Child welfare paramountcy: the donor conception paradox

By

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DEDICATION

This thesis is dedicated to my family:

My beautiful wife, Amanda,

My gorgeous children, Brydee and Angus,

My mother, Jane.

My dad, Hedley, my stepfather, Paul and my father, Rodney.

My brothers, Peter and Earl.

It is our connections with our family that makes us human.

WORKS ARISING FROM THESIS STUDIES

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SUMMARY

Introduction:

Donor conception is the use of a third person's gametes to achieve a pregnancy for a couple or person who may otherwise be unable to have a child. The donor-conceived child's welfare is to be treated as paramount in Australia under various pieces of legislation, regulation and international conventions. My significant original contribution to knowledge is that this thesis presents the firsts published systematic reviews on oocyte and sperm donation neonatal outcomes, as well as the first publication of the health outcomes of donor-conceived adults while assessing these outcomes through the child welfare paramountcy principle.

Study questions:

1) Are the health and welfare outcomes of donor-conceived people different from spontaneously conceived people?

2) Is the welfare of donor-conceived people being appropriately accommodated under the child welfare paramountcy principle?

What is known already:

People conceived with assisted reproductive technologies such as IVF have adverse perinatal outcomes, and there are concerns regarding their long-term health trajectories. Pregnancies implementing donor gametes/embryos are at an increased risk for hypertensive disorders of pregnancy, including preeclampsia which is also associated with adverse perinatal outcomes. Furthermore, donor conception frequently uses laboratory techniques, including freezing and embryo culture, which may adversely affect the gametes or embryos. The Developmental Origins of Health and Disease (DOHaD) phenomenon suggests that those born with adverse neonatal outcomes are more likely to suffer increased disease risks in adulthood.

Study design:

Three studies were conducted of donor-conceived people in comparison to those conceived spontaneously or through other technologies such as IVF:

1) A systematic review and meta-analysis of donor oocyte, sperm and embryo health outcomes.

2) A perinatal population-based study of donor sperm neonates.

3) A worldwide online health survey of donor-conceived adults.

Main results:

Donor sperm neonates were significantly more likely to be born of low birthweight (< 2500g) and with increased incidences of birth defects. Donor oocyte neonates were significantly more likely to born of low birthweight, very low birthweight (< 1500g), preterm delivery (< 37 weeks), preterm delivery with low birthweight, and of a lower mean gestational age.

Donor-conceived adults were significantly more likely to self-report being diagnosed with type 1 diabetes, thyroid disease, Hashimoto's disease, acute bronchitis, environmental allergies, sleep apnoea, having ear tubes/grommets surgically implanted, attention deficit disorder, autism and depressive disorder. They also reported increased incidences of having identity formation problems, learning difficulties, panic attacks, recurrent nightmares, alcohol/drug dependency, eating disorders, and seeing a mental health professional. DASS-21 analysis revealed that donor-conceived adults were also significantly more stressed.

Conclusion:

Donor-conceived people experienced a range of altered health outcomes neonatally as well as in adulthood. These outcomes are consistent with the DOHaD phenomenon and published studies. The welfare of donor-conceived people has not been treated as paramount as there has been no follow-up on their welfare. Some of these health outcomes are potentially modifiable by reducing the incidence of hypertensive disorders of pregnancy, particularly preeclampsia.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text.

Signed:

Date: September 28, 2020

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For the adult health study I would like to thank the following organisations for their support in advertising the survey, VARTA – Victorian Assisted Reproductive Treatment Authority; Donor Children online registry; Donor Conception Network – United Kingdom; Donor Conception Support Group – Australia; FIOM – Netherlands; and VANISH – Victorian Adoption Network for Information and Self Help. I would also like to thank the administrators of the following Facebook groups; Worldwide Donor Conceived People Network; We Are Donor Conceived; RUDC; Donor Conceived Offspring, Siblings, Parents (Sperm or Egg); DNA for the Donor Conceived; TangledWebs; and the email list PCVAI – People Conceived Via Artificial Insemination, for advertising the survey on my behalf.

To all the donor-conceived and spontaneously conceived people who completed the online survey, I extend my sincerest thanks as the first study into adult health outcomes associated with donor conception would simply not have been possible without them taking part and trusting me with their responses.

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ABBREVIATIONS AND ACRONYMS

5'AS<7	Apgar score less than 7 at 5 minutes
ABS	Australian Bureau of Statistics
ADD	Attention Deficit Disorder
ADHD	Attention Deficit Hyperactivity Disorder
AFS	American Fertility Society
AID	Artificial Insemination by Donor
ART	Assisted Reproductive Technology
ASD	Autism Spectrum Disorder
ASRM	American Society for Reproductive Medicine
BD	Birth Defects
BH	Benjamini-Hochberg
BMI	Body Mass Index
BPD	Borderline Personality Disorder
BW	Birthweight
CDC	Centers for Disease Control and Prevention
ChAb	Chromosomal Abnormalities
CI	Confidence Interval
cm	Centimetre
ConMal	Congenital Malformations
COPD	Chronic Obstructive Pulmonary Disease
DASS-21	Depression Anxiety Stress Scales (21 question version)
DC	Donor-Conceived
DI	Donor Insemination
DNA	Deoxyribonucleic Acid
DOHaD	Developmental Origins of Health and Disease
EENT	Ears Eyes Nose Throat
et al	et alia (and others)
FSA	Fertility Society of Australia
g	grams
GA	Gestational Age
GEE	Generalised Estimating Equations
gen pop	General Population
GERD	Gastroesophageal Reflux Disease

GIFT	Gamete Intrafallopian Transfer
HELLP	Haemolysis, Elevated Liver Enzymes, Low Platelet Count
HFEA	Human Fertilisation and Embryology Authority
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
ICSI	Intracytoplasmic Sperm Injection
ICU	Intensive Care Unit
IQ	Intelligence Quotient
IUGR	Intrauterine Growth Retardation (or Restriction)
IVF	Invitro Fertilisation
IVF-D	Invitro Fertilisation with Donor Sperm
JBI-MAStARI	Joanna Briggs Institute Meta-Analysis Statistics Assessment and Review Instrument
kg	Kilogram
LateD	Late-term Delivery (> 41 weeks)
LBW	Low Birthweight (< 2500g)
LGA	Large for Gestational Age (birthweight greater than 90th percentile)
MeSH	Medical Subject Headings
MRI	Medical Research International
mths	Months
Mult	Multiple delivery (triplets or more)
N or n	Sample size
NHMRC	National Health and Medical Research Council
NICU	Neonatal Intensive Care Unit
NPESU	National Perinatal Epidemiology and Statistics Unit
NSU	Neonatal Surveillance Unit
OCD	Obsessive-Compulsive Disorder
OI	Ovulation Induction
OR	Odds Ratio
PCOS	Polycystic Ovary Syndrome
PD	Preterm Delivery (< 37 weeks)
PE	Preeclampsia
PICOS	Participants, Interventions, Comparators, Outcomes, Study design

PIH	Pregnancy Induced Hypertension
PostD	Post-term Delivery (> 42 weeks)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD	Post-Traumatic Stress Disorder
RevMan	Review Manager Software (The Cochrane Collaboration)
RR	Risk Ratio
RTAC	Reproductive Technology Accreditation Committee
S	Singleton
SAPSC	South Australian Perinatal Statistics Collection
SART	Society for Assisted Reproductive Technology
SD	Standard Deviation
SEIFA	Socioeconomic Indexes for Areas
SES	Socioeconomic Status
SGA	Small for Gestational Age (birthweight less than 10th percentile)
sig	Significant
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TermD	Term Delivery (37 – 42 weeks)
Tw	Twin
UK	United Kingdom
UNCRC	United Nations Convention on the Rights of the Child
USA	United States of America
USD	United States Dollars
VARTA	Victorian Assisted Reproductive Treatment Authority
VLBW	Very Low Birthweight (< 1500g)
VPD	Very Preterm Delivery (< 32 weeks)
VSGA	Very Small for Gestational Age (birthweight less than 3rd percentile)
Wk	Week
yrs	Years

CHAPTER 1. DONOR CONCEPTION AND DOHAD

Infertility is a relatively common condition affecting approximately 9-18% of the general population[6] and approximately 15% of Australian couples/people of reproductive age.[7] Varying types of assisted reproductive technology (ART), including in-vitro fertilisation (IVF), but also donor conception, are used to assist people in overcoming infertility. Donor conception is the process of using a third party or parties to provide gamete(s) or embryos and has been used as a fertility treatment modality for countless people around the world. This fertility treatment has enabled them to overcome the emotional pain of infertility and provide them with the joy of having a baby.

Donor conception is not confined to just the actual physical treatment of infertility with donated gametes/embryos. It also includes other factors that enable its practice, such as legislation and regulation. An umbrella term used in this thesis to incorporate the entirety of the practice of donor conception is the 'paradigm'. The paradigm being how donor conception is practised and controlled through legislation and regulation in addition to the ART clinics actual practice. This paradigm is complex and contentious with considerable debate surrounding the issue of the welfare of donor-conceived (DC) people.[8-15] These welfare outcomes are significant considerations within the donor conception paradigm, specifically within the Australian context.

This thesis seeks to examine the welfare outcomes for people conceived with donated gametes/embryos. Welfare is generally considered to be comprised of both physical and mental wellbeing. Contributing to both physical and mental outcomes are material and social factors. In particular, the impact of social factors on outcomes for the DC person has been the subject of debate for some time.[16-19] However, the physical outcomes of donor-conceived people have been poorly addressed and under-investigated. This lack of investigation is a significant omission given that current knowledge suggests that conception and gestation are important components of a person's development and welfare. These debates, knowledge and lack of investigation of physical outcomes for the donor-conceived will be described in this thesis, but, first, a description of the history of donor conception and the global picture will be presented.

1.1 Introduction - Setting the Scene

In this section, a brief history of donor conception is described as a background to the welfare issues presented in this thesis. Detailed descriptions on the history of donor conception are presented in the works by Novaes,[20] Allan,[21] and Ombelet and Van Robays.[22]

The first use of donor sperm to achieve a pregnancy is credited to American William Pancoast in 1884.[23, 24] However, it was not until approximately 90 years later in the 1970s that assisted reproductive technology (ART) clinics and sperm banks became commonplace.[22, 25] It was during the 1980s that the use of donor oocytes and donor embryos started (both in 1984).[26, 27] In an Australian context, the first fertility clinic opened in Sydney in 1938.[28] While the use of artificial insemination (not necessarily donor insemination) was being used and advertised in South Australia from at least 1946,[29] and the first Australian sperm bank opened in Adelaide in 1972.[28]

It is not known how many people around the world have been conceived with donated gametes due to the secrecy often associated with donor conception.[30-32] Where data is known, for example, between 1996-2014, there were 74,892 ART cycles performed using donor sperm in the USA.[33] The percentage attributable to donor sperm increased over that period from 3.8% of all ART cycles in 1996, to 6.2% in 2014.[33] However, this data does not include artificial insemination treatments with donor sperm which is arguably also a significant proportion of all donor sperm treatment modalities.

In Australia, the National Perinatal Epidemiology and Statistics Unit (NPESU) reported that in 2017, 362 live births occurred as a result of donor sperm in Australia.[34] However, data from the Victorian Assisted Reproductive Treatment Authority (VARTA) annual reports for Victoria, one state of Australia, showed that for the financial year 2017-2018, there were 473 pregnancies from donor sperm treatments.[35] Similarly, for the financial year 2016-2017, there were 446 pregnancies in Victoria.[36] Even if all Victorian donor sperm pregnancies did not result in a live birth due to stillbirth or miscarriage, the numbers reported by the NPESU are low in comparison to data reported by VARTA and one would suggest what would also be occurring in other Australian states. Furthermore, NPESU data for donor sperm treatments only extend as far back as 1979, and therefore it has not captured the number of people conceived from donated sperm in Australia before that date. Whatever the reason, current information on the number of DC people born in Australia is unclear. Indeed, this uncertainty was highlighted in a Federal Senate inquiry into donor conception practices held in 2010.[37]

Without accurate data on the number of people conceived with donor conception around the world, in the USA or Australia, it is impossible to stipulate how many people are affected by the subject of this thesis. Some further information regarding the estimated rather than actual numbers of DC people in Australia is provided later in Chapter 4.

With a history of almost 140 years in the case of donor sperm treatments, it may be somewhat surprising, at least to some, that there is still much to learn about the outcomes for those people conceived with donated gametes. In particular, there is much to learn about their health.[1, 3] Quantifiable health outcomes of DC people are the primary focus of this thesis.

1.1.1 The Health of Donor-Conceived People

The potential for a DC person to have their health negatively impacted has its origins in their very mode of conception. It has been established that children born following the use of ART, including IVF, have increased morbidities,[38-46] and other health outcomes including altered epigenetic profiles.[47-50] Moreover, perinatal outcomes from ART procedures are associated with increased incidences of birth defects (BD), preterm delivery (PD < 37 weeks), lower birth weights and increased mortality in comparison to those observed from spontaneous conceptions.[45, 47, 51-59] This data highlights the possibility for adverse health outcomes occurring by manipulating gametes in a clinic or laboratory and using assisted reproductive technologies.

Of particular relevance for this discussion is the issue of adverse perinatal outcomes. These outcomes, including low birthweight (LBW < 2500g), and PD, have been correlated with increased incidences of morbidity and mortality in adulthood.[60-64] The increased incidences of non-communicable diseases and poor health arising in later life as a result of factors occurring during the conception and prenatal/developmental periods is termed the 'Developmental Origins of Health and Disease' or DOHaD.

DOHaD provides the theoretical framework and mechanisms through which the health of DC people may be affected not only at birth but also in adulthood. This chapter will introduce DOHaD and provide the foundation from which it is shown that the health of DC people require investigation.

1.2 Developmental Origins of Health and Disease (DOHaD)

1.2.1 The Barker Hypothesis

David Barker first described concepts of DOHaD in 1990 in his article 'The fetal and infant origins of adult disease'.[62] Subsequently, it has been dubbed the 'Barker Hypothesis' or in an early stage by Barker himself as the 'Thrifty Phenotype'.[65] The Thrifty Phenotype was based on his research that showed reduced foetal growth in the womb leads to increased incidences of chronic diseases in adulthood such as coronary heart disease, type 2 diabetes mellitus, and hypertension (high blood pressure).[66-69] This reduced foetal growth was attributed to maternal under-nutrition. This under-nutrition subsequently (re)programmed the foetus to prepare for later life, whereby sufficient and proper nutrition may also be problematic. Hence the term 'thrifty' as the foetus had to prepare for the short supply of nutrients and adjust its growth accordingly. The Barker Hypothesis was relabelled the Foetal Origins of Adult Disease (FOAD) which was later changed to DOHaD, as the hypothesis was found to encapsulate more areas including development rather than just the foetal stage.

Some infants who suffered from poor foetal growth, which is termed intrauterine growth restriction or intrauterine growth retardation (IUGR)[a] were subsequently born small for gestational age (SGA).[b] These infants would then undergo catch-up growth in which their growth was accelerated to bring them closer to their normal peers.[70-74] This catch-up growth is then also associated with different body compositions for these children, including higher body fat mass.[75-79]

SGA/IUGR children whose metabolism has been altered to accelerate this growth are at increased risk of developing metabolic syndrome.[80-84] Alterations in the child's metabolism have also been observed in the neonatal period with changes including:

> "glucose intolerance, insulin resistance, catabolite accumulation, and altered amino acid metabolism" p267.[85]

Metabolic syndrome can involve the following conditions: abdominal obesity, hypertension, elevated blood sugar levels, low high-density lipoprotein (HDL) levels, high serum triglycerides, and insulin resistance.[82, 86, 87] These conditions, as part of metabolic syndrome, are associated with increased incidences of cardiovascular disease and diabetes,[81, 88-90] and increases the mortality rate in this population.[91-94] Simplistically, obesity and altered

[a] IUGR is the condition in which the foetus/neonate is smaller than it should be due to a poorer growth rate.
[b] SGA is the condition in which the neonate has a birthweight below the 10th percentile for neonates of the same gestational age

metabolism obtained in adulthood through lifestyle choices are also associated with an increased risk of cardiovascular disease and diabetes. However, the developmental period can influence this trajectory and increase the incidences of obesity and metabolic disorders.

Some have suggested that rapid neonatal fat accumulation may be a useful marker for a DOHaD aetiology.[95] In addition to neonatal fat deposition, early childhood fat accretion has been associated with being born SGA and developing metabolic syndrome.[96] Regardless of which markers are most predictive through the neonatal, childhood or adult periods, being born SGA/IUGR has demonstrated negative consequences for the long-term health of the person born.

Further complications of being born SGA/IUGR include brain injury,[97-99] respiratory problems including bronchopulmonary dysplasia and asthma,[99, 100] altered immune systems with increased infections/allergies,[99-101] short stature, polycystic ovary syndrome (PCOS), premature adrenarche,[102] and reduced longevity.[103] Evidence is, therefore, suggestive that being born SGA/IUGR is not beneficial for long-term health.

The odds ratio for having an SGA child is increased when the mother was also born SGA showing the ability for poor foetal and adult outcomes to be inherited or at least have transgenerational transmission as a result of DOHaD.[104-107] The possibility of inherited SGA is consistent with studies showing an association with a father who was born SGA or LBW.[108-110] Furthermore, an association has been observed in SGA outcomes for twins and siblings.[111-113] This illustrates a strong heritable association with being born SGA and carrying it into the subsequent generation(s). Inheritance can be attributed to not only genetics but also potentially epigenetics, which is described later in this chapter.

There has been considerable controversy surrounding the DOHaD hypothesis. The data that lead to the Barker hypothesis was infant mortality and birth record data, including birthweight from England and Wales, starting from the early 20th century and correlating birthweight with cardiovascular disease later in life. Given that SGA was suggested to be the result of poor maternal nutrition, SGA children who grew up in the same lower socioeconomic environment were unsurprisingly more likely to experience poorer health in adulthood than their more privileged peers. This finding would be an association of confounding, which is one of the most serious of DOHaD criticisms.[114] There are many other potential confounders such as smoking, education, maternal age, maternal body mass index (BMI), birth order, obstetric complications, and maternal health which may also contribute.[115-117] Additionally, concerning

DC offspring, any pre-existing fertility issues can potentially negatively impact neonatal outcomes, including SGA.[118] There is however the suggestion that confounders such as socioeconomic status can be stable across generations, will be present before and after birth and are therefore part of the causal pathway.[119]

Authors Lucas *et al.*, in the earlier period of discussing the hypothesis had argued that much of the studies up until 1999 that investigated DOHaD were:

> "flawed by incomplete and incorrect statistical interpretation." p245.[120]

A further argument is that the hypothesis provides too broad a basis for the outcomes and that subsequently, many other models could also be applied to the data to provide a similar pathway analysis.[121] In comparison to the too broad a basis argument, there has also been a considerable narrow focus on just birthweight and SGA as primary outcome measures to determine the risk for adult diseases. Birthweight is just one marker of a poor foetal-maternal environment, and a subsequent focus on just these outcomes may produce erroneous conclusions.[115] Other markers such as catch up growth and childhood adiposity are therefore also important. Tu *et al.*, suggest that some of the evidence for DOHaD may be a statistical artefact created from adjusting for current weights which may exaggerate the relationship.[122] However, others argue that adjusting for attained bodyweight is warranted.[119] While the postulation by Tu *et al.*, is based on computer simulations rather than an analysis of observational data, the outcomes do raise potential concerns for some existing studies.

Notwithstanding, the DOHaD hypothesis continues to gain support from continual investigation and is generally accepted among scientists.[123] Furthermore, and crucially, the hypothesis is supported by animal models that remove confounding. These have shown similar results of the links between being born SGA/IUGR with catch up growth and having poorer outcomes in later life such as increased obesity and altered insulin/glucose homeostasis,[124-129] cardiovascular disease,[81, 130-133] brain alterations and damage,[134, 135] asthma and allergies,[100, 136] as well as shortened life-spans.[137-140] In an analysis of the DOHaD hypothesis and the criticisms surrounding it through a review of the literature, Skogen and Overland argue that most of the criticisms and methodological shortcomings have been addressed and that the hypothesis still holds credence.[141] The mounting evidence and the addressed criticisms have turned some original sceptics into converts.[114] The data has also become strong enough to compel the World Health Organisation (WHO) to include LBW as a risk factor for cardiovascular disease.[142] Due to the evidence and scientific community acceptance, the DOHaD hypothesis is described by some researchers as a phenomenon.[143-146]

So how can the foetal-maternal environment not only affect adult life but also life in subsequent generations? The answer may potentially lie with epigenetics.

1.2.2 Epigenetics of DOHaD

Epigenetics was first described in 1942 with the introduction of the term epigenotype.[147] Epigenotype was an explanation of the total development pathways of an organism and outcomes on that organism. Now, epigenetics is the study of how endogenous and exogenous factors (the environment) can reversibly alter the expression of genes but without altering the actual genetic code.[148] The sequence of the ATGCs is unaltered;[c] however, other factors affect gene expression. The genotype then gets translated into the phenotype, the observed outcomes of the gene expression. Epigenetics is concerned with changes to gene expression that alter the phenotype.

Modification of gene expression through epigenetic modification can occur through several mechanisms. These involve chromatin remodelling (a complex of DNA, histones and RNA) through methylation or demethylation of the DNA, or histone modification (including acetylation, methylation, and phosphorylation among others), as well as nucleosome positioning, and alteration of various mRNAs (messenger RNAs). More simply this means that various genes may be switched on or off, have the amount of their expression altered, or the proteins created from the transcription of these genes either altered or amounts increased or decreased. These changes occur through environmental pressures. These environmental pressures are not entirely understood. However, there are numerous pressures which could induce epigenetic changes such as but not limited to: diet (including micronutrients), chemicals (medications, alcohol, tobacco, mutagens), exercise, stress, and infectious agents.[149-153]

Even though epigenetic changes occur as a result of environmental factors, these modifications can be passed on to subsequent generations,[154, 155] including the passing on of epigenetic induced disease.[156, 157] This epigenetic transgenerational inheritance has been suggested to be a critical component of disease aetiology and subsequent risk assessments.[158, 159] While some adverse modifications are corrected in the embryo; some have the potential to be inherited.[160-164] These epigenetic modifications, whether induced in a person directly

[c] ATGCs are the four nucleotide bases of DNA, being A= adenine, T = thymine, G = guanine, C = cytosine.

through the environment or inheritance, have the potential to result in or be associated with various disease states due to phenotypic alterations.

In the case of gametes and the developing foetus, epigenetics plays a crucial role in growth and health outcomes for the individual and future generations. The sperm epigenome has numerous windows of opportunity for modification by the environment,[160, 165] leading to epigenetic transgenerational inheritance.[159, 166] In a review of the literature on epigenetics in oocytes, Clarke and Vieux argue that methylation or demethylation of DNA, histone modification, and short RNA modifications can occur during oogenesis.[161] Considering that oocytogenesis, a primary stage of oogenesis in the creation of primary oocytes, occurs before or shortly after birth and that a woman is born with their total number of oocytes that they will have in their lifetime; there is an opportunity to induce epigenetic changes in oocytes in the foetal-maternal environment. Epigenetic changes in the sperm, oocyte and embryo highlight its intrinsic relationship with DOHaD.

Altered gene expression and epigenetics has been associated with diseases synonymous with DOHaD such as diabetes[167-169] and is implicated by numerous authors as a potential cause for cardiovascular disease.[170-175] Additionally, in an analysis of animal models of epigenetic changes related to DOHaD, Cutfield *et al.*, hypothesise through the available evidence that the embryonic environment can lead to epigenetic modifications that in turn alter growth and metabolism in later life.[176]

Epigenetic modifications have been linked with the issue of infertility itself, which is the core underlying condition relevant to this thesis, albeit donor conception does not treat infertility per se (as described in Chapter 5). A review of the literature on sperm epigenetics by Jenkins and Carrell showed data supporting the position that:

> "proper establishment and maintenance of the paternal epigenetic program is associated with appropriate gamete and embryonic development, disruption of which is associated with varied degrees of infertility." p731.[177]

Similarly, Nilsson and Skinner in their review posit:

> “Environmentally induced epigenetic transgenerational inheritance appears to be an important contributing factor to reproductive disease in many organisms, including humans.” p1.[178]

These statements place a spotlight on the circular nature and self-fulfilling prophecy of DOHaD and epigenetics. A poor start in life by being born SGA/IUGR is associated with poorer health outcomes in adulthood. Adverse adult health is associated with decreased rates of fertility and poorer perinatal outcomes - and around the circle, it goes.

Subsequently, regardless of where epigenetic modification occurs, preconception (such as gametogenesis or the manipulation of gametes), the formation of the zygote/embryo (embryogenesis), preimplantation embryo development, the development of the foetus in-utero or in-vitro, during childhood, or even adulthood - epigenetics plays a crucial role not only for the health of the person concerned including their longevity,[157] but also potentially for future generations.

With the process of epigenetics established as a scientific theory that can in some instances explain poor growth, disease states and inheritance, it is a requirement to show then that processes involved in and around donor conception have the potential to induce epigenetic alterations.

1.2.3 Donor Conception - A Potential Source of Epigenetic Change

With adverse perinatal outcomes associated with ART already established, why would outcomes from donor conception require special consideration and segregation from a broader ART data set? Two factors, in combination with each other, set donor conception apart:

1) a novel antigen eliciting a maternal immune response leading to increased incidences of poor obstetric outcomes such as preeclampsia and pregnancy-induced hypertension,

and

2) laboratory/clinic manipulation of gametes, including extensive use of cryopreservation (freezing) techniques, and culture of embryos.

However, while the laboratory/clinic manipulation of gametes is also present in other ART treatment modalities such as IVF, it is its combination with the novel antigen that imparts the difference. Pregnancy-induced hypertension (PIH) which is also known as gestational hypertension, is the condition of having high blood pressure during pregnancy and develops after week 20 of gestation. High blood pressure is not only dangerous for the mother but also for the baby from the perspective that it reduces the amount of blood able to get to the placenta which can lead to a lack of oxygen and nutrients for the foetus. Preeclampsia (PE) is essentially PIH but with the added problem of an abnormal kidney and possibly liver function in the mother leading to excess protein in the urine. PE has the potential to be fatal. While PIH and PE are interrelated, the main focus of this section will be on PE due to the fact it is a far more severe and dangerous condition for both the mother, foetus and resultant child.

1.2.3.1 Novel Antigen

The novel antigen that is represented by a donor oocyte/embryo or donor sperm has the potential to elicit a maternal immune response leading to obstetric complications of which the hypertensive disorders of pregnancy including PE and PIH are particularly relevant from a DOHaD perspective.

1.2.3.1.1 Preeclampsia

The increased incidences of PE are associated with fertility treatments using donated gametes.[179-188] The risk of PE is elevated further in the cases of double donation (sperm and oocyte), over and above those observed for oocyte donation alone.[189] Preeclampsia is an immune response,[186, 190-192] that may alter placentation,[193-196] and is a leading cause of foetal and maternal morbidity and mortality.[197, 198]

While the association between the use of donated oocytes and PE is strong, there have been some reports where no correlation between the use of donated sperm and PE have been found.[199, 200] However, a recent systematic review highlighted that an increased risk for PE exists that is correlated with donated sperm in comparison to the use of partner's sperm in ART.[201] The association is also supported theoretically through the following immunological mechanisms.

The immunological component in response to a novel antigen (sperm), is highlighted by the reduced incidence of PE in women who have had prior repeated exposure to the semen/seminal fluid of the same man.[181, 202-204] Furthermore, the novel antigen association is highlighted by increased incidences of PE with changed paternity in subsequent pregnancies of multiparous women who did not have PE in the prior pregnancy.[205-207] Increased incidences of PE are also a problem of primipaternity (first-time pregnancy with that father), due to this novel antigen eliciting an adaptive immune response.[203, 208] Stratification of PE pregnancies into donor oocytes and autologous oocytes (mothers own oocytes) highlights this novel antigen immune response further, as different pathophysiological mechanisms were observed between the two groups.[209]

Of particular relevance, the immune mechanism of PE is correlated with factors such as IUGR, SGA and PD,[210-215] which are known to affect the child's health adversely. Individuals born following a pregnancy complicated by PE have increased risks of hypertension,[216-219] cardiovascular disease,[219-222] congenital heart defects,[223] endothelial dysfunction,[224] higher body mass index (BMI),[225, 226] higher triglycerides and non-HDLs,[226] gastrointestinal

disease,[227] hospitalisation due to disease,[228] stroke,[220, 229] asthma and allergies,[230-232] ophthalmic morbidity,[233] as well as mental disorders,[220] including epilepsy,[234] neuropsychiatric morbidity,[235] behavioural problems,[236] attention deficit hyperactivity disorder,[237] and autism spectrum disorder.[238, 239] Long-term health sequelae has been shown up to 70 years later with adults born as a result of pregnancies complicated with PE experiencing psychiatric problems.[240] Outcomes for the offspring born from a preeclamptic pregnancy outlined are extensive but by no means complete, yet even those listed highlight the severity of long-term health trajectories.

With PE having a heritable component,[241-246] in addition to women who are born SGA having a higher incidence of PE in pregnancy,[211] a cycle of PE and metabolic syndrome in both the mother and offspring has been created through the use of donated gametes.

So far in this analysis, it has been established that children born through ART have increased incidences of poor perinatal outcomes such as SGA and PD, while long term outcomes include but not limited to elevated incidences of cardiovascular disease. It has also been established that being born with adverse perinatal conditions such as SGA in spontaneously conceived conceptions is also associated with increased incidences of cardiovascular disease. It would seem plausible that they were causatively linked. However, Valenzuela-Alcaraz *et al.*, concluded that SGA and ART were independent causes of foetal cardiac remodelling, which can lead to cardiovascular disease.[247] The use of ART and donated gametes as an influence on poor perinatal and adult outcomes should, therefore, not be dismissed in favour of maternal factors that are associated with PE.

The origins of preeclampsia are multifactorial, which can create confounding. Not only is PE associated with adverse neonatal outcomes but it is also associated with other maternal factors such as metabolic syndrome,[248-252] obesity,[253-258] advanced maternal age,[253, 259-261] pregravid diabetes,[257, 262-265] pregravid hypertension,[253, 254, 265, 266] subfertility,[267-270] and maternal cardiovascular disease.[271-274] The aetiology of preeclampsia is therefore highly complex. Regardless of these maternal factors, the influence of donated gametes in increasing the risk for PE is a significant factor.[179-187, 275] A driving component of some of these adverse outcomes for those offspring affected by PE may potentially be epigenetics.

Epigenetic modifications have been correlated to poor placentation in preeclamptic pregnancies.[276-281] Infants and umbilical cord blood cells of foetuses exposed to PE have been shown to have altered methylation of IGF-2 (insulin-like growth factor-2),[277, 282, 283] which is

correlated with metabolic diseases in later life.[283, 284] Additionally, altered epigenetic profiles affecting a variety of genes and systems has been observed in foetal cells as well as neonates born after the pregnancy became preeclamptic.[285-288] As the use of donor gametes is associated with PE, is there a concomitant increased risk for adverse perinatal outcomes in donor offspring that is elevated above those found in spontaneously conceived offspring or those conceived via other ART treatment modalities? It is plausible that increased incidences of PE result in worse perinatal outcomes for the donor offspring cohort; however, PE is only one part of the potential problem.

1.2.3.1.2 Pregnancy-Induced Hypertension

Similar to PE, an increased incidence of PIH has been associated with pregnancies implementing donor oocytes.[200, 275, 289-293] For donor sperm, some studies have suggested an association to PIH,[184] while others have contradicted it.[200, 294] Whether this may be because PE has been studied more extensively than PIH in terms of donor sperm, or possibly that those women who do suffer PIH associated with donor sperm use may be more likely to go on to develop PE is unknown. However, a study of surgically extracted partner sperm used for intracytoplasmic sperm injection (ICSI) but which the woman had not been exposed to, found a higher incidence of PIH than those that had been exposed to their partner's sperm.[295] Once again highlighting the importance of exposure to semen antigens for not only the reduction of PE but also PIH.

Neonates born after a pregnancy complication by PIH are more likely to suffer a range of outcomes including LBW, SGA/IUGR, PD, stillbirth/mortality and neonatal intensive care unit (NICU) admissions.[296-300] Resultant children/adults are then more likely to go on to have high blood pressures themselves,[226, 301-305] cardiovascular disease,[306] higher BMI,[226] diabetes,[307, 308] behavioural problems,[309] and mental disorders,[310-312] among other issues. Similarities can, therefore, be drawn with observed offspring outcomes associated with PE, with albeit not quite as severe or as numerous problems. Further similarities are found epigenetically, as it has been suggested that offspring born from a pregnancy complicated by hypertensive disorders of pregnancy including PIH have similar epigenome-wide DNA methylations to those resulting from a PE complicated pregnancy.[313]

While there is a considerable public health problem for both the current generation giving birth and the subsequent generation (the child), as a result of PE and PIH, the increased incidences associated with the use of donated gametes and the potential implications for

future generations is disconcerting. Compounding the issue of child welfare outcomes through the use of donated gametes/embryos and the correlation to PE and PIH is the implication for problems also arising from the manipulation of the gametes as part of the fertility treatment itself.

1.2.3.2 Laboratory/Clinic Manipulation

Even during the very first donor insemination procedure of 1884, gametes have been manipulated as part of the donor conception treatment process. Whether it is from simple manual handling of sperm or oocytes to more modern techniques such as the cryopreservation of gametes/embryos or the culture of embryos in the laboratory, each manipulation is a window of opportunity to introduce epigenetic pressures or to damage the gamete/embryo directly.

1.2.3.2.1 Cryopreservation

Donor conception utilises cryopreservation of gametes and embryos extensively. Cryopreservation was first introduced as a means to store sperm for extended periods. This storage allowed the clinician to treat a woman with donor sperm whenever she came into the clinic, and the donor sperm could simply be thawed and used then and there. That is opposed to the problem of using fresh sperm in which the sperm donation is timed to coincide within a relative time window of the female patient's visit. Cryopreservation also allowed for the transport of sperm between clinics as required. However, now the use of cryopreservation is mandated to allow for the testing of various communicable diseases, mainly sexually transmitted diseases, but also for the screening of certain inheritable diseases. Mandatory cryopreservation first occurred in Australia,[314] as a result of the transmission of HIV to mothers that were reported in 1985,[315] and then found to have also occurred elsewhere.[316-319] Other jurisdictions soon followed suit and mandated the use of cryopreserved donor sperm.[320, 321] The situation for donor oocytes/embryos is somewhat a little different in that fresh oocytes/embryos are still used in addition to cryopreservation depending on the situation.[322-324] Donor-conceived cohorts potentially represent a useful tool for the investigation of the effects that cryopreservation has on offspring outcomes.

Sperm cryopreservation has been shown to cause fragmentation in both nuclear DNA,[325-327] and mitochondrial DNA.[328] It is also damaging to chromatin[d] and acrosome[e] integrity.[329, 330] Furthermore, the sperm's morphology, motility and viability are adversely affected,[331-333] which are important markers of fertility.[334, 335] Manual handlings of sperm using various laboratory techniques to prepare the samples also can induce DNA fragmentation.[336-338] For cryopreserved sperm, however, oxidative stress has been proposed as a mediator of fragmentation,[339, 340] occurring directly from the cryopreservation process.[341]

In an attempt to reduce DNA fragmentation, cryopreservation techniques have often resorted to using antioxidants in the freezing media.[342, 343] Others implement vitrification (freezing without ice crystal formation) as an alternative to conventional freezing as it improves motility post-thaw. However, DNA fragmentation rates remain similar regardless of the cryopreservation process.[344] Others have argued that while DNA fragmentation does occur from cryopreservation, that various techniques and media can reduce the amount of fragmentation as well as improve motility.[333, 345] Regardless of the technique or antioxidants used, sperm does suffer from damage that may be irreparable.

Significant DNA damage may result in either non-fertilisation or that the embryo will fail to develop properly and subsequently not carried to term.[346] However, given that single base changes in DNA (called single nucleotide polymorphisms) are associated with cardiovascular disease,[347, 348] autism spectrum disorders and schizophrenia,[349, 350] infectious diseases,[351, 352] and cancer[353, 354] among countless others, the consequences that small scale DNA changes can have on the health of the child are potentially significant.

Unfortunately, DNA damage is unable to be repaired by the sperm as it has no repair mechanisms,[355, 356] even though it has some pathways that would suggest that it could occur. However, sperm are missing some vital downstream components.[357] The oocyte is therefore required to undertake DNA repair,[358-360] otherwise, the damage may lead to programmed cell death, or the damage gets passed on to the embryo. In some instances, programmed cell death would be the preferred outcome rather than to continue the development of an embryo containing a deleterious alteration.

[d] Chromatin is a complex of DNA and protein including histones. It is important in the packaging of DNA to fit into the nucleus and is critical for the expression of genes.
[e] The acrosome is the cap which covers the head of the sperm. It is essential for breaking down of the oocyte's membrane the zona pellucida to enable fertilisation.

In oocyte cryopreservation, toxic cryoprotectants are often used.[361-364] Some reports have shown increased incidences of DNA damage,[365-367] including chromosome misalignment that is correlated with oocyte cryopreservation.[368] Although, this increased DNA damage is disputed by others.[369, 370] Of relevance to this issue is a report by Stigliani *et al.*, who stated:

> "Gene Ontology analysis by DAVID bioinformatics resource disclosed that cryopreservation deregulates genes involved in oocyte function and early embryo development, such as chromosome organization, RNA splicing and processing, cell cycle, cellular response to DNA damage and to stress, DNA repair, calcium ion binding, malate dehydrogenase activity and mitochondrial activity." p2519.[371]

The proposed deregulation of a cryopreserved oocyte's DNA repair mechanism has implications for the oocyte's ability to fix DNA damage occurring in cryopreserved sperm. Regardless, it has been postulated that sperm DNA fragmentation is a severe concern for offspring conceived via ART,[372] as sperm DNA damage may be transmitted to the embryo,[373] which is consistent with the statement by Stigliani and co-authors. Cryo-damage to the oocyte is not confined to DNA but also affects the oocyte's membranes and mitochondria, which may lead to altered metabolism.[374, 375]

Not only is direct DNA damage a cause for concern in the developing embryo, evidence of the sperm epigenome (epigenetic changes that alter the expression of the sperm genome), suggests that sperm epigenetic changes also play a role in the developing embryo.[177, 376, 377] This is because the embryo not only obtains DNA from the sperm but also incorporates centrosomes, activation factors, mRNA and iRNAs (interfering RNA), from the sperm.[378, 379] Subsequently, it is not merely a matter of being concerned with sperm DNA alteration or damage but also whether any chromatin remodelling, methylation/demethylation, altered RNAs, or histone modification induced epigenetic changes have occurred which can then impact the embryo. Such epigenetic changes have been associated with various outcomes, such as poor embryogenesis and male factor infertility.[380-383]

Specifically, for the DOHaD hypothesis with an emphasis on foetal growth, aberrant methylation and loss of imprinting have also been linked with both SGA placenta,[384-387] and IUGR placenta.[388-391] It has been argued that these methylation patterns are important determinants and markers of the in-utero environment as methylation remains relatively constant during labour, but that gene expression may change during this period.[385] While methylation may remain constant during birth; the effect cryopreservation can have on methylation patterns is less clear. Some studies have shown altered methylation in the oocyte,[392-395] and resultant zygote/embryo,[396-400] in various models including animals. Also

linking with foetal growth is the correlation between the use of cryopreserved embryos and an increased incidence of PE,[401] which is then also correlated with SGA/IUGR.

Oxidative stress which is associated with sperm cryopreservation is also separately associated with altered methylation in sperm,[402-405] and oocytes.[403] Which, in turn, affects fertility and embryo development. Others argue cryopreservation itself does not alter methylation patterns in gametes/embryos.[406-408] While debate exists regarding epigenetic changes resulting from cryopreservation, what can be concluded from those studies, is that typically specific genes and methylation patterns were targeted for analysis and that we do not yet know what effect cryopreservation has on not only the methylation pattern of 'all' genes but also other epigenetic modifications. These epigenetic changes and the implications for the health of offspring has raised concerns with some researchers.[382, 383, 409] Especially when considering data from mice showed that histone methylation in sperm adversely affected the health of offspring transgenerationally [410], and that female mice offspring had altered adiposity and glucose tolerance when conceived with sperm exposed to oxidative stress.[411] Therefore, further investigation is required.

Moreover, there are concerns about epigenetic changes which have also been associated with various cancers.[412-417] There is considerable literature on the links between epigenetic changes and other diseases/disorders, including imprinting disorders,[418] in which a loss of imprinting is harmful to the foetus and leads to various diseases/disorders.[419] However, to list them all here would be too lengthy. Instead, the reference to an association with cancer is an example of how such changes can adversely affect the health of individuals. It is through epigenetic modification that we can see that pathways exist which can induce different health trajectories for individual's dependent on their environment, including foetal-maternal, as well as preconception through the manipulation of gametes.

Associations between the use of ART and imprinting disorders in offspring has already been established.[420-424] Others have argued that epigenetic variation at birth that is associated with ART mostly resolves at adulthood and therefore does not adversely affect health and development.[425] Problematically as is the case with other studies suggesting that cryopreservation does not alter methylation, this study was also limited in what markers were studied. It did not investigate the imprinting disorders of Angelman syndrome, Beckwith-Wiedemann syndrome, Prader-Willi syndrome, or Silver-Russell syndrome that others have shown a correlation with and that have epigenetic and genetic aetiologies.[426] Rather, they looked at other imprinting loci. Caution should, therefore, be taken before broad

overarching statements such as the following are made when the authors have not assessed all aspects of epigenetic variation:

> "Importantly, ART-associated epigenetic variation at birth largely resolves by adulthood with no direct evidence that it impacts on development and health." p3922.[425]

Due to the potential for DNA and epigenetic changes induced through the manipulation of gametes, it is important to monitor how cryopreservation and the handling of gametes in a clinical environment may impact the health of DC people. In a discussion on DNA damage in sperm which included an analysis on cryopreservation, Gavriliouk and Aitken, make a profound statement that can be equally applied to the use of cryopreserved oocytes and emphasises the core component of this thesis of offspring health:

> "The integrity of sperm (oocyte) DNA is vital for the subsequent health trajectory of the off-spring.....given the current widespread use of ART to achieve conceptions in vitro that could not have occurred in vivo; until the genetic consequences of such trends are understood, we may be inadvertently creating a health burden for our species that future generations will have to solve." (oocyte added) p42.[427]

1.2.3.2.2 Embryo Culture

Those donor conception treatment modalities that may implement embryo culture include oocyte donation, embryo donation (double gamete donation), IVF with donor sperm, ICSI with donor sperm and gestational surrogacy using a donor oocyte and possibly donor sperm. These modalities implement IVF methodologies to fertilise the oocyte and grow the zygote in culture to become an embryo before implanting into the womb. Over the decades of IVF practice, numerous techniques, methodologies and equipment have been used. Importantly in terms of epigenetic change is the use of various culture media and the actual culturing process in an artificial environment. Some have regarded embryo culture as having the highest potential for introducing epigenetic change.[428] In light of evidence from the impacts of cryopreservation, PE and PIH, this statement is debatable in the context of donor conception. However, the impacts of embryo culture are potentially profound.

Some have attributed the increased incidences of birth defects, morbidity and imprinting disorders to the implementation of embryo culture and the lack of protection against oxidative stress.[429] Embryo culture has been shown to alter DNA methylation of embryos,[430-433] with variations in culture media themselves inducing changes in methylation patterns.[426, 434-436] Others have suggested that evidence failed to show an increase in methylation in imprinting genes resulting from culturing in two different media.[437] Similarly, to earlier

criticisms levelled at other studies that suggested that there is no problem with IVF/donor conception this study only looked at two different media and is not a comparison of the many different media that is currently available. Therefore it should not be taken as a conclusive argument to counter claims that media does not influence methylation more broadly.

The impacts of the use of various culture media are not confined to the embryo but also appears to manifest in altered outcomes for the children. Studies have shown that different culture media alters measures such as birthweight, bodyweight, BMI, adiposity,[438-443] and increased developmental problems.[444] These outcomes are consistent with altered health trajectories already associated with the use of ART.

1.2.3.2.3 Intracytoplasmic Sperm Injection

Intracytoplasmic sperm injection (ICSI) has become the most commonly used IVF technique in recent years,[445] in which a single sperm is selected by an embryologist and injected into an oocyte. This process can implement both donated oocytes and donated sperm. However, it is also used with a partner's sperm. Regarding sperm donation, ICSI is sometimes used because a lower volume/amount of sperm is required. This situation enables donor sperm to be used for more women/treatments than intrauterine donor insemination.

In comparison to traditional IVF, some studies have reported an increased frequency of adverse outcomes perinatally and long-term, including birth defects,[446-448] as well as autism and mental disability.[449-452] In terms of the offspring's own fertility, males conceived from ICSI have been reported to have poorer semen and endocrine parameters[453, 454] which may be associated with the father's male-factor infertility.

Irrespective of phenotypic outcomes, there has been a range of epigenetic modifications associated with ICSI. These changes have included altered methylation,[455, 456] including imprinting genes,[457] and histone modification in the placenta.[458] Foetuses conceived through the use of ICSI have been shown to have altered methylation patterns.[459] While in the resultant children themselves, an increase in imprinting disorders have been associated with ICSI resulting from altered epigenetic profiles.[420, 422, 460] It has been argued that it is not clear at what stage these modifications are introduced.[461]

The mechanisms and current evidence shown above is disconcerting for the health and wellbeing of people conceived with ART. Notwithstanding, some studies are confounded due to subfertility and other maternal/paternal factors making it challenging to come to definite

conclusions.[462] Subfertility is less of an issue in donor conception analysis as the person who is infertile or subfertile is often taken out of the equation except for oocyte donation. However, the success of donor oocytes highlights that a considerable proportion of the infertility is an issue of old eggs. However, other factors that provide confounding are essential considerations.

1.2.4 The Role of Confounding

Many factors can impart confounding to an analysis of donor conception outcomes. For example, advanced maternal/paternal age and poor maternal/paternal health which are associated with infertility or subfertility are confounders in analysing offspring outcomes.[47, 58, 463-466] The underlying health conditions of the parents, linked with their fertility problem, contribute to these poorer outcomes in their babies. Confounding is sometimes used to postulate that it is not the ART procedure but rather parental health and infertility or subfertility that is a significant factor in these poor outcomes.[467-469] However, subfertility or infertility is typically not one of them in donor conception due to the use of gamete donors. Some of the significant confounders associated with donor conception will be discussed here which highlight that it is a combination of the ART treatments and confounding that is associated with adverse outcomes for those conceived with ART.

1.2.4.1 Multiplicity

The use of ART is associated with multiple births, including twins which are a well-known confounder of perinatal outcomes.[470-477] A simple way to control for multiplicity is to stratify data and analyse singletons and multiples separately. In singletons, it has been shown that ART pregnancies still result in worse perinatal outcomes such as LBW, PD, and congenital malformations (ConMal) compared to those conceived spontaneously.[52, 54, 478-483] Furthermore, they are more likely to be admitted to the NICU.[484] Preterm delivery was elevated in ART children even when compared to a sibling who was not conceived via ART, thereby removing maternal confounders.[52]

There has been a suggestion that the increased risk in singletons may potentially be due to double embryo transfers that resulted in singletons rather than single embryo transfers,[485] although others dispute this result.[486] In terms of development after birth, a meta-analysis of childhood growth found a significantly lower weight in ART children aged 0-4 years which was no longer significant after five years of age.[487] This could perhaps be an example of catch-up growth to make up for a lower birthweight under the DOHaD phenomenon.

Stratification into twins conceived via ART compared to spontaneously conceived twins shows similar adverse outcomes of LBW, PD and ConMal,[476, 488-491] and they are more likely to be admitted to the NICU.[492] Multiple births, including twins, are already known for having a disproportional amount of adverse perinatal outcomes than singletons in spontaneous conceptions.[493-496] Some of the differences are attributed to higher incidences of PD, and those that make it to term are argued to be not worse off.[497-499] Notwithstanding, the evidence of the negative effect of twins and multiples on perinatal and maternal health was strong enough that either elective single embryo transfer is now recommended in ART practice or that at the least higher-order multiple pregnancies are discouraged in some jurisdictions.[500-504] It would appear that regardless of whether the birth is a singleton or multiple, controlling for this confounding shows that the use of ART is associated with poorer perinatal outcomes.

As is the case with most conclusions in this field, it is not without contention with some studies suggesting no increased risk as a result of being conceived with ART (singletons or twins).[505-508] Some of these conflicting studies are of smaller cohorts and or are older publications. On balance, the weight of evidence, including meta-analysis points to poorer perinatal outcomes as a result of ART which are generally accepted to be a significant problem in the field of ART research.[47] Ombelet *et al.* support this proposition, whom after analysing over 1 million births made the following statement:

> "According to our results all ART pregnancies, whether due to IVF/ICSI or non-IVF treatment, have to be considered as risk pregnancies, irrespective of the number of foetuses." p193.[509]

1.2.4.2 Maternal Age

Advanced maternal age (AMA > 35 years) and very-advanced maternal age (VAMA > 45 years) are other well-known confounders of poor perinatal outcomes including LBW, PD, SGA, ConMal, NICU admissions,[260, 510-515], and also the obstetric outcome of PE.[260, 510, 514, 516-518] Conversely some have observed no difference in PE outcomes.[519] Problematically, women of AMA and VAMA are more likely to use ART,[519] due to the reduction in their fertility. In donor conception, the reduction in a woman's fertility due to age is more likely to be associated with the use of donor oocytes or donor embryos, whereas donor sperm can be used over the entire fecund age range.

Even though the mother's age may be advanced, the age of the oocyte donor is relatively young by comparison,[520] and is critical for improving the cumulative live birth rates.[521, 522] The use of 'young' oocytes in effect provides better outcomes in terms of producing a pregnancy and having a baby.[523] It is an aspect some ART clinics promote when advertising for oocyte

donors in which they seek women under the ages of 30-35.[524-529] The use of ART may provide a protective effect for older mothers with evidence suggesting that the effect of age may be worse in women conceiving spontaneously than those utilising ART.[530] Analysis of donor oocyte and donor embryo perinatal outcomes are therefore less likely to be influenced by AMA and VAMA than donor sperm perinatal outcomes. Nonetheless, the issue of maternal age is still significant.

1.2.4.3 Parity

Parity is the number of times that a woman has given birth. Nulliparity (zero previous births), and grand multiparas (4+ births) are associated with poorer obstetric and perinatal outcomes.[531-537] As grand multiparas are also associated with lower socioeconomic status, increased BMI and higher maternal age,[538] the association with poorer outcomes is not surprising. The link with nulliparity is perhaps a little tenuous as it is suggested that the link may be biased due to those women who have a poor pregnancy as their first may be less likely to have a second pregnancy and second child.[539]

1.2.4.4 Obesity

Obesity is another confounder associated with poorer outcomes and is the most common condition for reproductive-age women.[540] It is associated with infertility and obstetric complications such as gestational diabetes, hypertensive disorders, as well as perinatal outcomes such as large for gestational age (LGA = birthweight greater than 90th percentile), PD, and ConMal.[540-544] Problematically for the child and fitting in with the DOHaD phenomenon is that they are also more likely to become obese themselves and develop metabolic syndrome.[545-548]

1.2.4.5 Socioeconomic Status

Socioeconomic status (SES) as a confounder is far more complicated as it incorporates numerous factors. It has been argued that SES has little effect on perinatal outcomes.[549] Rather, the authors found associations to maternal drug use, hypertension and diabetes which are factors also associated with lower SES,[550-552] as is obesity,[553-555] and which has already been correlated to adverse perinatal health. Others have contradicted the lack of an association between low SES and perinatal outcomes.[556-560] The multifactorial nature of low SES makes it challenging to analyse this confounder. From an ART perspective, IVF is associated with higher SES,[561-564] however, after adjusting for confounding, SES did not influence perinatal outcomes in IVF pregnancies rather the perinatal outcomes were affected by the IVF treatment itself.[561]

1.2.4.6 Confounding Discussion

Donor conception provides an interesting subset of ART treatment outcomes in terms of confounding. Infertility and or subfertility is mostly abrogated as the process of donor conception often removes the person or the issue associated with infertility. Donor oocytes remove some of the issue associated with AMA or VAMA, due to the age of the donor. Finally, people utilising donor conception are typical of high SES. Changes in the DNA methylation patterns of children conceived with ART are independently linked with the fertility treatment itself and are not just a function of confounding by the infertility status of the patients.[50] Thereby highlighting the link between ART treatments and the health of offspring from an epigenetic and subsequent DOHaD perspective.

All studies should at least discuss confounding especially in the instances whereby they are not able to be controlled. In the studies conducted for this thesis, confounding was either controlled or assessed as part of the analysis. Regardless, Berntsen *et al.*, make a profound statement when they argue in their review and analysis of the literature, that where studies have done an excellent job of disentangling confounding from ART outcomes, that both confounding parental parameters (such as infertility and maternal age), and the ART procedure itself are all important and contribute to the health of the child.[47]

Following on from the discussion in this chapter, it is therefore imperative that the health outcomes for donor-conceived people are investigated to determine whether the health trajectories of DC people differ to their peers. The answer could be that even though mechanisms exist that would suggest that their outcomes could be worse, in reality, these may not come to fruition. Alternatively, perhaps gamete selection rather than conception through

chance, the manipulation of the gametes in the clinical setting, and certain epigenetic changes could be beneficial, and an improvement in outcomes may be observed. The question is, are DC people's physical welfare altered in any way?

1.3 Research Question and Aims

The purpose of this thesis is to investigate the health and welfare outcomes for people conceived with donated gametes. It is an attempt to fill quantifiable health outcome gaps in the literature while keeping a focus on the welfare and best interest of the child and subsequent adult created from such technologies. It does not seek to address outcomes such as child psychosocial development or family functioning.

The research question: Is the physical and mental health of donor-conceived people different from those observed for people conceived as a result of spontaneous conceptions (donor sperm comparison cohort), and autologous oocytes (donor oocyte/embryo comparison cohort)?

1.3.1 Research Aims

1. The primary aim of the research is to obtain quantifiable physical and mental health data on DC people for two stages of life:
a) perinatally (physical health outcomes);
b) adulthood (physical and mental health outcomes).

2. Determine if the quantifiable health of DC people is altered when compared to their appropriate comparator group.[f]

3. Determine if adult DC people have health outcomes that have been potentially influenced by their mode of conception and which are implicated in the DOHaD phenomenon.

4. Assess health outcome data within the donor conception paradigm to determine if the welfare of DC people is appropriately considered in Australia.

[f] Comparator data was also collected. Comparators are the control/comparison groups of those conceived spontaneously (sperm donation offspring comparison) and those conceived through IVF using autologous/own oocyte (oocyte/embryo donation offspring comparison).

1.3.2 Thesis Overview

A flow chart of the structure of this thesis is presented in Figure 1.1. The flow of the thesis is as follows:

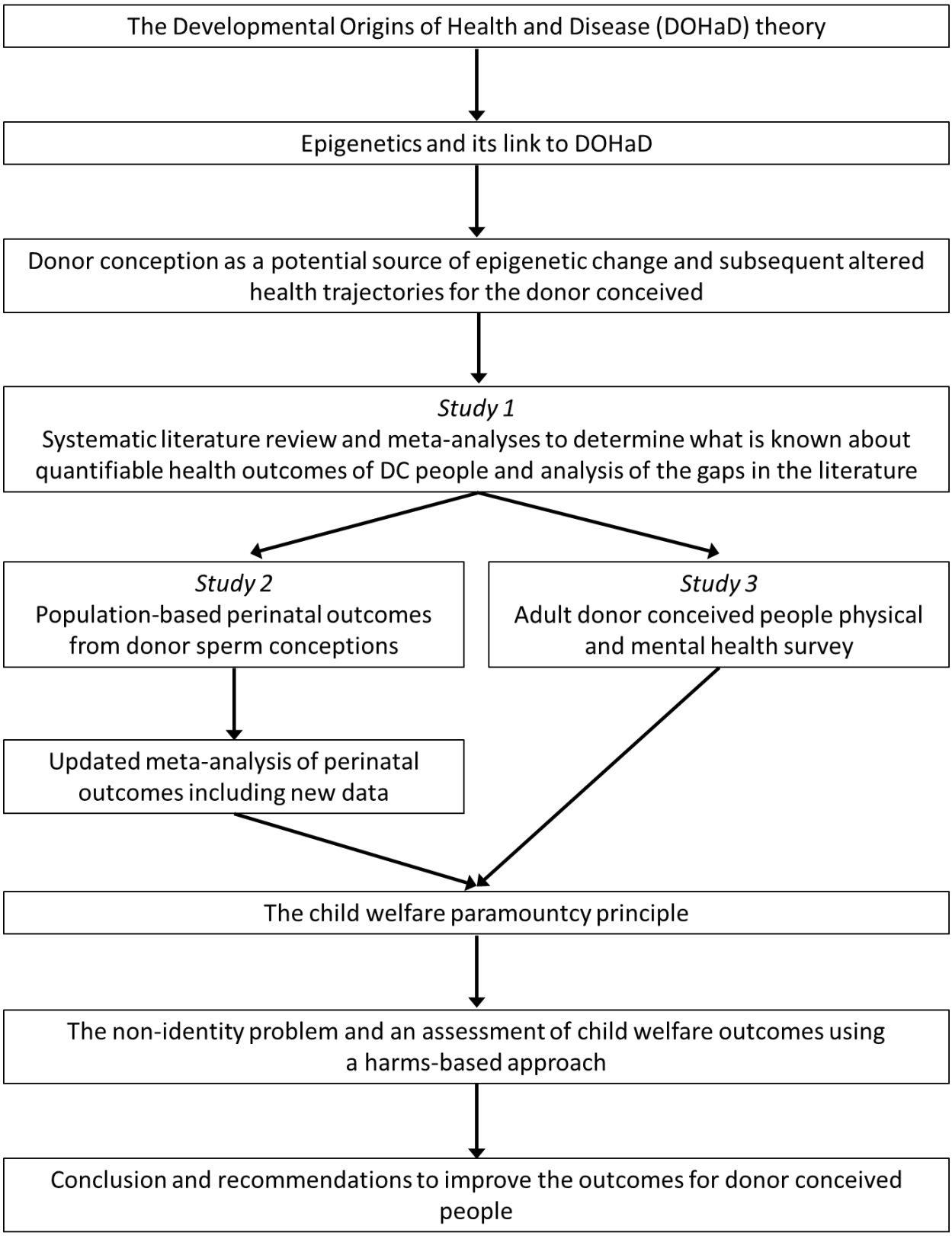

Figure 1.1 Thesis flow chart

Chapter 1: Describes donor conception and the Developmental Origins of Health and Disease (DOHaD) phenomenon, including DOHaD epigenetics and how donor conception creates mechanisms through which DC people may have their health trajectories altered.

Chapter 2: Study 1 – a systematic literature review and meta-analyses to determine what is currently known on the health of DC people and to identify gaps in the literature.

Chapter 3: Study 2 – comprised of two parts, the first of which investigated perinatal outcomes for donor sperm-conceived neonates in a population-based study in South Australia. The second part is an updated meta-analysis of donor sperm outcomes, including new data from the perinatal study in addition to newly published studies.

Chapter 4: Study 3 – a health survey of adult DC people from around the world in comparison to those adults conceived spontaneously. This study is separated into two parts, physical health outcomes and mental health outcomes.

Chapter 5: The thesis changes direction and explores the ethical and legal principle of child welfare paramountcy and how the physical and mental health outcomes from the preceding three chapters are related to this concept within the donor conception paradigm.

Chapter 6: Provides a description and rebuttal of the substantive ethical argument of the non-identity problem which is sometimes used to forward the position that any adverse welfare outcomes DC people experience, is the cost of existence. It then presents a synthesis and summary of the research, which is then used to analyse the welfare outcomes under the child welfare paramountcy principle using a harms-based approach.

Chapter 7: Thesis conclusion. Recommendations are made that could lead to improvements in both the welfare of DC people and donor conception policy more broadly to facilitate the child welfare paramountcy principle. Further recommendations are presented for future research.

CHAPTER 2. DONOR-CONCEIVED OFFSPRING HEALTH OUTCOMES – A SYSTEMATIC REVIEW

This chapter represents an updated and reworked discussion from a systematic review and meta-analyses that analysed outcomes from donor oocyte and donor sperm conceptions and which were published in the manuscripts:

Adams DH, Clark RA, Davies MJ, de Lacey S. A meta-analysis of neonatal health outcomes from oocyte donation. J Dev Orig Health Dis. 2016;7(03):257-272.[1] (Appendix 1.1).

Adams DH, Clark RA, Davies MJ, de Lacey S. A meta-analysis of sperm donation offspring health outcomes. J Dev Orig Health Dis. 2017;8(1):44-55.[3] (Appendix 1.2).

 Outcomes pertaining to donor embryos has not been published previously.

Attribution of authorship for both manuscripts:
DA (80%) and SdeL contributed to the design of the systematic review. DA (100%) conducted the computerised searches of the databases. DA (90%) and SdeL assessed articles for eligibility. Data extraction was conducted by DA (100%). Data analysis was performed by DA (80%), RC (10%), MD (5%) and SdeL (5%). DA (90%) drafted the manuscripts with all other authors (RC, MD, and SdeL) providing edits and revisions.

Note: A requirement of Flinders University for the inclusion of published manuscripts (or components of a published manuscript) in a thesis is that the student must be the primary author and that there is a clear statement in prose at the start of the chapter describing the contribution of each author.

2.1 Introduction

In the preceding chapter, the need for a study investigating the health outcomes for DC people was established. Before a study was planned and designed, there was first an imperative to conduct a review of the literature pertaining to health outcomes for DC people. This review was conducted as a systematic review. It is the first study in a sequence of three studies that form the substantive content of this thesis. These three studies underpin the review of the DC paradigm that concludes this thesis. This chapter presents the systematic review and therefore, the current knowledge as of November 2012 regarding the health outcomes of DC

people. It is an investigation of the outcomes from all three treatment modalities of donor oocytes, donor sperm, and donor embryos (double donation).

In the methods section below the method used for the systematic review is presented. This method covered all three treatment modalities as the search and analysis were conducted at the same time. The search results are also presented together. Stratified results and discussions about each modality are presented separately and are followed by a conclusion examining all three together.

2.2 Methods

The systematic review and reporting were conducted following the PRISMA guidelines.[565] The PRISMA checklist is presented in Appendix 1.3.

2.2.1 Literature Search

To identify publications reporting health outcomes of DC people, a computerised search of the literature from the online databases of Cochrane Reviews, EMBASE and PubMed[g] was performed. Selection of these databases was based on the methodology for conducting a systematic review of Wright *et al*.[566] The authors argued in 2009 (not long before this search was conducted), that there was only a 34% overlap between PubMed and EMBASE. Furthermore, they argued that PubMed had better coverage of American publications while EMBASE had better coverage of European publications and that Cochrane Reviews provided additional coverage for randomised control trials. This strategy of using these three databases enabled the authors to obtain reasonable coverage of the literature with minimal duplication. The search was conducted on November 15, 2012, was not restricted by date and included all articles published up to November 15, 2012, except for EMBASE which only allowed searches from 1980 onwards.

A 3-stage process was implemented as the search process. The first stage included all relevant articles known to Damian Adams to identify keywords. The keyword identification was coupled with a search of the Medical Subject Headings (MeSH) database of the U.S. National Library of Medicine to identify suitable search headings. The second stage was the searching of the online databases using the MeSH terms and other keywords. Analysis of search results allowed the analysis of the search specificity to allow refinement of search terms as presented in the next paragraph. The third and final stage was the examination of references of

[g] The PubMed database also incorporates the databases of MEDLINE and Index Medicus.

identified articles to find further articles that may have been inadvertently missed by the search strategy.

The three treatment modalities of 'oocyte donation', 'embryo donation' and 'artificial insemination' were used in conjunction with 'reproductive techniques' to create four search categories to be called 'techniques'. The term 'reproductive technique' was utilised as a catch-all term, while the term 'artificial insemination' was used in favour of the terms, 'sperm donation' or 'semen donation' due to the long history of its use in the literature. Furthermore, other search terms, including the descriptors described hereafter, were implemented to cover those articles not identified by the search using the artificial insemination term. The descriptors used were 'donor' and 'human' which filtered out treatments using autologous (own) gametes/embryos and animal studies. Additional filtering was obtained using three qualifiers which were added to each of the four techniques and two descriptors. These qualifiers were 'adverse effects', 'morbidity', and 'outcome*'. Implementation of the '*' wildcard covered studies with either of the keywords, outcome or outcomes.

The National Library of Medicine specifies the above terms of 'insemination, artificial', 'oocyte donation' and 'reproductive techniques' as MeSH terms and descriptors. 'Human' is a MeSH term descriptor. 'Donor' is an entry term of the MeSH heading 'tissue donors'. 'Morbidity' is an entry term of the qualifier 'epidemiology'; however, using the morbidity term returned more results than epidemiology. 'Adverse effects' is classed as a qualifier. In EMBASE, outcome, morbidity, and adverse effects were used as keywords.

2.2.2 Eligibility and Selection

The following PICOS criteria were used to determine article eligibility. Damian Adams determined article eligibility with verification performed by supervisor Sheryl de Lacey.

Participants; cohorts of neonates, children and or adults from which health data was presented in a published study.

Interventions; the treatment cohort groups must contain people conceived through donated sperm, oocytes or embryos. Treatment cohort data was required to be stratified and separated from comparison cohort data. Furthermore, they should not be contained within larger datasets that combined data and would bias analysis.

Comparators; for oocyte/embryo donation outcomes the comparison cohort could contain spontaneous conceptions as general population data or as a specific cohort, and or offspring

conceived through ART treatments using autologous oocytes/embryos as applicable. For sperm donation outcomes, the comparison cohort could contain spontaneous conceptions as general population data or as a specific cohort.

Outcomes; included studies must report either neonatal or child/adult health outcomes. Neonatal outcomes include categories such as but not limited to: BW (birthweight), LBW (low birthweight < 2500g), VLBW (very low birthweight < 1500g), GA (gestational age), SGA (small for gestational age, BW < 10^{th} percentile for GA), IUGR (intrauterine growth retardation), PD (preterm delivery < 37 weeks), TermD with LBW (term delivery 37–42 weeks with LBW), BD (birth defects), ChAb (chromosomal abnormalities), and ConMal (congenital malformations). Child/adult health outcomes could include any data that provided numerical values such as BMI or incidences of various conditions. Neonatal studies were excluded if they were only case studies investigating a single or few births, or if they only reported live-birth rates.

Study design; to avoid variation between populations and periods, studies were restricted to observational case-controlled studies with an appropriate comparison cohort. Furthermore, studies could be included, if the comparison cohort was publicly available health data or published public health data provided the data was from the same region and was also published/reported within ten years of the publication of the study.

Search results from each database were downloaded into Endnote (Clarivate Analytics, Philadelphia, United States). Titles and abstracts were analysed for suitability. Non-English language articles were excluded to enable scrutiny of the terminology, methodology and data. Those articles that could not be excluded via title and abstract analysis were submitted to a full-text review to determine suitability. Disagreements regarding the inclusion/exclusion of articles were resolved by discussion between Damian Adams and Sheryl de Lacey.

2.2.3 Data Extraction

A specially designed data extraction form was used to record all appropriate offspring data from the included studies (Appendix 1.4). From the eligible studies, the following data were recorded: citation (author(s) and year), country, treatment type and sample size (donor sperm, donor oocyte, donor embryo), control type and sample size (cohort, autologous oocyte/embryo, published data), whether cryopreservation of gametes/embryos was used, ages of cohorts, and health outcomes. Specific outcomes recorded included BW, LBW, VLBW, SGA, IUGR, GA, PD, TermD with LBW, BD, ChAb, ConMal, and IQ (intelligence quotients). A secondary data extraction form was used to record all appropriate confounding data from the

included studies which included maternal age, parity and multiplicity (Appendix 1.5). Authors of eligible studies were not contacted regarding obscure or missing data.

2.2.4 Meta-Analysis

Dichotomous outcomes were used in a meta-analysis implementing Mantel-Haenszel methods that incorporated a fixed-effects model. The meta-analysis was used to generate risk ratios (RR), 95% confidence intervals, *p* values, I^2 statistic, forest plots and funnel plots. Risk ratios are simple interpretations of data to determine if one outcome is more likely than the other. A RR value over 1 shows that the outcome is more likely due to a higher incidence of occurrence. While a value of less than 1 determines that the outcome is less likely due to a lower incidence. The dichotomous outcomes included LBW, VLBW, PD, PD with LBW, TermD with LBW, and BD. Meta-analysis of the continuous data of mean GA and mean BW was performed using inverse-variance, also with a fixed-effects model and 95% confidence intervals.

Heterogeneity of the studies was assessed using the I^2 statistic and visual interpretation of the symmetry of funnel plots. Higgins *et al.* suggested that an I^2 statistic value of 75% was considered to show high heterogeneity. However, we have selected a more stringent value of greater than 65%.[567] Cochrane's Q (chi-squared statistic) which has historically been used as a measure was not used as it has been described as being "poor at detecting true heterogeneity among studies".[567] A significant level of heterogeneity shows a high level of variation between the studies, reducing the confidence in the analysis result. Review Manager software (RevMan, version 5.2.8), was used to perform all statistical analysis (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, 2012). Continuous and dichotomous data are presented as forest plots as generated by RevMan. Funnel plots were assessed for asymmetry by visual analysis to determine publication bias. Funnel plot analysis was performed by Damian Adams and verified by Robyn Clark.

Where studies reported overlapping data, a sensitivity analysis was performed to determine the effect of the overlapping data. Sensitivity analysis was conducted by subtracting the study providing the overlapping data and reconducting the meta-analysis. Published data which did not have a comparison cohort but rather referenced either previous publications or databases of general population statistics, were excluded from all meta-analyses.

2.2.5 Risk of Bias in Individual Studies

The risk of bias present in the individual studies and their methodological quality was evaluated through the use of the *Joanna Briggs Institute Meta-Analysis Statistics Assessment and Review Instrument* (JBI-MAStARI),[568] which was modified for these meta-analyses. The JBI-MAStARI is a tool that enables critical appraisal of comparable case-control or cohort studies. Assessment of the studies was based on the following criteria:

> "1) Are patients in cohorts' representative of patients typically receiving fertility treatment?
> *For example, do they only include patients who may have been treated for ovarian cancer?*
> 2) Are the patients at a similar point in the course of their condition/illness?
> *Do they describe how many times the patient had received treatment?*
> 3) Has bias been minimised in relation to the selection of cases and comparators?
> 4) Was singleton versus multiple births identified and strategies to deal with them stated?
> *If singleton versus multiples was described, but all of the outcome data relevant to the review was not stratified, then = No.*
> 5) Are other confounding factors identified and strategies to deal with them stated?
> 6) Was cryopreservation of gametes or the use of fresh gametes adequately described, and were they appropriately stratified if both were included?
> 7) Are outcomes assessed using objective criteria?
> 8) Were outcomes measured reliably?
> 9) Was an appropriate statistical analysis used?" p259.[1]

2.3 Search Results

A total of 3,129 articles were identified for this study. Of which 3,110 were identified through computerised searches of the three databases. The remaining 19 were identified by searching through publication references. Potential articles for inclusion were reduced to 1,279 after the removal of duplicates. Screening of article titles and their abstracts restricted the potential articles down to 108 for full-text analysis. After reviewing the complete text of the 108 articles, 35 studies fulfilled the inclusion criteria and were included in this review. Of these, 27 were included in the various meta-analyses. The PRISMA flow diagram of article selection is presented in Figure 2.1.

Table 1.1 lists the included studies and their summary characteristics. Those studies that were removed after complete text analysis and the reasons for their exclusion are presented in Appendix 1.6.

Meta-analysis was only conducted for comparable sperm and oocyte outcomes due to the heterogeneity of published outcomes. Meta-analysis could not be performed on embryo donation outcomes due to a lack of comparable outcomes. Studies that were excluded from the meta-analysis did not report comparable outcome data. Subsequently, these have been summarised in the text.

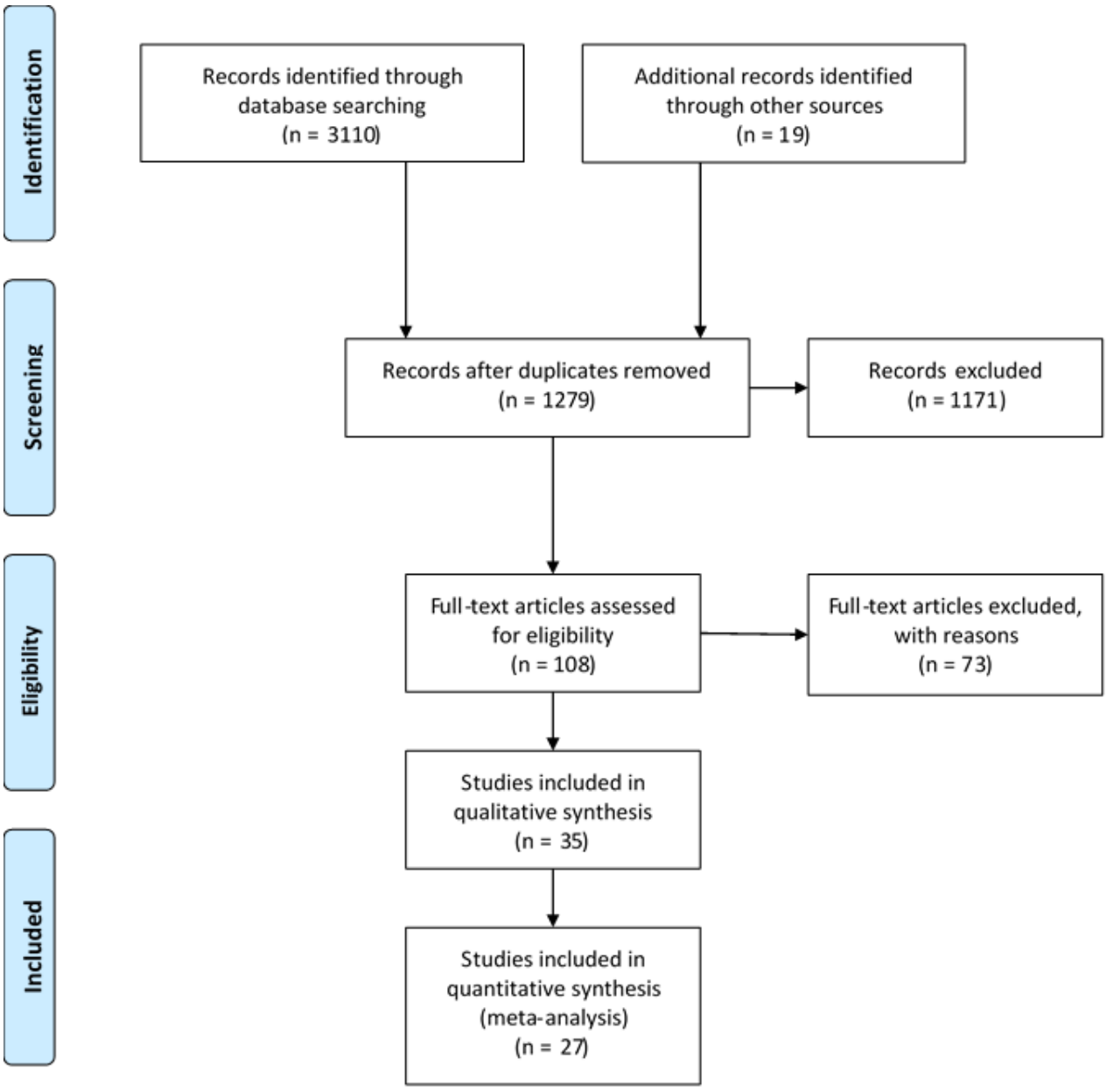

Figure 2.1 PRISMA flow diagram for the identification of studies meeting the inclusion criteria.

Table 1.1 Characteristics of studies included in the systematic review

Study	Donation Treatment(s) & Sample Size	Comparison & Sample Size	Frozen or Fresh	Ages	Specific Results
Sperm donation					
Thapar *et al.* (2007) United Kingdom	Sperm 170 AID as IVF (IVF-D)	Homologous IVF 378 & General population Published data	Not Specified	5-9yrs	LBW (all births) 19.6% sperm v 14.7% homologous IVF v 8% gen pop LBW (singletons) 8% sperm v 6.7% homologous IVF (gen pop singleton LBW not specified) Multiplicity 24.1% sperm v 20.1% homologous IVF
Gaudoin *et al.* (2003) United Kingdom	Sperm 35	Partners sperm 97 & General population 109302	Unknown	Neonates	BW 3149 ± 233g (donor) v 2921 ± 165g (partner) v 3301 ± 4g (comparison) LBW 11.4% (donor) v 22.7% (partner) v 7.1% (gen pop) PD 5.7% (donor) v 15.5% (partner) v 6.9% (gen pop)
Hoy *et al.* (1999) Australia	Sperm 1603	General population 7516	Frozen	Neonates	LBW 7.3% v 6.8%, RR 1.1 BD 3.6% v 3.2%, RR 1.1 Perinatal death 1.2% v 1.1%, RR 1.4 Stillborn 0.9% v 0.6%, RR 1.5 Neonatal death 0.4%v 0.5%, RR 0.8 ChAb 0.4% v 0.2%, RR 2.5 PD 6.4% v 6.6%, RR 1 Multiplicity 3.1% v 2.7% RR 1.2
Amuzu *et al.* (1990) USA	Sperm 481	General population Published data	Both	3mths - 15yrs (ave 5yrs)	BW (7.5lb ± 1.3) and birth length (20.1 inches ± 1.2) same as gen pop Major anomalies (2.9% at birth, 6.2% at time of study v 2% and 5%) ChAb 0.2% v not specified Developmental milestones same as gen pop Learning disabilities 5.8% v not specified Gifted and talented program 10.5% v not specified
Iizuka *et al.* (1968)	Sperm	General population	Both	N=40 ≥ 2.5yrs	BW and Length better in AID

Japan	54	Published data	(frozen = 9)	(oldest 11.8yrs) N=14 ≤ 2.5yrs	IQ of donor sperm children higher range than controls (better)
Davies *et al.* (2012) Australia	Sperm 428	General population 293314	Not Specified	Neonates	BD 8.4% v 5.7%, OR 1.51 (adjusted OR 1.37)
Lansac *et al.* (1997) France	Sperm (AID) 18128 AID as IVF (IVF-D) 3405	General population 13631	Frozen	Neonates	BW 3281 ± 491g (N=8943) v 3300 ± 600g (N=13631) LBW 4.7% (singleton) v 6.2% (national register of natural conceptions) Malformations (1.9% AID, no sig diff to gen pop, not specified) Malformations (2.74% IVF-D v 2.99% husband sperm, no sig diff) PD 4.8% (singleton) v 5.9% (national register of natural conceptions) ChAb 0.25% v 0.2% (Paris $p < 0.05$) v not specified (Strasbourg et Marsailles, no sig diff)
Forse *et al.* (1985) Canada	Sperm 395	General population Published data	Fresh	Neonates	ChAb 0.75% v 0.15%
Oocyte donation					
Gibbons *et al.* (2011) USA	Oocyte 10176	Autologous oocyte 49252	Fresh	Neonates	BW 3236 ± 652.7g v 3240.1 ± 607.4g LBW Odds Ratio 1.21 v 1 VLBW Odds Ratio 1.28 v 1 Gestational age 37.4 ± 2.4 weeks v 37.7 ± 2.2
Zegers-Hochschild *et al.* (2010) South and Central America	Oocyte 73	Autologous oocyte 90	Unknown	Neonates	Singleton BW 2980 ± 446g v 3170 ± 517g Tw BW 2390 ± 577g v 2057 ± 572g ($p < 0.05$) Mult BW 1658 ± 452g v 1365 ± 465g ($p = 0.05$) Singleton GA 37.6 v 38.5 (not significant) Tw GA 36.3 v 34.7 (not significant)
Krieg *et al.* (2008)	Oocyte	Autologous oocyte	Not	Neonates	BW 2835.6 ± 693.52g v 3081.6 ± 674.29g ($p = 0.02$)

USA	71 (pregnancies)	108 (pregnancies)	Specified		GA 37.0 (3.00 SD) v 38.1 (2.61 SD) weeks (p = 0.01) Not significant when adjusted for multiple gestations IUGR OR 1.35 (0.67─2.72)
Soderstrom-Anttila *et al.* (1998) Finland and Sweden	Oocyte 61 (67.2% S, 32.8% Mult)	Autologous oocyte 126 (54% S, 46% Mult)	Both	Neonates	BW singletons 3338 ± 740g v 3475 ± 630g LBW singletons 10% v 7% PD singletons 13% v 7% SGA singletons 5% v 6% Singletons in hospital (>7days) 36 v 13 (p < 0.01) BW multiples 2216 ± 689g v 2582 ± 556g (p < 0.05) LBW multiples 50% v 39% PD multiples 30% v 48% SGA multiples 40% v 24% Multiples admitted to ICU 60 v 24 (p < 0.01)
Porreco *et al.* (1997) USA	Embryo/oocyte 35 (pregnancies)	Autologous oocyte 32 (pregnancies)	Not Specified	Neonates	BW 2446 ± 784g v 2442 ± 687g GA all births 36.9 ± 2.8 v 37.2 ± 2.6 GA multiples 35.4 ± 2.6 v 35.8 ± 3.2 PD 39% v 29%
Friedman *et al.* (1996) USA	Oocyte 22	Autologous oocyte 22	Unclear	Neonates	BW 2924 ± 703g v 2374 ± 822g (p < 0.005) GA 35 (29─41) v 38 (35–42) (p < 0.01)
Nelson and Lawlor (2011) United Kingdom	Oocyte Total 144018 donor plus own	Autologous oocyte Included in N of 144018	Fresh	Neonates	LBW donor 1 v own 0.42 (0.26–0.68) (p < 0.001) PD donor 1 v own 0.41 (0.26–0.64) (p < 0.001)
Kalra *et al.* (2011) USA	Oocyte Fresh 5595 Frozen 3072	Autologous oocyte Fresh 20916 Frozen 10906	Both	Neonates	LBW fresh 11.5% v 10% LBW frozen 11.3% v 7.2% PD fresh 19.3% v 16% PD frozen 20.7% v 15.8% PD LBW fresh 32.7% v 34.1%

					PD LBW frozen 33.1% v 23.8% TermD with LBW fresh 2.2% v 2.5% TermD with LBW frozen 1.7% v 1.2%
Sunderam *et al.* (2009) USA	Oocyte 2995	Autologous oocyte 18603	Fresh	Neonates	LBW 12% v 9.3% ($p < 0.01$) VLBW 2.6% v 1.9% ($p < 0.01$) PD 17% v 13.4% ($p < 0.01$) PD LBW 9.3% v 6.7% ($p < 0.01$) PD VLBW 2.5% v 1.9% ($p < 0.01$) TermD with LBW 2.7% v 2.7% TermD with VLBW (0.1% v 0%)
Wright *et al.* (2008) USA	Oocyte 2864	Autologous oocyte 17642	Fresh	Neonates	LBW 11% v 9.5% ($p < 0.01$) VLBW 2% v 1.7% PD 16.9% v 13.4% ($p < 0.01$) PD LBW 9% v 6.9% TermD with LBW 2.1% v 2.7% ($p < 0.01$)
Thapar *et al.* (2007) United Kingdom	Oocyte 146	Autologous oocyte 378	Not Specified	5-9yrs	LBW singletons 13.6% v 6.7% LBW all deliveries 23.4% v 14.7% Multiplicity 24.1% v 20.1%
Wright *et al.* (2007) USA	Oocyte 2772	Autologous oocyte 17230	Fresh	Neonates	LBW 10.4% v 9.5% ($p < 0.01$) VLBW 1.9% v 1.8% PD 16.2% v 13.4% ($p < 0.01$) PD LBW 8.3% v 6.9% TermD with LBW 2.1% v 2.5% ($p < 0.01$)
Wright *et al.* (2006) USA	Oocyte 2507	Autologous oocyte 16082	Fresh	Neonates	LBW 11.2% v 9.3% ($p < 0.01$) VLBW 2.3% v 1.9% PD 17.6% v 13.4% ($p < 0.01$) PD LBW 9.1% v 6.9% ($p < 0.01$)

					TermD with LBW 2.1% v 2.4% ($p < 0.01$)
Wright *et al.* (2005) USA	Oocyte 2199	Autologous oocyte 14615	Fresh	Neonates	LBW 10.7% v 9.3% ($p < 0.01$) VLBW 2.1% v 1.9% PD 16.3% v 13.3% ($p < 0.01$) PD LBW 9% v 7% ($p < 0.01$) TermD with LBW 1.8% v 2.3% ($p < 0.01$)
Schieve *et al.* (2004) USA	Oocyte 6432 (total) 899 (1996) 1019 (1997) 1250 (1998) 1459 (1999) 1805 (2000)	Autologous oocyte 47586 (total) 6943 (1996) 8119 (1997) 9578 (1998) 10511 (1999) 12435 (2000)	Fresh	Neonates	LBW 15.2% v 13.7% (1996), 13% v 13.5% (1997), 13.1% v 12% (1998), 10% v 9.9% (1999), 10.6% v 9.1% (2000) VLBW 3.1% v 2.2% (1996), 3.8% v 3.1% (1997), 2% v 2.1% (1998), 1.9% v 1.8% (1999), 2.3% v 1.9% (2000) PD 18.5% v 13% (1996), 17.3% v 12.7% (1997), 18.2% v 13.1% (1998), 15.2% v 12.2% (1999), 16.2% v 13.1% (2000) PD LBW 8.8% v 6.7% (1996), 8.1% v 6.5% (1997), 8.9% v 6.7% (1998), 7.5% v 6.2% (1999), 8.2% v 6.4% (2000) TermD with LBW 6.3% v 6.9% (1996), 5% v 6.7% (1997), 4.1% v 5.2% (1998), 2.6% v 3.7% (1999), 2.4% v 2.5% (2000)
Sheffer-Mimouni *et al.* (2002) Israel	Oocyte 134	General population Published data	Not Specified	Neonates	PD 14.9% v 7% ConMal 2.2% v gen pop (no difference)
Corradetti *et al.* (2012) Italy	Oocyte 14	Autologous oocyte 28	Unclear	Neonates	IUGR 21.4% v 7.1% ($p < 0.011$)
Pados *et al.* (1994) Europe, Lebanon and South America	Oocyte 53	Autologous oocyte and General population Published data	Both	Neonates	IUGR 11.5% (donor) v 17% (own) v 3-7% (gen pop)
ASRM and SART (2000) USA	Oocyte 2458 (56.5% S, 37.5% Tw, 6% Mult)	Autologous oocyte 17677 (61.0% S, 31.8% Tw, 7.1% Mult)	Fresh	Neonates	BD 1.9% v 1.6%

ASRM and SART (1999) USA	Oocyte 1849 (59.7% S, 35.6% Tw, 4.7% Mult)	Autologous oocyte 14314 (61.0% S, 31.8% Tw, 7.1% Mult)	Fresh	Neonates	BD 1.3% v 1.8%
ASRM and SART (1998) USA	Oocyte 1743 (58.9% S, 35.8% Tw, 5.3% Mult)	Autologous oocyte 11342 (63.4% S, 29.6% Tw, 7% Mult)	Fresh	Neonates	BD 0.6% v 0.7%
ASRM and SART (1996) USA	Oocyte 1239 (61.8% S, 32.3% Tw, 5.9% Mult)	Autologous oocyte 6513 (63.7% S, 28.3% Tw, 6.5% Mult)	Fresh	Neonates	BD 2.1% v 2.7%
ASRM and SART (1995) USA	Oocyte 1018 (59.6% S, 35% Tw, 5.4% Mult)	Autologous oocyte 7034 (65.9% S, 27.5% Tw, 5.8% Mult)	Fresh	Neonates	BD 1.8% v 2.3%
AFS and SART (1994) USA	Oocyte 735 (62.9% S, 31.5% Tw, 4.1% Mult)	Autologous oocyte 5798 (67.3% S, 26% Tw, 6.2% Mult)	Fresh	Neonates	BD 1.7% v 1.9%
SART and AFS (1993) USA	Oocyte 372 (66.8% S, 27.6% Tw, 5.6% Mult)	Autologous oocyte 3930 (70% S, 25% Tw, 4.8% Mult)	Fresh	Neonates	BD 2.1% v 1.5%
MRI *et al.* (1992) USA	Oocyte 167 (45.8% S, 40.2% Tw, 14% Mult)	Autologous oocyte 3110 (52.8% S, 37.1% Tw, 10.1% Mult)	Fresh	Neonates	ConMal 0.56% v 1.22% ChAb 0% v 0.7%
MRI *et al.* (1991) USA	Oocyte 112 (47.3% S, 44.6% Tw, 8.1% Mult)	Autologous oocyte 2876 (50.8% S, 39.5% Tw, 9.7% Mult)	Fresh	Neonates	ConMal 2.7% v 0.9% ChAb 2.7% v 1.2%

MRI *et al.* (1990) USA	Oocyte 50 (46% S, 48% Tw, 6% Mult)	Autologous oocyte 2133 (56.9% S, 33.4% Tw, 9.7% Mult)	Fresh	Neonates	ConMal 0% v 0.84% ChAb 0% v 0.75%
Embryo donation					
Porreco *et al.* (1997) USA	Embryo/oocyte 35 pregnancies	Homologous IVF 32 pregnancies	Not Specified	Neonates	BW 2446 ± 784 (n=32) v 2442 ± 687 (n=34) GA all births 36.9 ± 2.8 v 37.2 ± 2.6 GA multiples 35.4 ± 2.6 v 35.8 ± 3.2 PD 39% v 29%
Thapar *et al.* (2007) United Kingdom	Embryo 31	Homologous IVF 378	Not Specified	5-9yrs	LBW singletons 12.5% v 6.7% LBW all deliveries 16.7% v 14.7% Multiplicity 16.7% v 20.1%

S = singleton, Tw = twin, Mult = multiple (triplets or greater), BW = birthweight, LBW = low birthweight <2500g, VLBW = very low birthweight <1500g, GA = gestational age, PD = preterm delivery (< 37 weeks), TermD = term delivery, SGA = small for gestational age, IUGR = intrauterine growth retardation, BD = birth defects, ConMal = congenital malformation, ChAb = chromosomal abnormalities, AID = artificial insemination by donor, ICU = intensive care unit, IVF-D = in vitro fertilisation with donor sperm, RR = risk ratio, OR = odds ratio, sig = significant, gen pop = general population, p values for significance is only provided where $p < 0.05$.

Data are presented as the donor group v comparison group. The comparison group is a cohort unless otherwise specified. Studies citing comparison group of the general population or autologous oocyte cohort data that was published elsewhere are denoted as "published data". General population data is of spontaneous conceptions.

Autologous oocytes and Homologous IVF represent the same procedure, that is IVF involving the mother's own oocyte and her partner's sperm but has been labelled differently in the oocyte and embryo sections to represent the segregation between the two groups.

This table is a combination of the two equivalent tables published in the oocyte[1] and sperm donation[3] systematic reviews with the added data from the embryo donation systematic review.

2.4 Oocyte Donation Results

2.4.1 Oocyte Donation Outcomes

Meeting the inclusion criteria for health outcomes of oocyte DC people was a total of 28 studies. Of these studies, 23 were able to be included in meta-analyses.[474, 500, 569-590] A qualitative analysis was conducted on the other five studies.[292, 591-594] All meta-analyses were comparisons of donor oocyte-conceived neonates compared to those conceived with autologous oocytes. No comparable data were available of childhood or adult health outcomes for analysis of long-term health trajectories. Of the five studies included for qualitative analysis, two studies included spontaneous conceptions as the comparison group. However, data were not comparable to allow for meta-analysis. Combining all studies allowed for the inclusion of 201,628 donor oocyte neonatal health outcomes and 432,361 autologous oocytes neonatal health outcomes.

As a result of some studies presenting overlapping data,[569, 576-578] the number of offspring is over-reported. This over-reporting pertains to data the studies obtained from databases maintained by the Society for Assisted Reproductive Technology (SART) in which the authors used data from the same year. Sensitivity analysis was conducted by removing the overlapping studies to determine their effect on the results and is presented later.

Types of data and more specifically, the actual health outcome categories presented by each study varied considerably, with no consensus on the data reported. Most of the data (71.4%) represented data obtained from national collection databases such as those maintained by the Human Fertilisation and Embryology Authority (HFEA) in the United Kingdom, and the SART and Centers for Disease Control and Prevention (CDC) in the United States of America.

Some studies reported oocyte cryopreservation information. Those studies reporting cryopreservation were poorly stratified and could not be used for meta-analysis of cryopreservation outcomes. Furthermore, some studies reported that the cryopreservation occurred after embryos were created from fresh donor oocytes and were therefore excluded from meta-analysis as it does not address the question of how oocyte cryopreservation affects outcomes. These studies are noted in Table 2.1. Data presented subsequently reflects both cryopreserved and fresh oocyte outcomes unless specified.

2.4.2 Oocyte Donation Birth Weights

Birth weights and the related categories of LBW, VLBW, LBW with PD, LBW at term, SGA and IUGR were the most frequently reported outcome. The outcomes of LBW associated with either PD or term delivery will be discussed in the next section that investigates gestational ages specifically.

Combined singleton and multiple delivery donor oocyte neonates had a lower mean BW than their autologous oocyte-conceived peers which were not statistically significant (mean difference -5.58g, CI: -19.19g–8.02g, $p = 0.42$, $I^2 = 76\%$), and contained significant heterogeneity (Figure 2.2). This analysis included 10,482 donor oocyte neonates and 49,697 autologous conceived neonates. The mean BW difference for singletons was mostly unchanged although there was an improvement in heterogeneity (mean difference -4.91g, CI: -18.63g–8.81g, $p = 0.48$, $I^2 = 26\%$) (Figure 2.3). This analysis of singletons included 10,239 donor oocyte neonates and 49,345 autologous conceived neonates, highlighting that singletons comprised 97.7% and 99.3% of the total mean BW outcomes, respectively. The vast majority of the data was provided by the study published Gibbons *et al.* The authors presented a dataset combining 3-years of United States national data from the SART collections.[569]

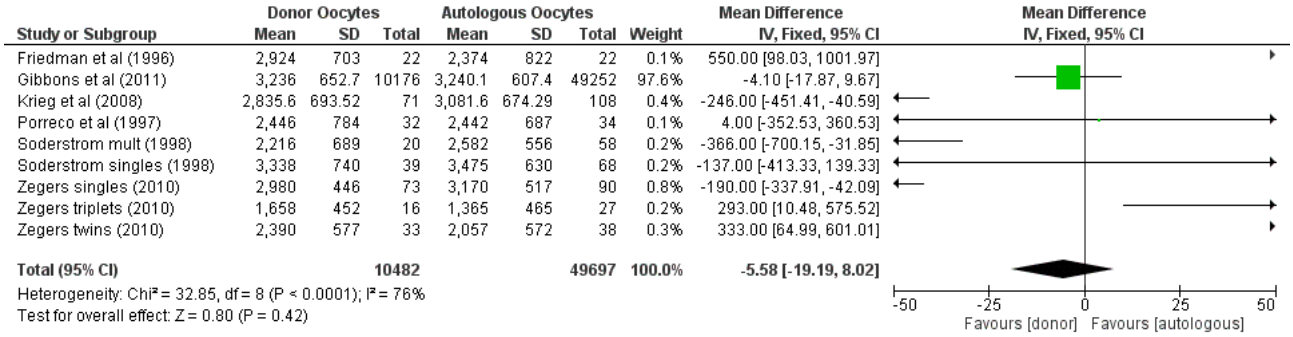

Figure 2.2 Forest plot of mean birth weight outcomes comparing donor oocyte versus autologous oocyte neonates (singletons and multiples).

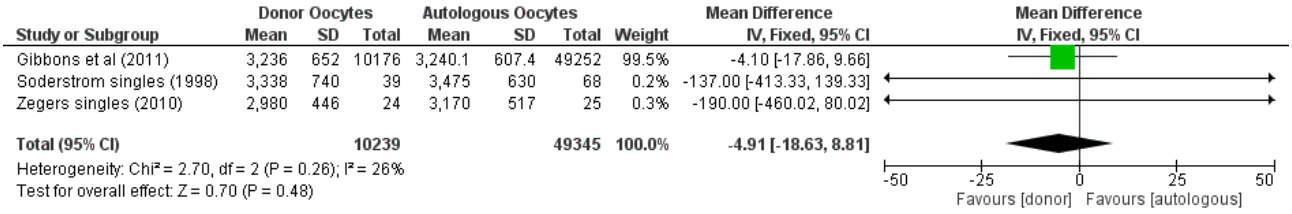

Figure 2.3 Forest plot of mean birth weight outcomes comparing donor oocyte versus autologous oocyte neonates (singletons only).

Donor oocyte-conceived neonates had a higher risk for being born smaller than 2500 grams (LBW) compared to those conceived with autologous oocytes (RR: 1.18, CI: 1.14–1.22, $p < 0.00001$, $I^2 = 36\%$) (Figure 2.4). This analysis included 38,817 donor oocyte neonates and 213,336 autologous conceived neonates. The publication of Schieve *et al.* presented data that was stratified into years. For consistency between this study and others that reported annual SART and CDC data, each year was treated separately. However, the 3-year dataset presented by Gibbons *et al.,* could not be stratified and treated the same way as their data were combined. Meta-analysis of singleton outcomes showed an increased risk of being born LBW (RR: 1.17, CI: 1.12–1.23, $p < 0.00001$, $I^2 = 59\%$) (Figure 2.5), and included 15,284 donor oocyte neonates and 79,854 autologous conceived neonates.

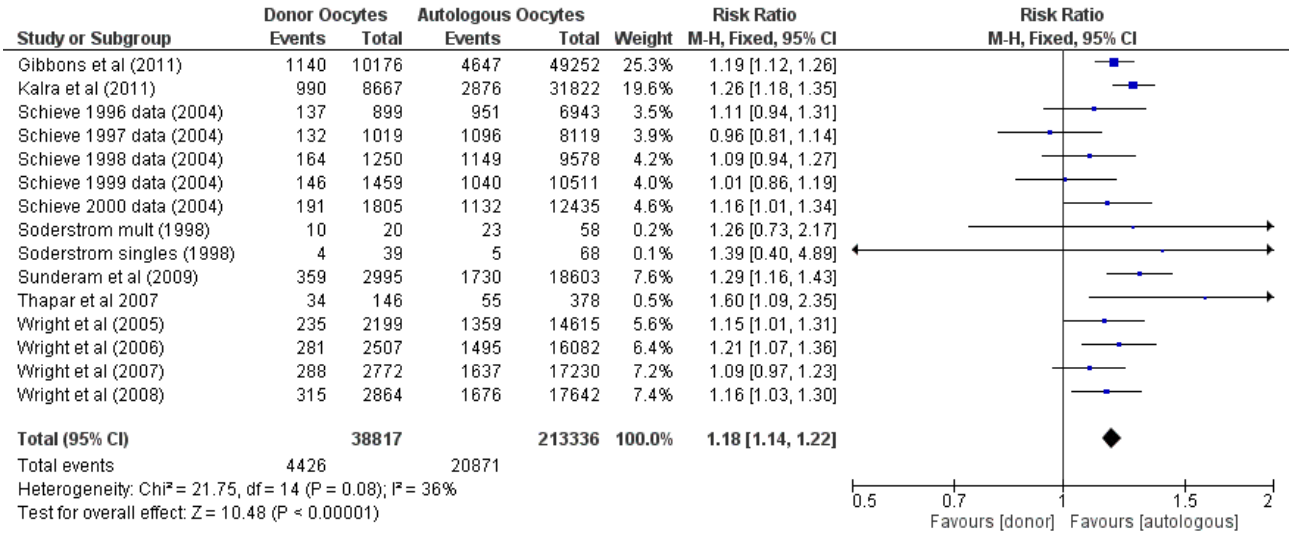

Figure 2.4 Forest plot of low birthweight (< 2500g) outcomes comparing donor oocyte versus autologous oocyte neonates (singletons and multiples).

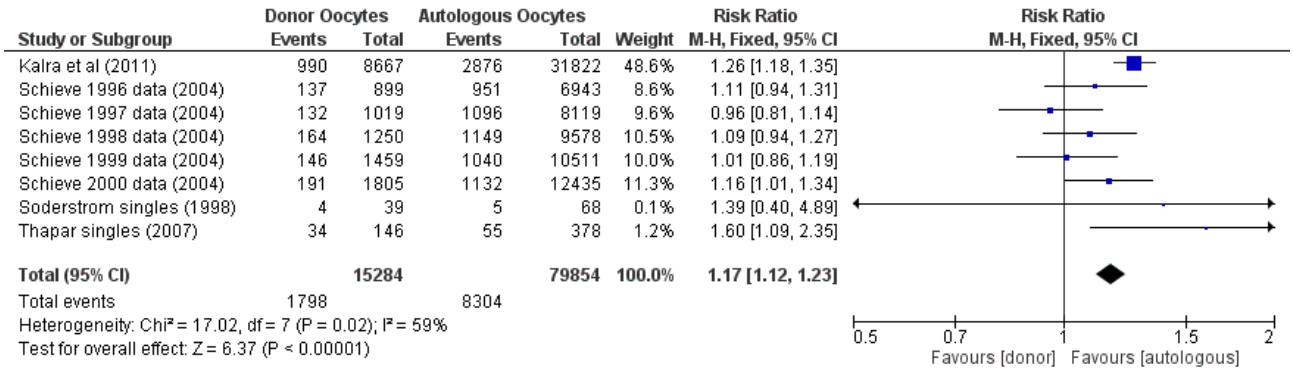

Figure 2.5 Forest plot of low birthweight (< 2500g) outcomes comparing donor oocyte versus autologous oocyte neonates (singletons only).

An increased risk of being born smaller than 1500g (VLBW) was also observed for donor oocyte-conceived neonates in comparison to autologous oocyte neonates (RR: 1.24, CI: 1.15–1.35, $p < 0.00001$, $I^2 = 32\%$) (Figure 2.6). This analysis included 29,945 donor oocyte neonates and 181,010 autologous conceived neonates. Meta-analysis of singleton outcomes indicated an increased risk of being born VLBW (RR: 1.31, CI: 1.11–1.54, $p = 0.001$, $I^2 = 65\%$) (Figure 2.7), and included 6,432 donor oocyte neonates and 47,586 autologous conceived neonates. Singleton meta-analysis showed heterogeneity at the cut-off for significance (65%). From the publications included in this systematic review, VLBW was the only outcome measure subjected to a meta-analysis that included fresh oocyte data only. All other meta-analysis included both cryopreserved and fresh oocyte data.

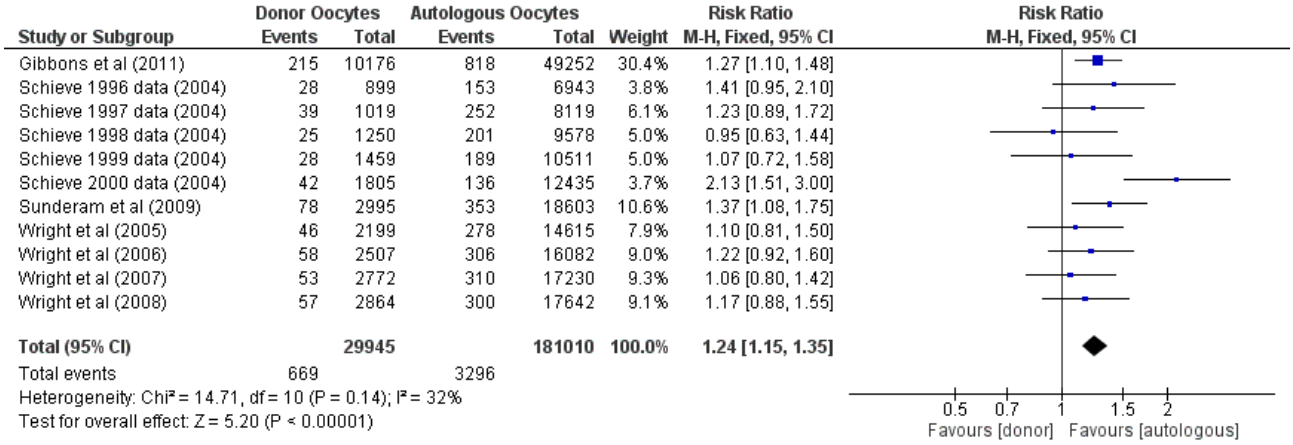

Figure 2.6 Forest plot of very low birthweight (< 1500g) outcomes comparing donor oocyte versus autologous oocyte neonates (singletons and multiples).

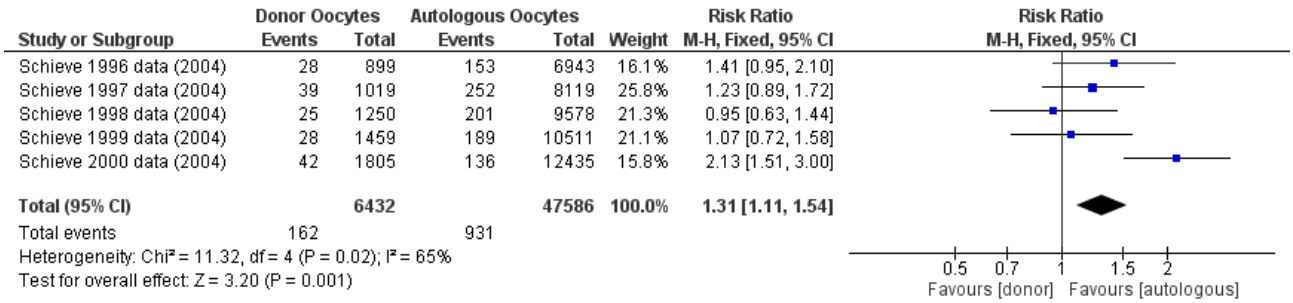

Figure 2.7 Forest plot of very low birthweight (< 1500g) outcomes comparing donor oocyte versus autologous oocyte neonates (singletons only).

All BW outcome data presented above included all gestational ages, including PD (< 37 weeks), TermD (37-42 weeks), and post-term (PostD > 42 weeks). Stratification and assessment of the association of BW to GA are presented in the next section.

Summary analysis of studies showed that of the included studies, ten reported that donor oocyte neonates were more likely to be adversely affected by BW outcomes than their autologous oocyte-conceived peers. These included a statistically reduced mean BW (p = 0.02),[571] increased incidences of LBW (p < 0.001,[591] p <0.01,[576-580] odds ratio 1.21 v 1),[569] increased odds of VLBW (1.28 v 1),[569] and IUGR (p < 0.011).[292] Soderstrom-Anttila *et al.*, only found a significant difference for mean BWs in multiples (p < 0.05), but not singletons.[572] Two further studies observed higher frequencies of LBW occurring in neonates conceived with donor oocytes. However, the authors did not perform statistical analyses.[575, 592]

Small sample sizes were associated with those studies reporting no significant differences in BW categories or even those reporting higher BWs.[570, 572-574] Large national cohorts conversely were associated with studies observing significant decreases in BW outcomes for donor oocyte neonates.[569, 575-580, 591]

Due to overlapping data, sensitivity analyses were conducted to determine the impact of the inclusion of the overlapped data. The overlap concerns the publications by Gibbons *et al.*, Kalra *et al.*, Wright *et al.*, and Sunderam *et al.* Specifically, Gibbons *et al.*, and Kalra *et al.*, presented data obtained from the SART between the years of 2004-2006, which covers the same years and data source as presented by Sunderam *et al.*, and Wright *et al.*[569, 575-578] The outcome measures that were presented were not all identical, and the samples had differences. All studies were, therefore included in the meta-analysis presented. However, a sensitivity analysis was performed by removing the data from both Kalra *et al.*, and Gibbons *et*

al., as those two studies represented the largest sample sizes. Sensitivity analysis highlighted that the risk ratios were comparable regardless of whether Kalra *et al.*, and Gibbons *et al.,* were include or excluded; LBW (excluded RR: 1.14, CI: 1.09–1.19, $p < 0.00001$, $I^2 = 31\%$, in comparison to the included RR: 1.18, CI: 1.14–1.22, $p < 0.00001$, $I^2 = 36\%$), and VLBW (excluded RR: 1.23, CI: 1.12–1.36, $p < 0.0001$, $I^2 = 39\%$, in comparison to the included RR: 1.24, CI: 1.15–1.35, $p < 0.00001$, $I^2 = 32\%$).

2.4.3 Oocyte Donation Gestational Ages

The second most frequently reported neonatal outcomes pertained to gestational ages of birth and in particular PD, as well as the categories of mean GA, PD with LBW, and TermD with LBW.

Combined singleton and multiple delivery donor oocyte neonates had a statistically significant lower GA of 0.3 weeks than their autologous oocyte-conceived peers (mean difference -0.3 weeks, CI: -0.35 weeks – -0.25 weeks, $p < 0.00001$, $I^2 = 40\%$) (Figure 2.8). This analysis included 10,282 donor oocyte neonates and 49,392 autologous conceived neonates. From this meta-analysis, the study by Zegers-Hochschild *et al.* was excluded due to the absence of standard deviation reporting in their study.[570] Mean GA meta-analysis could not be performed for singletons due to the lack of appropriately stratified data presented by Krieg *et al.,*[571] and Porreco *et al*.[573]

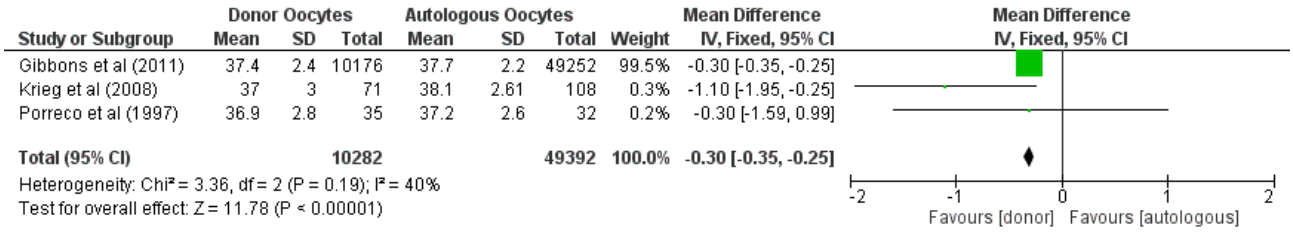

Figure 2.8 Forest plot of gestational age outcomes comparing donor oocyte versus autologous oocyte neonates (singletons and multiples).

Combined singleton and multiple delivery donor oocyte neonates exhibited a significantly increased risk of being born PD than their autologous oocyte-conceived peers (RR: 1.26, CI: 1.23–1.30, $p < 0.00001$, $I^2 = 0\%$) (Figure 2.9). This analysis included 28,516 donor oocyte neonates and 163,949 autologous conceived neonates. Meta-analysis of singleton outcomes also exhibited an increased risk of being born PD (RR: 1.27, CI: 1.22–1.32, $p < 0.00001$, $I^2 =$

5%) (Figure 2.10), and included 15,239 donor oocyte neonates and 79,719 autologous conceived neonates.

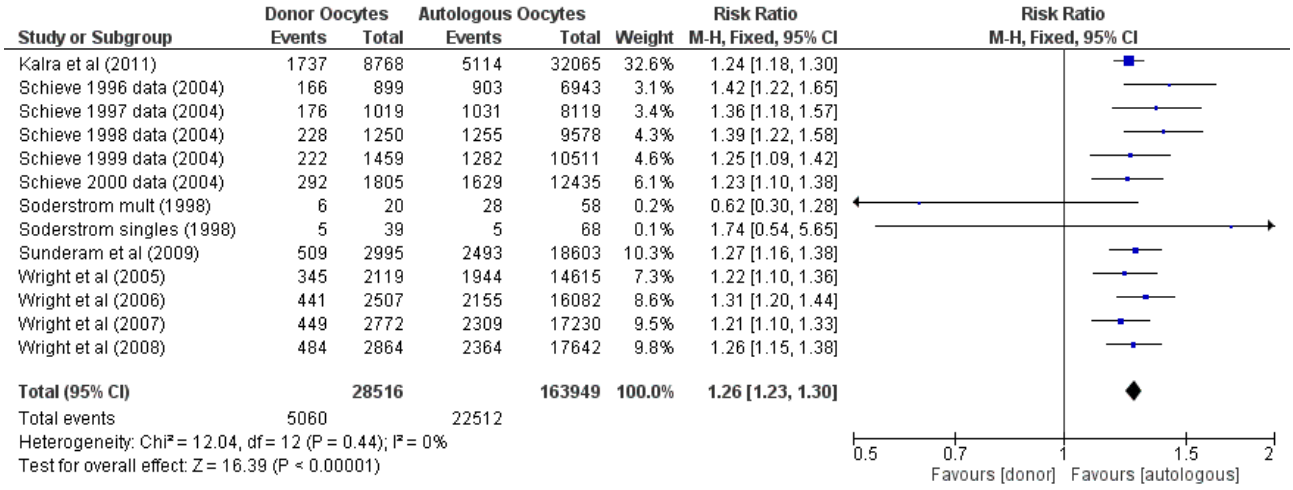

Figure 2.9 Forest plot of preterm delivery (< 37 weeks) outcomes comparing donor oocyte versus autologous oocyte neonates (singletons and multiples).

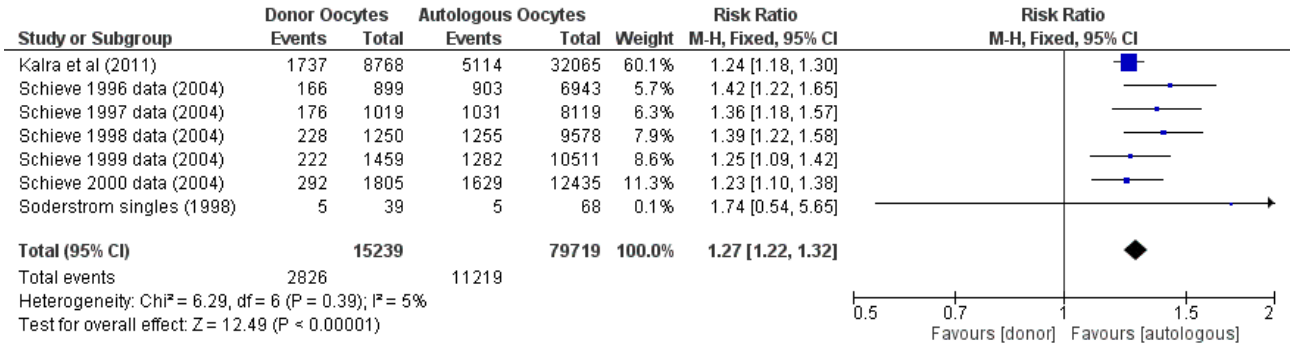

Figure 2.10 Forest plot of preterm delivery (< 37 weeks) outcomes comparing donor oocyte versus autologous oocyte neonates (singletons only).

Combined singleton and multiple delivery donor oocyte neonates showed a significantly increased risk of being born PD with LBW than their autologous oocyte-conceived peers (RR: 1.24, CI: 1.19–1.29, $p < 0.00001$, $I^2 = 46\%$) (Figure 2.11). This analysis included 21,405 donor oocyte neonates and 136,813 autologous conceived neonates. Meta-analysis of singleton outcomes also showed an increased risk of being born PD with LBW (RR: 1.17, CI: 1.10–1.24, $p < 0.00001$, $I^2 = 42\%$) (Figure 2.12), and included 8,148 donor oocyte neonates and 52,641 autologous conceived neonates.

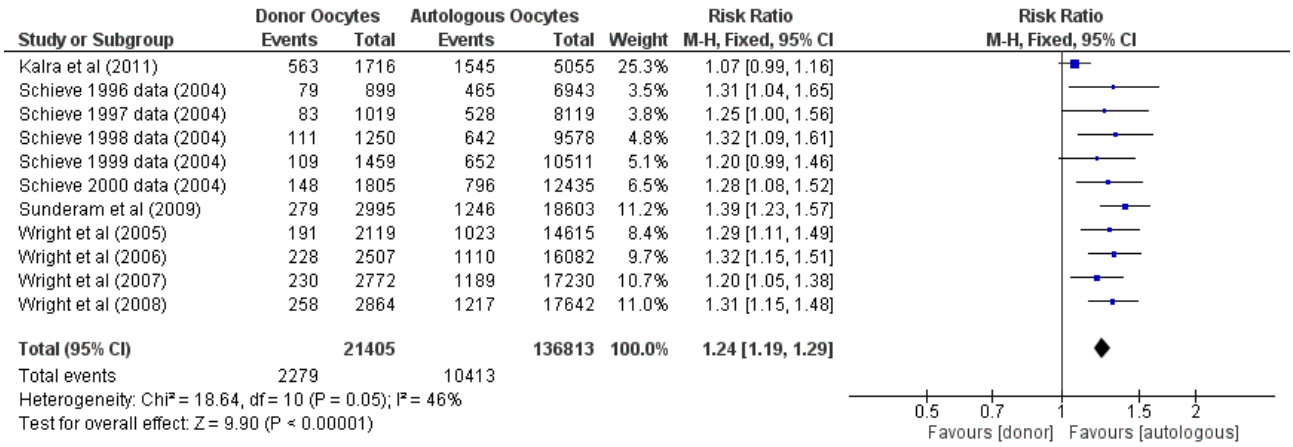

Figure 2.11 Forest plot of preterm delivery with low birthweight outcomes comparing donor oocyte versus autologous oocyte neonates (singletons and multiples).

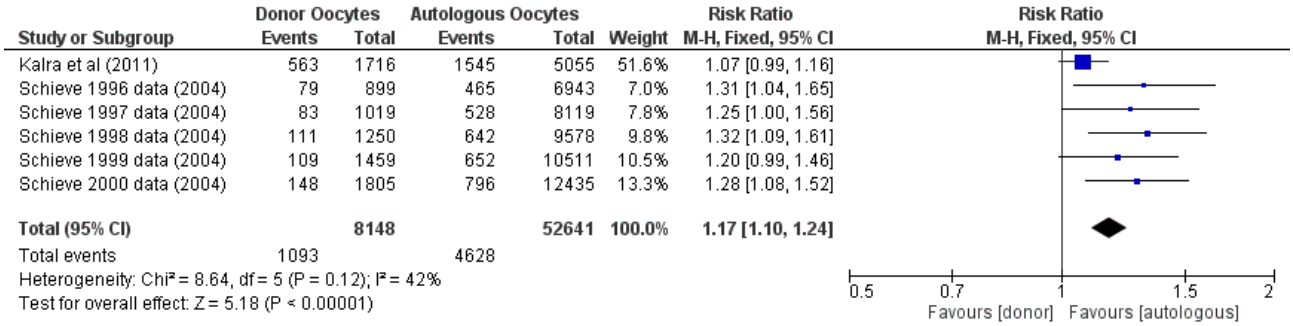

Figure 2.12 Forest plot of preterm delivery with low birthweight outcomes comparing donor oocyte versus autologous oocyte neonates (singletons only).

Conversely to previous outcome measures meta-analysis, combined singleton and multiple delivery donor oocyte neonates showed a significantly decreased risk of being born TermD with LBW than their autologous oocyte-conceived peers (RR: 0.86, CI: 0.80–0.93, $p = 0.0003$, $I^2 = 0\%$) (Figure 2.13). This analysis included 26,380 donor oocyte neonates and 157,597 autologous conceived neonates. Meta-analysis of singleton outcomes also showed a decreased risk of being born term with LBW (RR: 0.86, CI: 0.77–0.96, $p = 0.007$, $I^2 = 2\%$) (Figure 2.14), and included 13,043 donor oocyte neonates and 73,425 autologous conceived neonates.

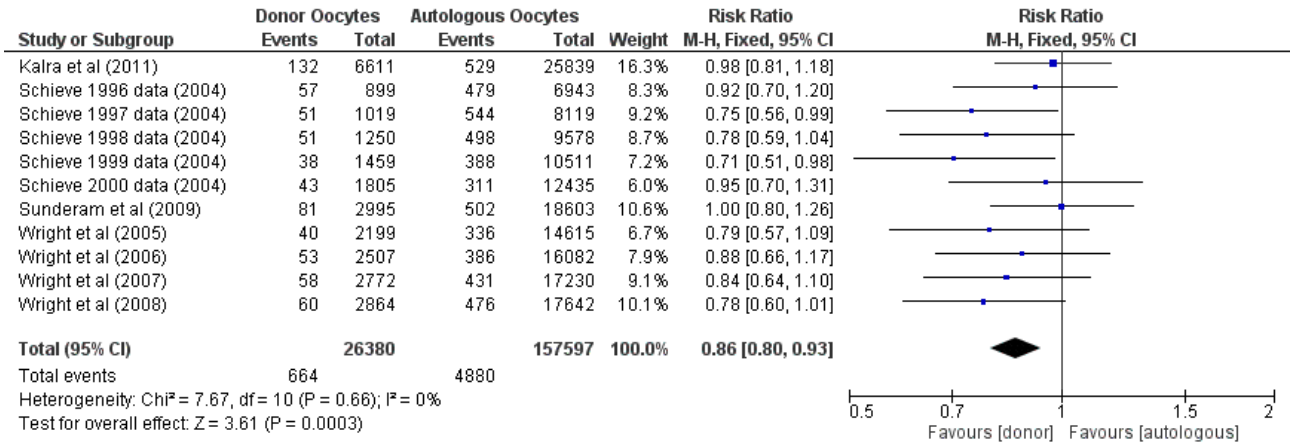

Figure 2.13 Forest plot of term delivery with low birthweight outcomes comparing donor oocyte versus autologous oocyte neonates (singletons and multiples).

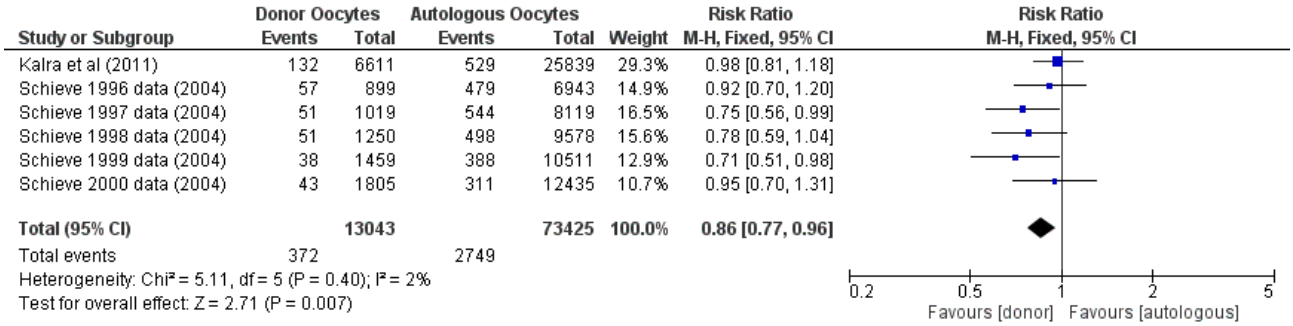

Figure 2.14 Forest plot of term delivery with low birthweight outcomes comparing donor oocyte versus autologous oocyte neonates (singletons only).

Summary analysis of studies showed that of the five studies reporting mean gestational age, two studies observed that donor oocytes neonates were more likely than their autologous conceived peers to be born with a lower GA ($p < 0.01$).[571, 574] Yet the remaining three studies ($p = 0.563$),[569] (p value not reported),[570, 573] reported no significant difference. Unlike the BW data in which the largest study by Gibbons *et al.*, found significant differences in BW characteristics, the same authors found no difference in gestational age characteristics. The study by Krieg *et al.* reported that GA data was associated with a reduced mean BW.

Six of ten studies reporting on the incidences of PD observed that donor oocyte-conceived neonates were significantly more likely than their autologous conceived peers to be born PD ($p < 0.001$),[591] ($p < 0.01$).[576-580] Porreco *et al.* reported no significant difference between the groups (p value not reported).[573] Of the remaining four studies, the two studies of Schieve *et*

al., and Kalra *et al.,* did not analyse the donor versus autologous oocyte outcomes statistically.[474, 575]

Three of seven studies reporting on the incidences of PD with LBW found significantly increased incidences for donor oocyte-conceived neonates in comparison to autologous oocyte-conceived neonates ($p < 0.01$).[576, 579, 580] Another study reported an increase in the incidence of donor oocyte neonates being born PD with VLBW ($p < 0.01$).[576] Statistical analysis was not performed in all studies with some reporting frequencies including the study by Schieve *et al.,* in which a higher proportion of donor oocyte-conceived neonates were born PD with LBW than their autologous oocyte-conceived peers for each year data (1996 = 8.8% v 6.7%, 1997 = 8.1% v 6.5%, 1998 = 8.9% v 6.7%, 1999 = 7.5% v 6.2%, and 2000 = 8.2% v 6.4%).[474]

Four of seven studies reported a significant decrease in the incidence of LBW at term (TermD with LBW $p < 0.01$).[577-580] Another two studies reported reduced frequencies including the study by Kalra *et al.*, (2.2% v 2.5%), and in each of the 5 years of the study reported by Schieve *et al.*, (1996 = 6.3% v 6.9%, 1997 = 5.0% v 6.7%, 1998 = 4.1% v 5.2%, 1999 = 2.6% v 3.7%, and 2000 = 2.4% v 2.5%), but both studies did not provide statistical analysis.[474, 575] While one study reported the same frequency of TermD with LBW, and also a non-significant increase in the frequency of TermD with VLBW.[576]

2.4.4 Oocyte Donation Birth Defects

The meta-analysis of birth defects (BD) in combined singleton and multiple delivery donor oocyte neonates showed no significant difference in the risk of being born with a BD in comparison to their autologous oocyte-conceived peers (RR: 0.89, CI: 0.75–1.05, $p = 0.15$, $I^2 = 48\%$) (Figure 2.15). This analysis included 9,734 donor oocyte neonates and 74,727 autologous conceived neonates and incorporated only fresh oocytes. No cryopreserved oocyte outcomes were included in this meta-analysis. Due to a lack of stratified singleton outcome data, a meta-analysis of singleton outcomes could not be performed.

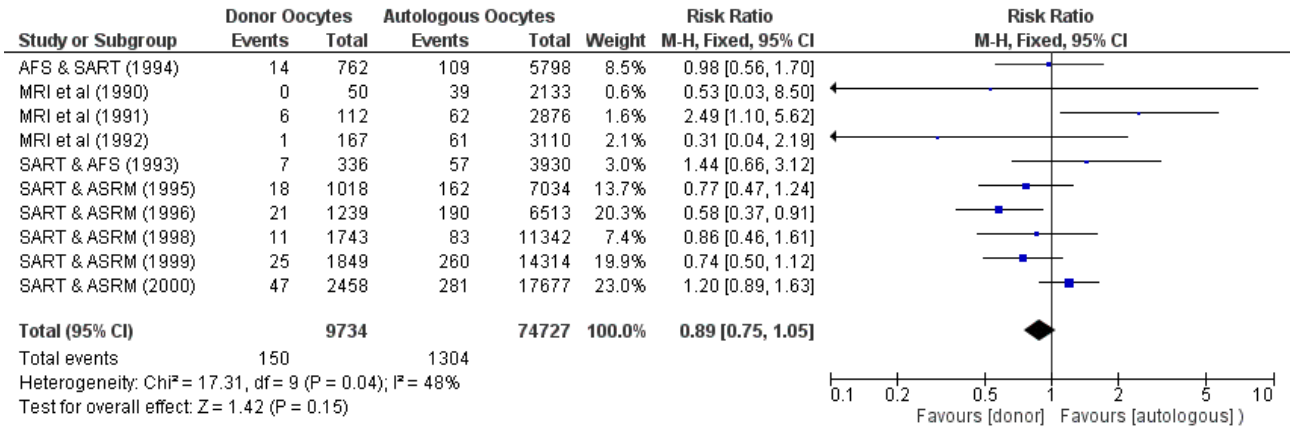

Figure 2.15 Forest plot of birth defect outcomes comparing fresh donor oocyte versus fresh autologous oocyte neonates (singletons and multiples).

Birth defect data was reported in earlier studies,[581-585, 588-590, 595] but was missing from later studies. These reports provided frequency percentages rather than statistical analysis in which a decreased percentage of birth defects were reported for seven of the ten years (Table 2.1). The study conducted by Sheffer-Mimouni *et al.* reported no significant differences between donor oocyte neonates and general population data for Israel (statistics were not reported).[593]

2.4.5 Oocyte Donation Other Outcomes

One study reported other perinatal outcomes of neonatal intensive care unit (NICU) or neonatal surveillance unit (NSU) admissions and the length of stay in hospital before going home. Soderstrom-Anttila *et al.* reported that donor oocyte-conceived singletons were more likely to have an increased hospital stay ($p < 0.01$) than their autologous oocyte-conceived singleton peers. Furthermore, donor oocyte neonates born as a twin or higher-order multiple were more likely to be admitted to the NICU/NSU ($p < 0.01$), in comparison to autologous oocyte-conceived multiples.[572]

2.4.6 Oocyte Donation Effects of Multiplicity

Multiplicity of births, including twins and higher-order multiples is associated with ART treatments and a known confounder for increased incidences of adverse neonatal outcomes. Subsequently, we conducted a meta-analysis of comparable data to determine whether there was an increased risk of being born as a twin or higher-order multiple in the included studies. Meta-analysis of multiplicity outcomes exhibited an increased risk for donor oocyte neonates

to be born as a twin or higher-order multiple than their autologous oocyte-conceived peers (RR: 1.10, CI: 1.07–1.13, $p < 0.00001$, $I^2 = 25\%$) (Figure 2.16), and included 9,985 donor oocyte neonates and 75,262 autologous conceived neonates.

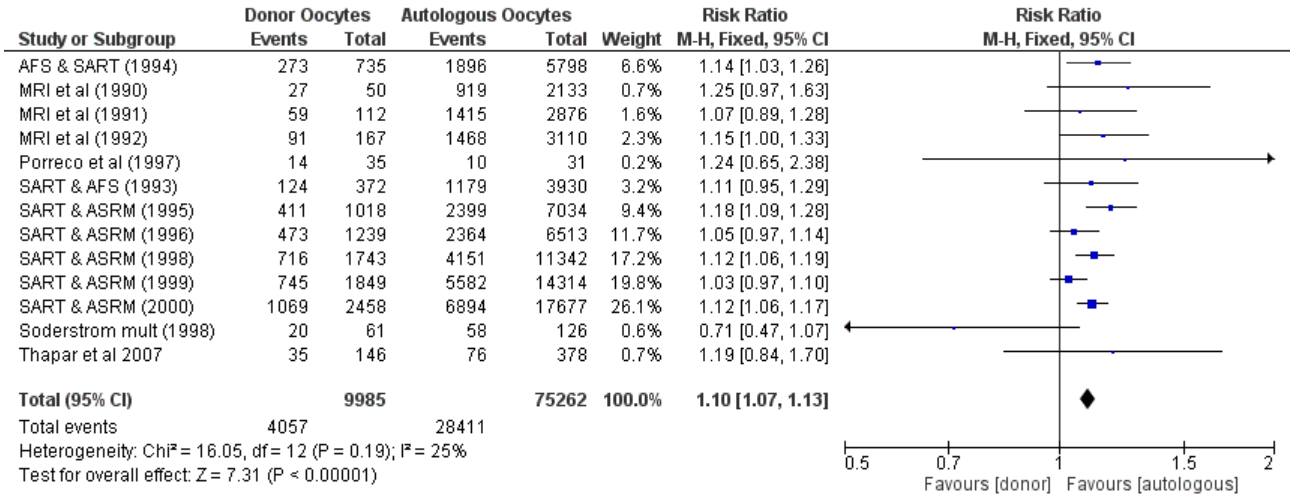

Figure 2.16 Forest plot of multiplicity outcomes comparing donor oocyte versus autologous oocyte neonates.

The majority of studies that reported higher incidences of multiplicity were from data collections occurring before 2000. The exception is the study by Thapar *et al.,* published in 2007, including data collected for three years previous.[592] In the 2000s there became an increased awareness of the necessity to reduce multiplicity by reducing the number of embryos that would be implanted at one time. This awareness can be seen in recommendations made by the ASRM starting in 1998, which have then been adjusted over time, leading to a reduction in multiple pregnancies.[500] Due to the lack of comparable stratified data in the included studies, we could not test if the risk of multiplicity was reduced in more recent times. However, conducting equivalent meta-analyses on all singleton outcomes is important to determine confounding by multiplicity in the results of his systematic review. All singleton meta-analysis was presented alongside the all births meta-analysis in the previous sections for ease of comparison. Controlling for multiplicity did not alter the risk for the observed outcomes and all significant associations of LBW, VLBW, PD, PD with LBW, and TermD with LBW remained significant.

2.4.7 Oocyte Donation Risk of Bias

A modification of the JBI-MAStARI instrument was used to assess methodological quality and the risk of bias of the included studies (Table 1.2). The length of time of treatment for the woman, including the total number of attempts to achieve a pregnancy was poorly reported. When this data was reported, it was not stratified to allow a comparison between donor oocyte and autologous oocyte treatment outcomes. Other confounders such as maternal demographics including maternal age, maternal BMI, parity, SES as well as infertility aetiology were also either frequently lacking or not stratified for analysis. Multiplicity and the reporting of segregated singleton data were lacking in several of the studies.

The two common confounders of maternal age and parity are presented in Table 1.3. These were reported in nine of the included studies. The largest study authored by Gibbons *et al.*, controlled for both maternal age and parity and accounts for 97.6% of mean BW data.[569] Subsequently, a significant proportion of the data included in this systematic review has appropriately controlled for both maternal age and parity. The association between LBW and maternal age in the studies is conflicting. Sunderam *et al.* observed an increased risk of LBW and VLBW with increased maternal age in the donor oocyte outcomes.[576] Whereas Gibbons *et al.*, reported no association between maternal age and LBW.[569] The association between maternal age and PD was only reported in one study. Sunderam *et al.* observed an increased incidence of PD and PD with LBW in the donor oocyte cohort, which had proportionally higher maternal ages than the autologous oocyte treatment cohort.[576] Studies reporting birth defects did not record maternal age or parity details.

Outcomes of mean BW, LBW, VLBW, SGA, IUGR, mean GA, PD, PD with LBW, and TermD with LBW were classified as reporting objective data and criteria. Birth defects, however, are more subjective and are potentially overlooked in the perinatal period due to their complex nature. Reports from five studies highlighted this issue directly with statements to the effect that BD reporting was inadequate and therefore the data presented was likely not to contain all BD data for that cohort.[583-586]

The comparison cohort was adequately described in most studies except for Corradetti *et al.*.[292] A further study did not provide its own comparison cohort but rather referenced previously published data.[594]

Table 1.2 Risk of bias and critical assessment of included donor oocyte studies

Study	Criterion								
	Representative patients	Similar point in condition	Minimised case selection bias	Singleton v multiples	Other confounders	Cryo-preservation	Objective criteria	Reliable outcomes	Appropriate statistics
Gibbons *et al.* (2011)	Yes	Unclear[a]	Yes	No[a]	Yes	Yes	Yes	Yes	Yes
Zegers-Hochschild *et al*. (2010)	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Yes
Krieg *et al*. (2008)	Yes	Unclear	Yes	No[a]	Yes	No	Yes	Yes	Yes
Soderstrom-Anttila *et al*. (1998)	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Porreco *et al*. (1997)	Yes	Unclear	Yes	No	No	No	Yes	Yes	Yes
Friedman *et al*. (1996)	Yes	Unclear	Yes	No	Yes	No	Yes	Yes	Yes
Nelson and Lawlor (2011)	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Kalra *et al*. (2011)	Yes	Unclear[a]	Yes	Yes	No[a]	Yes	Yes	Yes	No[b]
Sunderam *et al*. (2009)	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Wright *et al*. (2008)	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Thapar *et al*. (2007)	Yes	Unclear	Yes	Yes	No[a]	No	Yes	Yes	No[b]
Wright *et al*. (2007)	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Wright *et al*. (2006)	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Wright *et al*. (2005)	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Schieve *et al*. (2004)	Yes	Unclear	Yes	Yes	No[a]	Yes	Yes	Yes	No[b]
Sheffer-Mimouni *et al*. (2002)	Yes	Unclear	Yes	Yes	No[a]	No	Yes	Yes	No[b]
Corradetti *et al*. (2012)	Yes	Unclear	Unclear	No	No	No	Yes	Yes	Yes
Pados *et al*. (1994)	Yes	Unclear	No[c]	No[a]	No[a]	No	Yes	Yes	No
ASRM and SART (2000)	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
ASRM and SART (1999)	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
ASRM and SART (1998)	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
ASRM and SART (1996)	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
ASRM and SART (1995)	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
AFS and SART (1994)	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and AFS (1993)	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
MRI *et al*. (1992)	Yes	Unclear	Yes	No[a]	No	No	Yes	No	No
MRI *et al*. (1991)	Yes	Unclear	Yes	No[a]	No	No	Yes	No	No

MRI *et al*. (1990)	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No

[a] = data was presented but was not stratified as donor v autologous, or the data was not used in statistical analysis; [b] = statistics were used appropriately, but the authors did not analyse donor v autologous outcomes; [c] = a comparison group was used but was from previously published data, not a comparison cohort. [1]

Table 1.3 Maternal age and parity as reported in included donor oocyte studies

Study	Maternal Age Details	Parity Details
Gibbons *et al*. (2011)	adjusted for maternal age	adjusted for parity
Zegers-Hochschild *et al*. (2010)	(14% ≤ 34 yrs, 25.1% 35–39 yrs, 60.9% ≥ 40 yrs) v (50% ≤ 34 yrs, 34.6% 35–39 yrs, 15.4% ≥ 40 yrs)	-
Krieg *et al*. (2008)	(42.7 ± 4.4 yrs) v (41.3 ± 1.84 yrs)	(0.32 ± 0.528) v (0.35 ± 0.569)
Soderstrom-Anttila *et al*. (1998)	(33.5 ± 4.7 yrs) v (33.4 ± 3.7 yrs)	84% v 69% nulliparous
Porreco *et al*. (1997)	(38.8 yrs (range 27–50)) v (38.7 yrs (range 34–44))	89% v 78% nulliparous
Sunderam *et al*. (2009)	(12% < 35 yrs, 11.7% 35–37 yrs, 17.3% 38–40 yrs, 16.2% 40–42 yrs, 42.8% > 42 yrs) v (56.3% < 35 yrs, 25.1% 35–37 yrs, 14.3% 38–40 yrs, 3.5% 40–42 yrs, 0.8% > 42 yrs) *	-
Thapar *et al*. (2007)	(37.88 ± 5.89 yrs) v (34.14 ± 3.53 yrs)	-
Corradetti *et al*. (2012)	(range 32–50 yrs) v (range 30–46 yrs)	-

Only studies reporting maternal age and parity details are recorded in the table. * = function of live birth delivery rates. [1]

Funnel plots were used for determination of publication bias,[596] and are presented in Appendix 1.7 for all previous meta-analyses. Funnel plot analysis of all births (singleton and multiples) found that publication bias was present in BD outcomes. Mean BWs were too heterogeneous from visual analysis coupled with the I^2 statistic > 65% (I^2 = 76%). The outcome measures of LBW, VLBW, GA, PD, PD with LBW, and TermD with LBW in all births were interpreted as symmetrical as was the incidence of multiplicity. Analysis of singleton outcome funnel plots found that mean BWs was again too heterogeneous from visual analysis; however, the I^2 statistic was satisfactory (I^2 = 26%). The singleton outcomes of LBW, PD, and TermD with LBW were viewed as symmetrical. Conversely, VLBW and PD with LBW were deemed to be asymmetrical and therefore showing reporting bias. The I^2 statistic was 65% for VLBW, also highlighting the level of heterogeneity.

Funnel plots are typically used to determine publication bias. However, some authors argue that they are not an accurate prediction of publication bias.[597, 598] Recommendations have subsequently been made to improve interpretation of funnel plots,[599] which the authors argued are perhaps better suited to a meta-analysis of randomised trials than the studies included in this review. Nonetheless, Terrin *et al.*, found that researchers could not identify publication bias accurately by visual interpretation,[600] and therefore, the interpretations presented here should be treated with caution.

2.5 Oocyte Donation Limitations of Study

Even though the search strategy as described by Wright *et al.*, highlighted the benefits of using those three databases, it is still a limitation as eligible publications may be present in other databases and may have been inadvertently omitted. Further limitations are present due to the limited amount of hand-searching of reference lists as well as the exclusion of publications in languages other than English. Meta-analysis was hampered due to issues associated with data and methodological quality in earlier publications which prevented their inclusion in meta-analyses.

The lack of statistical analysis by studies included in this review is problematic as is the lack of appropriate stratification of data which subsequently meant some studies were excluded from the meta-analyses. Studies from national cohorts in America represent a form of self-reporting by the American Fertility Society (AFS), American Society for Reproductive Medicine (ASRM), and the Society for Assisted Reproductive Technology (SART). However, these were hampered by incomplete data capture and therefore, inaccurate reporting. Specifically, this pertains to the reporting of BDs and the statements that "more stringent requirements for follow-up and reporting" would be implemented in the following years suggesting that the data capture for this outcome needed improvement.[583-586] Later, in 2000, the same organisational annual report suggested that limitations still existed in the collection of outcome data.[581] Therefore, it could be postulated that the incidences of BDs in donor and autologous oocyte cohort groups are underreported.

Multiplicity reporting was inconsistent and was not always stratified appropriately to enable comparisons of outcomes between singletons and multiples. Further multiplicity stratification issues were apparent in the neonatal outcome data, such that meta-analysis could not be conducted on the various outcomes based on singletons versus multiples as the outcomes were not stratified themselves by multiplicity but were instead combined. Stratification issues had the effect of decreasing the number of studies included in various meta-analyses of singleton outcomes. When such meta-analysis was performed, similar risk ratio outcomes were observed even though the number of studies included was reduced. Therefore, multiplicity did not adversely bias the outcomes presented.

In general, the quality of the studies improved methodologically in a systematic manner over time. More recent studies were able to address the question of the impact the source of the oocyte had on neonatal outcomes better. Improvements over time were also observed in

terms of the reporting of confounding. However, improvements could be made particularly in terms of cryopreservation but also in the reporting of maternal age, multiplicity, parity, SES, and the length of time the mother had received fertility treatment before becoming pregnant.

2.6 Oocyte Donation Discussion

This study was the first systematic review and meta-analysis to be published on the neonatal outcomes of donor oocytes in comparison to autologous oocytes. Shortly after, other systematic reviews were also published. These will be discussed in the systematic review conclusion in this chapter.

The use of donor oocytes was correlated with an increased risk of neonates being born of LBW, VLBW, PD, and PD with LBW. Similarly, donor oocyte neonates were also more likely to be born of lower GA and were more like to be born as a twin or higher-order multiple. Those donor oocyte-conceived neonates that made it term were less likely to be born of LBW. These correlations remained after controlling for multiplicity with singletons having comparable risks for poorer neonatal outcomes in comparison to the donor oocyte-conceived cohorts that included multiple deliveries (all births). The presence of reporting bias in singleton VLBW and PD with LBW outcomes highlight that further data is required to confirm or refute these findings.

All the studies included in the meta-analyses reported autologous oocyte data as the comparison cohort. Whereas two small sample size studies reporting spontaneous conception comparison data were not included in the meta-analyses.[593, 594] As described in the preceding chapter detailing DOHaD and the mechanisms present in various fertility treatments that may influence neonatal outcomes, autologous oocyte treatments are the most appropriate comparison cohort. This is because autologous oocytes have been exposed to similar if not the same manipulation and treatments in the laboratory as donor oocytes. Subsequently, while laboratory treatments may affect outcomes as evidenced by IVF neonates having adverse outcomes, the increased frequency of adverse outcomes for donor oocyte neonates compared to autologous oocytes suggests other aetiologies such as maternal complications including PE may have influenced the observed differences. The inclusion of only autologous oocyte outcomes as the comparison cohort in the meta-analyses is a strength of the study.

Interestingly there was a general trend to decreased frequencies of reported TermD with LBW in each of the subsequent years of the United States SART data reported by Schieve *et al.*, which stabilised with the publications by Wright *et al.*, followed by an increase reported by

Sunderam *et al.*, (donor oocyte TermD with LBW = 6.3%, 5.0%, 4.1%, 2.6%, 2.4%, 1.8%, 2.1%, 2.1%, 2.1%, 2.7%). The reason for this remains unclear; however, it may be possible that with better monitoring and treatment of various maternal factors that the ability to get a pregnancy to term with a lower incidence of LBW regardless of the treatment modality has improved. A similar decreased trend in the incidences of LBW were observed in the same cohorts (15.2%, 13.0%, 13.1%, 10.0%, 10.6%, 10.7%, 11.2%, 10.4%, 11.0%, 12.0%), but which was less noticeable in PD (18.5%, 17.3%, 18.2%, 15.2%, 16.2%, 16.3%, 17.6%, 16.2%, 16.9%, 17.0%), highlighting an improvement over time in regard to outcomes in general.

The incidence of birth defects in fresh donor oocyte-conceived neonates was not statistically different to the incidence observed in their fresh autologous oocyte-conceived peers, although a non-significant trend to reduced BDs in donor oocyte neonates was observed. The analysis of birth defects, unlike the other neonatal outcomes, could not be controlled for multiplicity due to the nature of the BD data reported in the included studies not being appropriately stratified and therefore only reflects outcomes for all births. Further studies are required to clarify the effect of the use of donor oocyte on BD incidences, however, Hansen *et al.*, reported that the incidence of BD in ART treatments, in general, is higher than that observed in this study (ART birth defects RR: 1.32, CI: 1.24–1.42, $p = 0.000$, $I^2 = 47\%$).[51] The non-significant reduction in BD observed in this review is consistent with and supported by evidence that donor oocytes are typically donated by women who are younger than the recipient mother,[520, 521] which subsequently lowers the incidences of the use of poor quality oocytes including those that may be aneuploid.[601, 602]

One study investigated the length of stay in the hospital in addition to admissions to the NICU and NSU and found that donor oocyte-conceived neonates had increased admissions and length of stays.[572] There have been other studies that have also looked at this outcome for oocyte donations since the census date of this review and will be discussed in the systematic review conclusion section.

The systematic review will now address the outcomes for people conceived from donor sperm.

2.7 Sperm Donation Results

Due to the considerable amount of heterogeneity in the outcomes reported in the included studies, meta-analyses were only conducted on comparable outcomes.

2.7.1 Sperm Donation Outcomes

Meeting the inclusion criteria for health outcomes of sperm DC people was a total of eight studies. Of these studies, three were able to be included in meta-analyses.[183, 447, 603] A qualitative analysis was conducted on the other five studies and is presented in the text.[592, 604-607] All meta-analyses were comparisons of donor sperm-conceived neonates compared to those conceived spontaneously. While qualitative analysis also included partner IVF conceptions as a comparison group in addition to spontaneous conceptions. Spontaneously conceived cohort data was taken from data on the general population. No comparable data were available of adult health outcomes for analysis of long-term health trajectories. Combining all studies allowed for the inclusion of 24,699 donor sperm health outcomes and 423,763 outcomes from spontaneous or partner ART conceptions.

2.7.2 Sperm Donation Birth Weights

All included studies except for Forse *et al.*,[605] reported BW outcomes of either mean BWs or incidences of LBW. Mean BW data was not comparable between studies, and therefore meta-analysis could not be conducted. The study by Davies *et al.* included mean BW data; however, these could not be used in a meta-analysis as they were subsumed as part of a larger ART cohort incorporating outcomes from all ART treatment modalities.[447] No study reported a significant difference between the BWs of donor sperm-conceived neonates and those conceived spontaneously in the general population (see Table 1.1). The data presented by Lansac *et al.* was of donor sperm singleton outcomes in comparison to all births of those conceived spontaneously, including multiples rather than singletons, thereby introducing confounding.[607]

Donor sperm-conceived neonates were not significantly different to those conceived spontaneously in terms of being born of LBW (RR: 1.04, CI: 0.86 – 1.25, $p = 0.71$, $I^2 = 0\%$) (Figure 2.17). This analysis included 1,638 donor sperm neonates and 116,818 spontaneously conceived neonates.

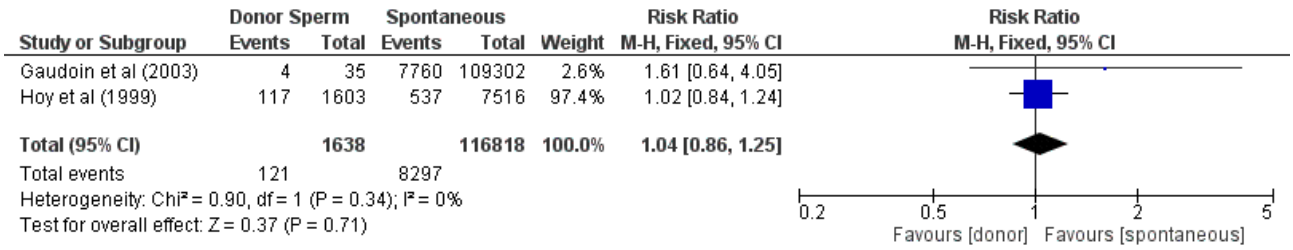

Figure 2.17 Forest plot of low birthweight (< 2500g) outcomes comparing donor sperm versus spontaneously conceived neonates.

Differences were observed in LBW crude frequency comparisons in various studies, primarily that donor sperm neonates had higher frequencies than those conceived spontaneously. For example, Hoy *et al.* observed a non-significant increased risk of being born of LBW in comparison to those conceived spontaneously (7.3% v 6.8%, RR: 1.1).[183] Thapar *et al*. also observed a higher frequency of LBW in all births including multiples of IVF neonates conceived with donor sperm (19.6%), homologous IVF with partner's sperm IVF (14.7%), and spontaneously conceived neonates (8%).[592] These differences in frequencies were decreased when controlling for multiplicity in the same cohorts, as singleton donor sperm neonatal LBW frequencies (8%) were only marginally larger than homologous IVF LBW frequencies (6.7%), but were stated to be not different to the general population even though singleton data for the general population was not reported, only all births. An increased frequency of LBW in donor sperm-conceived neonates (11.4%) in comparison to those spontaneously conceived (7.1%) was also observed by Gaudoin *et al*.[603] However, the frequency was lower than that observed when using the partner's sperm (22.7%), which was the converse of that observed by Thapar *et al*. The only study to report a lower frequency of LBW in the donor sperm-conceived neonatal cohort was that of Lansac *et al.*, who reported 4.7% v 6.2%.[607]

2.7.3 Sperm Donation Preterm Delivery

Meta-analysis of the studies reporting PD outcomes showed no significant difference between donor sperm and spontaneously conceived neonates (RR: 0.91, CI: 0.75 – 1.12, $p = 0.38$, $I^2 = 0\%$) (Figure 2.18). This analysis included 1,638 donor sperm neonates and 116,818 spontaneously conceived neonates. While three studies reported PD outcomes, the study by Lansac *et al.*, was excluded from meta-analysis due to the absence of comparable data for the spontaneously conceived cohort. Frequencies of PD outcomes of donor sperm neonates were

reduced in all studies in comparison to the general population of spontaneously conceived neonates (4.8% v 5.9%;[607] 6.4% v 6.6%;[183] 5.7% v 6.9%[603]).

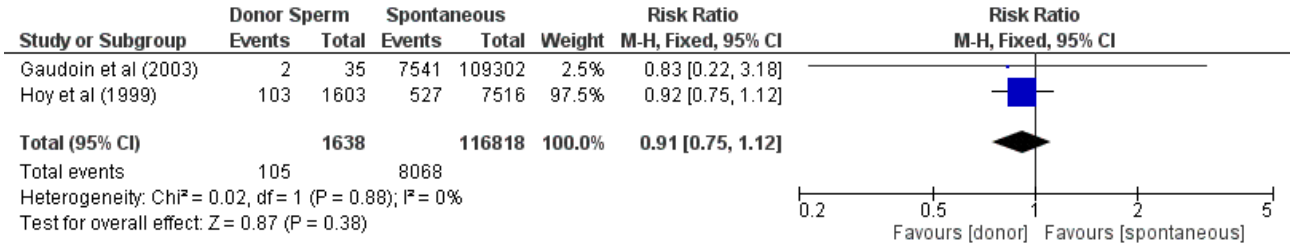

Figure 2.18 Forest plot of preterm delivery (< 37 weeks) outcomes comparing donor sperm versus spontaneously conceived neonates.

2.7.4 Sperm Donation Birth Defects

A meta-analysis of the studies reporting BD outcomes showed no significant difference between donor sperm and spontaneously conceived neonates (RR: 1.20, CI: 0.97 – 1.48, p = 0.09, I^2 = 57%) (Figure 2.19). This analysis included 2,031 donor sperm neonates and 300,830 spontaneously conceived neonates. Davies *et al.* reported a significantly increased risk of BD associated with sperm donation (8.4% v 5.7%, Odds Ratio (OR) 1.5, 95% CI 1.08 – 2.11).[447] However, this outcome was no longer significant (OR 1.37, 95% CI 0.98 – 1.92), when adjusting for extensive confounding of:

> "maternal age (categorized in 5-year age groups), parity, fetal sex, year of birth, maternal race or ethnic group, maternal country of birth, maternal conditions in pregnancy (pre-existing hypertension, pregnancy-induced hypertension, preexisting diabetes, gestational diabetes, anemia, urinary tract infection, epilepsy, and asthma), maternal smoking during pregnancy, socioeconomic disadvantage on the basis of the postal code of the mother's residence (according to the Socio-economic Indexes for Areas), and maternal and paternal occupation, coded according to the Australian Standard Classification of Occupations."[447]

Others also reported higher frequencies of birth defects that were not significantly different according to the authors (2.9% versus 2%;[606] 3.6% v 3.2%, RR 1.1[183]). One of the few longer-term data presented in the studies investigating sperm donation outcomes found a higher frequency of malformations in donor sperm-conceived children of an average of 5 years of age (6.2% versus 5%).[606] Lansac *et al.* reported no significant differences in the malformation rates of donor sperm-conceived neonates. However, the authors omitted reporting the actual data for those conceived spontaneously in the general population.

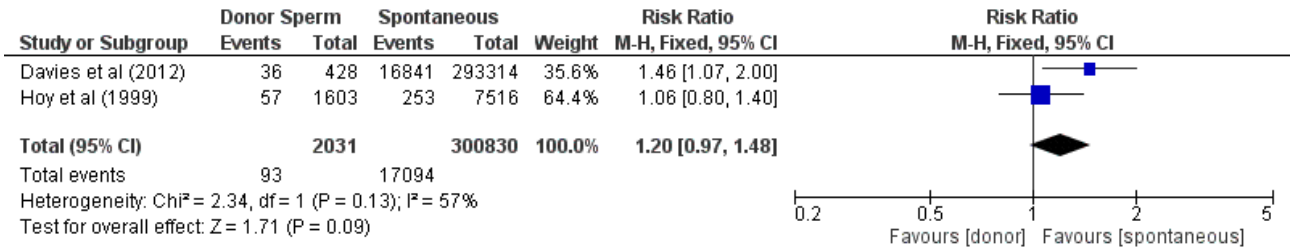

Figure 2.19 Forest plot of birth defect outcomes comparing donor sperm versus spontaneously conceived neonates.

Four studies reported chromosomal abnormalities (ChAb); however, the data was not comparable, and meta-analysis could not be performed. Two studies observed a higher frequency of aneuploidy,[183, 605] while another observed a significant increase in comparison to one general population cohort in France (Paris $p < 0.05$) but not significantly different to another general population cohort (Strasbourg et Marsailles not significant).[607] The final study did not report the ChAb frequency for the spontaneously conceived cohort.[606]

2.7.5 Sperm Donation Other Outcomes

The study by Hoy *et al.*, reported on mortality rates, specifically perinatal death (1.2% v 1.1%, RR: 1.4), stillbirth (0.9% v 0.6%, RR: 1.5), and neonatal death (0.4% v 0.5%, RR: 0.8).[183] These differences in frequencies were reportedly not statistically significant.

One study reported IQ for children conceived with donor sperm. Iizuka *et al.* reported that donor sperm-conceived children had a higher IQ,[604] than that observed in the general population, which was from previously published data and not a cohort.[608] Another study reported the frequency of donor sperm-conceived children with learning disabilities (5.8%), and who had been enrolled in gifted and talented programs (10.5%).[606] However, the authors did not report outcome frequencies for spontaneously conceived children for comparison.

2.7.6 Sperm Donation Effects of Cryopreservation

Two studies specifically reported the use of cryopreserved sperm in their donor sperm-conceived cohorts.[183, 607] Three other studies would have had neonates conceived with cryopreserved sperm even though they did not report it, because their respective jurisdictions mandated the use of cryopreserved sperm (see the section on 'Cryopreservation' in Chapter 1).[447, 592, 603] Consequently, the three studies that were included in the meta-

analyses all included neonates conceived with cryopreserved sperm. Two of the studies were from mandated jurisdictions while the other was a self-report of the use of cryopreservation.

Those outcomes that were reported as being significantly worse for the cryopreserved donor sperm-conceived cohort compared to those conceived spontaneously in each of the studies included LBW (OR: 1.73, CI: 0.26 – 11.69),[603] aneuploidy (RR: 2.5),[183] and chromosomal anomalies ($p < 0.05$).[607] Crude BD was also significantly increased (OR: 1.51, CI: 1.08 – 2.11); however, this was ameliorated when adjusted for confounding (OR: 1.37, CI: 0.98 – 1.92).[447] Thapar *et al.*, also reported a higher frequency of LBW outcomes in cryopreserved donor sperm-conceived neonates, but no statistical analysis was reported.[592]

In contrast, other studies found no difference between cryopreserved donor sperm neonates and those conceived spontaneously in terms of malformation rates,[607] and BD.[183] Without sufficient data and studies addressing the fresh versus cryopreserved sperm question, the effect that cryopreservation has on the neonatal and long-term health outcomes of those conceived with cryopreserved sperm cannot be elucidated.

2.7.7 Sperm Donation Effects of Multiplicity

Multiplicity was poorly recorded in several studies, and or the data was not appropriately stratified into comparable data to allow meta-analysis to be conducted on the incidence of multiplicity. The three studies that were included in the meta-analyses were methodologically better than the others in terms of either controlling for multiplicity or reporting of multiplicity.[183, 447, 603] Others were inconsistent from the perspective that they provided multiplicity data for the donor sperm-conceived cohort but failed to report the equivalent data for the spontaneously conceived cohort.[592, 606, 607] Where comparison cohort multiplicity data was provided, it pertained only to outcomes from IVF with donated sperm (IVF-D),[607] and homologous IVF.[592] The only study reporting data that compared donor sperm and spontaneously conceived cohort frequencies was Hoy *et al.*, who reported a higher frequency of multiplicity, but which was not statistically significant (3.1% v 2.7%, RR: 1.2, CI: 0.9 – 1.7).[183] Due to the lack of comparable data for meta-analysis of multiplicity, no inferences can be made on the effect of multiplicity on the neonatal health outcomes of LBW, PD and BD for those conceived with donor sperm.

2.7.8 Sperm Donation Risk of Bias

A modification of the JBI-MAStARI instrument was used to assess methodological quality and the risk of bias of the donor sperm studies included (Table 1.4). Similar to the assessment of donor oocyte studies, the length of time of treatment for the woman, including the total number of attempts to achieve a pregnancy was not reported. Other confounders, including maternal demographics including maternal age, maternal BMI, parity, SES as well as infertility aetiology, were also poorly reported. Alternatively, when they were reported, they were not stratified to allow comparison between donor sperm-conceived neonates and those conceived spontaneously.[447] The study by Davies *et al.*, was the most comprehensive in the control of confounding.[447]

Reporting of mean BW, mean GA, cryopreservation, and multiplicity was lacking in the majority of studies or were non-comparable, resulting in the inability to conduct a meta-analysis on those outcomes. In comparison, the meta-analyses conducted were hampered by a lack of studies that could be included - thereby inducing bias. Outcome reports of mean BWs, LBW, PD, and ChAb were considered to be objective outcomes. Birth defects and malformations were considered to be more subjective as BD, in general, is not a well-defined category. The exception is the study by Davies *et al.*, which was objective in the classifications of BDs by implementing the 'British Paediatric Association Modification of the International Classification of Diseases' (9th Revision).[447] Historically BD's have been potentially underreported in ART cohorts with reports by the AFS, ASRM, and SART, acknowledging that "more stringent" reporting of BD was required to avoid missing BDs in the neonatal period.[583-586]

Also problematic is the instances of studies referencing previously published data as their comparison cohort but did not report detailed figures or information.[592, 604-607]

All BW data reported including mean BWs and incidences of LBWs were not controlled for gestational age in the same manner as for oocyte donation outcomes (for example comparing outcomes of PD with LBW or term delivery with PD). Preterm delivery outcomes were deemed to suffer from publication bias through funnel plot analysis (Appendix 1.8), while others were deemed to be symmetrical. As described previously, funnel plot analysis should be treated with caution, especially considering the lack of studies included in the meta-analysis.

Table 1.4 Risk of bias and critical assessment of included donor sperm studies

Study	Criterion								
	Representative patients	Similar point in condition	Minimised case selection bias	Singleton v multiples	Other confounders	Cryo-preservation	Objective criteria	Reliable outcomes	Appropriate statistics
Thapar *et al.* (2007)	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	No[b]
Gaudoin *et al.* (2003)	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes
Hoy *et al.* (1999)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes[d]	Yes	Yes
Amuzu *et al.* (1990)	Yes	No	Yes[a]	No	No	No	Yes[d]	No	No[b]
Iizuka *et al.* (1968)	Yes	Unclear	No[a]	No	Yes	No	Yes	Yes	No
Davies *et al.* (2012)	Yes	Unclear	Yes	Yes	Yes	No[c]	Yes	Yes	Yes
Lansac *et al.* (1997)	Yes	Unclear	Yes[a]	No	Yes	Yes	Yes[d]	No	No[b]
Forse *et al.* (1985)	Yes	Unclear	Yes[a]	No	No	No	Yes[d]	Yes	No

a = comparison group was not a comparison cohort but data published elsewhere; b = statistics were used appropriately but did not report specific results in the analysis to the comparison group; c = cryopreservation was not recorded however cryopreservation was mandated in the jurisdiction of and during the period of those studies; d = included both objective and subjective data. [3]

The confounders of maternal age and parity are presented in Table 1.5 in the same manner as they were for oocyte donation outcomes. Five studies did not report parity, two reported frequencies of nulliparity (which was controlled for by *Davies et al.*,) and primiparity (not controlled by Hoy et al.,), while only the study by Gaudoin *et al.*, exclusively reported nulliparous data. Maternal age data reporting was inconsistent, thereby preventing meta-analysis. Five studies reported mean maternal ages of the donor sperm treated mothers, one reported frequencies of various age ranges and another the frequency of maternal age greater than or equal to 35 years. Spontaneously conceived comparison cohort maternal age data was missing from five of the eight studies.

Table 1.5 Maternal age and parity as reported in included donor sperm studies

Study	Maternal Age Details	Parity Details
Thapar *et al.* (2007)	33.88 ± 3.82 yrs (donor) v 34.14 ± 3.53 yrs (homologous IVF) v unknown (general population)	-
Gaudoin *et al.* (2003)	33.1 (31.9–34.3 95% CI, donor) v 32.4 (31.6–33.1, partner) v 25.9 (25.9–25.9, general population)	all nulliparous
Hoy *et al.* (1999)	16% ≥ 35 yrs v 10% ≥ 35 yrs	53.4% v 40.5% primiparous
Amuzu *et al.* (1990)	29.3 ± 4.2 yrs v unknown	-
Iizuka *et al.* (1968)	30.1 ± 2.7 yrs v unknown	-
Davies *et al.* (2012)	(2.2% 20–24 yrs, 22.2% 25–29 yrs, 44.4% 30–34 yrs, 26.2% 35–39 yrs, 5.1% ≥ 40 yrs) v (20.8% 20–24 yrs, 37.7% 25–29 yrs, 29.4% 30–34 yrs, 10.5% 35–39 yrs, 1.7% ≥ 40 yrs)[a]	65.3% v 37.5% nulliparous
Lansac *et al.* (1997)	[b]	-
Forse *et al.* (1985)	28.9 yrs[c]	-

a = maternal age and parity data are from larger assisted conception cohort that also includes donor sperm outcomes; b = no maternal age data of sperm donor outcomes versus comparison, rather maternal age data were presented within sperm donation outcomes stratified as healthy infants versus malformed infants; c = used comparison data for the population with same maternal age distribution. [3]

2.8 Sperm Donation Limitations of Study

As described previously in the oocyte limitations of study section, the donor sperm outcome study was also limited by the use of the three databases described by Wright et al.,[566] the hand-searching of references and the restriction to the English language. Furthermore, it was also limited in the number of studies fulfilling the inclusion criteria and the dearth of comparable data to allow meta-analysis. It thereby resulted in meta-analysis with only two studies for each outcome measure. Stratification of data by multiplicity was inconsistent with only two studies reporting singleton outcomes,[447, 603] whereas singleton data was subsumed into all birth data in other studies preventing meta-analysis.

Consistency in the reporting of outcome measures would assist in meta-analysis as would reporting of actual comparison cohort data which was missing for several studies rather than referencing previously published material. Consideration for confounding could be improved with only one study which controlled for multiple confounding.[447] Large national databases of ART outcomes are kept in countries such as the USA, UK and Australia. However, donor sperm outcomes are mostly overlooked in favour of recording donor oocyte, IVF and other ART treatment modalities. The inclusion of yearly sperm donation treatment data and outcomes would considerably improve the understanding of the effects of donor sperm conception.

2.9 Sperm Donation Discussion

This study was the first systematic review and meta-analysis to be published on the neonatal outcomes of donor sperm conceptions in comparison to those who have been spontaneously conceived. The donor sperm outcome review had far fewer studies that could be included and a lack of comparable data compared to the donor oocyte outcome review.[1] The small number of studies included would suggest that donor sperm neonates have been understudied. Additionally, unlike the donor oocyte review, no other researchers have followed up from this review with a systematic review of their own. However, we have been able to improve the number of studies included in a subsequent re-analysis that will be presented in Chapter 3.

Meta-analysis exhibited that donor sperm-conceived neonates were not at a significantly increased risk of having higher incidences of LBW, PD or BD in comparison to spontaneously conceived neonates. One included study suggested that they were also not at increased risk of stillbirth, neonatal death or perinatal death.[183] There was little evidence to support any correlations between the use of donor sperm and learning disabilities or IQ in the children.

Conflicting reports from different studies in reviews are not uncommon. One example is the study of Iizuka *et al.*, who reported an increase in BWs of the donor sperm-conceived cohort,[604] which is in contrast to other reports which found no difference in mean BWs. The authors posited that the environment of Tokyo and surrounding areas from which participants were recruited in the 1960s possibly contributed to the increased BW. This contribution to BW is in contrast to those that would be born and raised in other areas of Japan, which were less affluent. Another possibility is parental confounding. The parents of the children in the study reportedly had higher education levels than their spontaneous conception parental peers which potentially can be associated with a higher SES leading to

improved access to health/medical resources and better diets which may influence foetal growth.

Studies that did not control for multiplicity may adversely affect BW outcome analysis. For example, Lansac *et al.*, compared donor sperm-conceived singletons to spontaneously conceived all births, including multiples.[607] Considering that multiplicity reduces BWs,[609, 610] singleton weights for the spontaneously conceived comparison group could be higher depending on the rate of multiplicity. Subsequently, any actual effect may be overlooked due to inadequate controlling of the data.

No significant differences were observed in BD outcomes from the meta-analysis of donor sperm neonatal outcomes. One study reported a statistically significant increase in BDs associated with the use of donor sperm; however, this was ameliorated when controlled for numerous confounders.[447] Reports of ChAb were conflicting with one study showing a significant increase in comparison to one spontaneously conceived cohort but not another.[607] While another reported no significant difference even though the observed relative risk was 2.5.[183] These observed increases could be attributed to higher maternal ages,[611, 612] as well as sperm donor ages,[613] instead of being attributed to the use of donor sperm specifically. Supporting this postulation is the study by Lansac *et al.*, which associated both increased maternal and sperm donor age with increases in trisomy 21.[607] The only study investigating malformation rates in childhood found a higher frequency of malformations in donor sperm-conceived children than those observed in spontaneously conceived children.[606]

The implications of sperm cryopreservation on the DNA and function of sperm is of considerable interest, particularly concerning the health of any resultant offspring. One study specified the use of fresh sperm,[605] while four others specified that cryopreserved sperm was either exclusively used or in combination with fresh sperm.[183, 604, 606, 607] The three remaining studies,[447, 592, 603] were conducted after the introduction of mandatory cryopreservation in their respective jurisdictions and therefore would have exclusively used cryopreserved sperm.[315, 614] Without studies investigating fresh versus cryopreserved outcomes it is impossible to make conclusions about the effect of sperm cryopreservation on the health of those conceived as it needs to be disentangled from confounding of physical manipulation. Comparing cryopreserved donor sperm outcomes to spontaneous conceptions is unable to answer this question properly. The problem of having an appropriate model to study the question is exacerbated by the mandating of cryopreservation of donor sperm in various

jurisdictions. Studies investigating the use of fresh or cryopreserved partner's sperm in IVF treatments may be a better model for examining the effects of cryopreservation.

One study which has investigated such a scenario observed a significantly lower incidence of LBW in donor sperm singletons using cryopreserved donor sperm and fresh autologous oocytes than that observed when using non-donor sperm.[33] Problematically, no data was provided on the fresh or cryopreserved status of non-donor sperm, an issue noted by the authors meaning the cryopreservation question still cannot be answered. However, there were many confounding factors that potentially also have an impact on the results reported. For example, those utilising non-donor sperm had higher incidences of seeking treatment due to male factor infertility which may account for the increased incidence of LBW due to reduced sperm quality.

Nonetheless, examining outcomes from cryopreserved donor sperm may provide some insights and avenues of enquiry. While meta-analysis failed to reveal any significant differences in BD or other outcomes, that result may be more indicative of the low number of studies that were included in each meta-analysis. Individual studies reported significantly increased incidences of BD or ChAb,[447, 607] even though one would then be attenuated and no longer significant after controlling for confounding and the other found a significant difference to one comparison cohort population but not to another. Others reported non-significant increased frequencies of BD and or chromosomal abnormalities,[183, 605, 606] and therefore, it may also be a function of having comparable data reported and studies being underpowered to detect differences. The statement by Davies *et al.*, cautioning that the donor sperm-conceived cohort data that was adjusted for confounding was adversely affected by a small sample size supports this postulation.[447]

Further support for the problem of power and sample size to detect BD outcomes is the publication by Khoury and Holtzman who analysed the effect of well-known teratogens and BD inducing agents, such as thalidomide, valproic acid and isotretinoin.[615] They stated that even in a system monitoring 25,000 births/year, that it may require more than 20 years of monitoring to observe a significant effect.[615] This is due to the frequency of exposure, or the lack of exposure, which by comparison donor sperm treatment is also a low exposure treatment in the general population. The effect of sperm cryopreservation on the health outcomes in the neonatal, childhood and adulthood periods remains unclear, and further studies which may need to occur over decades might be required before an accurate picture is obtained.

The one study that investigated IQ outcomes in children suggested that donor sperm-conceived children had higher IQs than their spontaneously conceived peers.[604] IQ is influenced by numerous factors, including those that are environmental and genetic.[616] While more recent evidence suggests that intelligence has a strong genetic component and is highly heritable,[617-620] the environment and SES has also been shown to have an influence.[621, 622] Iizuka *et al.*, reported that the parents of the donor sperm-conceived children with higher IQs also had higher levels of education themselves. These genetic and environmental factors coupled with reports that sperm donors in this early period of donor conception were often recruited from a pool of medical school university students and or university students in general,[604, 623-625] including this specific study, suggests that the children's higher IQ may be a function of both genetic and social influences.

The recruitment of sperm donors in this early period was often but not exclusively achieved through an approach by lecturers or doctors to students directly,[314, 624] or through advertising in university student newspapers.[623, 624, 626] More recent changes to recruitment have included the use of the internet to expand the potential recruitment pool in an attempt to meet the demand.[627, 628] Recruitment via the internet has expanded to include advertising on social media platforms which may also advertise travel and financial inducements (see Appendix 1.9). Subsequently, the IQ of donors may now be more representative of the general population.

One donor sperm-conceived cohort was reported to have 5.8% of the children with learning difficulties, but no comparison cohort data was provided.[606] Considering that the American Academy of Pediatrics expressed that "learning disabilities are complex",[629] there can be variation in the reported prevalence's. For example, it has been argued that there is variation between geographic locations which can potentially be attributed to inconsistent identification of learning difficulties.[630] The variation between geographic location poses difficulties in comparing the outcome of 5.8% to other published data. Notwithstanding this limitation, the study by Amuzu *et al.* included children from the United States in which some authors have estimated the prevalence of learning difficulties to be 5%,[631] or 6.5%.[632] These prevalence's, location, and time-period of studies are consistent with that of Amuzu *et al.*, suggesting that donor sperm-conceived children did not have increased incidences of learning difficulties compared to the general population.

Amuzu *et al.*, additionally reported that 10.5% of donor sperm-conceived children were enrolled in gifted and talented programs which were also not compared to a comparison

cohort.[606] Published incident rates vary widely and can range from 1% to 15-20%, also due to inconsistent assessment criteria.[633] The reported frequency of gifted and talented donor sperm children is, therefore, not outside the bounds of what has been reported elsewhere. The outcomes of IQ, giftedness and learning difficulties have a paucity of evidence to suggest that they are adversely affected. What evidence that is available is suggestive that donor sperm-conceived children develop these attributes in line with those conceived spontaneously and that any variation could be attributed to genetic or environmental (including SES) factors.

The results of the systematic review and meta-analysis of oocyte donations highlighted the increased risk of neonates being born of LBW, VLBW, PD, PD with LBW, and lower GA.[1] However, there is a paucity of evidence to suggest that donor sperm-conceived neonates are negatively affected to the same extent. Furthermore, there is a dearth of evidence to show that their outcomes are different from those conceived spontaneously. The lack of studies that could be included in the meta-analysis infers that caution should be taken when interpreting the results and that more studies need to be conducted. Outcomes from oocyte donation had a higher degree of rigour with a more comprehensive and systematic reporting of outcomes, thereby inferring greater confidence in the data.

The systematic review will now address the outcomes for people conceived from embryo donation.

2.10 Embryo Donation Results

Due to a lack of included studies and comparable outcomes, meta-analyses could not be conducted for embryo donation outcomes. Summary qualitative analysis of the two included studies is summarised and presented in the text.

2.10.1 Embryo Donation Outcomes

Only two studies that investigated the health outcomes of people conceived via donated embryos fulfilled the inclusion criteria in which donor embryos were compared to own embryos (homologous IVF) with reported outcome data.[573, 592] One study involved a national cohort which represents data from the United Kingdom (UK).[592] The reported sample size represents only 0.3% of the data size of sperm donation data and 0.03% of the donor oocyte data size. Combining both studies allowed for the inclusion of approximately 66 donor embryo neonatal health outcomes and approximately 410 outcomes from homologous IVF neonates. Approximately half of the sample was comprised of pregnancies rather than actual births, and therefore the samples size may be larger if any of the pregnancies involved twins or higher-order multiples.

2.10.2 Embryo Donation Birth Weights

Of the two studies reporting birthweight data comparing the use of donor embryos versus homologous IVF, Thapar *et al.*, found a difference between the use of donor embryos and homologous IVF in terms of frequency of LBW (< 2500g) in singletons (12.5% v 6.6%, no statistical analysis), and all births (16.7% v 14.7%, no statistical analysis).[592] Contrastingly Porreco *et al.* found no significant difference in mean birth weight (2446 ± 784g v 2442 ± 687g).[573] While both had similar sample sizes for the treatment group (donor embryos), the study showing the correlation had a larger control cohort (n = 378 v 32).

2.10.3 Embryo Donation Gestational Ages

The study by Porreco *et al.* reported mean GA and the frequencies of PD. The authors reported no statistically significant differences in terms of the mean GA for all births 36.9 ± 2.8 v 37.2 ± 2.6 (weeks), mean GA for multiple births 35.4 ± 2.6 v 35.8 ± 3.2 (weeks), or the incidences of PD 39% v 29%, between donor embryo neonates and those conceived with autologous oocytes.[573]

2.10.4 Embryo Donation Effects of Multiplicity

Thapar *et al.* reported a reduction in the frequency of multiplicity 16.7% v 20.1% (no statistical analysis) comparing donor embryo outcomes to those from homologous IVF.

2.10.5 Embryo Donation Risk of Bias

The studies included in the embryo donation review were also included in the oocyte review. These studies presented data from both oocyte and embryo donation outcomes. The risk of bias in both instances is the same. Nevertheless, a modified table showing the critical appraisal using the modified JBI-MAStARI instrument of the studies reporting embryo donation outcomes is presented in Table 1.6 for convenience. The study by *Porreco et al.* describes results from what they term donor embryo transfer; however, a close examination of the study shows that while donor oocytes were used that they were either fertilised with donor sperm or their partner's sperm and therefore represent both donor oocyte and donor embryos (double donation).[573] As this study was not stratified, the data was included in both donor oocyte and donor embryo analysis.

The confounders of maternal age and parity are presented in Table 1.7. Maternal ages were controlled in the study by Porreco *et al.*, (donor cohort mean age 38.8 years (range 27-50) v autologous cohort 38.7 years (range 34-44).[573] However, Thapar *et al.*, reported a higher mean age for their donor cohort (41.23 ± 6.21 years), compared to the homologous IVF cohort (34.14 ± 3.53 years) (no statistical analysis provided by authors).[592] Nulliparous rates were reported as not significant by Porreco *et al.*, at 89% for the donor cohort and 78% for the homologous IVF cohort.[573] Advanced maternal age is associated with adverse neonatal outcomes including LBW even in women using ART when their age is higher than 40,[634] which may explain the report of higher LBW frequencies associated with donor embryo conceptions found in the study by Thapar *et al.*,[592] even though the oocytes used are typically from younger women.

Table 1.6 Risk of bias and critical assessment of included donor embryo studies

Study	Criterion								
	Representative patients	Similar point in condition	Minimised case selection bias	Singleton v multiples	Other confounders	Cryo-preservation	Objective criteria	Reliable outcomes	Appropriate statistics
Porreco *et al*. (1997)	Yes	Unclear	Yes	No	No	No	Yes	Yes	Yes
Thapar *et al*. (2007)	Yes	Unclear	Yes	Yes	No[a]	No	Yes	Yes	No[b]

[a] = the data was not used in statistical analysis; [b] = statistics were used appropriately, but the authors did not analyse donor v autologous outcomes. The table presented is a modification of the oocyte outcome risk of bias and critical appraisal. The original table: © Cambridge University Press and International Society for Developmental Origins of Health and Disease 2016. Reprinted with permission.[1]

Table 1.7 Maternal age and parity as reported in included donor embryo studies

Study	Maternal Age Details	Parity Details
Porreco *et al*. (1997)	(38.8 yrs (range 27–50)) v (38.7 yrs (range 34–44))	89% v 78% nulliparous
Thapar *et al.* (2007)	41.23 ± 6.21 yrs (donor) v 34.14 ± 3.53 yrs (homologous IVF) v unknown (general population)	

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2.11 Embryo Donation Discussion

In comparison to both donor oocyte and donor sperm neonatal outcomes, there was a paucity of data reporting donor embryo outcomes with only two studies being included in the review.

There was conflicting data from the two studies reporting on birth weights of embryo donation versus homologous IVF neonates. Maternal age and parity confounders were only reported for the studies analysing BW data. Thapar *et al.*, reported an increase in the incidences of LBW in singletons and all births from donor embryos which was correlated with a higher mean maternal age, whereas Porreco *et al.*, found no difference in birth weights in the two groups in which maternal age and parity were also not significantly different. Mean GA and the incidence of PD were not statistically different in the data presented by Porreco *et al.*, and the study by Thapar *et al.*, reported a reduced frequency in multiplicity but did not analyse this outcome statistically. The sample sizes of the included studies are underpowered to determine differences between donor embryo and homologous IVF outcomes, and therefore, caution should be taken with the interpretation of the results presented in those studies.

Considering that embryo donation utilises a donor oocyte it is plausible that donor embryo outcomes would either be at least comparable to those observed for donor oocyte outcomes if not slightly worse due to the use of donor sperm that may provide a second novel antigen. Subsequently, further studies may also show an increase in the incidences of LBW, VLBW, PD, PD with LBW, have a lower GA, and an increase in multiplicity in donor embryo neonates. No health outcome for donor embryo children or adults was found in this review.

2.12 Systematic Review Conclusion

The size of the cohorts in this systematic review are as follows: donor sperm = 24,699 (comparison = 423,763), donor oocyte = 201,628 (comparison = 432,361), and donor embryo = 66 (comparison = 410). Interestingly the donor oocyte cohort was approximately eight times larger than the donor sperm cohort even though it has only been practised for a far shorter period. The paucity of evidence on donor embryo outcomes in comparison to donor oocyte outcomes was somewhat surprising. However, this may be a reflection of the low numbers of embryos donated,[635] which may be due to the emotional connection the parents who created the embryos have and who liken embryo donation with adoption.[636] Instead, many parents choose to discard their embryos rather than donate.[637-639]

Meta-analysis highlighted that donor oocyte-conceived neonates were at increased risk of being born LBW, VLBW, PD, PD with LBW, have a lower GA, and an increase in the incidence of multiplicity. By contrast, there was a lack of evidence to suggest that donor sperm and donor embryo neonates also had higher incidences of poor neonatal outcomes. However, this may be due to the lack of data available rather than a reflection of the actual incidences.

Thapar *et al.* suggested that adverse perinatal outcomes are "mainly attributable" to maternal age and multiplicity.[592] However, meta-analyses of singleton outcomes showed that at least in donor oocyte neonatal outcomes, multiplicity had little effect on outcomes. Adverse neonatal outcomes were still observed to be significant in singletons.

There is considerable evidence in the published literature highlighting that maternal age is associated with adverse neonatal outcomes,[260, 511, 513-515] as also suggested by Thapar *et al.*, however, the largest study included in the review by Gibbons *et al.*, appropriately controlled for maternal age. The study by Gibbons *et al.* found that donor oocyte-conceived neonates were significantly more likely to be born LBW, VLBW and with a lower mean gestational age. Furthermore, in meta-analyses, the study provided 99.5% of weighted GA data, 25.3% of weighted LBW data and 30.4% of weighted VLBW. It would, therefore, be simplistic and premature to dismiss the results found in the meta-analysis as a result of confounding by maternal age. Especially when considering that there is evidence suggesting that women who have used ART, are less likely to have pregnancies with adverse neonatal outcomes associated with maternal age than those who conceive spontaneously,[530] and that poorer neonatal outcomes such as LBW are only evident in advanced maternal ages of over 40 years.[634] Furthermore, the issue of advanced maternal age and the use donor oocytes is highlighted by an increased risk for adverse singleton neonatal outcomes including PD and SGA when comparing donor oocyte to autologous oocyte IVF in 40-43 year-old women.[640]

Another confounding factor that may potentially lead to reduced BWs is the observed increased incidence of elective early caesarean section deliveries present in women using ART.[641-644] However, these increased incidences of elective early caesarean section would not adversely affect PD data as elective caesarean is typically not conducted before 37 weeks which is the GA cut-off for PD. Nor would it affect outcomes such as SGA, IUGR or BD.

Outcomes that could not be included in meta-analysis such as the increased incidences of NICU admissions and length of hospital stay in donor oocyte-conceived neonates (including in singletons) reported by Söderström-Anttila *et al.*, has been supported by subsequent studies.

Malchau *et al.* reported that donor oocyte-conceived singletons were more likely to be admitted to the NICU (24.2% v 7.6%, $p < 0.0001$), and that their length of stay in the NICU was significantly increased (2.5 ± 7.5 days v 0.9 ± 5.8 days, $p = 0.002$).[645] Luke *et al.*, also reported an increased NICU admission frequency in singleton donor oocyte-conceived neonates compared to singleton autologous oocyte neonates (fresh 10.5% v 7.9%; cryopreserved 10.4% v 8.3%, no statistical analysis provided).[646] Further studies in this area are subsequently required.

The results of this systematic review into donor oocyte outcomes which was the first one published are supported by and consistent with further publications that have been conducted since the census date of the review. Several other researchers have reported increased adverse neonatal outcomes associated with oocyte donation in comparison to autologous oocytes including LBW, VLBW, PD, very PD (VPD < 32 weeks), SGA, very SGA (VSGA birthweight less than the 3rd percentile), and stillbirth.[45, 293, 645, 647-653] Furthermore, others have also conducted systematic reviews of donor oocyte outcomes, all reporting similar adverse neonatal outcomes.[275, 654-656] The increased risk of adverse neonatal outcomes associated with donor oocytes appears to therefore not be in dispute but is now accepted as a known complication.

In contrast to the adverse neonatal outcomes listed above, donor oocyte-conceived neonates that make it to term have a better outcome regarding reduced incidences of LBW. This finding is supported by Dude *et al.*, who found a lower incidence of SGA and perinatal death when gestational age was controlled.[650] It appears that the issue may be getting donor oocyte foetuses to term, which is problematic due to the increased incidence of PE and PIH. Those that do make it to term may be less affected by PE and PIH, and subsequently have improved outcomes due to the better-quality oocytes of the younger donor.

Results suggest that the incidences of BD and or ConMal are not associated with fresh donor oocyte conceptions. However, data should still be collected on the incidences of BD and ConMal associated with cryopreserved donor oocyte conceptions to verify if cryopreservation alters outcomes. Considering that oocyte cryoprotectants often incorporate genotoxic chemicals,[361] such data collection is pertinent. The limited amount of evidence on cryopreservation induced damage in oocytes which can be conflicting has been claimed to be controversial.[375] However, what data is available on the question of fresh versus cryopreserved autologous outcomes appears to be reassuring in terms of BD and congenital malformations.[657, 658]

Furthermore, other adverse neonatal outcomes of LBW, PD and SGA have been shown in some autologous oocyte studies to have been improved through the use of cryopreserved oocytes.[45, 659, 660] Or that other outcomes such as LGA have increased frequencies associated with cryopreservation.[659, 661, 662] The risk for the outcomes above may partially be dependent on the type of freezing used (vitrification versus slow-freeze),[663] or the embryonic stage that the cryopreservation is implemented.[664] Others have also shown no difference in long-term health outcomes in children associated with embryo cryopreservation.[665, 666] It could be argued that cryopreservation may provide some protection against adverse outcomes. This protection may be because poor-quality oocytes/embryos are less likely to survive the freeze-thaw process. Subsequently, better-quality oocytes/embryos are used, which potentially reduces the incidences of adverse neonatal outcomes.

The outcomes from sperm donation appear to be reassuring from the perspective that donor sperm-conceived neonates are not as adversely affected as donor oocyte-conceived neonates. Problematically, the lack of case-controlled studies that could be included in meta-analyses means that caution should be used in interpreting the results and that other studies are required to improve the quality of each meta-analysis. The dearth of published case-controlled studies is a surprise considering both the extensive use and period sperm donation has been used as a treatment modality. Since the systematic review census date, other studies have been published, including one that was conducted as part of this thesis. That study and the others that have been published will be presented in the following chapter (Chapter 3), to expand and improve upon the knowledge of neonatal outcomes resulting from sperm donation.

Outcomes from embryo donation (double gamete donation), were mostly absent from this systematic review. Due to the nature of embryo donation, oocyte donation outcomes can be used to guide knowledge and advice on the use of donor embryos. Donor oocytes have been shown to have increased incidences of poor maternal and neonatal outcomes which have also been shown to be present in double donation (oocyte v embryo donation outcomes).[667] Some have argued for an increase in the risk for PE resulting from double donation over oocyte donation.[189] Each of these relatively recent studies would be improved with increased sample sizes.

Further studies would also substantially improve knowledge in this area. Notwithstanding the low amount of evidence from embryo donation, the substantive evidence from oocyte donation outcomes suggests that those conceived with a donor embryo would at the

minimum, be equally affected. Donor oocyte outcomes provide evidence enabling the answering of the question of whether donor embryo-conceived people had been affected by their conception. Subsequently, donor sperm neonatal outcomes and not embryo donation neonatal outcomes will be the focus of the next chapter.

What is also clear from the systematic review is the paucity of long-term health outcomes for those conceived with donated gametes not only in childhood but also adulthood. More specifically, there were no studies included in the systematic review that investigated the physical health of DC adults. What evidence has been published on long-term health outcomes from ART modalities in general and not explicitly restricted to donor conception are conflicting, and this is an emerging area of research.[57, 668-671] Even since the census data of the systematic review, no studies investigating the quantifiable health of DC adults have been published. Combining the concerns raised by the implications of DOHaD for DC people, the adverse neonatal outcomes observed in donor oocyte neonates, and the conflicting evidence currently available for the long-term health outcomes of ART conceived people in general, studies investigating long-term health trajectories of DC people are clearly warranted. The first study investigating the health of DC adults is presented in Chapter 4. The following chapter (Chapter 3) reports the investigation of perinatal outcomes from donor sperm-conceived neonates compared to spontaneously conceived neonates in a population-based study to fill the gap in the donor sperm neonatal outcome literature identified in the systematic review.

CHAPTER 3. DONOR SPERM PERINATAL OUTCOMES – A REDUX

Content contained within this chapter represents updated and reworked data and discussion from two publications. The first was an investigation of perinatal outcomes from sperm donation in a population-based cohort, and the second was an updated and expanded meta-analysis of donor sperm outcomes.

Adams D, Fernandez R, Moore V, Willson K, Rumbold A, de Lacey S, Scheil W, Davies M. Sperm donation perinatal outcomes in an Australian population cohort. J Obstet Gynaecol Res. 2017;43(12):1830-1839.[2] (Appendix 2.1)

Attribution of authorship:
DA (80%), MD (10%), RF (5%) and VM, KW, SdeL, and WS (5% total) contributed to the design of the study. RF (100%) wrote the code for and performed the data extraction. Data analysis was performed by RF (75%), DA (15%), MD (5%) and VM (5%). DA (80%) drafted the manuscript with all other authors (RF, VM, KW, AR, SdeL, WS and MD) providing edits and revisions.

Adams DH, Clark RA, Davies MJ, de Lacey S. Update on: a meta-analysis of sperm donation offspring health outcomes - 2018 update. J Dev Orig Health Dis. 2018;9(5):561-562.[4] (Appendix 2.2)

Attribution of authorship:
DA (100%) contributed to the design of the updated meta-analysis. DA (100%) conducted the updated, computerised searches and assessment of articles for eligibility. Data extraction was conducted by DA (100%). Data analysis was performed by DA (80%), RC (10%), MD (5%) and SdeL (5%). DA (90%) drafted the manuscript with all other authors (RC, MD, and SdeL) providing edits and revisions.

3.1 Introduction

In the previous chapter, the need for empirical knowledge about the health outcomes of all DC people, including neonates, was established. The objective of this chapter is to report the findings of such a study in order to improve and expand knowledge concerning health outcomes for donor sperm-conceived people. The conduct and findings of a retrospective analysis of data drawn from a population-based cohort in South Australia are first presented in Part A. Secondly, the findings from the retrospective database analysis were added to studies published on donor sperm neonatal outcomes that were sourced further to the initial systematic review. This additional data has been inserted into the meta-analysis reported in Chapter 2 in order to obtain further understanding of the outcomes for neonates conceived with donated sperm and is presented here in Part B as an updated meta-analysis.

3.2 Part A: A South Australian Population Cohort of Donor Sperm Neonatal Outcomes

3.2.1 Background

The systematic review of donor sperm neonatal outcomes presented in the previous chapter[3] revealed that there were very few studies published investigating the health outcomes of donor sperm-conceived neonates. Furthermore, not only were there few studies investigating these health outcomes, but the included studies were sometimes compromised due to poor methodological quality and lack of comparable outcomes.

By contrast, pregnancy rates and rates of live births from donor sperm conceptions have been reported far more extensively in other literature.[33, 672-683] Clinical outcomes of pregnancy and live births are important to both the patient and the ART clinic. However, the health of those conceived through donor conception treatment modalities is the primary focus of this thesis. The systematic review reported in Chapter 2 appeared reassuring in that donor sperm-conceived neonates were not at increased risk for being born with the neonatal outcomes of LBW, PD, or with BD, in comparison to those conceived spontaneously. Nevertheless, such a conclusion is tempered due to the lack of studies able to be included in the review.

Qualitative analysis of the studies included in the review found reports of increased frequencies of adverse perinatal outcomes. In particular, concerns were raised regarding a potential increase in ChAb or ConMal,[183, 605-607] which in some instances may be associated with cryopreservation. Another publication reported an increased risk for donor sperm-conceived singletons born with BD (OR =1.51 (1.08–2.11)), which was no longer significant

after controlling for confounding (OR = 1.37 (0.98–1.92)).[447] The authors cautioned that the amelioration of risk might have been an issue associated with power and the low number of events in the study.

The number of events associated with birth defects is an issue, particularly for smaller studies, as is statistical power.[684, 685] Even when larger population studies are available, the frequency of defects reported have been increasing over time,[686] thereby suggesting a change in the classification and or reporting. Even though the relative risk may not change through different periods,[686] comparisons between different periods may affect analysis due to sample sizes and weighting.

Large population-level studies that systematically investigate a wide variety of perinatal outcomes are therefore warranted to not only improve the knowledge of the effect that sperm donation treatment has on the resultant offspring but also to improve confidence in outcome analysis. This information is clinically significant to the ART clinics such that they can then provide information to their patients for fully informed consent to donor conception procedures as well as maintaining patient autonomy. Keeping the patients informed fully also enables their ability to make decisions not only for themselves but also for the health and welfare of their child. The first of two studies in this chapter investigated the perinatal outcomes from donor sperm conceptions compared to those conceived spontaneously in the population of South Australia.

3.2.2 Methods

The study was conducted following guidelines contained in the STROBE statement and reported following the STROBE checklist (Appendix 2.3).[687]

3.2.2.1 Ethical Approval

Ethical approval for the study was obtained from the Flinders University Social and Behavioural Research Ethics Committee (reference number: 7277) (Appendix 2.4) and was conducted in accordance with the Declaration of Helsinki (Tokyo revision 2004).[688] Data on the participants had previously been collected and stored in the South Australian Perinatal Statistics Collection (SAPSC) database. Subsequently, consent was not a requisite from the participants as approved by the ethics committee. However, approval for access to the SAPSC data was required, and further ethical approval was granted as follows; Australian Government, Australian Institute of Health and Welfare (AIHW) Ethics Committee (reference number: EO2013/3/51); SA Human Research Ethics Committee (reference number:

HREC/15/SAH/80, and amendment reference number: HREC/15/SAH/80/AM03); Site Specific Assessment (SSA reference number: SSA/18/WCHN/142).[h]

3.2.2.2 Study Design

All births in South Australia are recorded in the SAPSC as a requirement by law. Subsequently, the study is a retrospective cohort study at the population level. Clinical data, including pregnancies and births resulting from treatments conducted at South Australian ART clinics, including donor sperm treatments, were linked to SAPSC data. Perinatal outcomes, as described in the "Outcome variables" section, of donor sperm-conceived neonates, were compared to perinatal outcomes of spontaneously conceived neonates.

3.1.2.3 Setting

All births recorded in the SAPSC from January 1986 to December 2002 were included in the study. The population recorded for South Australia by the Australian Bureau of Statistics (ABS) in 1986 was 1.346 million,[689] and in 2002 it was 1.52 million.[690] For each year of the study, there were approximately 17,000 births recorded. All donor sperm-conceived neonates during this period were conceived with cryopreserved sperm under the mandate.[314]

The compulsory reporting of all births, including stillborn when the birth weight was a minimum of 400g or occurred at a minimum gestational age of 20 weeks is also mandated. Consistency of reporting was achieved through the use of a standardised notification form. Medical terminations of pregnancy occurring at a minimum gestational age of 20 weeks are also mandatorily reported. Maternal characteristics data of age, parity, SES (using the Socio-economic Indexes for Areas (SEIFA)),[691] ethnicity, and pre-existing conditions of diabetes, hypertension, epilepsy, asthma, and anaemia are recorded enabling the analysis and control of confounding. Further obstetric characteristics of PIH and gestational diabetes are also recorded.

3.1.2.4 Participants

All neonates born in South Australia between the period of January 1986 and December 2002 were participants. Mothers of those neonates born during that period are secondary participants in that their characteristics are reported and used for statistical analysis of perinatal outcomes. Excluded from the study were all neonates conceived through other ART treatment modalities including IVF, donor oocytes, donor embryos and ICSI. The ART

[h] Letters of ethical approval to access the SAPSC data are held by the other authors of the published study and are therefore not presented in an appendix.

treatment modality included was restricted to donor insemination conceptions which also included those donor inseminations used in patients where IVF had failed previously. However, modalities of IVF with donor sperm (IVF-D), and gamete intra-fallopian transfer (GIFT) with donor sperm were excluded to remove confounding due to the extra manipulation and culture of gametes/embryos involved in those modalities. All data were de-identified.

3.1.2.5 Outcome Variables

BW and GA were analysed as continuous outcomes, while dichotomous outcomes analysed were LBW, VLBW, PD, very preterm delivery (VPD < 32 weeks), LateD (late-term delivery > 41 weeks), PD with LBW, TermD with LBW, SGA (birth weight < 10th percentile),[692] LGA (birth weight > 90th percentile),[692] Apgar score less than 7 at 5 minutes (5'AS<7), neonatal death (ND death in first 28 days post-delivery), and stillbirth.

3.1.2.6 Statistical Analysis

Continuous outcomes of BW and GA are summarised and reported as means with standard deviation (SD). A two-tailed, Student's T-Test was implemented to determine the significance of continuous outcomes. Dichotomous outcomes were analysed using logistic regression, implementing generalised estimating equations (GEE), producing odds ratios (OR) and 95% confidence intervals (CI). GEE was used in the logistic regression due to the problem of large datasets including multiple covariate measures which would otherwise inherently produce a correlation.[693, 694] Results were classified as significant when $p < 0.05$. Statistical analysis was performed using Stata V.14. (StataCorp, College Station, Texas, USA). Renae Fernandez wrote the code to extract the data from the SAPSC and conducted the logistic regression analysis.

Exclusions from the data for consistency were as follows. There were no higher-order multiples of triplets or greater in the donor sperm-conceived cohort and subsequently, all higher-order multiples in the spontaneously conceived cohort were excluded. All analysis was therefore restricted to singletons and twins. Zygosity of twins was not recorded in the SAPSC data. Only one mother younger than the age of 20, had received donor insemination treatment. Accordingly, all births attributed to mothers under the age of 20 were excluded from both donor sperm-conceived and spontaneously conceived cohorts. Furthermore, neonates of indeterminate or unknown sex were not present in the donor sperm-conceived cohort, and therefore neonates of indeterminate or unknown sex from the spontaneously conceived cohort were also excluded.

All analyses were initially conducted for all births (singletons and twins) and then stratified by multiplicity (singletons and twins) which were then analysed separately. Continuous and dichotomous outcomes were adjusted for the a priori confounding of maternal age (stratified into 5-year age groups), parity, SES based on SEIFA (stratified into quartiles), ethnicity, and sex of the neonate. The change in estimate approach[695] was implemented when the following confounders produced a greater than 10% change (plus or minus) in the main effect estimate in the fully-adjusted model: pre-existing maternal conditions of hypertension, diabetes, epilepsy, anaemia, asthma, and the maternal conditions of pregnancy of PIH and gestational diabetes. Dichotomous outcome odds ratios were adjusted for the confounders of maternal age, parity, SES, ethnicity, and the sex of the neonate to account for clustering within the mother. Further adjustments to dichotomous outcome odds ratios were made for all maternal conditions of pregnancy, including both pre-existing and pregnancy-induced conditions.

Donor sperm treatments are sometimes combined with ovulation induction (OI) for women with irregular menstrual cycles, which is induced through the use of medications such as clomiphene citrate or gonadotropins as an endeavour to improve pregnancy outcomes.[696, 697] The effect of OI in donor sperm perinatal outcomes were determined by further stratification into OI cycles and natural cycles for comparison.

3.2.3 Results

A total of 299,424 births were recorded in the 17 years between January 1986 to December 2002. These were stratified into two categories of live births and stillbirths. A total of 297,756 live births which also incorporates 939 neonatal deaths were recorded along with 1,668 stillbirths. The characteristics of these births, including maternal characteristics, are presented in Table 2.1 according to the birth outcome (live versus stillbirth), and mode of conception (spontaneous versus donor sperm).

As a result of the low number of events occurring in donor sperm-conceived stillbirths, all description of results hereafter refers to all births data unless otherwise stated. Mothers using donor sperm to conceive were older than those mothers conceiving spontaneously with regard to live births. The increased maternal age is evident from the greater proportion of mothers in the three 5-year age groups over the age of 30 years in the donor sperm conceiving cohort. This increased proportion was statistically significant ($p < 0.001$). The donor sperm conceiving mothers were also statistically more likely to be primigravid (40.8% v 28.6%, $p < 0.001$), nulliparous (54.0% v 37.6%, $p < 0.001$), and suffer from pre-existing diabetes (0.8% v 0.3%, $p = 0.027$) and PIH (13.5% v 8.8%, $p < 0.001$), than their

spontaneously conceiving peers. The increased incidences of PIH were associated with singletons (p = 0.007), but not twins (p = 0.116) (data not shown). Furthermore, mothers who had used donor sperm to conceive were also significantly more likely to be classified as Caucasian (97.1% v 93.4%, p = 0.001). The SES of mothers, as determined by SEIFA quartiles, were not statistically different between the cohorts.

The male to female ratio was increased but not significantly in the donor sperm-conceived cohort (1.03), while the male to female ratio was decreased but also not significantly in the spontaneously conceived cohort (0.93). In effect, there was a greater proportion of donor sperm-conceived males and a greater proportion of spontaneously conceived females. Neonates conceived with donor sperm were significantly more likely to be born as a twin than those neonates conceived spontaneously (9.0% v 2.4%, $p < 0.05$).

Stillbirth and neonatal death data are presented in Table 2.2. There were no statistically significant differences observed between donor sperm-conceived and spontaneously conceived foetuses for the risk of stillbirth. However, comparing twins to singletons in each conception cohort showed that twins had higher frequencies of stillbirth (2.3% v 0.7% donor sperm; 2.0% v 0.5% spontaneously conceived). Furthermore, no statistically significant differences between donor sperm-conceived and spontaneously conceived foetuses were observed for the risk of neonatal death. In the donor sperm-conceived cohort, there were no incidences of neonatal death. Similar to stillbirth, the frequency of neonatal death was higher for spontaneously conceived twins in comparison to singletons (1.9% v 0.3%).

Table 2.1 Characteristics of live births and stillbirths by mode of conception (spontaneous versus donor sperm)

	Live births					Stillbirths				
	Spontaneous n = 297,280		Donor n = 476		*p* value	Spontaneous n = 1,664		Donor n = 4		*p* value
Age, n (%)*					**<0.001**					0.090
20-24 years	62,186	(20.9)	21	(4.4)		386	(23.2)	0	(0.0)	
25-29 years	112,494	(37.8)	141	(29.6)		571	(25.9)	1	(25.0)	
30-34 years	87,145	(29.3)	198	(41.6)		431	(25.9)	2	(50.0)	
35-39 years	30,632	(10.3)	107	(22.5)		221	(13.3)	0	(0.0)	
40+	4,813	(1.6)	9	(1.9)		55	(3.3)	1	(25.0)	
Primigravid, n (%)*	84,947	(28.6)	194	(40.8)	**<0.001**	501	(30.1)	2	(50.0)	0.387
Parity, n (%)*					**<0.001**					0.369
0	111,696	(37.6)	257	(54.0)		699	(42.0)	2	(50.0)	
1	107,488	(36.2)	175	(36.8)		460	(27.6)	2	(50.0)	
2+	78,096	(26.3)	44	(9.2)		505	(30.4)	0	(0.0)	
Socioeconomic quartile, n (%)					0.113					0.762
Lowest	69,521	(23.4)	120	(25.2)		448	(26.9)	0	(0.0)	
Low-middle	78,739	(26.5)	103	(21.6)		485	(29.2)	2	(50.0)	
Middle-high	74,694	(25.1)	126	(26.5)		409	(24.6)	1	(25.0)	
Highest	73,410	(24.7)	127	(26.7)		295	(17.3)	1	(25.0)	
Caucasian, n (%)*	277,744	(93.4)	462	(97.1)	**0.001**	1493	(89.7)	4	(100.0)	0.499
Sex ratio (M:F)	0.93		1.03		0.314	0.92		3		0.280
Twin gestation, n (%)*	7,018	(2.4)	43	(9.0)	**<0.001**	144	(8.7)	1	(25.0)	0.246
Maternal conditions, n (%)										
Pre-existing hypertension	3,280	(1.1)	8	(1.7)	0.228	62	(3.7)	0	(0.0)	0.694
PIH*	26,064	(8.8)	64	(13.5)	**<0.001**	158	(9.5)	1	(25.0)	0.292
Pre-existing diabetes*	869	(0.3)	4	(0.8)	**0.027**	17	(1.0)	0	(0.0)	0.839
Gestational diabetes	3,322	(1.1)	5	(1.1)	0.889	19	(1.1)	0	(0.0)	0.830
Epilepsy	1,566	(0.5)	0	(0.0)	0.112	18	(1.1)	0	(0.0)	0.834
Asthma	12,538	(4.2)	18	(3.8)	0.636	90	(5.4)	0	(0.0)	0.633
Anaemia	17,864	(6.0)	34	(7.1)	0.298	148	(8.9)	0	(0.0)	0.532

* Significantly different between groups for the comparison between spontaneous and donor sperm live births ($p < 0.001$). PIH = pregnancy-induced hypertension.

Table 2.2 Stillbirth and neonatal death among all births, singletons and twins by mode of conception, spontaneous or donor sperm

	All births			Singletons			Twins		
	Spontaneous n = 298,944	**Donor n = 480**	***p* value**	**Spontaneous n = 291,782**	**Donor n = 436**	***p* value**	**Spontaneous n = 7,162**	**Donor n = 44**	***p* value**
Stillbirth, n (%)	1664 (0.6)	4 (0.8)	0.416	1,520 (0.5)	3 (0.7)	0.626	144 (2.0)	1 (2.3)	0.900
Neonatal death, n (%)	939 (0.3)	0 (0.0)	0.219	806 (0.3)	0 (0.0)	0.272	133 (1.9)	0 (0.0)	0.362

Previously published table only reported singletons and twins outcomes which have been combined for all births in this table for completeness. [2]

Perinatal continuous and dichotomous outcomes from live births as well as stratified singleton and twin outcomes are presented in Table 2.3. Odds ratios could not be calculated for the outcomes in all births, singletons and twins of VLBW, VPD, LateD, TermD with LBW, and 5'AS<7 due to a low number of events. Furthermore, odds ratios could not be calculated for the outcomes of SGA and LGA in the twins' stratified group. However, the number of events was included in the tables for reference. Adjustment data for all maternal conditions of pregnancy, including pre-existing and pregnancy-induced, are not presented as they did not result in any alteration in the effect estimates.

Neonates conceived with donor sperm were not statistically different to those neonates conceived spontaneously in terms of BW regardless of whether singleton or twins were analysed separately. They were however significantly more likely to be born of lower GA than those neonates conceived spontaneously (mean difference: -0.25 weeks, CI: -0.45 – -0.06, p = 0.012). This difference was attenuated when analysing singletons and twins independently (mean GA difference in singletons: -0.13 weeks, CI: -0.31–0.05, p = 0.169; mean GA difference in twins: +0.51 weeks, CI: -0.34–1.36, p = 0.243).

Neonates conceived with donor sperm were significantly more likely than those neonates conceived spontaneously to be born PD with LBW (7.1% v 3.8%, OR: 1.74, CI: 1.16–2.61, p = 0.008). Controlling for singletons and twins eliminated any significance (singletons: 4.2% v 3.0%, OR: 1.37, CI: 0.84–2.23, p = 0.208; twins: 37.2% v 37.2%, OR: 0.95, CI: 0.42–2.13, p = 0.892).

Neonates conceived with donor sperm in comparison to those neonates conceived spontaneously, exhibited a non-significant increased risk for PD (9.5% v 6.5%, OR: 1.34, CI: 0.92–1.93, p = 0.125). Controlling for singletons and twins reduced the odds ratio (singletons: 5.5% v 5.5%, OR: 0.97, CI: 0.63–1.50, p = 0.903; twins: 48.8% v 47.9%, OR: 1.19, CI: 0.50–2.82, p = 0.688). Similarly, a non-significant increased risk of LBW was observed for neonates conceived with donor sperm in comparison to those neonates conceived spontaneously (8.2% v 5.7%, OR: 1.34, CI: 0.92–1.94, p = 0.129), which was also attenuated when controlling for singletons (singletons: 5.1% v 4.7%, OR: 1.07, CI: 0.69–1.66, p = 0.768). Controlling for twins exhibited a non-significant decreased risk (twins: 39.5% v 49.2%, OR: 0.62, CI: 0.27–1.39, p = 0.243).

Table 2.3 Perinatal outcomes among singleton and twin live births by mode of conception, spontaneous or donor sperm

		All births			Singletons			Twins		
		Spontaneous	**Donor**	***p* value**	**Spontaneous**	**Donor**	***p* value**	**Spontaneous**	**Donor**	***p* value**
All	n	297,280	476		290,262	433		7,018	43	
Birth weight †	Mean (SD)	3,377 (573)	3,312 (604)	0.242	3,400 (552)	3,392 (554)	0.912	2,430 (609)	2,510 (492)	0.247
	Diff (95% CI)	0 (-)	-35 (-93,23)		0 (-)	3 (-51,58)		0 (-)	107 (-74,288)	
Gestational age	Mean (SD)	39.1 (1.9)	38.9 (1.9)	**0.012**	39.2 (1.8)	39.1 (1.7)	0.169	35.8 (3.1)	36.4 (2.0)	0.243
	Diff (95% CI)	0 (-)	-0.25 (-0.45,-0.06)		0 (-)	-0.13 (-0.31,0.05)		0 (-)	0.51 (-0.34,1.36)	
PD	n (%)	19,265 (6.5)	45 (9.5)	0.125	15,901 (5.5)	24 (5.5)	0.903	3,364 (47.9)	21 (48.8)	0.688
	OR (95% CI)	1 (-)	1.34 (0.92,1.93)		1 (-)	0.97 (0.63,1.50)		1 (-)	1.19 (0.50,2.82)	
VPD ‡	n (%)	3,027 (1.0)	6 (1.3)	0.599	2,448 (0.8)	5 (1.2)	0.479	579 (8.3)	1 (2.3)	0.158
	OR (95% CI)	-	-		-	-		-	-	
LateD ‡	n (%)	4,858 (1.6)	3 (0.6)	0.084	4,856 (1.7)	3 (0.7)	0.112	2 (0.03)	0 (0)	0.912
	OR (95% CI)	-	-		-	-		-	-	
LBW †	n (%)	16,986 (5.7)	39 (8.2)	0.129	13,530 (4.7)	22 (5.1)	0.768	3,456 (49.2)	17 (39.5)	0.243
	OR (95% CI)	1 (-)	1.34 (0.92,1.94)		1 (-)	1.07 (0.69,1.66)		1 (-)	0.62 (0.27,1.39)	
VLBW †,‡	n (%)	2,710 (0.9)	6 (1.3)	0.424	2,160 (0.7)	4 (0.9)	0.664	550 (7.8)	2 (4.7)	0.438
	OR (95% CI)	-	-		-	-		-	-	
PD with LBW†	n (%)	11,370 (3.8)	34 (7.1)	**0.008**	8,761 (3.0)	18 (4.2)	0.208	2,609 (37.2)	16 (37.2)	0.892
	OR (95% CI)	1 (-)	1.74 (1.16,2.61)		1 (-)	1.37 (0.84,2.23)		1 (-)	0.95 (0.42,2.13)	
TermD with LBW †,‡	n (%)	5,603 (1.9)	5 (1.1)	0.181	4,756 (1.6)	4 (0.9)	0.242	847 (12.1)	1 (2.3)	**0.050**
	OR (95% CI)	-	-		-	-		-	-	
SGA †,‡	n (%)	30,126 (10.1)	42 (8.8)	0.259	29,464 (10.2)	40 (9.2)	0.341	662 (9.4)	2 (4.7)	0.284
	OR (95% CI)	1 (-)	0.82 (0.59,1.15)		1 (-)	0.84 (0.59,1.20)		-	-	
LGA †,‡	n (%)	29,442 (9.9)	46 (9.7)	0.893	28,753 (9.9)	44 (10.2)	0.712	689 (9.8)	2 (4.7)	0.256
	OR (95% CI)	1 (-)	1.02 (0.74,1.42)		1 (-)	1.06 (0.76,1.49)		-	-	
5'AS<7 ‡	n (%)	4,340 (1.5)	5 (1.1)	0.457	4,119 (1.4)	5 (1.2)	0.642	221 (3.1)	0 (0)	0.237
	OR (95% CI)	-	-		-	-		-	-	

Odds ratios account for clustering within mother and are adjusted for maternal age, parity, ethnicity, SES quartile and baby's sex.

†Twenty-four spontaneously conceived births were missing birth weight information. ‡ Chi-square *p* values provided. Odds ratios and 95% confidence intervals could not be calculated due to sparse data. SD = standard deviation; CI = 95% confidence interval; PD = preterm delivery <37 weeks gestation; VPD = <32 weeks; LateD = late-term delivery > 41 weeks; LBW = low birthweight <2500 grams; VLBW = very low birthweight <1500 grams; TermD = term delivery; SGA = small for gestational age <10th percentile; LGA = large for gestational age >90th percentile, 5'AS<7 = Apgar score less than 7 at 5 minutes. [2]

Neonates conceived with donor sperm in comparison to those neonates conceived spontaneously, exhibited a non-significant decreased risk for being born SGA (8.8% v 10.1%, OR: 0.82, CI: 0.59–1.15, $p = 0.259$). Controlling for singletons showed a similar risk (9.2% v 10.2%, OR: 0.84, CI: 0.59–1.20, $p = 0.341$). The risk of being born LGA was similar between donor sperm-conceived neonates and spontaneously conceived neonates in both all births (9.7% v 9.9%, OR: 1.02, CI: 0.74–1.42, $p = 0.893$), and singletons separately (singletons: 10.2% v 9.9%, OR: 1.06, CI: 0.76–1.49, $p = 0.712$).

Perinatal outcomes stratified by ovulation induction cycles and natural cycles in the donor insemination (DI) groups of all births, singletons and twins are presented in Table 2.4. OI cycles were associated with twin pregnancies ($p < 0.001$). In terms of all births, OI cycles were significantly associated with a lower mean BW (3226 ± 631g v 3352 ± 587g, $p = 0.033$), and lower mean GA (38.6 ± 2.1 weeks v 39.0 ± 1.8 weeks, $p = 0.025$), in comparison to natural cycles. OI cycles were also significantly associated with an increased risk for being born PD (14.4% v 7.2%, $p = 0.011$), and PD with LBW (11.1% v 5.3%, $p = 0.021$). Controlling for singletons and twins showed that only mean GA remained significantly lower for twins conceived with donor sperm and OI cycles in comparison to natural cycle donor sperm-conceived twins (35.9 ± 2.1 weeks v 37.3 ± 1.6, $p = 0.038$).

Table 2.4 Perinatal outcomes by use of ovulation induction in the donor insemination (DI) groups

		All DI Births			DI Singletons			DI Twins		
		Natural cycle	OI cycle	*p* value	Natural cycle	OI cycle	*p* value	Natural cycle	OI cycle	*p* value
Total	n	326	155		312	125		14	30	
Birth weight†	Mean (SD)	3352 (587)	3226 (631)	**0.033**	3387 (572)	3404 (506)	0.763	2600 (362)	2466 (544)	0.409
Gestational age†	Mean (SD)	39.0 (1.8)	38.6 (2.1)	**0.025**	39.1 (1.8)	39.2 (1.6)	0.544	37.3 (1.6)	35.9 (2.1)	**0.038**
PD†	n (%)	23 (7.2)	22 (14.4)	**0.011**	17 (5.5)	7 (5.7)	0.953	6 (42.9)	15 (51.7)	0.586
VPD†	n (%)	4 (1.2)	2 (1.3)	0.950	4 (1.3)	1 (0.8)	0.667	0 (0.0)	1 (3.5)	0.482
LateD†	n (%)	2 (0.6)	1 (0.7)	0.965	2 (0.7)	1 (0.8)	0.857	0 (0.0)	0 (0.0)	-
LBW†	n (%)	21 (6.5)	18 (11.8)	0.051	16 (5.2)	6 (4.8)	0.884	5 (35.7)	12 (41.4)	0.722
VLBW†	n (%)	4 (1.2)	2 (1.3)	0.950	4 (1.3)	0 (0.0)	0.203	0 (0.0)	2 (6.9)	0.314
PD with LBW†	n (%)	17 (5.3)	17 (11.1)	**0.021**	13 (4.2)	5 (4.0)	0.934	4 (28.6)	12 (41.4)	0.416
TermD with LBW†	n (%)	4 (1.2)	1 (0.7)	0.559	3 (1.0)	1 (0.8)	0.872	1 (7.1)	0 (0.0)	0.145
SGA†	n (%)	30 (9.3)	12 (7.8)	0.604	29 (9.4)	11 (8.9)	0.867	1 (7.1)	1 (3.5)	0.590
LGA†	n (%)	32 (9.9)	14 (9.2)	0.794	31 (10.0)	13 (10.5)	0.888	1 (7.1)	1 (3.5)	0.590
5'AS<7†	n (%)	4 (1.2)	1 (0.7)	0.559	4 (1.3)	1 (0.8)	0.667	0 (0.0)	0 (0.0)	-
Stillbirth	n (%)	3 (0.9)	1 (0.7)	0.761	3 (1.0)	0 (0.0)	0.273	0 (0.0)	1 (3.3)	0.490
Neonatal death	n (%)	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-

Excludes terminations (n=1). †Live births only. OI = ovulation induction; SD = standard deviation; PD = preterm delivery <37 weeks gestation; VPD = <32 weeks; LateD = late-term delivery > 41 weeks; LBW = low birthweight <2500 grams; VLBW = very low birthweight <1500 grams; TermD = term delivery; SGA = small for gestational age <10th percentile; LGA = large for gestational age >90th percentile; 5'AS<7 = Apgar score less than 7 at 5 minutes. [2]

3.2.4 Discussion

This population-based study into the perinatal outcomes that are associated with the use of cryopreserved donated sperm in comparison to those conceived spontaneously represents the most comprehensive analysis of these outcomes at the time of publication (2017). Significantly increased incidences of poor perinatal outcomes were not observed in this cohort with a few exceptions. The donor sperm-conceived cohort did not appear to be as adversely affected as those observed in the systematic reviews of donor oocyte outcomes.[1, 275, 654-656] This is even though the increased incidences of PE and DNA damage that have been associated with the use of donor sperm and sperm cryopreservation,[182-184, 197, 216, 225, 229, 294, 339, 340, 698-706] suggest that donor sperm-conceived neonates may potentially have poorer outcomes than spontaneously conceived neonates.

The two exceptions observed were that neonates conceived with donated sperm (all births), were significantly more likely to be born of a lower mean GA and to be at significantly increased risk of being born PD with LBW than those conceived spontaneously. This association was observed even after adjusting for confounding of maternal age, parity, ethnicity, SES and sex of the neonate; however, the association was attenuated when stratifying by multiplicity and analysing singletons and twins independently. Stratification reduced the number of events in both singletons' and twins' groups to ≤ 24 events for each of the outcomes of LBW, PD, and PD with LBW. Subsequently, the findings should be considered with caution. The power of this study would be improved with the addition of more recent data from births in South Australia since the census data, which may either confirm or refute these findings.

The significantly reduced lower mean GA and increased incidences of PD with LBW observed in the South Australian donor sperm-conceived cohort was correlated with the observed increased incidence of maternal PIH. The association between the use of donor sperm and increased incidences of PIH is controversial, with studies showing conflicting results.[184, 200, 294] Considering that PIH and PE are related,[299] and that the implementation of donor sperm is associated with an increased incidence of PE,[181-184, 294, 701] it is plausible that some studies may observe an increased risk for PIH as was evident in this study. The risk for PE in this study could not be calculated as the incidences of PE in South Australia were not available from the SAPSC. However, a finding of increased incidences of PE in mothers undertaking donor insemination would be consistent with the evidence. Considering that PE is correlated with

PD, SGA, and IUGR,[210-215, 707] hypothetically, increased incidences of PE in the South Australian donor sperm conception cohort could potentially account for the lower mean GA and increased risk of PD with LBW.

Neonates conceived with donor sperm were significantly more likely to be born as a twin, which was correlated with OI, and is supported by published evidence.[708, 709] DI cycles combined with OI treatments have been a common treatment modality aimed at improving pregnancy outcomes, especially for women with irregular menstrual cycles,[696, 697] including in Australian women during the study period.[183] OI induction includes the use of drugs such as clomiphene citrate, tamoxifen, letrozole and gonadotropins. Letrozole was introduced as an ovulation induction agent after the study period,[710] and is therefore irrelevant to this study. However, clomiphene citrate has been the OI drug of choice for approximately 50 years,[711] including the study period.

It has been argued that a need to find an alternative to clomiphene citrate has been known since the 1990s due to its "antiestrogenic effects on the endometrium, cervical mucus, and prolonged accumulation in tissues leading to prolonged depletion of estrogen receptors" p93.[710] Additionally clomiphene citrate has been associated with maternal issues including perimenopausal symptoms and increased hospitalisation,[708] and increased incidences of LBW, VLBW, PD, VPD, SGA.[708, 712, 713] While it has been suggested to increase the frequency of BD,[714-716] this is disputed by others.[717, 718] Children conceived with the assistance of OI, in general, are more likely to have long-term illnesses and hospitalisation.[708] These outcomes increase concerns regarding the use of OI and clomiphene citrate.

While it was possible to analyse for the use of OI in this study, there was insufficient statistical power to stratify by and analyse the effect of individual OI drugs such as clomiphene citrate. However, OI cycles in comparison to natural cycles were associated with a lower mean BW, reduced GA, and increased risk of being born PD, and PD with LBW in all births. A lower mean GA was also associated with OI cycles in twins, while the other associations were no longer significant when controlling for multiplicity and analysing singletons and twins independently.

The low number of adverse outcomes observed in the South Australian donor sperm-conceived cohort is suggestive that there may be no DNA damage occurring as a result of cryopreservation, or that the amount of DNA damage is minimal, or that perhaps if damage has occurred, that it is not influencing perinatal outcomes substantially. There are a few

factors that may contribute to this finding. The quality of the sperm has been shown to influence the amount of cryopreservation induced DNA damage.[719, 720] Considering that a sperm donor is screened for the quality of their sperm as part of the process of them being accepted as a donor; it would not be surprising if the amount of cryopreservation induced DNA damage in these men was lower than that observed for other men. Provided that the damage is not substantive, the oocyte is sometimes able to repair the DNA damage that has been introduced by the spermatozoa.[358]

The freezing and thawing process may also assist as a positive selection pressure towards better quality sperm as DNA damaged spermatozoa are less likely to lead to the fertilisation of an oocyte as evident by the contribution of DNA damage in sperm to infertility.[721] An example of this is the study by Gerkowicz *et al.*, who found by examining 19 years of national data from the United States and when adjusting for maternal age, the use of donor sperm increased the live birth rates in comparison to the partners' sperm.[33] Thereby suggesting that the quality of donor sperm, in general, is marginally better. Furthermore, DNA damage occurring in sperm has been associated in a systematic review with reduced pregnancy rates in various ART treatments,[722] as well as being correlated with recurrent pregnancy loss.[723, 724]

Summarising the factors mentioned above, mechanisms that may explain why the perinatal outcomes for neonates conceived with donated sperm were not substantively different in a wide range of outcomes than those conceived spontaneously may include:
1) Good quality sperm obtained from donors.
2) Artificial selection pressures induced by the freeze/thaw process with a reduced quality or damaged sperm not fertilising the oocyte.
3) Natural selection pressures through donor insemination rather than artificially selected sperm occurring in IVF and ICSI.
4) The repair mechanism of the oocyte which may correct DNA damage.
5) A reduced probability of an abnormal embryo resulting from fertilisation by DNA damaged sperm being able to implant in the uterus.[725]
6) The inability to carry a poor quality embryo and resultant foetus to term.

Notwithstanding, the donor sperm-conceived cohort sample size could be improved, and the lack of power for some analysis due to the low number of events suggests that the possibility for an increased risk of adverse outcomes cannot be ruled out. Supporting this is data showing modest differences which were not statistically significant. Improving the analysis was explored in the next section by incorporating into the previous meta-analysis, the results from

this study along with data from other studies published since the review census date. Nonetheless, the increased risk for adverse neonatal outcomes observed in donor oocyte conceptions,[1, 275, 654-656] was not present to the same extent in the South Australian donor sperm-conceived cohort.

Preeclampsia is an immune-mediated condition,[190, 191, 726] induced in donor conception through the presence of novel antigens which is more marked in oocyte donation. Novel oocyte antigens are not a normal exposure in the history of humans and have only been experienced by women in recent decades through the introduction of ART technologies, which is unlike the situation of novel sperm antigens which women have always experienced. Subsequently and hypothetically, perinatal outcomes resulting from oocyte donation are more likely to be worse than those from sperm donation due to the significantly increased immunological challenge. This scenario is consistent with the current findings on both donor oocyte and donor sperm neonatal outcomes in which donor oocyte neonates have been observed to have poorer outcomes. However, due to the lack of studies investigating donor sperm outcomes, the question of whether that is what is occurring cannot be answered conclusively. Further studies are required to advance the understanding of the health outcomes for those who are conceived with donated sperm.

The results of this study would potentially be reassuring to clinicians, patients and donor sperm-conceived people. However, caution should be taken with undertaking ovulation induction treatment regimens due to the increased risk of PD, PD with LBW, and lower mean BW and GA. While donor sperm-conceived people were born with an increased risk of PD with LBW, this was attenuated when considering singletons and twins separately and the lower GA of 0.2 weeks is unlikely to be clinically significant. A caveat for this reassurance is that the current associations hold or improve with the addition of further studies to the meta-analysis. Results of an updated meta-analysis are presented in the next section. Furthermore, as the census date for this study was from January 1986 to December 2002, additional data from subsequent years of the SAPSC would be of considerable interest and improve the study's statistical power. Especially for those outcomes in which a low number of events was observed.

3.3 Part B: Updated Donor Sperm Neonatal Outcomes Meta-Analysis

3.3.1 Background

The 2017 publication of the systematic review and meta-analysis on donor sperm-conceived people's health outcomes,[3] highlighted a dearth of studies that investigated the health of this specific donor conception cohort. From studies included up to the census date of November 2012, only eight studies were eligible for inclusion in the review, from which only three provided comparable outcome data for meta-analysis.[183, 447, 603] More specifically, only two studies were able to be included in each outcome meta-analysis.

As a result of the dearth of studies in the systematic review, the South Australian population-based study reported above was conducted. This study represents the most comprehensive and systematic investigation of perinatal outcomes from donor sperm conceptions at the time of publication.[2] Also, a further two studies were published since the census date, which also meet the inclusion criteria of the original systematic review.[678, 712] The addition of these three further studies to the meta-analysis not only substantially increased the level of evidence available but also enabled an analysis of whether the original findings are supported or refuted.

Revisiting the findings of the original systematic review it was observed that donor sperm-conceived neonates were not statistically different to spontaneously conceived neonates in terms of risk of being born LBW (RR: 1.04, CI: 0.86 – 1.25, $p = 0.71$, $I^2 = 0\%$); PD (RR: 0.91, CI: 0.75 – 1.12, $p = 0.38$, $I^2 = 0\%$); or with increased risks of BD (RR: 1.20, CI: 0.97 – 1.48, $p = 0.09$, $I^2 = 57\%$).[3]

Adding these three newer studies to the meta-analysis not only increased the number of studies and sample size but also enabled a more comprehensive range of neonatal outcomes to be analysed.

3.3.2 Methods

The methods used in this meta-analysis followed the methods as described in the systematic review chapter (See Chapter 2; Methods). A new systematic computerised search and a systematic analysis of search results were not conducted. Instead, a simplified search of the databases was conducted which identified the two other new studies. Secondly, the obstetric outcomes of PE, caesarean section, induction of labour and forceps delivery were also extracted from all studies, including those incorporated previously.

3.3.3 Results

The new studies provided a total of 3,984 donor sperm outcomes and 529,707 outcomes from spontaneous or partner ART conceptions which when added to the original systematic reviews sample size of 24,699 donor sperm outcomes and 423,763 outcomes from spontaneous or partner ART conceptions, provided a total of 28,683 donor sperm health outcomes and 953,470 outcomes from spontaneous or partner ART conceptions. The summary characteristics and health outcome data of the offspring obtained from the three new studies have been added to the original table of donor sperm studies and presented in Table 2.5.

Table 2.5 Characteristics of studies included donor sperm studies in the updated meta-analysis

Study	Donation Treatment(s) & Sample Size	Comparison & Sample Size	Cryo or Fresh	Ages	Specific Results
Thapar *et al.* (2007) United Kingdom	Sperm 170 AID as IVF (IVF-D)	Homologous IVF 378 & General population Published data	Not Specified	5-9yrs	LBW (all births) 19.6% sperm v 14.7% homologous IVF v 8% gen pop LBW (singletons) 8% sperm v 6.7% homologous IVF (gen pop singleton LBW not specified) Multiplicity 24.1% sperm v 20.1% homologous IVF
Gaudoin *et al.* (2003) United Kingdom	Sperm 35	Partners sperm 97 & General population 109302	Unknown	Neonates	BW 3149 ± 233g (donor) v 2921 ± 165g (partner) v 3301 ± 4g (comparison) LBW 11.4% (donor) v 22.7% (partner) v 7.1% (gen pop) PD 5.7% (donor) v 15.5% (partner) v 6.9% (gen pop)
Hoy *et al.* (1999) Australia	Sperm 1603	General population 7516	Frozen	Neonates	LBW 7.3% v 6.8%, RR 1.1 BD 3.6% v 3.2%, RR 1.1 Perinatal death 1.2% v 1.1%, RR 1.4 Stillborn 0.9% v 0.6%, RR 1.5 Neonatal death 0.4%v 0.5%, RR 0.8 ChAb 0.4% v 0.2%, RR 2.5 PD 6.4% v 6.6%, RR 1 Multiplicity 3.1% v 2.7% RR 1.2
Amuzu *et al.* (1990) USA	Sperm 481	General population Published data	Both	3mths - 15yrs (ave 5yrs)	BW (7.5lb ± 1.3) and birth length (20.1 inches ± 1.2) same as gen pop Major anomalies (2.9% at birth, 6.2% at time of study v 2% and 5%) ChAb 0.2% v not specified Developmental milestones same as gen pop Learning disabilities 5.8% v not specified Gifted and talented program 10.5% v not specified
Iizuka *et al.* (1968) Japan	Sperm 54	General population Published data	Both (frozen = 9)	N=40 ≥ 2.5yrs (oldest 11.8yrs) N=14 ≤ 2.5yrs	BW and Length better in AID IQ of donor sperm children higher range than controls (better)

Davies *et al.* (2012) Australia	Sperm 428	General population 293314	Not Specified	Neonates	BD 8.4% v 5.7%, OR 1.51 (adjusted OR 1.37)
Lansac *et al.* (1997) France	Sperm (AID) 18128 AID as IVF (IVF-D) 3405	General population 13631	Frozen	Neonates	BW 3281 ± 491g (N=8943) v 3300 ± 600g (N=13631) LBW 4.7% (singleton) v 6.2% (national register of natural conceptions) Malformations (1.9% AID, no sig diff to gen pop, not specified) Malformations (2.74% IVF-D v 2.99% husband sperm, no sig diff) PD 4.8% (singleton) v 5.9% (national register of natural conceptions) ChAb 0.25% v 0.2% (Paris $p < 0.05$) v not specified (Strasbourg et Marsailles, no sig diff)
Forse *et al.* (1985) Canada	Sperm 395	General population Published data	Fresh	Neonates	ChAb 0.75% v 0.15%
Adams *et al.* (2017) Australia	Sperm 480	General population 298,944	Frozen	Neonates	BW 3392 ± 554g v 3400 ± 552g (singletons) GA 39.1 ± 1.7weeks v 39.2 ± 1.8weeks (singletons) LBW 5.1% v 4.7% (singletons) VLBW 0.9% v 0.7% (singletons) PD 5.5% v 5.5% (singletons) VPD 1.2% v 0.8% (singletons) PostD 0.7% v 1.7% (singletons) PD + LBW 4.2% v 3.0 (singletons) TermD + LBW 0.9% v 1.6 (singletons) SGA 9.2% v 10.2% (singletons) LGA 10.2% v 9.9% (singletons) 5'AS < 7 1.2% v 1.4% (singletons)
Huang *et al.* (2016) China	Sperm 1623	General population 1014	Frozen	Neonates	BW 3.32 ± 0.46kg v 3.34 ± 0.43kg (all births) LBW 1.99% v 2.27% (singletons) Macrosomia (BW > 400g) 8.18% v 4.93% (singletons)

					BD 1.42% v 0.29% (all births)
Malchau *et al.* (2014)	Sperm	General population	Not	Neonates	BW 3505 ± 590g v 3515 ± 557g (singletons)
Denmark	1881	229,749	Specified		GA 278.5 ± 13.7days v 278.7 ± 12.5days (singletons)
					LBW 5.0% v 3.4% (singletons) $p < 0.001$
					VLBW 0.7% v 0.6% (singletons)
					PD 4.0% v 3.1% (singletons)
					VPD 0.8% v 0.7% (singletons)
					SGA 3.9% v 2.7% (singletons) $p < 0.001$
					LGA 3.2% v 3.1% (singletons)
					NICU admissions 11.3% v 7.8% $p < 0.001$

BW = birthweight, LBW = low birthweight <2500g, VLBW = very low birthweight <1500g, GA = gestational age, PD = preterm delivery (< 37 weeks), VPD = preterm delivery (< 32 weeks), PostD = post-term delivery > 42 weeks, TermD = term delivery, SGA = small for gestational age, LGA = large for gestational age, BD = birth defects, ChAb = chromosomal abnormalities, 5'AS < 7 = 5 minute Apgar score of less than 7, NICU = neonatal intensive care unit, AID = artificial insemination by donor, IVF-D = in vitro fertilisation with donor sperm, RR = risk ratio, OR = odds ratio, sig = significant, gen pop = general population, *p* values for significance is only provided where $p < 0.05$.

Data are presented as the donor group v comparison group. The comparison group is a cohort unless otherwise specified. Studies citing comparison group of the general population or autologous oocyte cohort data that was published elsewhere are denoted as "published data". General population data is of spontaneous conceptions. This table is a combination of the equivalent donor sperm outcome table published in the sperm donation systematic review[3] with the newly added data from the three newer studies.

3.2.3.1 Sperm Donation Birth Weights

Birth weight data including the categories of LBW and VLBW were the most frequently reported outcomes in the updated meta-analysis which showed that neonates conceived with donated sperm were more likely to be born of LBW (RR: 1.17, CI: 1.03 – 1.33, $p = 0.02$, $I^2 = 52\%$), than those conceived spontaneously (Figure 3.1). They were not however significantly more likely to be born with a lower mean BW (mean difference -12.5g, CI: -32.03g–7.02g, $p = 0.21$, $I^2 = 0\%$) (Figure 3.2), or VLBW (< 1500g) (RR: 1.22, CI: 0.76 – 1.97, $p = 0.4$, $I^2 = 0\%$) (Figure 3.3).

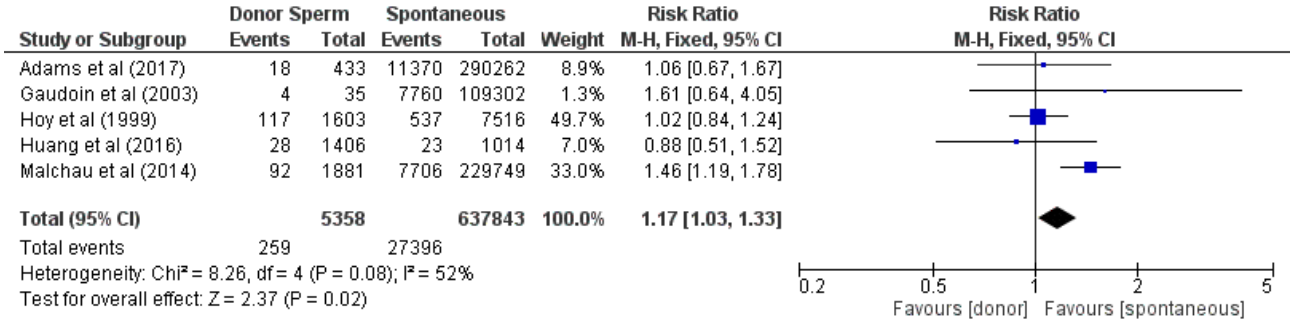

Figure 3.1 Updated meta-analysis forest plot of low birthweight (< 2500g) outcomes comparing donor sperm versus spontaneously conceived neonates.

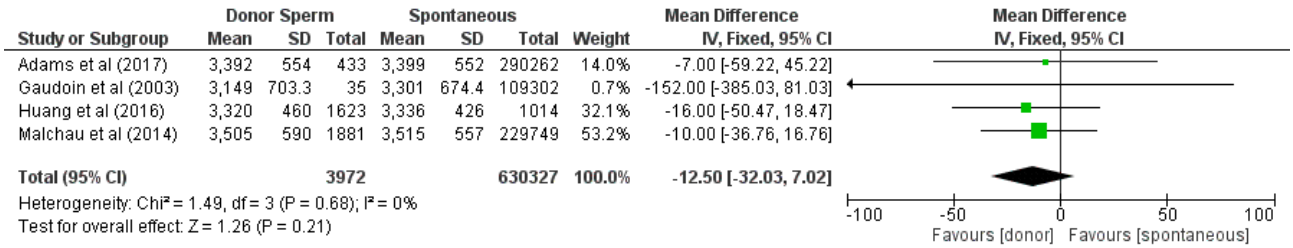

Figure 3.2 Updated meta-analysis forest plot of mean birthweight outcomes comparing donor sperm versus spontaneously conceived neonates.

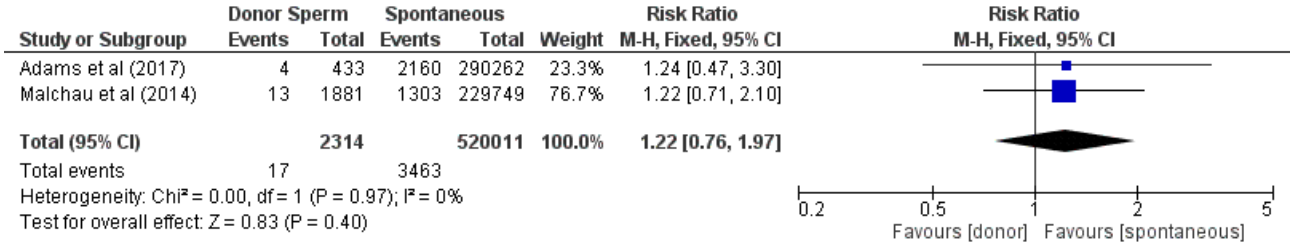

Figure 3.3 Updated meta-analysis forest plot of very low birthweight (< 1500g) outcomes comparing donor sperm versus spontaneously conceived neonates.

3.2.3.2 Sperm Donation Preterm Delivery

The next most frequently reported neonatal outcomes are those pertaining to preterm delivery and gestational age. The updated meta-analysis showed that neonates conceived with donated sperm were not different in terms lower mean GA (mean difference -0.02 weeks, CI: -0.10w–0.05w, $p = 0.55$, $I^2 = 12\%$) (Figure 3.4), than those conceived spontaneously. Furthermore, neonates conceived with donated sperm were also not significantly more likely to be born PD (RR: 1.05, CI: 0.91 – 1.21, $p = 0.47$, $I^2 = 52\%$) (Figure 3.5), or VPD (RR: 1.17, CI: 0.75 – 1.81, $p = 0.49$, $I^2 = 0\%$) (Figure 3.6).

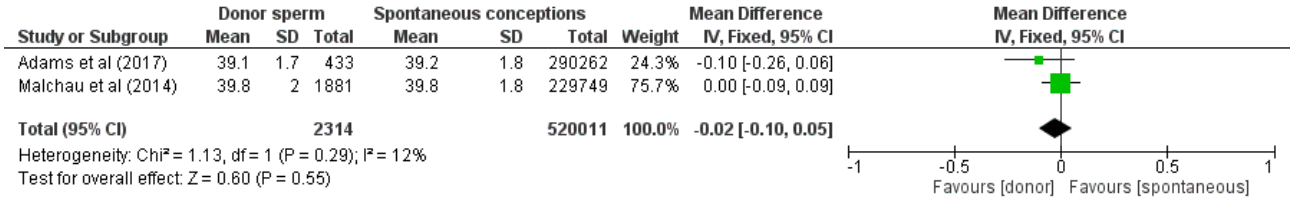

Figure 3.4 Updated meta-analysis forest plot of mean gestational age outcomes comparing donor sperm versus spontaneously conceived neonates.

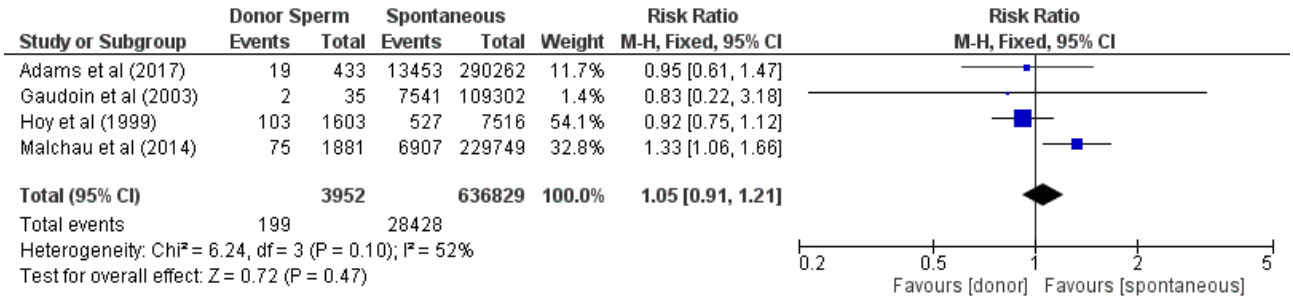

Figure 3.5 Updated meta-analysis forest plot of preterm delivery (< 37 weeks) outcomes comparing donor sperm versus spontaneously conceived neonates.

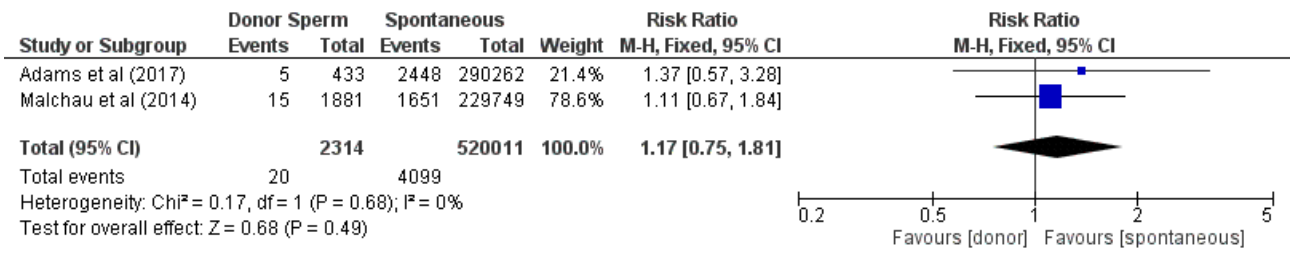

Figure 3.6 Updated meta-analysis forest plot of very preterm delivery (< 32 weeks) outcomes comparing donor sperm versus spontaneously conceived neonates.

3.2.3.3 Sperm Donation Birth Size Adjusted for Gestation Age

The updated meta-analysis showed that neonates conceived with donated sperm were not significantly more likely to be born SGA (RR: 1.19, CI: 0.99 – 1.42, $p = 0.06$, $I^2 = 82\%$) (Figure 3.7), or LGA (RR: 1.04, CI: 0.86 – 1.38, $p = 0.71$, $I^2 = 0\%$) (Figure 3.8), than those conceived spontaneously.

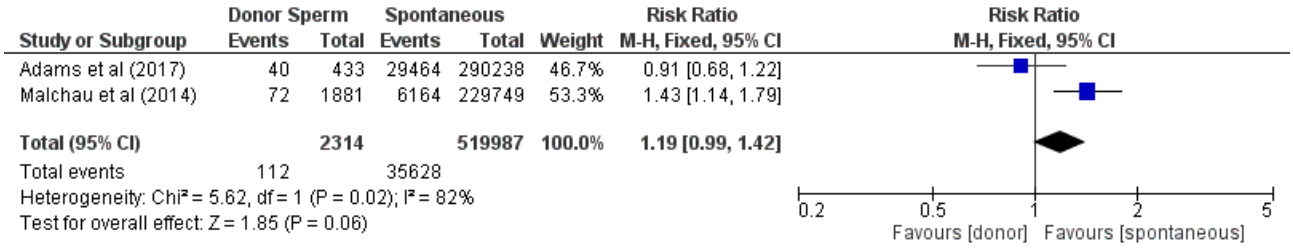

Figure 3.7 Updated meta-analysis forest plot of small for gestational age (birth weight < 10th percentile) outcomes comparing donor sperm versus spontaneously conceived neonates.

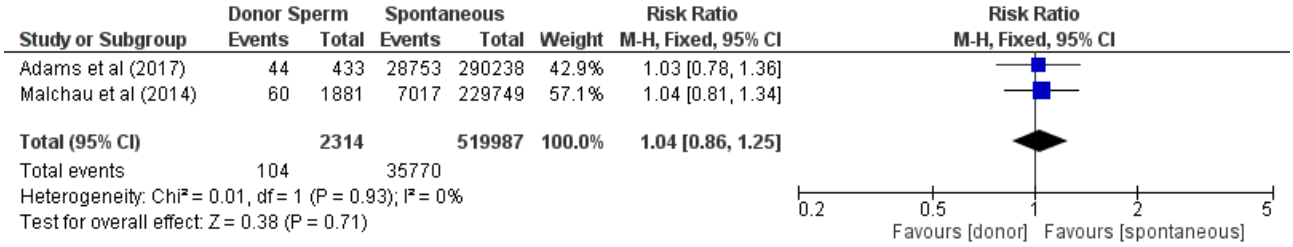

Figure 3.8 Updated meta-analysis forest plot of large for gestational age (birth weight > 90th percentile) outcomes comparing donor sperm versus spontaneously conceived neonates.

3.2.3.4 Sperm Donation Birth Defects

The updated meta-analysis showed that neonates conceived with donated sperm were significantly more likely to be born with increased incidences of BD (RR: 1.30, CI: 1.05 – 1.59, $p = 0.01$, $I^2 = 72\%$) (Figure 3.9), than those conceived spontaneously.

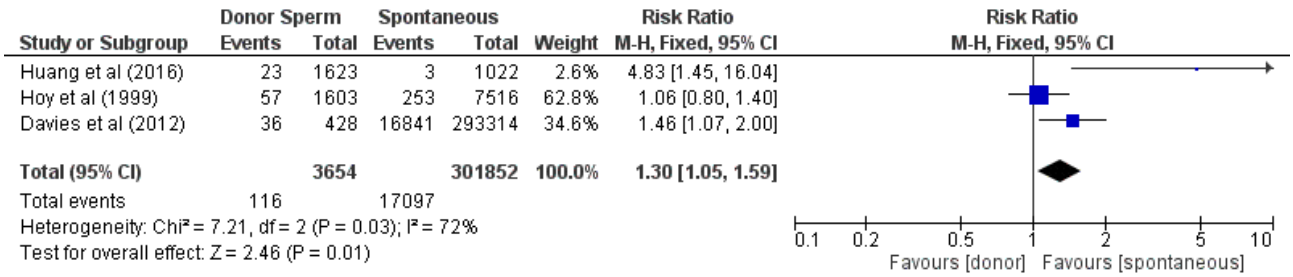

Figure 3.9 Updated meta-analysis forest plot of birth defect outcomes comparing donor sperm versus spontaneously conceived neonates.

3.2.3.5 Sperm Donation Mortality

The updated meta-analysis showed that neonates conceived with donated sperm were not significantly different to those conceived spontaneously in terms of altered perinatal mortality (RR: 0.93, CI: 0.59 – 1.45, $p = 0.74$, $I^2 = 0\%$) (Figure 3.10).

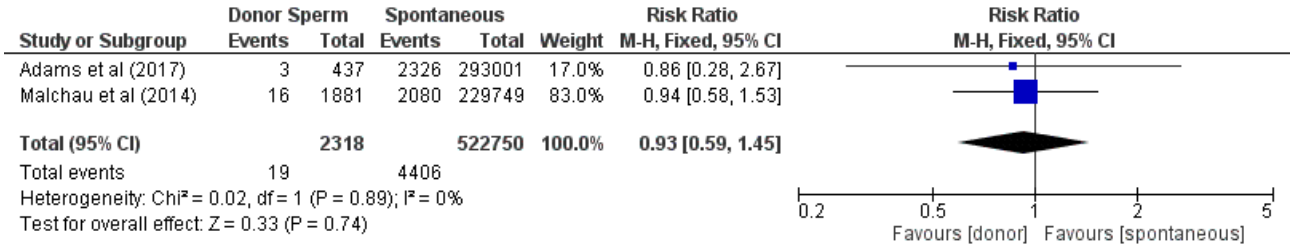

Figure 3.10 Updated meta-analysis forest plot of altered perinatal mortality outcomes comparing donor sperm versus spontaneously conceived neonates.

3.2.3.6 Sperm Donation Other Outcomes

There was one study which investigated neonatal admissions to the NICU, in which a significantly increased frequency associated with the use of donor sperm in comparison to those conceiving spontaneously was reported (11.3% v 7.8%, $p < 0.001$).[7,12]

3.2.3.7 Sperm Donation Obstetric Outcomes

While the focus of this meta-analysis and thesis is on the outcomes and welfare of those conceived through donor conception, the lack of information recorded on obstetric outcomes is also interesting as these outcomes may help inform patients and clinicians. The following obstetric outcomes are not recorded in the summary characteristics table (Table 3.5) but are reported in the forest plots.

The meta-analysis showed that mothers conceiving with donated sperm were significantly more likely than mothers who conceive spontaneously with their partner's sperm to suffer from PE (RR: 1.61, CI: 1.33 – 1.94, $p < 0.00001$, $I^2 = 0\%$) (Figure 3.11), to undergo induction of labour (RR: 1.34, CI: 1.25 – 1.43, $p < 0.00001$, $I^2 = 0\%$) (Figure 3.12), to have a caesarean section (RR: 1.46, CI: 1.40 – 1.52, $p < 0.00001$, $I^2 = 100\%$) (Figure 3.13), and to have a forceps delivery (RR: 1.45, CI: 1.29 – 1.62, $p < 0.00001$, $I^2 = 14\%$) (Figure 3.14). The study by Malchau *et al.* reported the frequencies of hypertensive disorders of pregnancy which included the following conditions; "gestational hypertension, preeclampsia, haemolysis, elevated liver enzymes, low platelet count (HELLP), and eclampsia",[712] but the incidences of PE and PIH (gestational hypertension) were not stratified and therefore could not be used in meta-analysis.

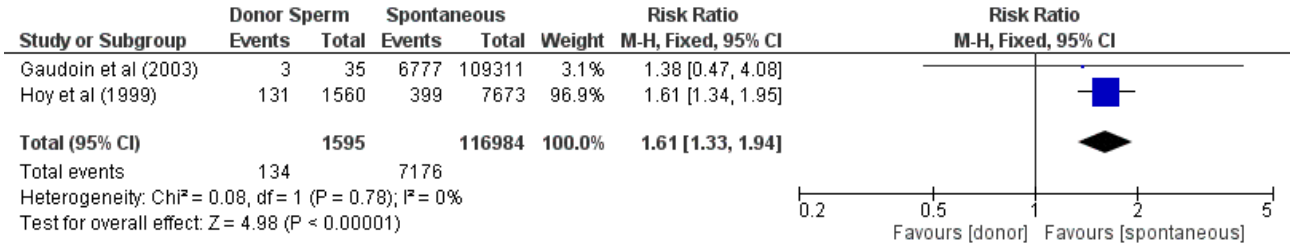

Figure 3.11 Updated meta-analysis forest plot of preeclampsia outcomes comparing donor sperm versus spontaneously conceived neonates.

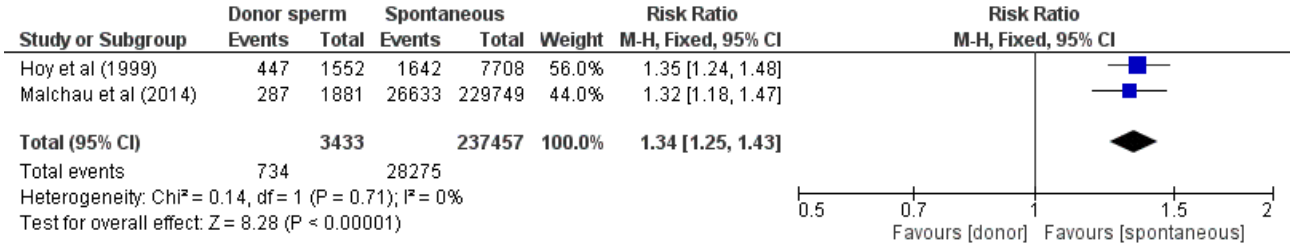

Figure 3.12 Updated meta-analysis forest plot of induction of labour outcomes comparing donor sperm versus spontaneously conceived neonates.

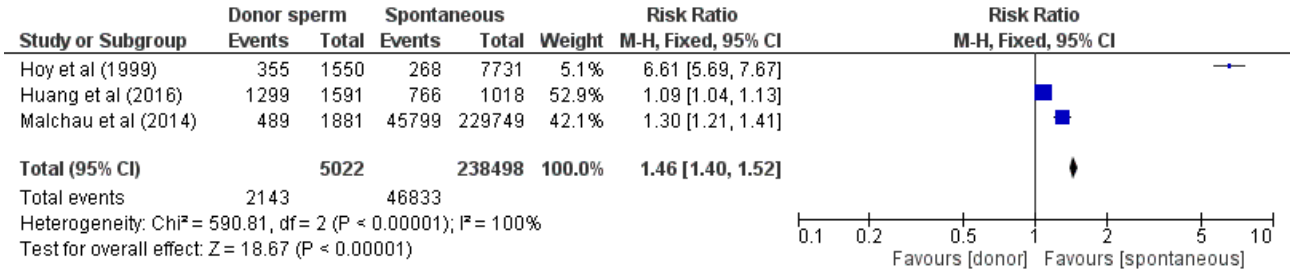

Figure 3.13 Updated meta-analysis forest plot of caesarean section outcomes comparing donor sperm versus spontaneously conceived neonates.

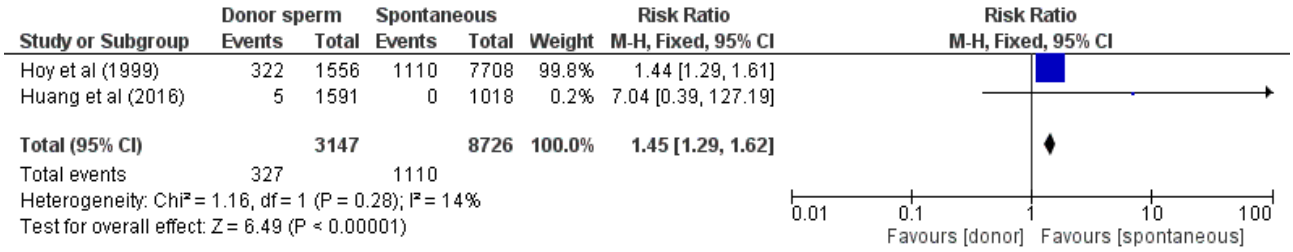

Figure 3.14 Updated meta-analysis forest plot of forceps delivery outcomes comparing donor sperm versus spontaneously conceived neonates.

3.3.4 Risk of Bias

The modified JBI-MAStARI instrument was used to assess the risk of bias and the methodological quality of the donor sperm studies incorporating the newer studies into the original donor sperm table (Table 2.6). The following qualitative assessment only reports on the three newly included studies. Multiplicity was appropriately controlled for in two studies to remove confounding by multiplicity. Adams *et al.* stratified singleton and twin births and compared to all births,[2] while Malchau *et al.*, restricted the analysis to singletons only.[712]

Maternal age and parity confounding data was reported differently across the studies and is presented in Table 2.7. The three newly included studies appropriately reported maternal ages, while only two of these studies appropriately adjusted for maternal age.[2, 712] The remaining study by Huang *et al.*, reported no statistically significant difference between the mean maternal ages of those mothers who had conceived with donated sperm versus those conceiving spontaneously.[678] Parity was adjusted appropriately in the reports of both Malchau *et al.*, and Adams *et al.*[2, 712]

Outcome meta-analysis showing significant heterogeneity ($I^2 > 65\%$), was observed in the data for the outcomes of BD, SGA and caesarean section. Funnel plot analysis showed symmetry for the outcome measures of mean BW, LBW, VLBW, mean GA, VPD, SGA, and LGA; while BD, PD, and perinatal mortality were asymmetrical thereby showing the presence of bias (Appendix 2.5). The obstetric outcomes of PE, induction of labour, caesarean section and forceps delivery also exhibited asymmetry and therefore, bias.

These findings should be interpreted with caution. While the meta-analysis was considerably strengthened with the addition of three studies, more studies are required, especially for

those meta-analyses that have few studies included. Furthermore, some meta-analyses have significant heterogeneity and bias as observed through the I^2 statistic and funnel plot analysis, respectively. A continual undertaking of and reporting of studies investigating the outcomes of donor sperm conception are required to improve the meta-analyses and the understanding of how the use of this treatment modality affects the health of not only those conceived but also the mothers who carry these babies. The use of specific OI drugs such as clomiphene citrate which are also associated with the use of DI should also be studied in greater detail considering that they are also correlated with increased incidences of poor neonatal outcomes,[603, 708, 712, 713] and have been associated with poorer obstetric outcomes such as PE, PIH, gestational diabetes and caesarean section in ART treatments.[727-729]

Table 2.6 Risk of bias and critical assessment of included donor sperm studies in the updated meta-analysis

Study	Criterion								
	Representative patients	Similar point in condition	Minimised case selection bias	Singleton v multiples	Other confounders	Cryo-preservation	Objective criteria	Reliable outcomes	Appropriate statistics
Thapar *et al.* (2007)	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	No
Gaudoin *et al.* (2003)	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes
Hoy *et al.* (1999)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes[d]	Yes	Yes
Amuzu *et al.* (1990)	Yes	No	Yes[a]	No	No	No	Yes[d]	No	No[b]
Iizuka *et al.* (1968)	Yes	Unclear	No[a]	No	Yes	No	Yes	Yes	No
Davies *et al.* (2012)	Yes	Unclear	Yes	Yes	Yes	No[c]	Yes	Yes	Yes
Lansac *et al.* (1997)	Yes	Unclear	Yes[a]	No	Yes	Yes	Yes[d]	No	No[b]
Forse *et al.* (1985)	Yes	Unclear	Yes[a]	No	No	No	Yes[d]	Yes	No
Adams *et al.* (2017)	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Huang *et al.* (2016)	Yes	Unclear	Yes	No	No	Yes	Yes	Yes	Yes
Malchau *et al.* (2014)	Yes	Unclear	Yes	Yes	Yes	No[c]	Yes	Yes	Yes

[a] = data was presented but was not stratified as donor v autologous, or the data was not used in the analysis; [b] = statistics were used appropriately, but the authors did not analyse donor v autologous outcomes; [c] = a comparison group was used but was from previously published data, not a comparison cohort. This table is a combination of the equivalent donor sperm outcome table published in the sperm donation systematic review[3] with the newly added data from the three newer studies.

Table 2.7 Maternal age and parity as reported in included donor sperm studies in the updated meta-analysis

Study	Maternal Age Details	Parity Details
Thapar *et al.* (2007)	33.88 ± 3.82 yrs (donor) v 34.14 ± 3.53 yrs (homologous IVF) v unknown (general population)	-
Gaudoin *et al.* (2003)	33.1 (31.9–34.3 95% CI, donor) v 32.4 (31.6–33.1, partner) v 25.9 (25.9–25.9, general population)	all nulliparous
Hoy *et al.* (1999)	16% ≥ 35 yrs v 10% ≥ 35 yrs	53.4% v 40.5% primiparous
Amuzu *et al.* (1990)	29.3 ± 4.2 yrs v unknown	-
Iizuka *et al.* (1968)	30.1 ± 2.7 yrs v unknown	-
Davies *et al.* (2012)	(2.2% 20–24 yrs, 22.2% 25–29 yrs, 44.4% 30–34 yrs, 26.2% 35–39 yrs, 5.1% ≥ 40 yrs) v (20.8% 20–24 yrs, 37.7% 25–29 yrs, 29.4% 30–34 yrs, 10.5% 35–39 yrs, 1.7% ≥ 40 yrs)[a]	65.3% v 37.5% nulliparous
Lansac *et al.* (1997)	[b]	-
Forse *et al.* (1985)	28.9 yrs[c]	-
Adams *et al.* (2017)	(4.4% 20–24 yrs, 29.6% 25–29 yrs, 41.6% 30–34 yrs, 22.5% 35–39 yrs, 1.9% ≥ 40 yrs) v (20.9% 20–24 yrs, 37.8% 25–29 yrs, 29.3% 30–34 yrs, 10.3% 35–39 yrs, 1.6% ≥ 40 yrs)	40.8% v 28.6% primiparous
Huang *et al.* (2016)	27.62 ± 3.64 yrs v 27.69 ± 3.75 yrs	
Malchau *et al.* (2014)	34.4 ± 4.4 yrs v 30.7 ± 4.9 yrs	69.5% v 43.4% nulliparous

This table is a combination of the equivalent donor sperm outcome table published in the sperm donation systematic review[3] with the newly added data from the three newer studies.

3.3.5 Discussion

This updated meta-analysis highlighted that the risk of adverse neonatal outcomes as a result of being conceived with donated sperm could change when more studies are added to the meta-analysis. Originally, evidence suggested that neonates conceived with donated sperm were not at a significantly elevated risk of being born of LBW, PD or with BD, in comparison to those spontaneously conceived. Subsequent meta-analyses highlighted that conclusions to such effect were premature as updated analysis suggests that donor sperm-conceived neonates fare significantly worse in terms of both LBW and BD. However, they were not significantly disadvantaged in terms of mean BW, VLBW, mean GA, PD, VPD, SGA, LGA or perinatal mortality.

Meta-analyses of obstetric outcomes suggest that mothers using donor insemination are at greater risk of experiencing PE, induction of labour, caesarean section and forceps delivery. These meta-analyses were hampered by low numbers of studies, bias and significant heterogeneity of studies included. Of particular note is the 100% I^2 statistic value for the caesarean section meta-analysis. The I^2 statistic simply is the amount of error not caused by

sampling error. Some suggest that the caesarean section data, therefore, have nothing in common and that the pooled results should not be reported.[730] However, there is evidence that perhaps this result should not be ignored as will be described forthwith.

The obstetric outcome meta-analysis is hampered by the selection of studies based on neonatal and childhood outcomes, whereas studies investigating obstetric outcomes without neonatal outcomes have been published. From existing literature, the outcome of significantly increased PE associated with the use of donated sperm is consistent with previously published studies,[181, 182, 294, 701] as is the significantly increased risk for caesarean section.[731, 732] Furthermore, another study has shown a higher absolute frequency of labour induction.[732] An increased risk for caesarean section has also been correlated with the use of donated oocytes.[275, 656] Notwithstanding the limitations, these obstetric outcomes, even when treated with caution, are consistent with adverse outcomes previously published and should also be considered in future studies to improve the confidence in the meta-analysis.

Inclusion of the three newer studies improved the meta-analysis and understanding of donor sperm-conceived neonatal outcomes compared to spontaneously conceived neonates. The updated meta-analysis is suggestive that neonates conceived with donated sperm are at increased risk of being born of LBW and with increased incidences of BD. One included study also reported a significantly increased frequency of donor sperm-conceived neonates requiring admission to the NICU,[712] which is consistent with reports from donor oocyte-conceived neonates.[572, 645, 646]

3.4 Summary

The following outcomes have been observed when collating data from the systematic reviews, perinatal study, updated meta-analysis and previous publications:

1) Donor oocyte neonates have a significantly increased risk of being born of low birthweight, very low birthweight, preterm delivery, preterm delivery with low birthweight, and with a lower mean gestational age in comparison to those conceived with autologous oocytes. However, donor oocyte-conceived neonates that make it term have a significantly decreased risk for being born of low birthweight.
2) Donor sperm neonates have a significantly increased risk of being born of low birthweight and with increased incidences of birth defects in comparison to those conceived spontaneously. However, donor sperm-conceived neonates were not significantly different in terms of their mean birthweight, and mean gestational age. They were also not significantly different in terms of the incidences of being born of very low birthweight, preterm delivery, very preterm delivery, small for gestational age, large for gestational age or perinatal mortality.
3) Donor-conceived neonates were more likely to be admitted to the NICU and have longer hospital stays than their autologous oocyte or spontaneously conceived peers.
4) Donor sperm treatment modalities are associated with the implementation of ovulation induction treatments which are also correlated with a significantly increased risk of a lower mean birthweight, lower mean gestational age, preterm delivery, and preterm delivery with low birthweight.
5) Mothers achieving a pregnancy with donated gametes are at an increased risk for developing preeclampsia, pregnancy-induced hypertension, and for having a caesarean section delivery. At the same time, mother's using donor insemination treatments are also at increased risk of induction of labour and forceps delivery.
6) There has been little progress made in determining the full impact of cryopreservation on the health of those conceived from frozen gametes/embryos.
7) There was minimal data on the health outcomes for DC people in childhood, and no data available as adults.

3.5 Donor Sperm Perinatal Outcomes - A Redux Conclusion

Conclusions on the health and wellbeing of sperm DC neonates based on the original systematic review and meta-analysis were not substantiated as the addition of more studies altered the risk for two outcomes. The same could be postulated for this update and particularly for those outcomes implementing a small number of studies and or sample sizes. Further studies are subsequently required.

However, the shift towards adverse outcomes is consistent with the correlation between donated sperm use and increased risks of PE, which is also correlated with adverse outcomes both in the perinatal period and long-term. It is also consistent with the increased incidences of poorer outcomes observed in oocyte donation outcomes,[1, 275, 654-656] but to a less severe extent fitting with the lower immunological challenge presented. The increased risk for BD has also been associated with the use of ICSI in non-donor IVF treatments.[446]

Whether these increased risks in the donor sperm-conceived cohort are a direct result of increased incidences of PE,[294] the cryopreservation of sperm leading to DNA damage,[325] ovulation induction drugs,[712, 713] embryo culture from IVF/ICSI with donor sperm, intervention by obstetricians, or any combination of the factors mentioned above is unclear and requires further elucidation.

The number of studies investigating the outcomes from oocyte donation is suggestive that there have been concerns about the health of donor oocyte-conceived people at least in the perinatal period. However, from the dearth of studies investigating the outcomes for those conceived with donor sperm which has been practised for a far more extended period, perhaps some had mistakenly believed that their outcomes would be no different from those conceived spontaneously. This assumption has been a misconception.

From the DOHaD perspective, the neonatal outcomes presented in the previous chapters have implications for an altered health trajectory in adulthood. While such an altered trajectory appears plausible, it is not a simple case of fait accompli. Studies of DC adults and their health must be conducted to determine if the increased incidences of adverse neonatal and obstetric outcomes manifest in or are more specifically associated with changes in the health outcomes for adult DC people. It may be the case that these adverse neonatal outcomes do not influence the health trajectories of DC people at all. Nevertheless, without data, we simply do not know.

The focus of this thesis now turns to this issue. The next chapter will present the findings of a self-reported health status survey of adult DC people and people who were conceived spontaneously.

CHAPTER 4. DONOR-CONCEIVED ADULT HEALTH OUTCOMES – GROWING UP WITH DOHAD

Content contained within this chapter represents updated and reworked data and discussion from one publication, which presented the physical health outcomes from the study of health outcomes for DC adults. This study also investigated mental health outcomes which has not yet been published

Adams DH, Gerace A, Davies MJ, de Lacey S. Self-reported physical health status of donor sperm conceived adults. J Dev Orig Health Dis. 2020. Accepted July 20, 2020.[5] (Appendix 3.1)

Attribution of authorship:
DA (90%) and all other authors AG, MD and SdeL, contributed to the design of the study. DA (100%) distributed the survey to the appropriate online support groups and donor conception organisations. DA (100%) conducted the survey and extracted the data. Data analysis was performed by DA (95%) with input from all other authors. DA (90%) drafted the manuscript with all other authors (AG, MD, and SdeL) providing edits and revisions.

4.1 Introduction

The findings of the systematic review and perinatal study reported in the preceding chapters suggested that adverse perinatal outcomes are associated with donor conception. The DOHaD phenomenon describes that these adverse outcomes in early life may alter their health trajectories into adulthood, thereby affecting the long-term health of DC people. This chapter reports the second study of this thesis that sought to fill gaps in the literature that was identified in the systematic reviews. Specifically, there appear to have been no studies on the physical health outcomes of DC adults and no quantitative studies investigating their mental health. Therefore, this study represents both the first study conducted into the physical health of DC adults and the first quantitative study of their mental health. While the research

contained in this thesis has focussed primarily on physical health outcomes, conducting a self-reported health survey represented an excellent opportunity to obtain mental health outcomes in addition to physical outcomes. As the mental health data collection occurred during the same survey, the methods sections of this chapter will present the entire method for collecting and analysing both sets of data. The results and discussion sections will address the physical and mental health outcomes separately before culminating in a conclusion.

4.2 Background

A short summation of information from previous chapters that are pertinent to why a study investigating adult health outcomes is required is as follows. Neonates born from ART treatments including donor conception are significantly more likely to be adversely affected by a range of outcomes such as LBW, VLBW, SGA, PD, VPD, and a higher incidence of congenital abnormalities and perinatal mortality.[1, 4, 45, 52, 54, 447, 478, 480, 481, 654, 733]

The DOHaD phenomenon,[62] has highlighted that adverse neonatal outcomes such as those listed are associated with altered physical and mental health trajectories in adulthood.[60, 61, 220, 235, 237, 239, 734-736] These increased incidences of adverse neonatal outcomes have prompted the investigation of the long-term health of people conceived with IVF and other ART treatment modalities.[38, 42, 57, 737, 738] However, donor conception has been largely ignored by these investigations.

There continue to be studies conducted investigating the health and psychological functioning of DC children,[739] but to date, adult studies are still missing from the literature. Donor-conceived adults, therefore, represent an interesting population subset of ART treatment modalities that have not been explicitly studied in terms of their physical and mental health outcomes quantitatively. There are; however, some adult studies investigating psychological, emotional and mental outcomes from a qualitative perspective as described in Chapter 6.

4.2.1 Recruitment Issues

Unlike the previous studies in this thesis of meta-analyses and a perinatal study which implemented either already published data or data that was available through a perinatal statistics collection, the conduct of this study was challenged with regard to the recruitment of participants.

Obtaining clinically sound health outcome data on adult DC people could be achieved via two main methods, which could be categorised as fitting in with gold standard practice. The first

that was considered was to have both donor-conceived and spontaneously conceived adults visit a laboratory/clinic whereby a general health assessment and a variety of tests (e.g. blood tests, glucose tolerance tests, respiratory tests, blood pressure), could be conducted. Additionally, various anthropometric measurements could be taken (e.g. height, weight). Such data would provide a non-biased and standardised approach producing rigorous findings. However, this approach was considered not to be feasible because this would require either a sufficiently large sample size of people in a given community to attend a laboratory/clinic, and or the laboratory would have to go 'on the road' by visiting major cities in an attempt to obtain a large enough sample size. Further issues concerning the recruitment of DC people from a specific community will be described later.

The second approach considered was to obtain patient health data from doctor/physician records. These records would contain data that has been clinically diagnosed by an independent third party. However, the standardisation may not be consistent between physicians in addition to inconsistencies between test data from using different equipment and protocols. Furthermore, those records are subject to doctor-patient confidentiality. An exception would be those records that could be made available through data linkage studies. As there are no data linkage projects currently linking adult health records to the person's mode of conception, this option was also not feasible.

Problematically, neither of the two options described above are feasible for social reasons. Adding to the usual issues of recruiting participants is the issue of low disclosure rates. It is challenging to recruit DC people when the majority are unaware that they were conceived with donated gametes, and subsequently, in these circumstances, any sample cannot be truly representative. While recently reforms have been made regarding disclosure, studies conducted in the period of donor conception practice relevant to potential participants for this study have reported that the majority of DC people were not aware of their donor conception.[740-744]

Non-disclosure is particularly relevant for the older generation of offspring as it was recommended that parents keep it a secret.[745, 746] In a systematic review and meta-analysis, only 21% of donor sperm-conceived children had been told[747] (excluding those planning to tell as intent does not always result in disclosure even when the parents support openness),[748] and only 23% of donor oocyte-conceived children had been told of their conception. More recent studies still suggest that most recipient parents are not disclosing,[749] except for single mothers by choice.[750] Nonetheless, in most cases, disclosure is still not

occurring even in adulthood, as observed in a small Australian study that showed only 11% of DC adults were aware of their method of conception.[751] These factors significantly reduce the potential recruitment pool of DC people in Australia or around the world.

At the 2010 Australian Federal Inquiry into donor conception, it was estimated that there were approximately 20,000-60,000 DC people in Australia,[37] which has been referenced in the literature concerning the numbers of Australian DC people.[12, 752-755] Using the upper bound approximation of 60,000 and the 2,000 per year that was also used to derive that figure, then by the start of this study the maximum potential number of Australian DC people would be 74,000. If the number of children under the age of 18 years is removed from that total (17 years = 34,000), then the recruitment pool drops to 60,000. By using the disclosure rates reported by Tallandini *et al.*, then the approximate recruitment pool available drops down to rounded figures of 8,000 - 9,000 DC people. It was therefore considered highly unlikely that a sufficient sample size of DC people willing to come into a laboratory/clinic could be achieved. By comparison, studies of Australian adults conceived with IVF, from which there is a larger potential pool for recruitment has shown a wide variety of sample sizes obtained from a few (N = 14),[756] to a reasonable sample size (N = 193).[670] Therefore, an alternative approach needed to be taken.

There are numerous online network and support groups, including those on Facebook that either contain DC people only or DC people with recipient parents and donors.[757] It is these online networks that were used as the primary vehicle for advertising a questionnaire that was used to gather self-reported health information. Some of these online networks are specifically for Australians, while others include other countries around the world (worldwide), which allowed the expansion of the potential recruitment pool significantly.

4.2.2 Online Surveys

Online surveys provide a readily accessible platform to administer a questionnaire; however, they are not without drawbacks. For example, in a 2016 meta-analysis of response rates comparing web surveys versus other survey methods, Wengrzik *et al.*, found that web surveys had a 13% lower response rate.[758] While Sue and Ritter state that web-based surveys have an approximate response rate of 30%.[759] With little in the way of current consensus of an acceptable online survey response rate, the figure of 30% may still be representative.

Notwithstanding the response rate problem, Baltar and Brunet stated that snowball sampling using online networks such as Facebook improve response rates over traditional snowballing

techniques due to the trust engendered in the researcher due to their personal information being directly available and due to their presence and interaction in those networks.[760] Of which Adams has a considerable and long-standing presence already. However, in accordance with ethics approval, Adams did not advertise the survey personally, rather administrators of those groups advertised on his behalf to avoid issues of respondents feeling compelled to take part due to pre-existing relationships.

In addition to conducting surveys online, recruitment using online methods are becoming increasingly popular. Online recruitment methodologies, including Facebook, have been argued as a viable methodology to target small, hard to access sub-populations.[761-763] Furthermore it has been stated that Facebook is an effective means of recruiting participants in surveys,[764, 765] that is easy, quick and economical,[766] and that it is also suitable specifically for medical research.[765-768] Any sample obtained from online recruitment, including Facebook, will be a non-probability, convenience sample.

In a discussion on sample size for non-probability samples, it was argued that seldom is there justification of sample sizes that are less than 30 participants or greater than 500,[769, 770] but that in general the larger, the better.[759] It was also argued that within those limits, the sample size should reflect 10% of the parent population. The parent population which is the total number of DC adults in the sampling frame cannot be known due to reasons described in the 'Methods' section and subsequently cannot be used as a means to select the target sample size.

4.2.3 Previous Surveys of Donor-Conceived People

Given that access to physical postal addresses or phone numbers of large numbers of DC people (the sampling frame), is impossible, there was little option but to use online options. Despite limitations, online surveys have been successfully used previously to recruit adult DC people. For example, a 2010 survey of adult DC people from around the world using online support networks for recruitment obtained 85 respondents.[771] No survey timeframe was provided by the authors.

A study showing a smaller response sample size of 29 DC offspring was conducted in 2011, which was restricted to Australian offspring recruited through online forums and email requests.[772] No survey timeframe was provided by the authors for their study either.

Larger cohorts have been achieved by researchers implementing the Donor Sibling Registry (DSR), as a sampling frame.[i] The members of the DSR include recipient parents and donors in addition to DC people of all ages, not just DC adults. The DSR has also been involved in survey research with a 2016 study receiving 419 DC responses, of which 77% were adults (adult n = 323), over 95 days.[773] This highlighted the potential for substantial recruitment to be achieved via online surveys of DC people. That survey was posted on the DSR as well as other online support groups for Single Mothers by Choice, Circle Surrogacy, various Facebook (FB) groups, and in other online facilities such as Craigslist.

A large sample size of donor sperm-conceived adults was obtained by the 'My Daddy's Name is Donor' study.[774] This study has received criticism for among other things; not being published in a peer-reviewed journal, that it did not have Institutional Ethical Board approval for the study, and that the group conducting the research represent a special interest group and therefore may potentially bias any interpretation of the results.[775] Notwithstanding any of these criticisms, the study obtained 562 responses from adult donor sperm-conceived people. This sample size was achieved by sending invitations to 670,524 members of the SSI SurveySpot Web Panel over 18 days. A total of 48,637 people logged into the survey (7.3%), 90.1% of whom were spontaneously conceived, 2.5% adoptees, 1.5% DC people, and 5.9% represented missing/incomplete surveys.

A yearly online survey of DC people has also been conducted on the We Are Donor Conceived website, with further advertising conducted mainly in Facebook groups. The 2017 survey managed to attract 82 responses from DC people over 55 days,[776] the 2018 survey received 127 responses over 57 days,[777] the 2019 survey received 312 responses over 57 days,[778] and the 2020 survey received 481 responses over an undisclosed period.[779] While these surveys show the sample size that is possible through advertising in Facebook groups that are restricted to DC people; it also shows how these groups expand over time[j] with more people taking part in the research.

[i] As of January 15, 2017, the DSR reported that the DSR had 52,833 members. https://donorsiblingregistry.com/ accessed January 15, 2017.
[j] The We Are Donor Conceived survey notes the sizes of each Facebook group which were used to advertise the survey in 2018 but not for 2017, however, these groups have been continually expanding each and every year.

4.2.4 Surveying Adult Donor-Conceived People and DOHaD

While donor sperm was first reported to have been used to create a live birth in 1884,[24] donor oocytes and donor embryos were not implemented until 1984.[26, 27] The number of older donor oocyte and donor embryo adults are thereby considerably less than donor sperm-conceived adults. Nevertheless, even those donor oocyte or donor embryo-conceived people from the earlier period are now in adulthood with some in their early 30s. Subsequently, this study provided an opportunity to assess how all DC people, regardless of treatment type used to conceive them, are faring in terms of their overall health in adulthood.

Returning to the DOHaD phenomenon, a study investigating the adult health outcomes for DC people would enable us to gain some insight as to whether the method of conception (donor gametes/embryos) and any technology used (cryopreservation), has any negative or positive impact on the long-term health of people thus conceived. Without access to a suitable population sampling frame due to low disclosure rates, it is not possible to obtain a representative cross-section of DC adults. However, the use of online platforms for the recruitment of participants of a hard to reach population does provide valuable data. Therefore, this is an exploratory study which can then be used to determine if further studies should be conducted investigating this area.

4.3 Methods

The study was conducted following guidelines contained in the STROBE statement and reported following the STROBE checklist (Appendix 2.3).[687] The method described below pertains to the whole survey, which captured both physical and mental health outcomes.

4.3.1 Ethical Approval

Ethical approval for the study was obtained from the Flinders University Social and Behavioural Research Ethics Committee (reference number: 7827) (Appendix 3.2) and was conducted in accordance with the Declaration of Helsinki (Tokyo revision 2004).[688] This study meets the Australian ethical standards and guidelines of *The National Statement on Ethical Conduct in Human Research*,[780] in accordance with the *National Health and Medical Research Council Act*.[781]

4.3.2 Study Design

As a probability sample is not possible for this study, a convenience sample is sufficient, particularly considering it is an exploratory study. The convenience sample is that of a cross-sectional cohort study design with participants who would remain anonymous.

4.3.3 Setting

The questionnaire was posted online on the SurveyMonkey website (SurveyMonkey Inc., San Mateo, CA, USA), https://www.surveymonkey.com/. It was available to anyone in the world and was completed anonymously. The survey ran for four months between December 1, 2017, until March 31, 2018. The survey became available on December 1, 2017, when the first advertisements were posted. Due to the anonymous nature of the study, no-follow ups to obtain missing data were conducted.

4.3.4 Participants

Adults (individuals aged 18 years and over), who were either donor-conceived or spontaneously conceived from around the world, and who could understand English and had access to the internet were eligible to participate. Participants were self-selected after responding to advertisements seeking respondents as described in the next section 'recruitment'.

A sample size of 30 was described as a minimum sample size by Alreck and Settle,[769] and Hill,[770] would not be appropriate when assessing self-reported incidences of illnesses that would typically have a low incident rate in the general population. Therefore, a target sample size of 100 was selected as one that would be attainable, that fits within the range stated by Sue and Ritter,[759] and that could potentially differentiate self-reporting of more common, rather than rare, illnesses.

4.3.5 Recruitment

A 6-prong recruitment strategy was implemented to obtain a non-probable convenience sample in an attempt to overcome the potential for only obtaining a small sample size. The first strategy targeted existing donor conception networks that had been identified as the primary sampling frame for recruiting DC adult participants. These online support groups with member numbers (as of August 21, 2017) are shown in Table 3.1.

Some of the groups mentioned contain recipient parents, donors, and other interested parties. Subsequently, the exact number of DC people in each of those groups was unknown except

where 'donor-conceived only' was specified. Furthermore, some cross-pollination occurs in those groups where a specific person may belong to multiple groups. The wording of the online support group advertisements is presented in Appendix 3.3.

Table 3.1 Donor conception support groups and numbers of members.

Group Name	Type/Location	Membership
People Conceived Via Artificial Insemination (PCVAI)	Email group	291
Are You Donor Conceived (RUDC)	Facebook	250
Worldwide Donor Conceived People Network	Facebook	224
Donor Conceived Offspring, Siblings, Parents (Sperm or Egg)	Facebook	3766
DNA for the Donor Conceived	Facebook	772
We Are Donor Conceived	Facebook	126
TangledWebs	Facebook	46
Donor Children	Online registry	1343

The memberships of PCVAI; RUDC; Worldwide Donor Conceived People Network; We Are Donor Conceived are exclusively DC people. The memberships of Donor Conceived Offspring, Siblings, Parents (Sperm or Egg); DNA for the Donor Conceived; TangledWebs; Donor Children include DC people, recipient parents, donors and other interested parties.

The second strategy involved targeting DC adults directly through organisations who provide support to DC people and infertile people. These organisations were able to notify members through newsletters, email, and or online, and assist in advertising the study. Organisations approached were:

- VARTA (Victorian Assisted Reproductive Treatment Authority);
- Donor Conception Network (UK);
- Donor Conception Support Group of Australia;
- FIOM - International Social Service (Netherlands);
- VANISH (Victorian Adoption Network for Information and Self Help) - also supports DC people.

Numbers of DC people belonging to each of these organisations could not be determined online; therefore, ascertaining an accurate number of DC people initially targeted via these organisations was impossible. These organisations used the same advertisement as described for the online support groups.

The third strategy was direct advertising on Facebook using Facebook Ads. These advertisements were placed on the Flinders University Facebook page by the Flinders University Office of Communication and Engagement. The advertisements ran from March 9 till March 31, 2018, and were set to target an equal ratio of men and women (50/50) in all

ages above 18 years. Initially, these were restricted to Australia until March 20, when the target audience was expanded to include the United States. The targeting and choice of countries were made to ensure enough spontaneously conceived control cohort people were obtained from those countries. The following images of 'a woman's hands at the keyboard', 'IVF treatment', and 'an embryo sonogram' were chosen by the Flinders University Office of Communication and Engagement to accompany the advertisements (Figures 4.1 – 4.3).

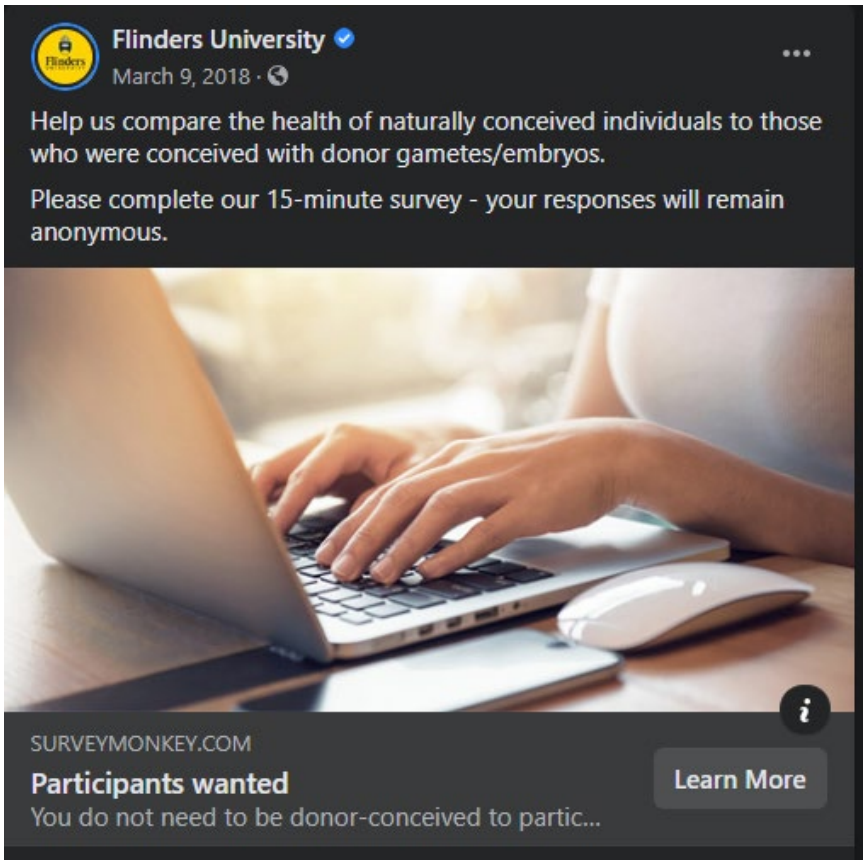

Figure 4.1 Facebook advert of the survey using 'woman's hands at the keyboard' image

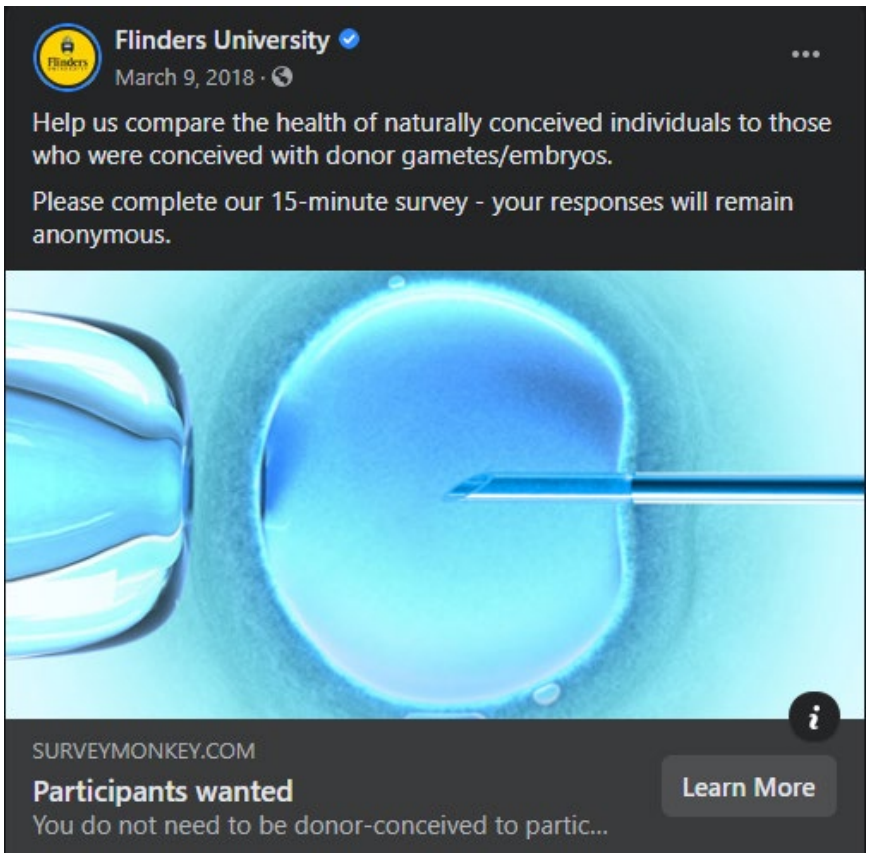

Figure 4.2 Facebook advert of the survey using 'IVF treatment' image

Figure 4.3 Facebook advert of the survey using 'an embryo sonogram' image

The fourth strategy was the placement of an advertisement on the Flinders University 'Participate in research studies' webpage on which the University's investigators (staff and students) can advertise their study to seek participants. This webpage is publicly accessible. This advertisement was live between February 16, 2018, until March 31, 2018.
https://www.flinders.edu.au/research/research-study
The wording for this advertisement fulfilling the University's template is presented in Appendix 3.4.

The fifth strategy was the use of a dedicated online community of people from around the world who participate in surveys hosted by a website-based company called Prolific.
https://prolific.ac/
Marquardt *et al.* reported a similar method of recruiting respondents through a 3rd party.[774] Prolific has been successfully used by researchers at universities such as Harvard, Oxford, Yale, Cambridge and Stanford, and at the time of the survey had 125,915 individuals whom would be eligible to participate, representing a substantial recruitment pool of people that are frequently willing to complete questionnaires. Prolific is a website that enables researchers to obtain participants in surveys from around the world.

Prolific provides demographic screening and uses a micropayment system to reward participants in lieu of their time. They recommend a rate of $6.50 per hour as an ethical reward. For a 15-minute survey, this would equate to $1.63. The researchers can also alter the rate. We felt that an amount equal to $2.50 per 15 minutes would be a more ethical rate while still maintaining that the amount was not coercive or an attraction for respondents to participate for the sake of the financial reward. The wording for the Prolific advertisement is provided in Appendix 3.5.

Prolific advertising started on February 19 and was completed by March 24, 2018. Preliminary data obtained on SurveyMonkey allowed for the targeting of participants based on country of residence in an attempt to reflect the proportions of countries observed in the DC adult respondents that had already completed the survey. Subsequently, the countries of the United Kingdom, the United States, Australia, Belgium, Canada, the Netherlands, and New Zealand were selected as demographics choices for participants as was the minimum age of 18 years. These selections restricted the eligible pool of possible respondents to 23,741 out of 125,915 initially available.

The sixth and final strategy was snowball sampling. Snowball sampling strategies have been described as an effective way of attracting respondents of specifically defined, hard to reach populations,[759, 782] which applies to the DC people sought here. Furthermore, it has been argued that snowballing is an essential strategy to gain an understanding of hidden and hard to reach populations, albeit a non-scientific, non-random understanding.[783]

The details in the advertisement requested that respondents assist in not only recruiting other DC people but also spontaneously conceived people as comparators through snowball sampling by stating in the advertisement; "Please feel free to share the details of the survey, and the link with anyone you feel may be interested in participating." Furthermore, the information sheet that is at the start of the survey on SurveyMonkey also requests assistance by stating; "We also invite participants who are donor-conceived to consider sending the survey off to a friend who is of a similar age so that we may have a large enough sample for comparison. This can be done by cutting and pasting the link to this survey and sending to friends, or by sharing the original message you received regarding this survey (e.g. from a Facebook group)."

In summary, the 6-prong recruitment strategy was:

1) Direct recruitment from online DC support groups;
2) Indirect recruitment through organisations involved in donor conception;
3) Facebook advertising (conducted by the Flinders University Office of Communication and Engagement);
4) Advertising on the Flinders University 'Participate in research studies' webpage;
5) Direct recruitment through survey recruitment website Prolific;
6) Snowballing.

4.3.6 Survey Questionnaire

The questionnaire was based on knowledge of DOHaD outcomes associated with the poor neonatal outcomes observed in the systematic reviews,[1, 4, 275, 655, 656] in combination with health questionnaires used in a variety of situations including health insurance, medical clinics, university's, and professional industry (such as Scuba diving, and Health and Fitness), to cover a wide variety of both physical and mental health outcomes. A list of online resources of health questionnaires used to assist the survey construction is presented in Appendix 3.6.

The survey as presented on SurveyMonkey, including the introduction page, participant information page, agreement to participate and the survey questions are presented in Appendix 3.7.

4.3.7 Outcome Variables

All questions were voluntary except for the compulsory characteristic questions of birth status (whether they were donor-conceived including sperm, oocyte, embryo or surrogacy conceived with donor gametes/embryo or whether they spontaneously conceived – so that they could be allocated to the appropriate cohort), their age, sex, and whether they had received ART treatments themselves.

Respondent characteristics included:
Age - in years;
Sex – male, female, or other;
Multiplicity of their birth – singleton, twin, or higher-order multiple;
Did their mother have maternal complications during pregnancy – yes, no, or don't know;
Did their mother smoke during pregnancy – yes, no, or don't know;
What was their highest level of education attained - less than high school, high school degree or equivalent, vocational qualifications, university/college undergraduate degree, or university/college postgraduate degree;
Height – in cm or feet;
Weight – in kg or lbs or stones;
Are they currently a smoker – yes or no;
Are they a former smoker – yes or no;
How many alcoholic drinks did they consume per week - 0-1, 2-4, 4-10, 10+;
How many times did they undertake low or moderate exercise such as walking per week;
How many times did they undertake high or strenuous exercise such as running per week;
Did they take prescribed medications – yes or no;
Did they take recreational or illicit drugs – yes or no;
Did they receive fertility treatment themselves – yes or no?

4.3.7.1 Physical Health Outcomes Questionnaire

The specific physical health questions encapsulated major health systems. These questions required binary answers of yes or no. Respondents were requested only to report 'yes' to a health condition if they had received a diagnosis from a recognised health professional such as a physician/general practitioner or a specialist. For any health condition that they were unsure of, they were requested to respond with an answer of 'no'. The health systems investigated are listed below. Individual health condition questions are listed in the appropriate tables presented in the results section.

Cardiovascular;
Chromosomal and genetic;
Dermatological;
EENT (ears, eyes, nose and throat);
Endocrinological;
Gastrointestinal;
Immunological;
Musculoskeletal;
Neurological;
Oncological;
Reproductive;
Respiratory;
Urogenital.

For each health system listed, respondents were also provided with the option of voluntarily entering information in a free text box. This free text box sought responses of any health condition that the respondent had been diagnosed with that belonged to that specific health system that was not already present in the survey. The free text box allowed the respondent to provide additional information that they felt may be beneficial that was not asked directly of them or of conditions that were inadvertently omitted.

4.3.7.2 Mental Health Outcomes Questionnaire

The mental health outcomes encapsulated those conditions diagnosed by a mental health professional and their mental health status, which reflected the respondent's own experience. The respondents were requested to respond in the same manner as the physical health outcomes questions in that they were required only to report 'yes' to a question if they had received a diagnosis from a recognised mental health professional such as a psychiatrist or

psychologist. Similarly, for any health condition that they were unsure of, they were requested to respond with an answer of 'no'. For the diagnosed mental health outcome category, a voluntary free text box option could be used to describe any other condition or illness that they may have been diagnosed with that was not covered by the listed conditions or illnesses. Similarly, a free text box option was available to list which mental health professional(s) the respondent had seen as part of the 'own experience' category.

Furthermore, the Depression Anxiety Stress Scale 21 instrument was used (DASS-21),[784] to assess how the respondent was feeling over the previous week. The DASS-21 is unlike all other reported measures which describe the history of the mental health of the respondent. Subsequently, the DASS-21 is more representative of their current mental health status.

4.3.8 Statistical Analysis

Respondents were grouped into the following categories; Spontaneously Conceived, All Donor-Conceived (including donated sperm, oocyte, embryo and or surrogacy), and Donor Sperm-Conceived (donor oocyte, embryo and surrogacy respondents were excluded as a form of sensitivity analysis because they are known to have worse perinatal outcomes than their donor sperm-conceived peers). All statistical analysis was performed using IBM SPSS® Statistics V25. (IBM Corporation, New York, USA). All analyses were comparisons between either of the two DC cohorts and the spontaneously conceived cohort. Except for validation analysis that was conducted comparing the spontaneously conceived cohort to relevant reference data as described later.

Due to the low number of respondents received in the donor oocyte, donor embryo and surrogacy conceptions, further stratification of the donor sperm-conceived cohort only were conducted to enable separate analyses of the effect of sex, maternal complications, and country of birth on health outcome measures. The country of birth stratification was restricted to those born in Australia because Australians represented the largest sample of both donor sperm-conceived as well as spontaneously conceived adults.

Variables of height and weight were converted to centimetres and kilograms respectively for accurate comparison. Continuous variables of age, height, weight and BMI (body mass index) were summarised using their means and standard deviation (SD). These continuous variables were subjected to a two-tailed, Student's t-test to determine significance. Binomial outcomes of yes/no answers are reported as the total numbers of yes responses along with the total number of responses received for each question and then expressed as a percentage. These

were subjected to a two-tailed Pearson's chi-squared analysis using Phi and Cramer's V nominal association. Cross-tabulation of outcomes involving more than two outcomes were also subjected to a two-tailed Pearson's chi-squared analysis using Phi and Cramer's V nominal association. However, when cross-tabulation produced > 20% of cells with an expected count of less than 5, then a two-tailed Fisher's Exact Test was implemented for 2x2 tables, and two-tailed Likelihood Ratios were used for tables larger than 2x2 to determine significance.

Free text input in each health system allowed respondents to report diagnoses of other conditions not covered by the questionnaire. When free text input received greater than or equal to 20 responses for the DC cohort, these responses were then subjected to quantitative content analysis.[785] Themes were identified in the responses, which were then used to code and group the reported conditions. Where appropriate these were then collapsed and combined to form three of four main thematic groups which were subjected to a two-tailed Pearson's chi-squared analysis using Phi and Cramer's V nominal association and two-tailed Likelihood Ratios in the instance of > 20% of cells with an expected count of less than 5.

Analysis of DASS-21 results implemented means and SD, which were subjected to two-tailed, Student's t-test to determine significance.

This survey is relatively large in terms of the number of health questions that are being asked. Statistically, in any large study that has numerous comparisons such as this, inevitably, there will be some outcome analysis that will be statistically significant, which is caused by sample variability and chance. In effect, some of these positive associations may be false positives. There are several methods to correct for false positives with one of the most common being the Bonferroni correction.[786] However, this method is conservative due to its methodology, which becomes problematic as the number of comparisons increase and may also introduce false negatives.[787] A more powerful and sensitive alternative is the implementation of a false discovery rate which is recommended in preference to multiple correction methods such as the Bonferroni correction, particularly in the analysis of health studies.[788] For this study, the Benjamini-Hochberg (BH) procedure was implemented to correct for false discovery as it has been widely used in multiple comparisons and is also recommended in health studies in preference to the Bonferroni method.[789] A false discovery rate at the alpha 0.05 level was implemented in the BH adjustment.[790] Results were determined to be significant if $p < 0.05$.

Benjamini-Hochberg correction was not applied to the characteristics of respondents. It was also not applied to the DASS-21 analysis as this is a separate analytical instrument which is typically only assessed through the Student's t-test. Nor was it applied to the quantitative content analysis because these responses were grouped post-hoc rather than being specific questions that could be answered directly by the respondent.

Considering that the spontaneously conceived adult cohort is the comparison cohort from which DC adult outcomes are deemed to either be significantly different or not, it is important to investigate how representative this sample was regarding the frequencies of reported conditions. This determination was achieved through two analyses. Firstly, the Australian spontaneously conceived cohort was stratified then compared to equivalent health outcome frequencies that are publicly available from the Australian Bureau of Statistics, National Health Survey (ABS NHS).[791] The ABS NHS data dated 2017-2018 was used as the comparison as this corresponds to the census date of this survey. No comparable worldwide health frequency data exists for comparison that would encapsulate the countries and ethnicities observed in the worldwide spontaneously conceived cohort precisely. However, the worldwide spontaneously conceived cohort was compared to equivalent data that is also publicly available from the Centers for Disease Control and Prevention, National Health and Nutrition Examination Survey (CDC NHANES).[792] The CDC NHAES data from the same period 2017-2018 was also used for this analysis.

4.4 Survey Results

The total number of respondents was 1233. The number of respondents excluded because they chose not to take part was 19. The number of respondents who agreed to participate but did not answer the compulsory question on their mode of conception and was subsequently excluded was 53. A further two respondents were excluded due to the following reasons. One responded yes to almost every malady including all but one cancer which is not possible. The other respondent described that they included data for both the husband and wife.

After exclusions, the final sample consisted of 1159 respondents. By mode of conception the number of respondents were as follows: Spontaneous (n = 877), All Donor-Conceived (n = 282), Donor Sperm-Conceived (n = 272), Donor Oocyte-Conceived (n = 5), Donor Embryo-Conceived (n = 3), Surrogacy (n = 2). Those who were gestated with surrogacy were conceived with donated oocytes/embryos and were not conceived using the surrogate's own oocytes. Due to the low numbers of respondents who were conceived with donated oocytes,

embryos or surrogacy with donated gametes/embryos, these groups were not analysed separately. Rather they are only included as part of the all donor-conceived group to see if they influenced outcomes due to the higher risk for adverse neonatal outcomes observed in the systematic reviews and meta-analysis, and also for completeness.

The average amount of time taken to complete the survey was 10 minutes and 17 seconds. The completion rate was 78%, which reflects the number of respondents completing the survey as a function of the total number of people entering the survey on the SurveyMonkey website. It is not possible to calculate a response rate because the number of people viewing the advertisement is unknown. Furthermore, the number of DC adults around the world, let alone in each country is also unknown.

Facebook advertising reached a total of 26,280 people with a total of 1,262 clicks, of which greater than 90% were women in all ages above 25 years. The clicks per image are as follows 'a woman's hands at the keyboard' = 127, 'IVF treatment' = 354, and 'an embryo sonogram' = 781 clicks.

Three additional donor sperm-conceived adults were obtained through the Prolific advertising, out of a total of 299 respondents completing the survey through that site. Data determining the number of additional DC respondents was possible due to the use of a different collector on SurveyMonkey as links back to Prolific was required at the end of the survey to enable Prolific participants to receive their micropayment. The number of DC adults sourced from advertising external to the social media groups specifically for donor conception is unknown as separate collectors were not created for each advertising campaign, only for Prolific.

No negative messages or emails about the content of the survey were received from respondents. Three Prolific respondents reported problems with the completion code that provided them with the ability to claim their micropayment, which was rectified on the Prolific website. Another Prolific respondent reported an error with SurveyMonkey, which prevented them from completing the survey, which was a temporary issue associated with SurveyMonkey. While another Prolific respondent sent a message reporting how much they enjoyed the survey and that they felt that it was well constructed.[k]

[k] A Prolific respondent sent the following deidentified message: "Thank you for the considerable thought and effort which you have clearly expended in creating a Study with such an exceptionally well-designed User Interface.

4.4.1 Characteristics of Respondents

Participant characteristics as stratified by conception group is presented in Table 3.2. Both donor conception groups (all and sperm), were matched with those conceived spontaneously in terms of their general characteristics of the mean age in years, sex as designated by the participant (male, female or other), mean height, whether they smoke cigarettes/tobacco or cigars currently, the number of alcoholic drinks they consume per week, the amount of low or moderate level exercise they undertake per week such as walking, the amount of high or strenuous exercise they undertake per week such as running, and the incidence of fertility treatment they had received themselves. They were, however, significantly different to those conceived spontaneously in terms of having a lower BMI (all $p = 0.040$; sperm $p = 0.023$), while the donor sperm-conceived adults only also had a lower mean weight ($p = 0.035$). Both DC adult groups had higher levels of education, in particular, post-graduate qualifications from universities and colleges than those conceived spontaneously (all $p < 0.001$; sperm $p < 0.001$). They were also significantly more likely to be currently taking both prescribed medications (all $p = 0.002$; sperm $p = 0.002$), as well as recreational or illicit drugs (all $p = 0.027$; sperm $p = 0.047$). Only donor sperm-conceived adults were more likely to report being a former smoker ($p = 0.032$).

The gestational and birth characteristics of the participants showed that both DC cohorts were significantly more likely to be born as a twin (all $p = 0.001$; sperm $p = 0.004$). They also reported that their mothers were significantly more likely to have suffered maternal complications of pregnancy (all $p < 0.001$; sperm $p = 0.001$). Both donor and spontaneously conceived cohorts were matched for the self-reported incidences of their mothers smoking during the pregnancy involving their birth.

The countries of birth and countries of residence data exhibited considerable variation between the proportions of both donor and spontaneously conceived adults particularly for the five countries with the largest number of participants (n > 20 = Australia, Belgium, the Netherlands, the United Kingdom, the United States) (Table 3.3). The countries of Belgium, the Netherlands and the United States exhibited higher proportions of participants who were donor-conceived, while Australia and the United Kingdom exhibited higher proportions of participants who were spontaneously conceived. The complete descriptive table showing all

In particular, I felt that the explanatory Notes at the beginning were especially clear and informative. This is an area which can often be regarded as being little more than peripheral to the Study itself and thus given little thought. The entire Study is undoubtedly a credit to you."

countries of birth and residence is presented in Appendix 3.8, in which all other countries had less than 10 participants in each cohort.

Table 3.2 Characteristics of respondents

	Spontaneous	All Donor-Conceived		Donor Sperm-Conceived	
	n Total [877]	n Total [282]	*p*	n Total [272]	*p*
Age, Mean (SD)	33.2 (12.5)	32.2 (10.3)	0.177	32.6 (10.3)	0.395
Sex, %			0.081*		0.074*
Female	80.8	85.8		86.0	
Male	18.8	14.2		14.0	
Other	0.3	0		0	
Multiplicity of Own Birth, %			**0.001***		**0.004***
Singleton	98.5	94.7		95.2	
Twin	1.0	5.0		4.4	
Multiple (3 or more)	0.5	0.4		0.4	
Mother Had Maternal Complications, %			**< 0.001#**		**0.001#**
Yes	12.6	17.4		17.3	
No	75.0	63.0		63.1	
Don't know	12.4	19.6		19.6	
Mother Smoked During Pregnancy, %			0.552#		0.598#
Yes	16.0	15.2		15.1	
No	79.0	81.2		81.2	
Don't know	5.0	3.5		3.7	
Highest Level of Education Attained, %			**< 0.001#**		**< 0.001#**
Less than high school	2.5	3.2		2.6	
High school degree or equivalent	27.1	17.0		16.5	
Vocational qualifications	11.4	7.8		8.1	
University/College undergraduate degree	39.0	41.5		41.2	
University/College postgraduate degree	20	30.5		31.6	
Height, Mean cm (SD)	168.8 (9.2)	169.0 (9.3)	0.695	169.0 (9.3)	0.724
Weight, Mean kg (SD)	74.7 (18.6)	72.3 (17.6)	0.063	72.0 (17.4)	**0.035**
BMI, Mean (SD)	26.2 (6.4)	25.3 (6.0)	**0.040**	25.2 (6.0)	**0.023**
Currently Smoke, %	7.9	9.4	0.432	9.4	0.455
Former Smoker, %	30.0	23.8	0.058	22.9	**0.032**
Alcoholic Drinks Consumed Per Wk			0.637#		0.758#
0-1	62.7	59.8		60.3	
2-4	20.8	24.4		23.7	
4-10	13.0	12.0		12.1	
10+	3.5	3.8		3.9	
Low/Mod Exercise Per Wk, Mean (SD)	4.7 (5.0)	4.8 (4.3)	0.869	4.9 (4.3)	0.720
High/Stren Exercise Per Wk, Mean (SD)	1.4 (1.9)	1.3 (1.6)	0.504	1.3 (1.6)	0.546
Prescribed Medications, %	39.1	49.6	**0.002**	49.8	**0.002**
Recreational/Illicit Drugs, %	6.8	10.9	**0.027**	10.5	**0.047**
Fertility Treatment Themselves, %	6.7	3.7	0.075	3.9	0.094

[ ] = Total respondents.

p value using Students two-tailed TTEST versus spontaneously conceived unless specified by alternative test below.

= Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived.

* = Likelihood Ratio *p* value versus spontaneously conceived people used instead of Fisher's Exact Test for when > 20% of cells in chi-squared table have expected values less than 5 in Tables larger than 2x2.

Note, percentages may not equal 100% due to rounding.

Table 3.3 Countries of birth and residency (top 5 countries by number of participants)

	Spontaneous				All Donor-Conceived				Donor Sperm-Conceived			
	Birth n	Birth %	Resid. n	Resid. %	Birth n	Birth %	Resid. n	Resid. %	Birth n	Birth %	Resid. n	Resid. %
Australia	372	46.3	490	55.9	82	31.1	89	31.6	78	30.7	85	31.3
Belgium	23	2.9	21	2.4	16	6.1	19	6.7	16	6.3	19	7
Netherlands	89	11.1	70	8	58	22	60	21.3	57	22.4	59	21.7
United Kingdom	190	23.7	186	21.2	17	6.4	18	6.4	16	6.3	17	6.3
United States	86	10.7	90	10.3	81	30.7	88	31.2	77	30.3	84	30.9

Descriptive table of the respondent's country of birth and current residence.

4.5 Physical Health Outcomes Results

All positive self-reported physical health outcome responses were requested to have been of only those conditions that had been diagnosed by a medical professional such as a general practitioner or specialist. Those conditions in which no statistically significant differences were observed are also listed in the text and footnotes to provide greater detail about each condition and because non-significantly different findings are equally relevant as those that are significantly different.

4.5.1 Cardiovascular Outcomes

No significant differences were observed between both donor-conceived groups (all and sperm) and those adults conceived spontaneously for all self-reported incidences of diagnoses of various cardiovascular outcomes (Table 3.4). These cardiovascular outcomes included congenital heart disease, cardiovascular disease, bleeding disorders, heart murmur, palpitations, high blood pressure, low blood pressure, anaemia, poor peripheral circulation, high cholesterol, aneurysms, phlebitis, varicose veins, heart defects requiring surgery and other cardiovascular conditions, as described by the respondent.[1]

4.5.2 Chromosomal and Genetic Outcomes

Both DC groups self-reported no significant differences in the incidences of chromosomal or genetic abnormalities compared to those conceived spontaneously (Table 3.5).

[1] Further information pertaining to the cardiovascular conditions are as follows. Congenital heart disease includes abnormality of the heart that developed before birth. Cardiovascular disease includes the following conditions of angina, aneurysm, arteriosclerosis, atherosclerosis, cardiomyopathy, cerebrovascular disease, deep vein thrombosis, heart attack, peripheral arterial disease, rheumatic heart disease, and stroke. Bleeding disorders such as haemophilia. Heart murmurs are irregular sounds from blood flow of the heart. Palpitations are sensation of irregular, racing or pounding heartbeat. High blood pressure was described as pressure over 140/90 - either or both reading(s) could be higher. Low blood pressure was described as pressure below 90/60 - either or both reading(s) could be lower). Anaemia is the reductiobn in red blood cells. Poor peripheral circulation may include white/blue fingers and or toes (e.g. Raynaud's syndrome). Aneurysms is the abnormal swelling of blood vessels. Phlebitis is inflammation of the veins. Varicose veins are swollen veins just under the skin.

Table 3.4 Cardiovascular outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Congenital Heart Disease	7 (820)	0.9	1 (253)	0.4	0.689^	1.000	1 (245)	0.4	0.690^	0.976
Cardiovascular Disease	18 (819)	2.2	1 (253)	0.4	0.059^	0.290	1 (245)	0.4	0.094^	0.411
Bleeding Disorders	5 (824)	0.6	3 (252)	1.2	0.399^	0.773	2 (244)	0.8	0.662^	0.969
Heart Murmur	46 (820)	5.6	16 (251)	6.4	0.650	1.000	16 (243)	6.6	0.569	0.899
Palpitations	88 (818)	10.8	34 (250)	13.6	0.216	0.634	34 (242)	14.0	0.159	0.543
High Blood Pressure	86 (821)	10.5	18 (252)	7.1	0.118	0.454	18 (244)	7.4	0.152	0.534
Low Blood Pressure	123 (821)	15.0	40 (251)	15.9	0.712	1.000	40 (243)	16.5	0.574	0.899
Anaemia	227 (822)	27.6	64 (253)	25.3	0.468	0.822	60 (245)	24.5	0.333	0.746
Poor Peripheral Circulation	38 (823)	4.6	15 (253)	5.9	0.399	0.773	15 (245)	6.1	0.341	0.746
High Cholesterol	72 (820)	8.8	23 (252)	9.1	0.866	1.000	23 (244)	9.4	0.756	1.000
Aneurysm	2 (819)	0.2	0 (251)	0	1.000^	1.000	0 (243)	0	1.000^	1.000
Phlebitis	2 (820)	0.2	1 (252)	0.4	0.553^	0.907	1 (244)	0.4	0.543^	0.899
Varicose Veins	62 (822)	7.5	15 (253)	5.9	0.384	0.773	15 (245)	6.1	0.451	0.853
Heart Defect Surgery	6 (821)	0.7	2 (251)	0.8	1.000^	1.000	2 (243)	0.8	1.000^	1.000
Other	25 (818)	3.1	9 (252)	3.6	0.684	1.000	9 (244)	3.7	0.622	0.925

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table 3.5 Chromosomal and genetic outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Chromosomal or Genetic Abnormality	20 (839)	2.4	10 (261)	3.8	0.210	0.634	9 (252)	3.6	0.304	0.746

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people.

4.5.3 Dermatological Outcomes

Both donor-conceived groups were not more likely to self-report increased incidences of being diagnosed with various dermatological conditions than those conceived spontaneously (Table 3.6). These dermatological outcomes included eczema, psoriasis, urticaria and other dermatological conditions, as described by the respondent.[m]

Greater than 20 donor-conceived respondents submitted information on 'other' conditions that they had been diagnosed, and subsequently, these responses were subjected to quantitative content analysis. Responses were able to be grouped into the four categories of acne, colouring, infections and ungrouped conditions.[n] No significant differences were observed between both donor-conceived groups and those conceived spontaneously in terms of the incidences of being diagnosed with various dermatological conditions other than eczema, psoriasis and urticaria.

4.5.4 Ears Eyes Nose Throat (EENT) Outcomes

Both DC groups were significantly more likely to self-report than those conceived spontaneously of having undergone a surgical procedure to have ear tubes or grommets implanted (all 11.3% v 6.1%, $p = 0.041$; sperm 11.3% v 6.1%, $p = 0.046$) (Table 3.7). They were, however, not more likely to self-report being diagnosed with the other EENT conditions of eye disorders, corrective glasses or lenses, requiring eye surgery, hearing loss, total deafness, nasal allergies or hayfever, tonsils surgically removed, adenoids surgically removed, tinnitus, Meniere's disease and other EENT conditions, as described by the respondent.[o]

[m] Further information pertaining to the dermatological conditions are as follows. Eczema is a condition characterised by itchy and inflamed skin. Psoriasis is a condition characterised by scaly, itchy and dry skin. Urticaria is also known as hives, which is a skin rash.

[n] Further information pertaining to the 'other' dermatological conditions that were subjected to quantitative content analysis are as follows. The group titled 'acne' also included other conditions such as eccrine hidrocystoma, hidradenitis suppurativa, and hormonal cysts. The group titled 'colouring' included conditions that change the colour of the skin such as dermatitis, Henoch-Schonlein purpura, pityriasis rosea, rosacea, and vitiligo. The group titled 'infections' included conditions involving bacterial, fungal or viral infections including but not limited to cellulitis, impetigo, shingles, and tinea versicolour. The group titled 'ungrouped conditions' included all conditions that could not be placed into the three previously described categories.

[o] Further information pertaining to the EENT conditions are as follows. Eye disorders included conditions such as glaucoma and cataracts but excluding glasses or contact lenses. Tinnitus is a condition characterised by ringing or buzzing noises in the ear. Meniere's disease is an inner ear disorder characterised by hearing loss, vertigo and or tinnitus.

Table 3.6 Dermatological outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Eczema	200 (833)	24.0	68 (258)	26.4	0.444	0.803	64 (249)	25.7	0.585	0.899
Psoriasis	53 (829)	6.4	22 (257)	8.6	0.231	0.634	20 (248)	8.1	0.358	0.746
Urticaria	76 (831)	9.1	33 (255)	12.9	0.078	0.355	32 (246)	13.0	0.076	0.360
Other[#]	64 (820)	7.8	28 (254)	12.4	0.109	0.436	27 (246)	11.0	0.119	0.444
Acne	18 (820)	2.2	11 (254)	4.3	0.067	-	11 (246)	4.5	0.054	-
Colouring	37 (820)	4.5	14 (254)	5.5	0.513	-	13 (246)	5.3	0.615	-
Infections	6 (820)	0.7	1 (254)	0.4	1.000^	-	1 (246)	0.4	1.000^	-
Ungrouped	4 (820)	0.5	1 (254)	0.4	1.000^	-	1 (246)	0.4	1.000^	-

[#] = Other conditions not classified which were then subjected to quantitative content analysis which is reported below the dashed line.

Acne = also includes other conditions such as hormonal cysts, hidradenitis suppurativa, and eccrine hidrocystoma. Colouring = includes conditions that change the colour of the skin such as rosacea, dermatitis, pityriasis rosea, Henoch-Schonlein purpura, and vitiligo. Infections = includes conditions involving bacterial, viral or fungal infections of the skin such as impetigo, cellulitis, shingles, and tinea versicolour. Ungrouped = all other conditions not grouped into the above categories.

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people.

BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. BH correction not performed on content analysis.

^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table 3.7 EENT outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Eye Disorders	34 (832)	4.1	9 (259)	3.5	0.659	1.000	9 (250)	3.6	0.730	1.000
Corrective Glasses/Lenses	481 (831)	57.9	152 (258)	58.9	0.769	1.000	146 (249)	58.6	0.833	1.000
Eye Surgery	20 (827)	2.4	4 (255)	1.6	0.421	0.773	4 (246)	1.6	0.461	0.859
Hearing Loss	49 (831)	5.9	19 (259)	7.3	0.403	0.773	19 (250)	7.6	0.331	0.746
Deafness (total)	1 (826)	0.1	0 (257)	0	1.000^	1.000	0 (248)	0	1.000^	1.000
Nasal Allergies/Hayfever	327 (832)	39.3	121 (257)	47.1	0.027	0.158	115 (248)	46.4	0.047	0.241
Tonsilectomy	132 (830)	15.9	44 (256)	17.2	0.626	0.993	42 (248)	16.9	0.698	0.976
Ear Tubes/Grommets	51 (830)	6.1	29 (256)	11.3	0.006	**0.041***	28 (247)	11.3	0.006	**0.046***
Adenoidectomy	50 (830)	6.0	26 (257)	10.1	0.025	0.154	26 (248)	10.5	0.016	0.104
Tinnitus	70 (831)	8.4	29 (257)	11.3	0.163	0.557	29 (248)	11.7	0.117	0.444
Meniere's Disease	3 (829)	0.4	3 (258)	1.2	0.149^	0.524	3 (249)	1.2	0.140^	0.506
Other	35 (829)	4.2	14 (257)	5.4	0.408	0.773	12 (248)	4.8	0.677	0.976

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

4.5.5 Endocrinological Outcomes

Both DC groups were significantly more likely to self-report being diagnosed with type 1 diabetes (juvenile diabetes (all 3.1% v 0.4%, $p = 0.013$; sperm 2.8% v 0.4%, $p = 0.031$)), and thyroid disease (including conditions such as hyper or hypothyroidism, goiter, nodules, thyroiditis (all 8.8% v 3.9%, $p = 0.022$; sperm 8.7% v 3.9%, $p = 0.031$)) (Table 3.8), than those conceived spontaneously. They were not, however, more likely to self-report being diagnosed with the other endocrinological conditions of type 2 diabetes, pancreatitis, adrenal disorders, pituitary disorders and other endocrinological conditions, as described by the respondent.[p]

4.5.6 Gastrointestinal Outcomes

No significant differences were observed between both DC groups, and those adults conceived spontaneously for all self-reported incidences of diagnoses of various gastrointestinal conditions (Table 3.9). These gastrointestinal conditions included liver disease, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), ulcers, Coeliac disease, appendicitis, gall bladder problems, gastroesophageal reflux disease (GERD) and other gastrointestinal conditions, as described by the respondent.[q]

[p] Further information pertaining to the endocrinological conditions are as follows. Type 2 diabetes is adult-onset diabetes. Pancreatitis is inflammation of the pancreas. Adrenal disorders included consitions such as Addison's disease, Cushing's syndrome, congenital adrenal hyperplasia, pituitary tumours, pheochromocytoma, paraganglioma.
[q] Further information pertaining to the gastrointestinal conditions are as follows. Liver disease included conditions such as cirrhosis, hemochromatosis and fatty liver disease. Irritable bowel syndrome (IBS) is an intestinal disorder causing pain, wind, constipation and diarrhoea. Inflammatory bowel disease (IBD) included Crohn's disease and ulcerative colitis. Ulcers included stomach, gastric and or duodenal ulcers. Coeliac disease is an immune reaction to gluten. Appendicitis is inflammation of the appendix. Gastroesophageal reflux disease (GERD) is acid reflux/heartburn.

Table 3.8 Endocrinological outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Type 1 Diabetes	3 (842)	0.4	8 (262)	3.1	0.001^	**0.013***	7 (253)	2.8	0.002^	**0.031***
Type 2 Diabetes	21 (842)	2.5	1 (260)	0.4	0.034	0.190	1 (251)	0.4	0.038	0.212
Pancreatitis	5 (841)	0.6	1 (260)	0.4	1.000^	1.000	1 (251)	0.4	1.000^	1.000
Adrenal Disorders	9 (841)	1.1	2 (262)	0.8	1.000^	1.000	2 (253)	0.8	1.000^	1.000
Thyroid Disease	33 (840)	3.9	23 (262)	8.8	0.002	**0.022***	22 (253)	8.7	0.002	**0.031***
Pituitary Disorders	7 (841)	0.8	4 (260)	1.5	0.299^	0.766	4 (251)	1.6	0.288^	0.746
Other	18 (840)	2.1	9 (259)	3.5	0.226	0.634	9 (250)	3.6	0.193	0.593

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table 3.9 Gastrointestinal outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Liver Disease	13 (842)	1.5	9 (260)	3.5	0.053	0.272	9 (251)	3.6	0.043*	0.230
IBS	108 (842)	12.8	36 (261)	13.8	0.686	1.000	36 (252)	14.3	0.548	0.899
IBD	15 (840)	1.8	8 (259)	3.1	0.200	0.631	8 (250)	3.2	0.172	0.560
Ulcers	26 (841)	3.1	5 (261)	1.9	0.316	0.773	5 (252)	2.0	0.353	0.746
Coeliac	20 (837)	2.4	3 (261)	1.1	0.222	0.634	3 (252)	1.2	0.246	0.672
Appendicitis	63 (843)	7.5	21 (261)	8.0	0.760	1.000	20 (252)	7.9	0.807	1.000
Gall Bladder	47 (841)	5.6	12 (261)	4.6	0.534	0.898	12 (252)	4.8	0.610	0.925
GERD	106 (840)	12.6	31 (262)	11.8	0.736	1.000	29 (253)	11.5	0.624	0.925
Other	24 (841)	2.9	9 (262)	3.4	0.630	0.993	9 (253)	3.6	0.566	0.899

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people.

4.5.7 Immunological Outcomes

Both DC groups were significantly more likely to self-report being diagnosed with being allergic to anything (all 45.5% v 36.0%, $p = 0.041$; sperm 45.6% v 36.0%, $p = 0.046$), and Hashimoto's disease (autoimmune disease of the thyroid (all 3.9% v 0.8%, $p = 0.022$; sperm 4.0% v 0.8%, $p = 0.029$)), in comparison to adults conceived spontaneously (Table 3.10).

No significant differences were observed between both DC groups and those adults conceived spontaneously for all self-reported incidences of diagnoses of the remaining immunological conditions. These immunological conditions included arthritis, rheumatoid arthritis, spleen problems, gout, lupus, ankylosing spondylitis, connective tissue disorders, chronic infectious disease and other immunological conditions, as described by the respondent.[r]

Greater than 20 DC respondents submitted information on specific allergy diagnosis in a free text input, and subsequently, these responses were subjected to quantitative content analysis. Responses were able to be grouped into the four groups of environmental allergies, ingested allergies, medication allergies and ungrouped allergies.[s] Both DC groups were significantly more likely to self-report being diagnosed with an allergy to environmental allergens (all 29.6% v 16.7%, $p < 0.001$; sperm 29.4% v 16.7%, $p < 0.001$), than those conceived spontaneously (Table 3.10). They were however not more likely to self-report being allergic to ingested, medication or ungrouped allergens.

[r] Further information pertaining to the immunological conditions are as follows. Arthritis is an inflammatory condition of the joints causing pain. Rheumatoid arthritis is an autoimmune form of arthritis in which the joints are attacked by the immune system. Gout is an arthritic condition caused by uric acid crystals in the joints. Lupus is an autoimmune condition where the immune system attacks the person's own body. Ankylosing spondylitis is a condition characterised by inflammation of the spine often leading to fused vertebrae and a hunched back. Connective tissue disorders included Sjorgen's syndrome. Chronic infectious disease could include any chronic infectious disease.

[s] Further information pertaining to the 'other' immunological conditions that were subjected to quantitative content analysis are as follows. Environmental allergies included contact allergies to antigens from sources such as animals, cosmetics, latex, plants/pollen and moulds. Ingested allergies included all food type allergies except for medications. Medication allergies could include medications that were ingested, intravenous or applied topically. Ungrouped allergies included all other allergies not covered by the three categories as described earlier and included allergies to insect bites and stings.

Table 3.10 Immunological outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Arthritis	65 (829)	7.8	20 (256)	7.8	0.988	1.000	20 (248)	8.1	0.909	1.000
Rheumatoid Arthritis	18 (829)	2.2	7 (256)	2.7	0.600	0.971	7 (247)	2.8	0.544	0.899
Spleen Problems	1 (828)	0.1	1 (256)	0.4	0.417^	0.773	1 (248)	0.4	0.408^	0.797
Gout	10 (830)	1.2	2 (257)	0.8	0.742^	1.000	2 (248)	0.8	1.000^	1.000
Lupus	3 (830)	0.4	2 (256)	0.8	0.337^	0.773	2 (247)	0.8	0.324^	0.746
Ankylosing Spondylitis	3 (830)	0.4	1 (256)	0.4	1.000^	1.000	1 (247)	0.4	1.000^	1.000
Hashimoto's Disease	7 (828)	0.8	10 (256)	3.9	0.002^	**0.022***	10 (247)	4.0	0.001^	**0.029***
Connective Tissue Disorders	10 (822)	1.2	4 (255)	1.6	0.751^	1.000	4 (247)	1.6	0.541^	0.899
Allergic to Anything[#]	297 (826)	36.0	117 (257)	45.5	0.006	**0.041***	113 (248)	45.6	0.006	**0.046***
Chronic Infectious Disease	16 (826)	1.9	8 (255)	3.1	0.256	0.670	8 (246)	3.3	0.221	0.618
Other	18 (827)	2.2	8 (257)	3.1	0.392	0.773	8 (248)	3.2	0.345	0.746
Environmental	138 (827)	16.7	76 (257)	29.6	<0.001*	-	73 (248)	29.4	<0.001*	-
Ingested	82 (827)	9.9	34 (257)	13.2	0.133	-	32 (248)	12.9	0.180	-
Medication	111 (827)	13.4	31 (257)	12.1	0.573	-	29 (248)	11.7	0.478	-
Ungrouped	24 (827)	2.9	4 (257)	1.6	0.235	-	4 (248)	1.6	0.264	-

[#] = Allergies which had free text input and were then subjected to quantitative content analysis which is reported below the dashed line. Environmental = contact allergies such as animals, plants, pollen, cosmetics, mould, latex. Ingested = food type allergies (medication excluded). Medication = such as antibiotics (can be ingested, topical or intravenous). Ungrouped = other allergies not covered by the above categories such as insect bites and stings. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. BH correction not performed on content analysis. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

4.5.8 Musculoskeletal Outcomes

No significant differences were observed between both DC groups and those adults conceived spontaneously for all self-reported incidences of diagnoses of various musculoskeletal conditions (Table 3.11). These musculoskeletal conditions included joint problems, osteoporosis, scoliosis, growth disorder, muscular dystrophy and other musculoskeletal conditions, as described by the respondent.[t]

4.5.9 Neurological Outcomes

No significant differences were observed between both DC groups and those adults conceived spontaneously for all self-reported incidences of diagnoses of various neurological conditions (Table 3.12). These neurological conditions included epilepsy, migraines, multiple sclerosis, vertigo, cerebral palsy, fibromyalgia, Parkinson's disease and other neurological conditions, as described by the respondent.[u]

[t] Further information pertaining to the musculoskeletal conditions are as follows. Osteoporosis is a condition characterised by weak and brittle bones. Scoliosis is a condition characterised by abnormal curvature of the spine. Growth disorder included being excessively short or tall, i.e. dwarfism or gigantism. Muscular dystrophy is a group of inherited diseases leading to increasing weakness and loss of muscle mass and function.

[u] Further information pertaining to the neurological conditions are as follows. Epilepsy also included more generalised seizures. Tremors is a condition characterised by involuntary shaking. Migraines are debilitating headaches which can be associated with nausea and or light/sound sensitivity. Multiple sclerosis is a chronic disease affecting the myelin covering of nerves. Vertigo is a condition characterised by dizziness. Cerebral palsy is a permanent movement disorder. Fibromyalgia is a condition associated with muscle tenderness and pain, fatigue and altered sleep. Parkinson's disease is a progressive nervous system disorder adversely affecting movement and causing tremors.

Table 3.11 Musculoskeletal outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Joint Problems	135 (830)	16.3	56 (258)	21.7	0.045	0.241	55 (249)	22.1	0.034	0.199
Osteoporosis	9 (830)	1.1	3 (256)	1.2	1.000^	1.000	3 (247)	1.2	0.743^	1.000
Scoliosis	67 (827)	8.1	27 (257)	10.5	0.232	0.634	27 (248)	10.9	0.173	0.560
Growth Disorder	0 (830)	0	0 (258)	0	n/a	n/a	0 (249)	0	n/a	n/a
Muscular Dystrophy	3 (827)	0.4	0 (257)	0	1.000^	1.000	0 (248)	0	1.000^	1.000
Other	47 (818)	5.7	15 (255)	5.9	0.935	1.000	15 (246)	6.1	0.836	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table 3.12 Neurological outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Epilepsy/Seizures	26 (838)	3.1	6 (260)	2.3	0.506	0.877	6 (251)	2.4	0.558	0.899
Tremors	19 (839)	2.3	6 (262)	2.3	0.981	1.000	6 (253)	2.4	0.921	1.000
Migraines	232 (836)	27.8	75 (260)	28.8	0.731	1.000	71 (251)	28.3	0.868	1.000
Multiple Sclerosis	3 (834)	0.4	1 (261)	0.4	1.000^	1.000	0 (253)	0	1.000^	1.000
Vertigo	82 (839)	9.8	26 (261)	10.0	0.929	1.000	25 (252)	9.9	0.945	1.000
Cerebral Palsy	1 (836)	0.1	0 (261)	0	1.000^	1.000	0 (252)	0	1.000^	1.000
Fibromyalgia	18 (838)	2.1	8 (262)	3.1	0.400	0.773	8 (253)	3.2	0.354	0.746
Parkinson's Disease	3 (836)	0.4	0 (261)	0	1.000^	1.000	0 (252)	0	1.000^	1.000
Other	14 (834)	1.7	9 (257)	3.5	0.075	0.355	9 (248)	3.6	0.062	0.305

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

4.5.10 Oncological Outcomes

No significant differences were observed between both DC groups and those adults conceived spontaneously for all self-reported incidences of diagnoses of various cancers (Table 3.13). These cancers included those that affect the blood, skin, bowel, breast, prostate, bone, brain, lung/tracheal, pancreas and other malignancies, as described by the respondent.[v]

4.5.11 Reproductive Outcomes

Females in both DC groups were not more likely to self-report increased incidences of being diagnosed with various reproductive conditions than females conceived spontaneously (Table 3.14). These reproductive conditions included ovarian cysts, endometriosis, menstrual problems, polycystic ovary syndrome (PCOS), infertility and other female reproductive disorders, as described by the respondent.[w] No significant differences were also observed between groups in terms of pregnancy rates and parity.

Males in both DC groups were not more likely to self-report increased incidences of being diagnosed with various reproductive conditions than males conceived spontaneously (Table 3.15). These reproductive conditions included testicular problems, prostate problems, low sperm count and or poor sperm quality, infertility and other male reproductive disorders, as described by the respondent.[x]

[v] Further information pertaining to the oncological outcomes are as follows. Blood cancers included cancers such as lymphoma and leukemia. Skin cancers included melanoma and other skin cancers such as basal cell carcinoma or squamous cell carcinoma. Breast cancers were stratified by all sexes and females only.
[w] Further information pertaining to female reproductive outcomes are as follows. Endometriosis is a condition in which tissue that usually lines the inside of the uterus grows outside of the uterus. Menstrual problems included irregular menstruation. Polycystic ovary syndrome (PCOS) is a hormonal disorder leading to enlarged ovaries and a range of other health complications.
[x] Further information pertaining to male reproductive outcomes are as follows. Testicular problems included torsion, epididymal cysts or undescended testes. Prostate problems excluded prostate cancer.

Table 3.13 Oncological outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Blood Cancers	3 (837)	0.4	0 (260)	0	1.000^	1.000	0 (251)	0	1.000^	1.000
Skin Cancers	15 (838)	1.8	9 (260)	3.5	0.107	0.436	9 (251)	3.6	0.089	0.405
Bowel Cancer	0 (837)	0	0 (260)	0	n/a	n/a	0 (251)	0	n/a	n/a
Breast Cancer (all sexes)	5 (838)	0.6	3 (259)	1.2	0.402^	0.773	3 (250)	1.2	0.394^	0.782
Breast Cancer (females only)	4 (675)	0.6	3 (223)	1.3	0.373^	0.773	3 (215)	1.4	0.368^	0.754
Prostate Cancer (males only)	0 (161)	0	1 (37)	2.7	0.187^	0.612	1 (36)	2.8	0.183^	0.577
Bone Cancer	0 (836)	0	0 (260)	0	n/a	n/a	0 (251)	0	n/a	n/a
Brain Cancer	0 (831)	0	0 (260)	0	n/a	n/a	0 (251)	0	n/a	n/a
Lung/Tracheal Cancer	0 (835)	0	0 (260)	0	n/a	n/a	0 (251)	0	n/a	n/a
Pancreatic Cancer	0 (835)	0	0 (259)	0	n/a	n/a	0 (250)	0	n/a	n/a
Other	18 (827)	2.2	4 (259)	1.5	0.529	0.898	4 (250)	1.6	0.572	0.899

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table 3.14 Female reproductive outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Ovarian Cysts	115 (667)	17.2	44 (221)	19.9	0.370	0.773	41 (213)	19.2	0.504	0.899
Endometriosis	45 (666)	6.8	10 (219)	4.6	0.244	0.652	10 (211)	4.7	0.292	0.746
Menstrual Problems	201 (666)	30.2	64 (221)	29.0	0.731	1.000	63 (213)	29.6	0.867	1.000
PCOS	52 (664)	7.8	17 (221)	7.7	0.947	1.000	16 (213)	7.5	0.879	1.000
Infertility	59 (660)	8.9	15 (221)	6.8	0.318	0.773	15 (213)	7.0	0.387	0.780
Other	37 (667)	5.5	12 (221)	5.4	0.947	1.000	11 (213)	5.4	0.830	1.000
Pregnancy	342 (662)	51.7	120 (219)	54.8	0.421	0.773	117 (211)	55.5	0.337	0.746
Parity (Mean (SD))	1.90 (1.10)	-	1.60 (1.09)		0.013	0.084	1.63 (1.09)	-	0.025	0.154

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. Parity data is continuous data analysed by two-tailed student's t-test.

Table 3.15 Male reproductive outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Testicular Problems	11 (157)	7.0	2 (35)	5.7	1.000^	1.000	1 (34)	2.9	0.696^	0.976
Prostate Problems	2 (157)	1.3	0 (35)	0	1.000^	1.000	0 (34)	0	1.000^	1.000
Low Sperm Count/Quality	2 (157)	1.3	1 (35)	2.9	0.455^	0.811	1 (34)	2.9	0.447^	0.853
Infertility	1 (157)	0.6	1 (35)	2.9	0.332^	0.773	1 (34)	2.9	0.325^	0.746
Other	4 (156)	2.6	0 (35)	0	1.000^	1.000	0 (34)	0	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

4.5.12 Respiratory Outcomes

Both DC groups were significantly more likely to self-report being diagnosed with acute bronchitis (short term bronchitis (all 22.1% v 13.2%, $p = 0.011$; sperm 22.4% v 13.2%, $p = 0.008$)), and sleep apnoea (all 6.5% v 2.7%, $p = 0.038$; sperm 6.7% v 2.7%, $p = 0.037$), in comparison to adults conceived spontaneously (Table 3.16). No significant differences were observed between both DC groups and those adults conceived spontaneously for all self-reported incidences of diagnoses of the remaining respiratory conditions included asthma, chronic obstructive pulmonary disease (COPD), pneumonia and other respiratory disorders, as described by the respondent.[y]

4.5.13 Urogenital Outcomes

Both DC groups were not more likely to self-report increased incidences of being diagnosed with various reproductive conditions than those conceived spontaneously (Table 3.17). These urogenital conditions included kidney disease, kidney stones, bladder disease, urogenital defects and other urogenital disorders, as described by the respondent.[z]

[y] Further information pertaining to the respiratory outcomes are as follows. Asthma is an inflammatory condition of the airways leading to excess mucus and difficulty breathing. Chronic obstructive pulmonary disease (COPD) included emphysema and chronic (long term) bronchitis. Pneumonia is an infection of the lungs.

[z] Further information pertaining to the urogenital outcomes are as follows. Kidney disease is a condition that leads to renal failure. Kidney stones is a condition characterised by hard mineral deposits in the kidneys causing pain. Urogenital defects include those of the urinary tract or genital defects.

Table 3.16 Respiratory outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Asthma	213 (842)	25.3	77 (262)	29.4	0.189	0.612	74 (253)	29.2	0.210	0.601
COPD	4 (837)	0.5	3 (259)	1.2	0.366^	0.773	3 (250)	1.2	0.203^	0.597
Acute Bronchitis	111 (844)	13.2	58 (263)	22.1	< 0.001	**0.011***	57 (254)	22.4	< 0.001	**0.008***
Sleep Apnoea	23 (843)	2.7	17 (261)	6.5	0.004	**0.038***	17 (252)	6.7	0.003	**0.037***
Pneumonia	98 (838)	11.7	40 (262)	15.3	0.128	0.463	39 (253)	15.4	0.118	0.444
Other	19 (845)	2.2	6 (264)	2.3	0.982	1.000	6 (255)	2.4	0.922	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table 3.17 Urogenital outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Kidney Disease	6 (839)	0.7	2 (260)	0.8	1.000^	1.000	2 (251)	0.8	1.000^	1.000
Kidney Stones	28 (839)	3.3	12 (260)	4.6	0.336	0.773	12 (251)	4.8	0.286	0.746
Bladder Disease	8 (836)	1.0	6 (259)	2.3	0.110^	0.436	6 (250)	2.4	0.104^	0.426
Urogenital Defects	9 (837)	1.1	2 (260)	0.8	1.000^	1.000	1 (250)	0.4	0.469^	0.861
Other	18 (835)	2.2	4 (259)	1.5	0.540	0.898	4 (250)	1.6	0.584	0.899

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

4.5.14 Effect of Sex on Physical Health Outcomes

Both DC cohorts (all and sperm only) and the spontaneously conceived cohort had a majority of females with a greater than 80% proportion in each cohort. The cohorts were stratified by sex to determine the effect of sex on the rates of self-reported diagnoses. Due to the low numbers of respondents conceived via donor oocyte, embryo and surrogacy, stratification was restricted to the donor sperm cohort as described in the methods.

In both the donor sperm and spontaneously conceived cohorts, females and males were matched regarding their characteristics of mean age, whether they were born as a twin or multiple, whether their mother experienced maternal complications or smoked during pregnancy, the education levels that they obtained and whether they smoked currently or previously (Table 3.18). The mean height and mean weight of males was significantly greater than females ($p < 0.001$), as would be expected for typical male versus female population comparisons. However, they were not significantly different in terms of obesity, as was observed in their BMI. Males were significantly more likely to report greater amounts of alcohol consumption (sperm $p = 0.016$; spontaneous $p < 0.001$), but also a significantly reduced amount of prescription medicine use (sperm $p = 0.001$; spontaneous $p < 0.001$). Significantly higher incidences of self-reports of recreational/illicit drug use ($p = 0.013$), exercise amounts (low/moderate $p = 0.009$; high/strenuous $p = 0.012$), while a significantly lower incidence of receiving fertility treatment ($p = 0.001$), was observed in spontaneously conceived males in comparison to spontaneously conceived females, but not in donor sperm-conceived males.

Complete tables of all diagnosed physical health outcomes stratified by sex are presented in Appendix 3.9, while all significantly different outcomes are presented in Table 3.19. Spontaneously conceived females only were significantly more likely to report increased incidences of being diagnosed with acute bronchitis ($p = 0.007$), anaemia ($p < 0.001$), asthma ($p = 0.003$), gall bladder problems ($p = 0.038$), irritable bowel syndrome ($p = 0.007$), low blood pressure ($p = 0.002$), migraines ($p = 0.001$), nasal allergies/hayfever ($p = 0.001$), pneumonia ($p = 0.041$), tonsillectomy ($p = 0.019$), urticaria ($p = 0.001$), and varicose veins ($p = 0.001$), than their spontaneously conceived male peers (Table 3.19). Both donor sperm and spontaneously conceived males reported significantly lower incidences of being allergic to anything (sperm $p < 0.001$; spontaneous $p = 0.004$), than their female counterparts (Table 3.19). Content analysis of allergy type showed that spontaneously conceived females, but not donor sperm-conceived females, were significantly more likely to report having medication

allergies ($p < 0.001$) (Appendix 3.9). Donor sperm-conceived females reported significantly increased incidences of wearing corrective glasses/lenses ($p = 0.005$), than male donor sperm-conceived adults (Table 3.19).

Table 3.18 Characteristics of respondents by sex

	Spontaneous			Donor Sperm-Conceived		
	Female n Total [709]	**Male n Total [165]**	***p***	**Female n Total [234]**	**Male n Total [38]**	***p***
Age, Mean (SD)	33.3 (12.5)	33.4 (12.8)	0.939	33.0 (10.4)	30.3 (9.4)	0.110
Multiplicity of Own Birth, %			0.064*			0.710*
Singleton	98.2	100		94.9	97.4	
Twin	1.3	0		4.7	2.6	
Multiple (3 or more)	0.6	0		0.4	0	
Maternal Complications, %			0.266#			0.660#
Yes	14.3	5.5		17.9	13.2	
No	73.6	81.8		62.8	63.2	
Don't know	12.1	12.7		18.9	23.7	
Mother Smoked During Pregnancy, %			0.124#			0.366#
Yes	16.8	12.1		16.2	7.9	
No	78.8	80.6		79.9	89.5	
Don't know	4.4	7.3		3.8	2.6	
Highest Level of Education Attained, %			0.322#			0.565#
Less than high school	2.8	1.2		2.1	5.3	
High school degree or equivalent	26.8	27.4		16.2	18.4	
Vocational qualifications	12.2	7.9		7.3	13.2	
University/College undergrad. degree	38.7	40.9		42.3	34.2	
University/College postgrad. degree	19.5	22.6		32.1	29.0	
Height, Mean cm (SD)	166.1 (7.0)	180.2 (8.8)	**< 0.001**	166.8 (7.5)	182.4 (8.0)	**< 0.001**
Weight, Mean kg (SD)	72.7 (18.9)	82.7 (14.7)	**< 0.001**	70.5 (17.6)	81.0 (13.1)	**< 0.001**
BMI, Mean (SD)	26.3 (6.7)	25.6 (5.0)	0.118	25.4 (6.2)	24.4 (4.5)	0.292
Currently Smoke, %	7.5	9.9	0.308#	9.1	11.1	0.757^
Former Smoker, %	28.8	35.1	0.126#	22.7	24.2	0.845#
Alcoholic Drinks Consumed Per Wk			**< 0.001#**			**0.016***
0-1	66.3	46.9		64.3	36.1	
2-4	19.8	25.3		21.7	36.1	
4-10	11.0	21.6		10.4	22.2	
10+	2.9	6.2		3.6	5.6	
Low/Mod Exercise Per Wk, Mean (SD)	4.5 (5.0)	5.6 (4.7)	**0.009**	4.7 (3.7)	5.8 (7.0)	0.376
High/Stren Exercise Per Wk, Mean (SD)	1.3 (1.7)	1.8 (2.5)	**0.012**	1.3 (1.6)	1.5 (1.3)	0.344
Prescribed Medications, %	42.1	25.9	**< 0.001#**	53.8	25.0	**0.001#**
Recreational/Illicit Drugs, %	5.7	11.2	**0.013#**	10.0	13.9	0.555^
Fertility Treatment Themselves, %	8.2	0.6	**0.001#**	4.1	2.8	1.000^

[ ] = Total respondents.

p value using Students two-tailed TTEST versus spontaneously conceived unless specified by alternative test below.

= Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived. Chi-squared results are based on total chi-squared table results of all outcomes and not individual outcome groupings (i.e. all of the all donor-conceived outcomes versus all spontaneously conceived outcomes).

^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

* = Likelihood Ratio *p* value versus spontaneously conceived people used instead of Fisher's Exact Test for when > 20% of cells in chi-squared table have expected values less than 5 in Tables larger than 2x2.

Note, percentages may not equal 100% due to rounding.

Table 3.19 Significant physical health outcomes by sex

	Female		Male			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Spontaneous						
Low Blood Pressure	114 (660)	17.3	9 (159)	5.7	< 0.001	**0.002**
Anaemia	219 (660)	33.2	8 (160)	5.0	< 0.001	**< 0.001**
Varicose Veins	61 (660)	9.2	1 (160)	0.6	< 0.001	**0.001**
Urticaria	73 (669)	10.9	2 (160)	1.3	< 0.001	**0.001**
Nasal Allergies/Hayfever	285 (671)	42.5	41 (159)	25.8	< 0.001	**0.001**
Tonsilectomy	119 (670)	17.8	13 (158)	8.2	0.003	**0.019**
IBS	100 (679)	14.7	8 (161)	5.0	0.001	**0.007**
Gall Bladder	45 (678)	6.6	2 (161)	1.2	0.007	**0.038**
Allergic to Anything	258 (665)	38.8	38 (159)	23.9	< 0.001	**0.004**
Migraines	207 (675)	30.7	24 (159)	15.1	< 0.001	**0.001**
Asthma	190 (680)	27.9	23 (160)	14.4	< 0.001	**0.003**
Acute Bronchitis	103 (680)	15.1	8 (162)	4.9	0.001	**0.007**
Pneumonia	88 (675)	13.0	9 (161)	5.6	0.008	**0.041**
Donor Sperm-Conceived						
Corrective Glasses/Lenses	137 (216)	63.4	9 (33)	27.3	< 0.001	**0.005**
Allergic to Anything	99 (214)	46.3	0 (34)	0	< 0.001	**< 0.001**

Pearson chi-squared (two-tailed) *p* value females versus males. BH = Benjamini-Hochberg procedure adjusted *p* value females versus males.

4.5.15 Effect of Maternal Complications on Physical Health Outcomes

Maternal complications, including but not limited to PE, PIH and gestational diabetes, are known confounders of neonatal outcomes that are associated with altered health trajectories.[219, 793, 794] Subsequently, physical health outcome data were stratified by reports of maternal complications and was confined to donor sperm and spontaneously conceived outcomes as per other sub-analysis. Respondents reporting that they did not know if their mother experienced maternal complications during their pregnancy were excluded.

Both donor sperm and spontaneously conceived respondents whose mothers experienced maternal complications were not significantly different to their counterparts whose mothers did not experience maternal complications in their characteristics of multiplicity, maternal smoking, education levels, mean weight, BMI, current smoking status, amount of alcoholic drinks consumed per week, amount of exercise undertaken per week, use of prescription medications, recreational or illicit drug use and whether they had received fertility treatments themselves (Table 3.20). However, both donor sperm and spontaneously conceived respondents whose mothers experienced maternal complications had a lower mean age (sperm $p = 0.020$; spontaneous $p < 0.001$). While for those respondents whose mothers experienced maternal complications, donor sperm-conceived adults only were more likely to be a former smoker ($p = 0.017$), and spontaneously conceived adults only were more likely to

be female ($p < 0.003$), and to be shorter in mean height ($p < 0.001$), than their counterparts whose mothers did not experience maternal complications.

Table 3.20 Characteristics of respondents by maternal complication

	Spontaneous			Donor Sperm Conceived		
	Yes n Total [110]	No n Total [657]	*p*	Yes n Total [47]	No n Total [171]	*p*
Age, Mean (SD)	29.5 (11.3)	34.1 (12.3)	**< 0.001**	30.0 (8.2)	33.4 (10.6)	**0.020**
Sex, %			**0.003***			0.216*
Female	91.8	79.3		89.4	86.0	
Male	8.2	20.5		10.6	14.0	
Other	0	0.2		0	0	
Multiplicity of Own Birth, %			0.225*			0.642*
Singleton	96.4	98.8		93.6	95.3	
Twin	2.7	0.8		6.4	4.1	
Multiple (3 or more)	0.9	0.5		0	0.6	
Mother Smoked During Pregnancy, %			0.408			0.801
Yes	20.0	15.1		14.9	15.8	
No	75.5	80.7		83.0	80.1	
Don't know	4.5	4.3		2.1	4.1	
Highest Level of Education Attained, %			0.101			0.309*
Less than high school	4.5	2.1		2.1	1.8	
High school degree or equivalent	31.8	25.3		21.3	16.4	
Vocational qualifications	6.4	12.3		14.9	7.0	
University/College undergraduate degree	40.9	39.2		38.3	38.6	
University/College postgraduate degree	16.4	21.0		23.4	36.3	
Height, Mean cm (SD)	165.7 (9.0)	169.3 (9.3)	**< 0.001**	167.7 (7.3)	169.4 (9.4)	0.187
Weight, Mean kg (SD)	75.0 (22.7)	75.0 (17.7)	0.991	73.5 (17.6)	70.3 (15.9)	0.279
BMI, Mean (SD)	27.3 (7.9)	26.2 (6.0)	0.160	26.0 (5.8)	24.5 (5.2)	0.108
Currently Smoke, %	5.7	7.4	0.525	6.3	11.3	0.418^
Former Smoker, %	24.8	31.3	0.185	36.4	19.0	**0.017**
Alcoholic Drinks Consumed Per Wk			0.176			0.067
0-1	72.6	62.2		73.3	55.3	
2-4	13.2	21.6		20.0	26.1	
4-10	11.3	12.7		2.2	14.9	
10+	2.8	3.4		4.4	3.7	
Low/Mod Exercise Per Wk, Mean (SD)	5.1 (3.8)	4.7 (5.4)	0.354	5.4 (4.6)	4.7 (3.5)	0.324
High/Stren Exercise Per Wk, Mean (SD)	1.7 (2.1)	1.3 (1.9)	0.150	1.5 (1.7)	1.3 (1.6)	0.466
Prescribed Medications, %	45.7	38.3	0.150	51.1	47.8	0.697
Recreational/Illicit Drugs, %	9.5	6.5	0.250	6.7	11.8	0.421^
Fertility Treatment Themselves, %	4.7	7.5	0.300	4.4	3.1	0.647^

[ ] = Total respondents.

p value using Students two-tailed TTEST versus spontaneously conceived unless specified by alternative test below.

= Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived. Chi-squared results are based on total chi-squared table results of all outcomes and not individual outcome groupings (i.e. all of the all donor-conceived outcomes versus all spontaneously conceived outcomes).

^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

* = Likelihood Ratio *p* value versus spontaneously conceived people used instead of Fisher's Exact Test for when > 20% of cells in chi-squared table have expected values less than 5 in Tables larger than 2x2.

Note, percentages may not equal 100% due to rounding.

Complete tables of all diagnosed physical health outcomes stratified by maternal complications are presented in Appendix 3.10, while all significantly different outcomes are presented in Table 3.21. Donor sperm-conceived respondents born from a pregnancy with maternal complications were not significantly different from those donor sperm-conceived respondents born from an uncomplicated pregnancy (Appendix 3.10). However, spontaneously conceived adults born from a complicated pregnancy were significantly more likely than those born from an uncomplicated pregnancy to report being diagnosed with acute bronchitis ($p = 0.011$), blood cancers ($p = 0.026$), eczema ($p < 0.001$), migraines ($p < 0.001$), nasal allergies/hayfever ($p = 0.019$), and psoriasis ($p = 0.019$) (Table 3.21). Spontaneously conceived females born from a pregnancy involving maternal complications were significantly more likely to have been diagnosed with menstrual problems ($p = 0.004$) and were less likely to have experienced pregnancy themselves ($p = 0.033$).

Table 3.21 Significant physical health outcomes by maternal complications

	Spontaneous					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Eczema	42 (103)	40.8	131 (626)	20.9	< 0.001	**< 0.001**
Psoriasis	14 (103)	13.6	34 (623)	5.5	0.002	**0.019**
Nasal Allergies/Hayfever	55 (103)	53.4	233 (625)	37.3	0.002	**0.019**
Menstrual Problems	43 (93)	46.2	132 (491)	26.9	< 0.001	**0.004**
Pregnancy	38 (93)	40.9	277 (487)	56.9	0.004	**0.033**
Migraines	49 (104)	47.1	161 (628)	25.6	< 0.001	**< 0.001**
Blood Cancers	3 (104)	2.9	0 (629)	0	0.003^	**0.026**
Acute Bronchitis	25 (106)	23.6	75 (634)	11.8	0.001	**0.011**

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

4.5.16 Effect of the Country of Birth on Physical Health Outcomes

Access to health care and the criteria for the diagnosis of health conditions can potentially vary between countries. Subsequently, stratifying responses by country of birth provides a means of assessing whether bias is present in the outcomes of the cohorts due to the geographic location in which they were born. In both donor sperm and spontaneously conceived cohorts, the largest proportion was born in Australia (donor sperm 30.7%; spontaneous 46.3%) (Table 3.3), and therefore the responses from Australians were analysed separately.

Australian donor sperm-conceived adults had a significantly lower mean age ($p < 0.001$), and their mothers had experienced increased incidences of maternal complications ($p = 0.002$), than spontaneously conceived Australians (Table 3.22). They were, however, well-matched in terms of the characteristics of sex ratio, maternal smoking, education levels, mean height or weight, BMI, current and former smoking status, amount of alcoholic drinks consumed per week, amount of exercise undertaken per week, use of prescription medications, recreational or illicit drug use and whether they had received fertility treatments themselves.

Furthermore, donor sperm-conceived Australians were not significantly different to spontaneously conceived Australians for all primary physical health outcomes (Appendix 3.11). The only difference observed in physical health outcomes was a secondary measure obtained from content analysis in which donor sperm-conceived Australians were more likely to have environmental ($p < 0.001$), and ingested allergies ($p = 0.025$), even though the overall incidence of allergies was not statistically significant (Appendix 3.11).

Table 3.22 Characteristics of Australian respondents

	Spontaneous n Total [372]	Donor Sperm-Conceived n Total [78]	*p*
Age, Mean (SD)	33.4 (12.1)	29.6 (6.7)	**< 0.001**
Sex, %			0.164#
Female	90.0	84.6	
Male	10.0	15.4	
Other	0	0	
Multiplicity of Own Birth, %			0.111*
Singleton	98.1	94.9	
Twin	1.3	5.1	
Multiple (3 or more)	0.5	0	
Mother Had Maternal Complications, %			**0.002#**
Yes	11.8	17.9	
No	76.6	57.7	
Don't know	11.6	24.4	
Mother Smoked During Pregnancy, %			0.177#
Yes	15.1	7.7	
No	79.6	88.5	
Don't know	5.4	3.8	
Highest Level of Education Attained, %			0.054#
Less than high school	2.4	5.1	
High school degree or equivalent	24.3	15.4	
Vocational qualifications	14.6	6.4	
University/College undergraduate degree	40.7	50.0	
University/College postgraduate degree	18.1	23.1	
Height, Mean cm (SD)	168.2 (7.6)	168.9 (9.0)	0.518
Weight, Mean kg (SD)	74.6 (18.1)	74.3 (17.9)	0.897
BMI, Mean (SD)	26.3 (6.0)	26.2 (6.6)	0.863
Currently Smoke, %	5.4	5.6	1.000^
Former Smoker, %	28.9	18.3	0.069#
Alcoholic Drinks Consumed Per Wk			0.509#
0-1	62.4	65.3	
2-4	21.1	25.0	
4-10	14.5	8.3	
10+	2.0	1.4	
Low/Mod Exercise Per Wk, Mean (SD)	4.3 (3.8)	4.7 (5.0)	0.440
High/Stren Exercise Per Wk, Mean (SD)	1.4 (1.7)	1.4 (1.5)	0.973
Prescribed Medications, %	44.0	51.4	0.249#
Recreational/Illicit Drugs, %	5.1	9.7	0.166#
Fertility Treatment Themselves, %	8.0	2.8	0.117#

[ ] = Total respondents.

p value using Students two-tailed TTEST versus spontaneously conceived unless specified by alternative test below.

= Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived. Chi-squared results are based on total chi-squared table results of all outcomes and not individual outcome groupings (i.e. all of the all donor-conceived outcomes versus all spontaneously conceived outcomes).

^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

* = Likelihood Ratio *p* value versus spontaneously conceived people used instead of Fisher's Exact Test for when > 20% of cells in chi-squared table have expected values less than 5 in Tables larger than 2x2.

Note, percentages may not equal 100% due to rounding.

4.5.17 Validation of Comparison Group

The comparison cohort of spontaneously conceived people needs to be validated to ascertain the rigour of comparative analysis to the DC cohorts. This validation was done by comparing the Australian spontaneously conceived group to ABS NHS reference data, and by comparing the worldwide spontaneously conceived cohort to CDC NHANES reference data. Frequencies of comparable outcomes are presented in Table 3.23.

Spontaneously conceived respondents born in Australia represent 46.3% of all spontaneously conceived respondents worldwide. They were mostly representative in terms of reported frequencies of all conditions with the exceptions of eczema, low blood pressure and nasal allergies/hayfever in comparison to the worldwide spontaneously conceived group.

In comparison to the respective reference data, Australian and worldwide spontaneously conceived adults reported frequencies of conditions that were comparable, but also in several instances where they reported frequencies, which were either higher or lower. Australian spontaneously conceived adults reported frequencies that were lower in 2 of 2 respondent characteristics of being a former smoker and taking prescribed medications than those reported in the ABS NHS reference data. They also reported lower frequencies in 12 of 29 health outcome conditions and higher frequencies in 17 of 29 health outcome conditions.

Worldwide spontaneously conceived adults reported frequencies that were also lower in 2 of 2 respondent characteristics of currently smoking and taking prescribed medications than those reported in the CDC NHANES reference data. They also reported lower frequencies in 24 of 27 health outcome conditions, and higher frequencies of asthma and female infertility than that reported in the CDC NHANES reference data, while the frequency of blood cancers was the same.

Table 3.23 Spontaneous cohort comparisons

	Spontaneous (All Countries) %	CDC NHANES %	Spontaneous (Australia) %	ABS NHS %
Characteristics				
Currently Smoke	7.9	49.6	5.4	15.1
Former Smoker	30.0	-	28.9	29.2
Prescribed Medications	39.1	73.5	44.0	-
Cardiovascular				
Cardiovascular Disease	2.2	4.8[a]	1.8	6.2
Heart Murmur	5.6	-	6.3	1.6
High Blood Pressure	10.5	34.7	12.7	13.6
Low Blood Pressure	15.0	-	21.4	1.2
High Cholesterol	8.8	32.4	11.5	7.8
Varicose Veins	7.5	-	9.2	1.7
Chromosomal and Genetics				
Chromosomal and Genetic Abnormality	2.4	-	3.2	0.4[b]
Dermatology				
Eczema	24.0	-	29.1	0.6
Psoriasis	6.4	-	8.8	3.1
EENT				
Deafness and Hearing Loss (total)	6.0	-	6.4	12.9
Nasal Allergies/Hayfever	39.3	-	45.6	21.6
Endocrinological				
Diabetes (Types 1 & 2 (total))	2.9	10.0	2.0	6.2
Thyroid Disease	3.9	11.8[c]	4.9	5.0
Gastrointestinal				
Liver Disease	1.5	5.3[d]	1.4	-
Ulcers	3.1	-	2.9	3.2
Gall Bladder	5.6	11.5[e]	5.5	0.4[f]
Immunological				
Arthritis	7.8	30.4	8.5	18.3
Rheumatoid Arthritis	2.2	-	1.8	2.5
Gout	1.2	6.1	1.5	3.0[g]
Allergic to Anything	36.0	-	35.8	13.2
Ingested Allergy	9.9	-	8.2	6.4
Medication Allergy	13.4	-	16.8	5.6
Musculoskeletal				
Osteoporosis	1.1	12.9	1.5	5.0
Neurological				
Epilepsy	3.1	-	3.2	0.7
Migraines	27.8	-	29.8	7.6
Oncological				
Blood Cancers	0.4	0.4	0.6	-
Skin Cancers	1.8	2.4	2.0	0.7
Bowel Cancer	0	0.8	0	-
Breast Cancer (all sexes)	0.6	1.6	1.2	-
Prostate Cancer (males only)	0	1.7	0	-
Bone Cancer	0	0	0	-
Brain Cancer	0	0.1	0	-
Lung/Tracheal Cancer	0	0.4	0	-
Pancreatic Cancer	0	0	0	-
Other Cancers	2.2	3.5	2.3	1.6[h]
Reproductive (Female)				
Female Infertility	8.9	6.7	8.2	-
Pregnancy (females)	51.7	85.1	46.9	-
Respiratory				
Asthma	25.3	14.9	28.6	11.5
COPD	0.5	5.3	0	3.0
Urogenital				
Kidney Disease	0.7	-	0.6	1.2
Kidney Stones	3.3	9.9	3.4	-

CDC NHANES = Centers for Disease Control and Prevention, National Health and Nutrition Examination Survey, 2017-2018 data (USA), all ages. ABS NHS = Australia Bureau of Statistics, National Health Survey, 2017-2018, ages 18 and over. a = coronary heart disease as designated by CDC; b = chromosomal abnormalities but also includes congenital malformations and deformations; c = thyroid disease but also includes other thyroid problems; d = liver condition including disease; e = gall bladder surgery; f = gallstones; g = includes gout and other soft tissue disorders; h = Australian cancers other than skin and benign neoplasms or neoplasms of unknown nature. [5]

4.6 Physical Health Outcomes Discussion

Results of this study showed that for just over 100 physical health outcomes depending on conception modality (all v sperm), DC adults were not significantly different to those adults conceived spontaneously. However, donor sperm-conceived and all donor-conceived adults self-reported higher incidences of being diagnosed by a medical health professional with type 1 diabetes, thyroid disease, Hashimoto's disease, acute bronchitis, environmental allergies, sleep apnoea, and having ear tubes or grommets implanted surgically. These significant differences were present after controlling for false-discovery using the Benjamini-Hochberg procedure.[790]

Both DC groups (all and sperm) were well matched in their characteristics to the spontaneously conceived group in terms of their mean age, mean height, sex ratio, current smoking status, amount of alcohol consumption, levels of exercise, maternal smoking during pregnancy, and whether they had received fertility treatment themselves. However, DC adults were significantly more likely to have been born as a twin, have a lower BMI, to have achieved a higher level of education, to be taking prescribed medications, to be using recreational or illicit drugs, and their mothers were also more likely to have experienced complications during pregnancy. Donor sperm-conceived adults only reported a significantly lower current mean weight and were less likely to have smoked cigarettes/tobacco previously. Some of these findings have been reported previously in the literature.

An increased incidence of twins has been associated with both donor sperm,[2, 678] and donor oocyte treatment modalities.[581-585] An increased incidence of maternal complications during pregnancy has also been associated with both donor sperm,[2, 294] and donor oocytes.[275, 795, 796] Furthermore, maternal complications are also correlated with pregnancies involving twins/multiples.[56, 464]

The observed significantly increased incidences of prescription medication use in the DC group may potentially be associated with the increased incidences of type 1 diabetes, thyroid disease, Hashimoto's disease, acute bronchitis, environmental allergies, and sleep apnoea diagnoses, which all have prescribed medical treatments.

As males and females have differing experiences of health,[797, 798] with sex being argued as one of the most important modulators of disease risk,[799] an assessment of outcomes based on sex stratification was conducted. This assessment was pertinent, considering the high proportion of female respondents. Stratification was only conducted on the donor sperm-conceived

cohort due to the low numbers of respondents conceived with the other donor conception modalities. Where a significant difference was observed between females and males in their physical health outcomes, it was always females that reported the significantly increased diagnoses. These increased incidences included a range of conditions including acute bronchitis, anaemia, asthma, being allergic to anything, gall bladder problems, IBS, low blood pressure, migraines, nasal allergies or hayfever, pneumonia, tonsillectomy, urticaria, varicose veins, and wearing corrective glasses or lenses. Except for being allergic to anything and the wearing of corrective glasses or lenses, all other significant outcome differences by sex occurred in the spontaneously conceived cohort.

Non-significant outcomes may potentially be due to an issue of statistical power, and the relatively small sample size of male DC respondents (n = 38), as variation in the absolute frequencies was observed. The increased incidence of adverse outcomes in female respondents is consistent with the increased use of prescribed medications in both donor sperm and spontaneously conceived females.

The high proportion of females observed in this study of 85.8% of DC respondents and 80.8% of spontaneously conceived respondents is not unexpected. Previous studies of DC adolescents and adults have also reported higher proportions of females ranging from 74% - 85%.[771-773, 800-802] Furthermore, FB advertisement analysis showed that greater than 90% of clicks on the advertisement were from women. It is likely that the majority of these would be spontaneously conceived women and may, in some way, explain the high proportion of females also observed in the spontaneously conceived cohort. For whatever reason, taking part in the survey and or the subject matter was of greater interest to females.

Donor-conceived neonates are at increased risk for being born LBW, PD, and SGA,[1, 4, 275, 654-656] which is consistent with the DOHaD phenomenon correlating those birth characteristics with increased incidences of cardiovascular disease,[64, 803] hypertension,[736, 804] type 2 diabetes,[805, 806] and obesity[807, 808] in adulthood. However, increased incidences of cardiovascular disease, including hypertension, type 2 diabetes and obesity were not observed in the DC respondents in this study. In terms of obesity, they were conversely significantly more likely to have a lower BMI than the spontaneously conceived cohort. The observed current non-significant outcomes do not preclude DC people from increased incidences of cardiovascular disease, type 2 diabetes and obesity progression at a later age when their current age at the time of the study is considered. All donor-conceived (32.2 years) and donor sperm-conceived (32.6 years) respondents are relatively young from a burden of those diseases' perspective, and

therefore the findings may be a reflection of their current age and not a complete picture of their health trajectory under the DOHaD phenomenon.

Further considerations must be made concerning the SES of the respondents due to fertility treatments being positively correlated with the SES of parents.[809] The SES may potentially be linked with the DC characteristics such as lower BMI, weight and incidences of smoking previously. The increased post-graduate qualifications may potentially also be linked to SES in locations whereby college/university education has a considerable financial burden such as the United States. Subsequently, caution should be applied in the extrapolation of findings to age-related conditions such as cardiovascular disease from a DOHaD perspective due to the influence of socio-economic factors.

Maternal complications, such as hypertensive disorders of pregnancy, including PE and PIH, are a well-known confounder of perinatal outcomes,[810, 811] and are associated with long-term adverse health outcomes for the offspring.[812, 813] To ascertain whether maternal complications affected health outcomes, the data was stratified by those who reported that their mother had maternal complications. Similar to the sample size issue of male DC respondents in the effect of sex on outcomes analysis, the sample size of donor sperm-conceived respondents reporting maternal complications was relatively small (n = 47), also reducing the power to detect differences in some outcomes. All significant differences in the donor sperm-conceived cohort were ameliorated after adjusting for false-discovery using the Benjamini-Hochberg procedure. Therefore, no inferences can be made regarding the effect of maternal complications on the health of donor sperm-conceived adults.

Maternal complications were correlated with increased incidences of being diagnosed with acute bronchitis, blood cancers, eczema, menstrual problems (females), migraines, nasal allergies/hayfever, and psoriasis in spontaneously conceived respondents. Females whose mothers experience maternal complications were also significantly less likely to have been pregnant. The increased incidences of adverse outcomes observed are consistent with the literature correlating adverse long-term health outcomes with PE and PIH.[219, 220, 225, 226, 230, 306, 307] Other maternal complications such as placental praevia,[814, 815] and cervical insufficiency have not been associated with adverse offspring health outcomes. While the maternal complication of hyperemesis gravidarum has some evidence showing increased adverse outcomes in the offspring,[816-819] it has not been associated with donor conceptions, specifically donor oocytes.[290] Subsequently, hyperemesis gravidarum is unlikely to contribute

to the increased incidences of maternal complications observed in the DC cohort, and therefore unlikely to affect the observed increased adverse outcomes.

Health care varies between countries,[820, 821] and the ability for an individual to access appropriate health care can be affected by the country they were born, raised and live in, which has implications for their long-term health trajectories. The diagnostic criteria of various conditions can also vary between countries.[822, 823] By country of birth, the largest proportion of respondents (donor sperm 30.7%; spontaneous 46.3%) were born in Australia. Subsequently, an analysis was conducted on Australian donor-conceived and spontaneously conceived adults. All significant differences observed from the chi-squared analysis was no longer significant when controlling for false-discovery using the Benjamini-Hochberg procedure.

The majority of survey respondents (89.8%) were born in Australia, Belgium, Canada, Germany, Ireland, the Netherlands, New Zealand, Norway, Sweden, the United Kingdom, and the United States, which would all generally be regarded as having excellent healthcare. The significant differences in the worldwide analysis are therefore biased by these other countries but not by Australia. This lack of influence by Australia is due to the lack of differences observed in the Australian cohorts. Problematically, the issue of statistical power and sample sizes that affected stratification analysis by sex and maternal complications also affected Australian donor sperm analysis (n = 78). Caution should therefore be taken in concluding that Australian DC adults are equally healthy as spontaneously conceived Australians.

The physical health of adult DC people in this study was worse than those respondents who were conceived spontaneously. However, the comparison cohort of spontaneously conceived people needs to be validated to ascertain whether they are representative of the general population. Generally, the worldwide spontaneously conceived cohort was healthier than the CDC NHANES reference data averages with lower frequencies of conditions. However, the CDC stipulates that the NHANES data were oversampled regarding the ethnicities of non-Hispanic black, Hispanic and Asians, and therefore is not representative of the population in the USA.[792] However, this provides increased variability in ethnicity, which is more reflective of the respondents in this study which also included individuals from Asian and Eastern-European countries. The CDC also specified that the NHANES oversampled non-Hispanic whites over 80 years of age and non-Hispanic whites living at or below 185% of the Department of Health and Human Services poverty guidelines.[792] This study did not obtain data on poverty, but in terms of age, only one spontaneously conceived respondent was over the age of 80 years. The

CDC NHANES reference data is, therefore, more likely to be biased towards outcomes associated with lack of access to health care due to poverty as well as age-related conditions than the respondents in this survey. The findings of the worldwide spontaneously conceived cohort were therefore consistent with the CDC NHANES reference data.

Australian reference data from the ABS NHS in comparison to Australian spontaneously conceived respondents was variable in terms of having both lower and greater frequencies of conditions. The ABS NHS reference data reported that 28.3% of participants were between the ages of 0-19 years, while all respondents in this survey were adults over the age of 18 years. The respondents in this survey are, therefore, more likely to be biased towards age-related conditions than the ABS NHS data. Australian spontaneously conceived respondents provided approximately 42% of all worldwide spontaneously conceived data and were generally consistent with the worldwide cohort, which was also consistent with CDC NHANES reference data.

Both the ABS NHS and CDC NHANES reference data sets are well matched to the date of this study. They are also subject to the sample recall bias as the respondents in this survey of remembering if they had been diagnosed with a specific condition. There were differences observed between both of the reference data sets and the spontaneously conceived cohorts (worldwide and Australian). However, these are not surprising due to age (CDC NHANES and ABS NHS), and poverty (CDC NHANES), biases that were present in the reference data.

4.7 Mental Health Survey Background

The mental health and psychological adjustment of those conceived with donor gametes have been of interest for researchers investigating the role of parent-child biological relatedness and family functioning. A systematic review of 11 studies that investigated the psychological outcomes of adolescents (11-18 years), conceived from donor gametes concluded that DC adolescents were well adjusted psychologically.[824] However, four of these studies used the same sampling frame (the same participants), while another two studies contained adolescents that crossed over into both publications thereby reducing both the number of unique participants analysed and the strength of the conclusions drawn.

Studies of younger children have also concluded that they too are psychologically well-adjusted compared to their spontaneously conceived peers.[825-827] Some of these studies, both of young children and adolescents are under-powered with relatively small sample sizes, or they implement exclusion criteria restricting participants to healthy singletons making

conclusions about the overall mental health of DC children difficult even though the results so far are reassuring. Furthermore, such investigations are often limited by either the young person's lack of knowledge of their conception or that the researchers did not assess disclosure. It has been shown through a systematic review that most DC children and adolescents/young adults have not had their conception disclosed to them.[747] Similarly, of those studies included in the systematic review of adolescent psychological outcomes,[824] not all offspring were aware of their conception and, in the case for heterosexual parents, less than 10% had disclosed to their child about their conception. Without the children or adolescents knowing the nature of their conception, it is therefore difficult to examine the relationship between knowledge of conception and psychological outcomes.

While this flaw is noted, these previous studies provide data on the mental health outcomes of young DC people. Conversely, in the case of adult outcomes, there is a dearth of studies investigating the mental health of adults conceived with donor gametes in comparison to spontaneously conceived adults. However, there are reports in which some adult DC people have experienced negative feelings surrounding their conception, including feeling that they are victims who have been abandoned and deceived or experiencing symptoms of depression.[771, 800, 828-830] Adult studies by nature require the informed consent of the participant. Therefore, they represent a different subset of the DC population as these adults know that they are donor-conceived, unlike those studies investigating childhood outcomes. A different sample bias will therefore often be inherent in the adult studies through self-selection than those observed in the childhood studies where participation was decided by their parents and potentially involves non-disclosure of their donor conception status.

Regardless of disclosure and the family environment, significant to this thesis is the implication of DOHaD in mental health outcomes.[831] Particularly, pregnancies complicated by PE have been correlated with mental disorders,[220] including neuropsychiatric morbidities,[235] behavioural problems,[236] attention deficit hyperactivity disorder,[237] and autism spectrum disorder in the offspring.[238, 239] Furthermore, people born from pregnancies complicated by PIH have also been correlated with mental disorders[310-312] and behavioural problems.[309] Subsequently, it is pertinent to investigate the mental health outcomes for DC people. While these outcomes may occur independently of disclosure, it is not possible to study these outcomes in a survey without the DC adult knowing that they are donor-conceived.

Due to a lack of quantitative and systematic studies investigating the mental health of DC adults in comparison to those who are spontaneously conceived, studies are required to

examine not only the mental health status of DC adults but whether it differs from reports of outcomes of DC children and adolescents. The online survey investigating the physical health of DC adults provided an opportunity also to explore the mental health of the same DC individuals. This section reports the findings of the mental health data.

4.8 Mental Health Outcomes Results

Self-reported mental health outcomes were comprised of conditions that had been diagnosed by a medical professional such as a psychiatrist, psychologist or general practitioner, and conditions that were based on the respondent's own experience.

4.8.1 Diagnosed Mental Health Outcomes

In comparison to those conceived spontaneously, DC adults reported significantly higher incidences of being diagnosed by a mental health professional with depressive disorder (all 40.7% v 31.1%, $p = 0.041$), attention deficit disorder or attention deficit hyperactivity disorder (ADD/ADHD (all 11.1% v 3.9%, $p = < 0.001$; sperm 10.2% v 3.9%, $p = 0.004$)), and autism or autism spectrum disorder (autism/ASD (all 5.2% v 2.0%, $p = 0.041$; sperm 5.3% v 2.0%, $p = 0.044$)) (Table 3.24).

Donor-conceived adults also reported being diagnosed with significantly higher incidences of mental health issues not classified in the categories listed (all 13.1% v 7.2%, $p = 0.031$; sperm 13.2% v 7.2%, $p = 0.038$), and were able to describe these with free text input. Quantitative content analysis showed that the three groups with the most free text input responses were borderline personality disorder, obsessive-compulsive disorder and post-traumatic stress disorder. All other disorders/conditions were labelled as 'ungrouped' (such as oppositional defiance disorder, body dysmorphic disorder, adjustment disorders, schizophrenia, and panic disorders). No significant differences were observed between DC adults and those conceived spontaneously in the quantitative content analysis (Table 3.24). Furthermore, both DC groups did not report significantly increased incidences of anxiety disorder, and bipolar disorder diagnoses in comparison to those adults conceived spontaneously.

Table 3.24 Diagnosed mental health outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Depressive Disorder	255 (820)	31.1	103 (253)	40.7	0.005*	**0.041***	97 (245)	39.6	0.013*	0.089
Anxiety Disorder	258 (817)	31.6	93 (253)	36.8	0.125	0.463	88 (245)	35.9	0.204	0.597
Bipolar	13 (814)	1.6	3 (252)	1.2	0.775^	1.000	2 (244)	0.8	0.541^	0.899
ADD/ADHD	32 (815)	3.9	28 (253)	11.1	< 0.001*	**< 0.001***	25 (245)	10.2	< 0.001*	**0.004***
Autism/ASD	16 (818)	2.0	13 (252)	5.2	0.006*	**0.041***	13 (244)	5.3	0.005*	**0.044***
Other[#]	59 (816)	7.2	33 (251)	13.1	0.003*	**0.031***	32 (243)	13.2	0.004*	**0.038***
BPD	9 (816)	1.1	2 (251)	0.8	1.000^	-	2 (243)	0.8	1.000^	-
OCD	10 (816)	1.2	4 (251)	1.6	0.751^	-	4 (243)	1.6	0.538^	-
PTSD	29 (816)	3.6	15 (251)	6.0	0.091	-	14 (243)	5.8	0.126	-
Ungrouped	18 (816)	2.2	11 (251)	4.4	0.064	-	11 (243)	4.5	0.052	-

[#] = Mental health diagnoses in the 'Other' category which had free text input were then subjected to quantitative content analysis which is reported below the dashed line. Note that the N of the categories below the line do not equal those in 'Other' due to multiple responses for certain respondents and also some respondents not completing the free text input. BPD = borderline personality disorder. OCD = obsessive-compulsive disorder. PTSD = post-traumatic stress disorder. Other = all other disorders/conditions not grouped into the above categories such as oppositional defiance disorder, body dysmorphic disorder, adjustment disorders, schizophrenia, and panic disorders. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$). ADD = Attention Deficit Disorder, ADHD = Attention Deficit Hyperactivity Disorder, ASD = Autism Spectrum Disorder.

4.8.2 Own Experience Mental Health Outcomes

In terms of the respondent's experiences rather than formal diagnosis of mental health issues, DC adults were significantly more likely to report higher incidences of having experienced panic attacks (all 54.8% v 43.3%, p = < 0.015; sperm 53.7% v 43.3%, p = 0.038), recurrent nightmares (all 25.7% v 17.8%, p = < 0.041; sperm 26.1% v 17.8%, p = 0.038), having difficulty forming their identity (all 52.2% v 14.1%, p = < 0.001; sperm 51.8% v 14.1%, p = < 0.001), having an eating disorder (such as anorexia or bulimia (all 20.3% v 12.5%, p = 0.022)), alcohol/drug dependency (all 12.4% v 5.9%, p = 0.012; sperm 11.5% v 5.9%, p = 0.037), and to have reported learning difficulties (all 17.2% v 7.1%, p = < 0.001; sperm 16.9% v 7.1%, p = < 0.001) (Table 3.25). The only own experience mental health outcome that a significant difference was not observed, was for insomnia.

Free text inputs of the significantly increased incidences of seeing a mental health professional (all 70.0% v 49.5%, p = < 0.001; sperm 69.8% v 49.5%, p = < 0.001), were subjected to content analysis using the categories of psychologist (all 47.0% v 33.0%, p = < 0.001; sperm 46.5% v 33.0%, p = < 0.001), psychiatrist (all 22.5% v 16.2%, p = 0.021; sperm 21.6% v 16.2%, p = 0.048), and other mental health professional (all other medical health professionals as designated by the respondent such as general practitioner, psychotherapist, mental health nurse, counsellor, or cognitive behavioural therapist) (all 15.4% v 9.8%, p = 0.013; sperm 15.5% v 9.8%, p = 0.013).

Table 3.25 Own experience mental health outcomes

	Spontaneous		All Donor-Conceived				Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*	n (Total)	%	*p*	BH *p*
Panic Attacks	354 (817)	43.3	138 (252)	54.8	0.001*	**0.015***	131 (244)	53.7	0.004*	**0.038***
Identity Formation Difficulty	115 (818)	14.1	132 (253)	52.2	< 0.001*	**< 0.001***	127 (245)	51.8	< 0.001*	**< 0.001***
Recurrent Nightmares	146 (818)	17.8	65 (253)	25.7	0.006*	**0.041***	64 (245)	26.1	0.004*	**0.038***
Alcohol/Drug Dependency	48 (818)	5.9	31 (251)	12.4	0.001*	**0.012***	28 (243)	11.5	0.003*	**0.037***
Eating Disorder	102 (817)	12.5	51 (251)	20.3	0.002*	**0.022***	47 (243)	19.3	0.007*	0.051
Insomnia	217 (814)	26.7	81 (251)	32.3	0.083	0.365	78 (243)	32.1	0.097	0.411
Learning Difficulties	58 (812)	7.1	43 (250)	17.2	< 0.001*	**< 0.001***	41 (242)	16.9	< 0.001*	**< 0.001***
Seen Mental Health Professional #	404 (816)	49.5	177 (253)	70.0	< 0.001*	**< 0.001***	171 (245)	69.8	< 0.001*	**< 0.001***
Psychologist	269 (816)	33.0	119 (253)	47.0	<0.001*	-	114 (245)	46.5	<0.001*	-
Psychiatrist	132 (816)	16.2	57 (253)	22.5	0.021*	-	53 (245)	21.6	0.048*	-
Other	80 (816)	9.8	39 (253)	15.4	0.013*	-	38 (245)	15.5	0.013*	-

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. BH correction not performed on content analysis. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$). # = Mental health professional as designated by the respondent. Other = all other medical health professionals as designated by the respondent such as general practitioner, psychotherapist, mental health nurse, counsellor, cognitive behavioural therapist.

4.8.3 Depression, Anxiety and Stress Scales (DASS-21)

DASS-21 results are typically expressed as a function of the total mean score and a mean score for each scale of depression, anxiety and stress.[784] The results will, therefore, be discussed in terms of these four outcomes. However, results from each question are presented in the table for completeness (Table 3.26). The total DASS-21 score of DC adults was higher than those spontaneously conceived but was not significantly different. Donor-conceived adults were significantly more stressed in the past week when compared to spontaneously conceived adults (all 13.63 (SD = 9.77) v 11.65 (SD = 9.74), $p = 0.007$; sperm 13.43 (SD = 9.74) v 11.65 (SD = 9.74), $p = 0.013$), although they did not experience statistically significantly different levels of depression or anxiety.

Using the DASS-21 scoring system, mean anxiety and mean stress scores in each group were in the normal range (anxiety = 0-7; stress = 0-14). In comparison, mean depression scores for both DC groups were in the mild range (10-13) and was borderline between normal and mild for spontaneously conceived people (9.40), but not significantly different between groups.

The DASS-21 is a separate instrument from the rest of the data collected in the survey. It has been shown to have good invariance between females and males,[832] and high internal consistency.[833] While the DASS-21 has been shown to have invariance between quite different cultures,[834] good consistency of means has been observed in western countries particularly English-speaking ones.[835] From available data of those completing the country of their birth question, this survey was primarily comprised of English-speaking countries with the majority of respondents originating from the countries of Australia, Ireland, New Zealand, the United Kingdom and the United States. While other countries such as Canada and South Africa are members of the Commonwealth and are former British colonies, the Netherlands has a vast majority of citizens who speak English well, and Belgium has a considerable proportion who speak English.[836] Therefore, the percentage of respondents representing western countries with excellent English-speaking skills and subsequent good invariance across this survey increases to 97.5%. Accordingly, the DASS-21 was not subjected to stratification by sex, maternal complications of pregnancy and country of birth which the other mental health outcomes are subjected to in the following sections.

Table 3.26 DASS-21 outcomes

	Spontaneous Score [769]	All Donor-Conceived Score [234]	*p*	Donor Sperm-Conceived Score [227]	*p*
Total DASS 21 Score, Mean (SD)	*27.32 (25.14)*	*30.76 (24.62)*	*0.064*	*30.26 (24.55)*	*0.102*
Depression Score, Mean (SD)	*9.40 (10.50)*	*10.30 (10.18)*	*0.243*	*10.09 (10.06)*	*0.343*
No positive feelings	1.20 (1.65)	1.32 (1.70)	0.339	1.30 (1.70)	0.477
Difficult to find initiative	2.22 (1.96)	2.32 (1.97)	0.530	2.27 (1.98)	0.740
Nothing to look forward to	1.12 (1.76)	1.24 (1.75)	0.356	1.22 (1.74)	0.459
Felt down-hearted and blue	1.55 (1.79)	1.68 (1.76)	0.303	1.66 (1.76)	0.414
Unable to become enthusiastic	1.21 (1.72)	1.22 (1.63)	0.900	1.21 (1.62)	0.998
Felt worthless	1.23 (1.89)	1.45 (1.95)	0.123	1.40 (1.91)	0.236
Felt life was meaningless	0.87 (1.63)	1.06 (1.70)	0.140	1.04 (1.69)	0.190
Anxiety Score, Mean (SD)	*6.27 (7.77)*	*6.83 (7.60)*	*0.330*	*6.74 (7.66)*	*0.406*
Aware of dryness in mouth	1.19 (1.58)	1.21 (1.66)	0.876	1.19 (1.67)	0.978
Experienced breathing difficulty	0.65 (1.32)	0.68 (1.25)	0.743	0.68 (1.24)	0.788
Experienced trembling	0.66 (1.37)	0.55 (1.31)	0.263	0.55 (1.31)	0.265
Worried about panicking	1.21 (1.81)	1.34 (1.80)	0.317	1.32 (1.81)	0.401
Felt close to panic	0.87 (1.54)	1.11 (1.65)	**0.049***	1.08 (1.64)	0.084
Aware of heart rate without exertion	0.89 (1.54)	1.07 (1.68)	0.147	1.06 (1.68)	0.178
Felt scared with no good reason	0.81 (1.52)	0.87 (1.41)	0.557	0.86 (1.41)	0.614
Stress Score, Mean (SD)	*11.65 (9.74)*	*13.63 (9.77)*	***0.007****	*13.43 (9.74)*	***0.013****
Hard to wind down	2.12 (1.88)	2.37 (1.88)	0.081	2.32 (1.86)	0.168
Over-reacted to situations	1.67 (1.80)	1.77 (1.67)	0.433	1.74 (1.65)	0.605
Used a lot of nervous energy	1.33 (1.73)	1.82 (1.94)	**< 0.001***	1.79 (1.93)	**0.001***
Found myself getting agitated	1.83 (1.77)	1.96 (1.75)	0.326	1.95 (1.76)	0.374
Found it difficult to relax	1.98 (1.90)	2.38 (1.92)	**0.005***	2.33 (1.92)	**0.014***
Intolerant of anything preventing tasks	1.19 (1.57)	1.44 (1.78)	**0.047***	1.43 (1.77)	0.065
Felt I was rather touchy	1.53 (1.73)	1.89 (1.83)	**0.009***	1.88 (1.81)	**0.012***

[ ] = Total respondents included in analysis. Respondents that did not answer every question were excluded.

* = *p* value significant ($p < 0.05$) using Students two tailed t-test versus spontaneously conceived.

4.8.4 Effect of Sex on Mental Health Outcomes

Spontaneously conceived females were significantly more likely than spontaneously conceived males to self-report being diagnosed with depressive disorder (34.4% v 16.4%, $p < 0.001$), anxiety disorder (35.8% v 13.9%, $p < 0.001$), and other non-listed mental health conditions (8.5% v 1.9%, $p = 0.023$) (Table 3.27). Content analysis of free text input for other diagnosed conditions not listed revealed that female spontaneously conceived adults were also more likely to be diagnosed with post-traumatic stress disorder (PTSD) (4.3% v 0.6%, $p = 0.026$). Donor sperm-conceived females did not report any statistically significant differences in the frequencies of being diagnosed with depressive disorder, anxiety disorder, bipolar, ADD/ADHD, autism/ASD or any other non-listed mental health condition.

In terms of the respondent's own experience, spontaneously conceived females were significantly more likely than spontaneously conceived males to self-report experiencing panic attacks (48.5% v 21.4%, $p < 0.001$), recurrent nightmares (20.5% v 6.3%, $p < 0.001$), eating disorders (14.3% v 3.8%, $p = 0.007$), and seeing a mental health professional (53.1% v 34.6%, $p < 0.001$) (Table 3.28). Conversely, they were significantly less likely to self-report a dependency on alcohol or drugs (4.7% v 10.7%, $p = 0.023$). Content analysis of free text input for which mental health professional was consulted showed that females were more likely to visit a psychologist (36.5% v 18.2%, $p < 0.001$), and other mental health professionals such as a general practitioner, psychotherapist, mental health nurse, counsellor or cognitive behavioural therapist (11.3% v 3.8%, $p = 0.004$). No differences were observed between female and male spontaneously conceived adults in terms of self-reported frequencies of identity formation issues, insomnia or learning difficulties. Similar to diagnosed mental health outcomes, donor sperm-conceived females were no different from their donor sperm-conceived male peers in all outcome measures.

Stratifying outcomes by sex showed that the donor sperm-conceived cohort exhibited no differences between females and males in their mental health outcomes. In contrast, spontaneously conceived females fared worse than their spontaneously conceived male peers in a variety of mental health outcomes except for alcohol and drug dependency, which was elevated in males. DASS-21 results were not stratified by sex as it is a separate instrument.

Table 3.27 Diagnosed mental health outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Depressive Disorder	227 (659)	34.4	26 (159)	16.4	< 0.001	**< 0.001***	88 (211)	41.7	9 (34)	26.5	0.092	0.710
Anxiety Disorder	235 (657)	35.8	22 (158)	13.9	< 0.001	**< 0.001***	81 (211)	38.4	7 (34)	20.6	0.045	0.540
Bipolar	13 (653)	2.0	0 (159)	0	0.084^	0.255	2 (211)	0.9	0 (34)	0	1.000^	1.000
ADD/ADHD	26 (655)	4.0	6 (158)	3.8	0.921	1.000	22 (211)	10.4	3 (34)	8.8	1.000^	1.000
Autism/ASD	12 (659)	1.8	4 (157)	2.5	0.526^	0.835	7 (210)	3.3	6 (34)	17.6	0.004^	0.108
Other[#]	56 (656)	8.5	3 (160)	1.9	0.004	**0.023***	31 (209)	14.8	1 (34)	2.9	0.059^	0.637
BPD	9 (656)	1.4	0 (160)	0	0.218^	-	2 (209)	1.0	0 (34)	0	1.000^	-
OCD	10 (656)	1.5	0 (160)	0	0.224^	-	3 (209)	1.4	1 (34)	2.9	0.455^	-
PTSD	28 (656)	4.3	1 (160)	0.6	**0.026**	-	14 (209)	6.7	0 (34)	0	0.228^	-
Ungrouped	16 (656)	2.4	2 (160)	1.3	0.550^	-	11 (209)	5.3	0 (34)	0	0.371^	-

ADD = Attention Deficit Disorder, ADHD = Attention Deficit Hyperactivity Disorder, ASD = Autism Spectrum Disorder. [#] = Mental health diagnoses in the 'Other' category which had free text input were then subjected to quantitative content analysis which is reported below the dashed line. Note that the N of the categories below the line do not equal those in 'Other' due to multiple responses for certain respondents and also some respondents not completing the free text input. BPD = borderline personality disorder. OCD = obsessive-compulsive disorder. PTSD = post-traumatic stress disorder. Other = all other disorders/conditions not grouped into the above categories such as oppositional defiance disorder, body dysmorphic disorder, adjustment disorders, schizophrenia, and panic disorders. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

* = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table 3.28 Own experience mental health outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Panic Attacks	318 (656)	48.5	34 (159)	21.4	< 0.001	**< 0.001***	117 (210)	55.7	14 (34)	41.2	0.115	0.776
Identity Formation Difficulty	97 (657)	14.8	16 (159)	10.1	0.124	0.335	113 (211)	53.6	14 (34)	41.2	0.180	1.000
Recurrent Nightmares	135 (657)	20.5	10 (159)	6.3	< 0.001	**< 0.001***	59 (211)	28.0	5 (34)	14.7	0.102	0.734
Alcohol/Drug Dependency	31 (657)	4.7	17 (159)	10.7	0.004	**0.023***	21 (209)	10.0	7 (34)	20.6	0.085^	0.710
Eating Disorder	94 (656)	14.3	6 (159)	3.8	0.001	**0.007***	45 (209)	21.5	2 (34)	5.9	0.032	0.540
Insomnia	183 (655)	27.9	32 (157)	20.4	0.059	0.203	68 (209)	32.5	10 (34)	29.4	0.717	1.000
Learning Difficulties	46 (653)	7.0	11 (157)	7.0	0.987	1.000	31 (208)	14.9	10 (34)	29.4	0.037	0.540
Seen Mental Health Professional #	348 (655)	53.1	55 (159)	34.6	< 0.001	**< 0.001***	151 (211)	71.6	20 (34)	58.8	0.133	0.845
Psychologist	239 (655)	36.5	29 (159)	18.2	**< 0.001**	-	104 (211)	49.3	10 (34)	29.4	**0.031**	-
Psychiatrist	111 (655)	16.9	20 (159)	12.6	0.179	-	46 (211)	21.8	7 (34)	20.6	0.873	-
Other	74 (655)	11.3	6 (159)	3.8	**0.004**	-	35 (211)	16.6	3 (34)	8.8	0.246	-

= Mental health professional as designated by the respondent. Other = all other medical health professionals as designated by the respondent such as general practitioner, psychotherapist, mental health nurse, counsellor, cognitive behavioural therapist. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

4.8.5 Effect of Maternal Complications on Mental Health Outcomes

Stratifying by maternal complications revealed that those spontaneously conceived adults whose mothers experienced maternal complications during pregnancy were significantly more likely than those whose mothers did not experience any maternal complications to self-report being diagnosed with other non-listed mental health conditions (16.0% v 5.9%, p = 0.005) (Table 3.29). However, the content analysis did not reveal any significant differences in which conditions were diagnosed. Spontaneously conceived adults whose mothers experienced maternal complications were however no different to those gestated without maternal complications in terms of being diagnosed with depressive disorder, anxiety disorder, bipolar, ADD/ADHD, or autism/ASD. No differences were also observed between DC adults whose mothers experienced maternal complications and those who did not experience maternal complications in terms of frequencies of being diagnosed with depressive disorder, anxiety disorder, bipolar, ADD/ADHD, autism/ASD or any other non-listed mental health condition.

In terms of the respondent's own experience, spontaneously conceived adults whose mothers experienced maternal complications during pregnancy were significantly more likely to self-report experiencing recurrent nightmares (36.3% v 14.7%, $p < 0.001$), eating disorders (23.0% v 10.1%, p = 0.004), insomnia (42.0% v 24.0%, p = 0.004), learning difficulties (13.9% v 4.9%, p = 0.011), and seeing a mental health professional (67.3% v 46.3%, p = 0.003) (Table 3.30). Content analysis of free text input for which mental health professional was consulted revealed no differences between the cohorts. No differences were observed between spontaneously conceived adults in terms of self-reported frequencies of panic attacks, identity formation issues or dependency on alcohol and or drugs. Similar to diagnosed mental health outcomes, donor sperm-conceived adults whose mothers experienced maternal complications during pregnancy were not significantly different to those whose mothers did not experience any maternal complications in all outcome measures.

Stratifying outcomes by maternal complications showed that the donor sperm-conceived cohort exhibited no differences in their mental health outcomes. In contrast, spontaneously conceived adults reported increased incidences of adverse mental health outcomes if their mother had experienced maternal complications during pregnancy.

Table 3.29 Diagnosed mental health outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Depressive Disorder	38 (100)	38.0	179 (616)	29.1	0.071	0.241	16 (44)	36.4	58 (152)	38.2	0.829	1.000
Anxiety Disorder	43 (100)	43.0	181 (613)	29.5	0.007	0.053	16 (44)	36.4	53 (152)	34.9	0.855	1.000
Bipolar	2 (99)	2.0	10 (613)	1.6	0.678^	1.000	1 (44)	2.3	1 (151)	0.7	0.401^	1.000
ADD/ADHD	8 (100)	8.0	21 (612)	3.4	0.050^	0.179	6 (44)	13.6	15 (152)	9.9	0.579^	1.000
Autism/ASD	6 (101)	5.9	8 (614)	1.3	0.008^	0.054	3 (44)	6.8	6 (151)	4.0	0.425^	1.000
Other#	16 (100)	16.0	36 (613)	5.9	< 0.001	**0.005***	7 (44)	15.9	20 (151)	13.2	0.653	1.000
BPD	1 (100)	1.0	6 (613)	1.0	1.000^	-	0 (44)	0	1 (151)	0.7	1.000^	-
OCD	4 (100)	4.0	5 (613)	0.8	0.026^	-	0 (44)	0	2 (151)	1.3	1.000^	-
PTSD	9 (100)	9.0	18 (613)	2.9	0.008^	-	4 (44)	9.1	10 (151)	6.6	0.523^	-
Ungrouped	3 (100)	3.0	13 (613)	2.1	0.481^	-	3 (44)	6.8	5 (151)	3.3	0.383^	-

ADD = Attention Deficit Disorder, ADHD = Attention Deficit Hyperactivity Disorder, ASD = Autism Spectrum Disorder. # = Mental health diagnoses in the 'Other' category which had free text input were then subjected to quantitative content analysis which is reported below the dashed line. Note that the N of the categories below the line do not equal those in 'Other' due to multiple responses for certain respondents and also some respondents not completing the free text input. BPD = borderline personality disorder. OCD = obsessive-compulsive disorder. PTSD = post-traumatic stress disorder. Other = all other disorders/conditions not grouped into the above categories such as oppositional defiance disorder, body dysmorphic disorder, adjustment disorders, schizophrenia, and panic disorders. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

* = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table 3.30 Own experience mental health outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Panic Attacks	55 (101)	54.5	248 (614)	40.4	0.008	0.054	27 (44)	61.4	75 (151)	49.7	0.172	1.000
Identity Formation Difficulty	22 (101)	21.8	78 (614)	12.7	0.015	0.085	22 (44)	50.0	78 (152)	51.3	0.878	1.000
Recurrent Nightmares	37 (101)	36.6	90 (614)	14.7	< 0.001	**< 0.001***	13 (44)	29.5	33 (152)	21.7	0.280	1.000
Alcohol/Drug Dependency	5 (101)	5.0	37 (614)	6.0	0.670	1.000	9 (44)	20.5	13 (150)	8.7	0.054^	0.961
Eating Disorder	23 (100)	23.0	62 (614)	10.1	< 0.001	**0.004***	10 (44)	22.7	25 (150)	16.7	0.358	1.000
Insomnia	42 (100)	42.0	147 (612)	24.0	< 0.001	**0.004***	19 (44)	43.2	42 (150)	28.0	0.056	0.961
Learning Difficulties	14 (101)	13.9	30 (609)	4.9	0.001	**0.011***	7 (44)	15.9	21 (149)	14.1	0.764	1.000
Seen Mental Health Professional #	68 (101)	67.3	284 (613)	46.3	< 0.001	**0.003***	31 (44)	70.5	105 (152)	69.1	0.862	1.000
Psychologist	40 (101)	39.6	193 (613)	31.5	0.107	-	20 (44)	45.5	71 (152)	46.7	0.883	-
Psychiatrist	21 (101)	20.8	96 (613)	15.7	0.197	-	8 (44)	18.2	32 (152)	21.1	0.677	-
Other	13 (101)	12.9	60 (613)	9.8	0.343	-	9 (44)	20.5	18 (152)	11.8	0.144	-

= Mental health professional as designated by the respondent. Other = all other medical health professionals as designated by the respondent such as general practitioner, psychotherapist, mental health nurse, counsellor, cognitive behavioural therapist. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

4.8.6 Effect of the Country of Birth on Mental Health Outcomes

Stratifying by country of birth revealed that donor sperm-conceived Australians were not more likely than those Australians conceived spontaneously to self-report being diagnosed with depressive disorder, anxiety disorder, bipolar, ADD/ADHD, autism/ASD or any other non-listed mental health condition (Table 3.31).

Table 3.31 Diagnosed mental health outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Depressive Disorder	123 (339)	36.3	31 (70)	44.3	0.208	1.000
Anxiety Disorder	129 (339)	38.1	36 (70)	51.4	0.038	0.515
Bipolar	7 (338)	2.1	0 (70)	0	0.609^	1.000
ADD/ADHD	6 (335)	1.8	4 (70)	5.7	0.076^	0.760
Autism/ASD	7 (339)	2.1	6 (70)	8.6	0.013^	0.264
Other[#]	26 (336)	7.7	8 (70)	11.4	0.311	1.000
BPD	6 (336)	1.8	1 (70)	1.4	1.000^	-
OCD	4 (336)	1.2	2 (70)	2.9	0.277^	-
PTSD	11 (336)	3.3	2 (70)	2.9	1.000^	-
Ungrouped	10 (336)	3.0	3 (70)	4.3	0.476^	-

[#] = Mental health diagnoses in the 'Other' category which had free text input were then subjected to quantitative content analysis which is reported below the dashed line. Note that the N of the categories below the line do not equal those in 'Other' due to multiple responses for certain respondents and also some respondents not completing the free text input. BPD = borderline personality disorder. OCD = obsessive-compulsive disorder. PTSD = post-traumatic stress disorder. Other = all other disorders/conditions not grouped into the above categories such as oppositional defiance disorder, body dysmorphic disorder, adjustment disorders, schizophrenia, and panic disorders. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant ($p < 0.05$). ADD = Attention Deficit Disorder, ADHD = Attention Deficit Hyperactivity Disorder, ASD = Autism Spectrum Disorder.

In terms of the respondent's own experience, donor sperm-conceived Australians were significantly more likely to self-report having difficulty forming their identity (54.3% v 13.6%, $p < 0.001$), but not for the self-reported frequencies of panic attacks, recurrent nightmares, identity formation issues, dependency on alcohol and or drugs, eating disorders, insomnia, learning difficulties or visiting a mental health professional (Table 3.32).

Table 3.32 Own experience mental health outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Panic Attacks	168 (338)	49.7	48 (70)	68.6	0.004	0.098
Identity Formation Difficulty	46 (338)	13.6	38 (70)	54.3	< 0.001	**< 0.001***
Recurrent Nightmares	61 (338)	18.0	15 (70)	21.4	0.508	1.000
Alcohol/Drug Dependency	19 (338)	5.6	9 (70)	12.9	0.038^	0.515
Eating Disorder	48 (338)	14.2	11 (70)	15.7	0.743	1.000
Insomnia	86 (337)	25.5	21 (70)	30.0	0.438	1.000
Learning Difficulties	21 (337)	6.2	12 (70)	17.1	0.002	0.081
Seen Mental Health Professional #	208 (337)	61.7	50 (70)	71.4	0.125	0.912
Psychologist	162 (337)	48.1	39 (70)	55.7	0.244	-
Psychiatrist	60 (337)	17.8	11 (70)	15.7	0.675	-
Other	33 (337)	9.8	8 (70)	11.4	0.679	-

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. BH correction not performed on content analysis. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$). # = Mental health professional as designated by the respondent. Other = all other medical health professionals as designated by the respondent such as general practitioner, psychotherapist, mental health nurse, counsellor, cognitive behavioural therapist.

4.9 Mental Health Outcomes Discussion

This study highlighted that the adult DC respondents in this survey reported more mental health issues than their spontaneously conceived counterparts and were more likely to have seen a mental health professional. However, of the DASS-21 categories of recent depression, anxiety and stress, only stress was found to be significantly elevated in the DC cohorts. These findings reflect previous reports highlighting that some DC adults have issues with their conception mentally and emotionally.[837, 838]

The number of adverse mental health differences experienced by the DC participants in this study in comparison to those conceived spontaneously were more numerous than the physical health outcomes observed in the same cohorts.[5] Considering that some DC people feel that they suffer as a consequence of being separated from biological kin, the loss of family history, the lack of medical health history, and being deceived of their origins by their parents,[839] these may potentially be associated with the poorer mental health outcomes observed in this study.

The lack of significance for the DASS-21 depression score contrasts with the elevated reports of DC respondents being diagnosed with a depressive disorder. However, the DASS-21 assessment is of how the respondent felt during the previous week and is not necessarily indicative of their diagnosed mental health history.

In line with the outcome analysis of physical health outcomes after stratification by sex, maternal complications of pregnancy and country of birth, the mental health outcomes analysis was also hampered by a lack of statistical power in the DC cohorts due to sample size and the number of reports. Subsequently, no conclusions can be drawn on the effects that these may have had on the mental health outcomes of adult DC people except for an observed increase in the difficulty in forming their identity for Australian DC adults. The identity formation difficulty would be consistent with the literature.[839]

In spontaneously conceived people, females showed an increased incidence of adverse mental health outcomes including depressive disorder, anxiety disorder, PTSD, panic attacks, recurrent nightmares, eating disorders, and seeing a mental health professional. However, males were more likely to suffer from substance abuse issues with a dependency on alcohol or drugs. These sex-based differences are consistent with previously published data highlighting that females are more likely to experience mental health issues including anxiety, depression, PTSD and mood disorders, while men are more likely to experience substance abuse.[840, 841]

The association of maternal complications during pregnancy highlighted an increased risk for being diagnosed with various non-listed mental health conditions, and also for experiencing recurrent nightmares, eating disorders, insomnia, learning difficulties, and seeing a mental health professional. These results are also consistent with published data highlighting an association between PE and PIH with an increased risk for mental disorders in the offspring,[310, 311, 842] that also include depression,[843] ADHD and ASD.[237]

Despite child studies, generally showing positive results in terms of psychological adjustment and notwithstanding the limitations of those studies, adult participants in this survey had more self-reported adverse outcomes than their spontaneously conceived peers. While this study is not without limitations, the results are consistent with the observations of outcomes in qualitative adult donor conception studies.[771, 800, 828-830] Unlike some childhood studies in which the child is unaware of their conception as the parents had not disclosed, all adult DC respondents in the survey were aware of their donor origins.

Disclosure to a person of their DC status at an early age has been associated with less psychological trauma.[800, 844] Parental attitudes towards disclosure has changed over time from being mostly opposed to disclosure,[845-848] to increasing openness.[849-852] While the age of disclosure or conception discovery was not investigated, many participants in this study were conceived during a period when secrecy was the accepted practice. Respondents may have

had their conception disclosed in adulthood or may have reassessed their feelings and started searching for information and biological kin once they had started a family of their own, or after the death of a parent as seen with adoptees.[853] Therefore, their poorer mental health may potentially be influenced by adulthood triggers. Another cohort of people who suffer similar situations of biological family separation, loss of family and health histories, and being deceived of their origins are adoptees. Similarities between adoptees and DC people in this respect have been reported.[10, 853-855] Adult adoptees too have been shown to suffer worse mental health outcomes than non-adoptees,[856-859] and therefore, the results of this study are also consistent with studies on adult adoptee outcomes.

An alternative and possibly contributing factor is that developmental defects only become apparent through adult based psychological diagnoses and under conditions of adult functioning. This alternative is plausible if one considers variations in adult function as an extension of the already demonstrated increased risk of adverse perinatal outcomes in DC neonates.[4, 654, 655] Furthermore, studies have highlighted that perinatal outcomes such as low birthweight (< 2500g), are associated with poorer adult psychological outcomes and responses,[831, 860] including ADHD,[861, 862] as was found in this study.

4.10 Limitations of the Adult Health Survey Study

This adult health survey is the first study that has not only investigated the self-reported physical health outcomes of adult DC people but also quantitatively investigated their mental health rather than qualitatively. However, the study is limited due to the self-selecting nature of the sample. Therefore, it is not representative of a true cross-section of the adult DC community. Furthermore, the sample bias is influenced by the fact that the majority of DC adults in the community, in general, are not aware of how they were conceived.[747] Subsequently, the sample is best described as a subset of DC adults, and therefore the results should be treated with caution and not used to extrapolate to DC people as a whole. Given the issues associated with recruiting DC adults, it is not possible to get a true representative cross-section which has been noted by other researchers.[771, 800, 863, 864] This sample bias issue will continue to be an issue for researchers for as long as non-disclosure continues.

Further limitations are observed through the self-reporting of various health conditions in which the respondents may inadvertently provide false or misleading data. In an attempt to deal with this reporting or recall bias, it was requested that respondents only respond in the affirmative if they had been diagnosed with that condition by a medical health professional to

provide a professional objective perspective. The only conditions where this was not required were the person's own mental health experiences and responses to the DASS-21 questionnaire, which is a validated instrument for assessing depression, anxiety and stress. Additionally, in the respondent characteristics of birth questions in terms of maternal smoking and maternal complications, the respondent was also able to answer, 'do not know'. The approach of only requesting diagnosed responses appears to be partially successful due to the low number of physical health conditions that were significantly different from the spontaneously conceived cohort. Furthermore, the Benjamini-Hochberg procedure was implemented as a statistical control to adjust for false-discovery.

Due to recall bias, specific maternal complications such as PE or PIH were not requested. Instead, the question reflected a general category of maternal complications and therefore, could also reflect the reporting of a wide range of complications which may also potentially affect the outcomes.

The self-selection bias of the DC cohort is further exacerbated by the recruitment sources, with the primary source being social media and online DC groups, in particular Facebook support groups. It is not unreasonable to postulate that these support groups represent a further subset of DC individuals that may be looking for emotional support in dealing with issues surrounding being donor-conceived or that they are potentially seeking assistance in their search for information regarding their biological family including the donor.[772, 802] Notwithstanding these limitations, Facebook and online support groups have been used by other researchers to not only recruit DC people,[771, 773, 865] but are now viewed as a valid recruitment tool for health studies,[766] including hard to access populations.[762] This accurately describes not only the DC community but the study that was conducted.

Self-selection of participants in a health study has the potential to attract people who have adverse health conditions. This bias, however, would be reflected in both the donor-conceived and spontaneously conceived cohorts equally. Analysis of the spontaneously conceived cohort against the ABS NHS and CDC NHANES reference data validated the spontaneously conceived cohort, and therefore the study was not overtly influenced by this potential bias.

While the DC groups and spontaneously conceived group were well matched on numerous respondent characteristics data, there was a considerable sex selection bias, with over 80% of respondents in all groups being female. The sex-ratio imbalance was not unexpected considering previous studies of DC adolescents and adults reported 74% - 85% of participants

were female,[771-773, 800-802] and that FB advertisement data highlighted that females responded substantially better to the survey advertising. Nonetheless, while significant differences were observed in both physical and mental health outcomes as stratified by sex, the sex-ratio of each group was not statistically different and therefore not likely to have adversely impacted outcome comparisons. The differences in mental health outcomes by sex is consistent with data published by the World Health Organisation.[866] Additionally, good invariance between men and women,[832] and across English speaking countries,[835] have been found with the use of the DASS-21. Accordingly, the sex variation between females and males and countries of birth in this study should not affect DASS-21 outcomes.

Regardless of the limitations, a strength of the study is that both the DC cohorts and spontaneously conceived cohort were not significantly different in terms of the respondent's characteristics of mean age, the ratio of females to males, mean height, levels of alcohol consumption per week, whether they currently smoke cigarettes or tobacco, the amount and type of exercise they participated in per week, whether their mother had smoked during their pregnancy, and whether the respondent had undergone fertility treatment. Subsequently, the cohorts could be viewed as being matched well across a range of characteristics.

4.11 Adult Health Survey Conclusions

This study is the first to investigate the health outcomes, both physical and mental, in adult DC people in a quantitative manner. As identified in the systematic reviews, no studies of physical outcomes have been previously reported while the literature also highlights that previous mental health studies of adult DC people were sparse, more generalised and qualitative. This study showed that this subset of DC adults reported significantly increased incidences of adverse outcomes in a limited number of physical health conditions and a large variety of mental health outcomes in comparison to those conceived spontaneously. However, there were just over 100 health outcome categories, depending on the mode of conception (all v sperm), in which no significant differences were observed, thereby showing that for most health outcomes that DC people were not significantly different.

There are considerable limitations associated with this study as is present in all other studies previously published on child, adolescent and adult DC people. Nonetheless, it does represent important data from an interesting subset of DC adults that have not been studied in this manner previously. The importance and validity of this data are that the self-reports of adverse health outcomes is supported in the following ways:

• The adverse physical health outcomes are consistent with the increased incidences of birth defects that have been associated with donor sperm conceptions.[4]
• The adverse physical health outcomes are consistent with the DOHaD phenomenon linking the increased incidences of adverse neonatal outcomes associated with donor conception,[1, 4, 654] with increased incidences of adverse adult health conditions.
• The increased incidence of twins observed is consistent with other donor sperm conception studies,[2] as well as data showing that double embryo transfers are still being used in preference to single embryo transfers in various donor oocyte programs in the United States resulting in high multiple delivery rates.[867]
• The increased incidences of maternal complications observed in this DC cohort have been observed in donor gamete treatment modalities.[181, 185]
• The increased incidence of maternal complications and the correlation with adverse physical and mental health outcomes in the offspring is consistent with other studies.[232, 237, 310, 868]
• The increased incidences of adverse mental health outcomes are consistent with the framework and literature on psychosocial outcomes, which includes, but is not limited to identity formation issues which were observed in this DC cohort.[839]
• That increased incidences of adverse outcomes in both physical and mental health conditions exhibit a direct and indirect association with each other that is supported by the literature.[869]

On the last point raised above, it could be postulated that the increased incidence of physical health conditions may be due to the self-selection of participants who were already experiencing mental health issues as a reason for why they were in online support groups. Rather than this postulation diminishing the findings, it instead highlights the incredibly complex nature of investigating the long-term health outcomes for DC people and the issues surrounding recruitment. Regardless, the data is consistent with numerous other studies as well as mechanisms that support the findings and therefore, the findings should not be ignored, but instead used as an impetus for further investigation.

This study exceeded its expectation in the minimal sample size desired for the survey. The actual sample size of DC adults (n = 282) was larger than many previous studies of DC people,[771, 772, 800, 870, 871] however, it was smaller than some.[773, 801, 872] Unlike the study presented here, those studies with larger sample sizes also incorporated under-aged DC people (children and or adolescents), rather than adults separately. The use of an online

questionnaire and the various recruitment methodologies implemented have therefore proved effective in recruiting the hard to reach DC cohort.

Returning to the donor conception sources of epigenetic change that may influence long-term health outcomes, the increased incidence of maternal complications which include conditions such as PE and PIH was correlated with a range of adverse physical and mental health outcomes in the adult DC population investigated in this study. Any correlation with cryopreservation of donated gametes is unclear. A question was not included in the survey to elucidate if the respondents had details of whether they were conceived with cryopreserved gametes. Due to the problems that DC people have encountered in accessing records from ART clinics,[31] let alone the fact that any records about such information is more likely contained within their mother's treatment records and would require their mother to request this information rather than the DC person, this question was excluded from the survey.

A possible methodology would be to stratify by age and analyse those people from specific jurisdictions that would be known to have been conceived after mandated donor sperm cryopreservation. However, comparing those people to others who were conceived prior is problematic as cryopreservation had been in use since 1953 with dry ice,[873] and 1963 with liquid nitrogen,[874] and therefore any data from people in the earlier period would likely be contaminated with data from cryopreserved donor sperm conceptions. As described in the donor sperm systematic review section, a better method to assess the effect of cryopreservation would be to compare outcomes from fresh and cryopreserved partner's sperm in IVF treatments.

The effect of embryo culture on adult health outcomes is also unclear. In the same manner as the question pertaining to cryopreservation was not included in the survey, so too for embryo culture and the use of IVF or ICSI with donor sperm, a question regarding this was not included for the same reasons. What can be ascertained from demographic data of the respondent's ages is that 22.4% of respondents were born before the third baby ever produced from IVF was born in 1980.[875] Also, 70.6% of respondents were born before the first ICSI birth in 1992.[876] At least in the earlier period of IVF, the proportion of cycles implementing donor sperm would have been lower than the use of their partner's sperm. Subsequently, the proportion of people born from donor insemination would have outweighed those conceived from IVF with donor sperm. However, there would likely be some respondents who would have been conceived with donated sperm used in IVF or ICSI treatment modalities and whose outcomes may also be influenced by embryo culture.

Evidence from this study shows that there is a cohort of people who have been conceived with donated gametes who self-reported adverse physical and mental health outcomes in adulthood more often than a cohort of people who were conceived spontaneously. Increased incidences of maternal complications and multiplicity were observed in the DC cohort, which are well-known confounders. However, these confounders are intrinsically linked with the ART treatments themselves. Maternal complications such as PE and PIH are correlated with the use of donated gametes which introduce a novel antigen. While multiplicity is sometimes iatrogenically induced in donor sperm treatments when ovulation induction is implemented and in oocyte/embryo donation when double or multiple embryos are transferred. Subsequently, appeals to diminish the importance of the findings due to confounding are therefore problematic, especially when the findings are supported by and consistent with the published literature.

This investigation aimed to conduct an exploratory study that looked at the question of whether the long-term health of DC people was any different from those who were conceived spontaneously. It achieved that goal. Donor-conceived people in this study did have different health outcomes in adulthood than those conceived spontaneously. Due to limitations, the findings are by no means conclusive but should be used as an impetus to conduct further studies into donor conception outcomes which may in turn either dispute or support the findings. Furthermore, these findings can be used in conjunction with the meta-analyses and previously published literature to determine emerging issues of physical and mental health welfare of DC people. It is this question of how such findings may be incorporated in considerations of child welfare paramountcy to which this thesis now turns. In the following chapters, the ethico-legal concept of child welfare paramountcy and its relevance to donor conception is presented and discussed in light of the findings of these three original studies.

CHAPTER 5. THE CHILD WELFARE PARAMOUNTCY PRINCIPLE AND PROCREATIVE FREEDOMS

In the first part of this thesis, the findings of the investigation of perinatal and adult health outcomes showed that donor conception was associated with altered health outcomes for the offspring in the immediate and long-term. This finding raises questions regarding the clinical application and ethico-legal regulation of the practice of donor conception in Australia and elsewhere. This thesis now takes a different direction and proceeds to explore the findings of the studies presented within the context of the ethical and legal principle of child welfare paramountcy.

This chapter will start by presenting the ethico-legal principle of child welfare paramountcy, followed by how this principle is germane to discussions concerning DC people and their welfare. The welfare of a DC person incorporates many facets but also includes their physical and mental health from birth to adulthood. A common argument presented in debates regarding child welfare paramountcy, particularly in reference to disclosure to the child of their conception, is that parents are entitled to procreative freedom and choice.[838, 877, 878] However, the freedoms and choices of parents influence the welfare of the child more broadly. Both child welfare paramountcy and procreative freedoms will be discussed primarily in the Australian context. However, arguably the concerns are applicable in many other countries.

5.1 Introduction - A Definition of Child Welfare Paramountcy

In a description of the progress of donor conception practices through history, Allan describes that the paradigm was initially focused on the adults – i.e. potential parents and donor, while the interests of the offspring were mainly ignored.[21] Then starting in the 1980s legislation was gradually introduced in Sweden, and in the Australian states of Victoria and South Australia that would address some of the needs of the donor-conceived.[879-881] These pioneering pieces of legislation would then be followed by more legislation in other jurisdictions around the world in the coming decades. Donor-conceived people as a separate group to the general population had various aspects of their welfare enshrined and in some instances made of paramount importance.

As described by the Macmillan Dictionary (online), the definition of paramount is:

> "adjective: more important than all other things"[882]

The noun paramountcy regarding child welfare is, therefore, the principle that the welfare of the child is of greater importance than other members of the donor conception triad; that of the recipient parents and the donor. Specifically, the Macmillan Dictionary (online) also uses child welfare paramountcy in its description of the term paramount:

> "The interests of the child are paramount."[882]

Furthermore, the Australian Law Dictionary (online) describes the paramountcy principle as:

> "The overriding obligation on family courts to consider the best interests of the child as paramount, taking priority over…."[883]

The law dictionary here is referencing how courts are to view the paramountcy principle concerning the best interests of the child, which can be seen to stem from the normative interpretation of the word paramount. Such that the best interests of the child are to be held over and above those of other parties. The child welfare paramountcy principle in Australia has been viewed as essential and has subsequently been institutionalised through legislation, guidelines and conventions.

5.2 Institutionalisation of Child Welfare Paramountcy

Children deserve special consideration due to their vulnerability and the decisions that adults make on their behalf. Their welfare as a paramount concern forms the basis for numerous Australian state and federal legislation, guidelines, and conventions to be described hereafter. In the realm of ART, whereby the welfare of the child may be influenced by not only decisions made before their conception but the actual conception procedure itself, it is necessary to investigate whether this welfare paramountcy principle is being sufficiently and appropriately implemented.

At various stages in the remainder of the thesis, there will be discussions and descriptions about the welfare and interests of children. However, it should be noted they will go on to become adults themselves, and therefore the terms child, children, adults, people, and offspring can be used interchangeably when describing a DC person as befitting the situation. Their welfare as a paramount consideration should not be diminished when they become an adult as their adult welfare is affected by their conception, gestation and birth. It has also been the view of various state and federal inquiries and legislative reviews into donor conception in Australia that the welfare of DC children does not cease to be a paramount consideration when they become an adult.[37, 837, 838, 884-886]

Morally and ethically, there is a duty of care to safeguard that the welfare of people conceived through ART, including donor conception, are treated as paramount. In contrast to those conceived spontaneously, donor conception in Australia is institutionalised through legislation, regulation and codes of practice. All Australian ART clinics must receive accreditation by following the *Code of Practice for Assisted Reproductive Technology Units* from the Reproductive Technology Accreditation Committee (RTAC) which is the responsibility of the Fertility Society of Australia (FSA).[501] Additionally, the National Health and Medical Research Council's (NHMRC), *Ethical guidelines on the use of assisted reproductive technology in clinical practice and research*[887] must be followed along with relevant federal or state legislation.

The accreditation process enables ART clinics to practice fertility treatments which would otherwise be an offence under Commonwealth law.[888] The first state to enact legislation was Victoria with the *Infertility (Medical Procedures) Act (1984)*, which was assented by parliament in 1984 but not enacted till 1988.[880] Also enacted in 1988 was the South Australian *Reproductive Technology Act*.[881] These were followed by Western Australia,[889] and then New South Wales.[890] It is the states rather than the Commonwealth which legislate in the area of donor conception as health law is the jurisdiction of the states. Effectively, Australian ART clinics are self-governed by their own society while following various legislation, guidelines and codes of practice. Medicare, Australia's universal health insurance scheme, partly funds various fertility treatments through the public purse, further institutionalising the paradigm of donor conception in Australia.[891]

It is this institutionalisation and the intentionality of procreation with the use of donated gametes/embryos that elevates the responsibility of not only the government and clinics but also recipient parents and donors. From a legal perspective, this duty of care to the DC child's welfare has also been enshrined as paramount. For example, South Australia, which was one of the first states to enact legislation concerning donor conception, has the following passage written in its *Reproductive Technology Act 1988*.

> "The welfare of any child to be born in consequence of an artificial fertilisation procedure must be treated as of paramount importance, and accepted as a fundamental principle, in the formulation of the code of ethical practice." p7.[881]

The paramountcy principle was also echoed later in Victorian legislation,[892] and both the 2004 and 2007 NHMRC versions of the *Ethical guidelines on the use of assisted reproductive*

technology in clinical practice and research.[893, 894] However, the latest 2017 version of the Ethical guidelines reduced the welfare of a DC child from paramount to simply:

> "….promote the consideration of the interests and welfare of the person who may be born…." p75.[887]

Why the NHMRC reduced the importance of the welfare of the DC children is not made clear but rather the alteration is used to highlight the ever-changing face of legislation and guidance in Australia, even though other pieces of legislation to be described later clearly enshrine the paramountcy principle. Other state legislation concerning donor conception while not elevating the welfare of the child to a paramount consideration emphasises that the welfare of the child is important and must be assessed. Similar to the NHMRC stance, Western Australian legislation stipulates:

> "that the prospective welfare of any child to be born consequent upon a procedure to which this Act relates is properly taken into consideration." p13.[889]

While the welfare of the DC child in Western Australia is also of concern for legislators, what is meant by the term 'properly' is subject to interpretation. The other state that has donor conception legislation is New South Wales. The New South Wales legislation,[890] describes not only the welfare of the child from the perspective of disclosure of information and contact between the donor and child but also concerning adults who have a genuine interest in the welfare of the child. However, the welfare of the child is not described as a general principle of the Act. The rest of the Australian states and territories do not have specific legislation dealing with donor conception. Instead, each state and the clinics therein must follow the NHMRC Ethical guidelines.

While some states and previously the NHMRC, have placed child welfare as a paramount concern, other states and currently the NHMRC does not describe the welfare of the child as paramount. It is, however, still an important and vital consideration. South Australia went one step further through amendments made in 2009 that not only perpetuated the welfare paramountcy principle but elevated it as a core guiding principle of the Act:

> "The welfare of any child to be born as a consequence of the provision of assisted reproductive treatment in accordance with this Act must be treated as being of paramount importance, and accepted as a fundamental principle, in respect of the operation of this Act." p3.[895]

This amendment highlights the importance of the welfare principle in respect to DC people in South Australia that it is not just a single concern among many others that should be balanced but instead forms the ethos and paradigm for the operation of the Act.

5.3 Child Welfare Paramountcy in Other Legislation and Conventions

In other legislation around Australia, that deals explicitly with the welfare of the child; there are many other examples whereby the welfare of the child is deemed as paramount. Of particular relevance is the Commonwealth of Australia *Family Law Act* which references the best interests of the child as a paramount consideration in 16 sections/subsections including specifically 'Section 67ZC – Orders relating to welfare of children' p224.[896]

Adoption is another such area, and one which has remarkable similarities and parallels to donor conception.[10, 752, 854, 855, 897, 898] In adoption legislation, every single state and territory in Australia has enshrined the paramountcy principle in their Acts.[899-906] Additionally, there are other pieces of Australian legislation, including those at the federal level, which also stipulate this paramountcy principle. These include, but are not limited to the Commonwealth of Australia, *Family Law Act*;[896] New South Wales, *Children and Young Persons (Care and Protection) Act*;[907] Queensland, *Child Protection Act*;[908] Western Australia, *Children and Community Services Act*;[909] South Australia, *Children's Protection Act*.[910] Therefore, the child welfare paramountcy principle is a fundamental basis for the treatment of children in Australia.

External to the legal situation within Australia is Australia's responsibilities in an international context. Australia is a signatory to the United Nations Convention on the Rights of the Child (UNCRC). The UNCRC is the most widely and rapidly ratified international treaty on human rights. It has been ratified by 196 countries with the only member nation not to ratify the convention being the United States.[911] Although this convention does not have the force of the law in Australia in that it has not been put into legislation and is therefore not enforceable, it does provide important guidance on how children should be treated in Australia. The convention states:

> "Bearing in mind that, as indicated in the Declaration of the Rights of the Child, the child, by reason of his physical and mental immaturity, needs special safeguards and care, including appropriate legal protection, before as well as after birth" p1.[912]

The above statement highlights that conditions and events occurring before a child's birth which also includes the conception of a child, are important considerations when addressing their rights as further outlined in the convention. Of particular relevance is Article 3.1, which states:

> "In all actions concerning children, whether undertaken by public or private social welfare institutions, courts of law, administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration". p2.[912]

The above passage further highlights that the welfare of the child is of primary (a synonym of paramount) importance for the United Nations Committee on the Rights of the Child, which is also expressly described concerning adoption in Article 21:

> "States Parties that recognize and/or permit the system of adoption shall ensure that the best interests of the child shall be the paramount consideration…." p6.[912]

The amendments made to South Australian legislation which made the paramountcy principle a core guiding principle of the Act were reportedly introduced to reflect the state's obligation under the UNCRC as well as to reflect the Australian family law system, both of which are described above.[913] Furthermore, when the paramountcy principle has been assessed in Australian courts, the court has decided to apply a strong view.[914] That is the courts have taken a strong stance in ensuring the best interests of the child are paramount rather than a weaker position that includes more significant consideration of the interests of other parties such as the parents.[914] The specific Children's Court version of the Local Court Bench Book as written by the Judicial Commission of New South Wales also highlights that the paramountcy principle is reflected in the UNCRC and are relevant for determining the child's best interests.[915]

Therefore, by bringing all the federal and state legislation, regulation, legal precedence as well as international convention together, the welfare of the child is a fundamental principle in Australian society. Children are deemed to be the most vulnerable, and subsequently, those whose interests must be held over and above those of adults.

If, however, a child's welfare is held up as being paramount and above that of recipient parents, can that adversely impact an adult's ability to create a family through procreation? In a discussion of the impact of ART legislation and guidelines, Bromham and Lilford argue that laws and principles that are propounded for the benefit of one party, in this case, the child, "may restrain autonomy, beneficence and justice done to another", in this case, the recipient parents.[916] While their argument was focused on surrogacy; the concept equally applies to donor conception since surrogacy also uses donated gametes. They posit that restraining the autonomy of a person's reproductive choices should be kept to a minimum. In other words, a person should maintain full autonomy over their reproductive choices without undue external interference. The issue of procreative freedoms and autonomy will now be discussed.

5.4 Procreative Autonomy and Procreative Freedoms

A cornerstone of family life and society has been the freedom to procreate such that it may be viewed as a human freedom or right that is inalienable as described by the United Nations Universal Declaration of Human Rights:

> "Men and women of full age, without any limitation due to race, nationality or religion, have the right to marry and to found a family." p5.[917]

The term 'found a family' is open to interpretation and has been used as an argument for procreation and the ability to access ART services.[918] This is with the exception for certain legalities such as:

• The prohibition of marriage and procreation between siblings (referred to as consanguinity) in various countries such as Australia;[919]

• The prohibition on underage sex (age of consent laws vary by each state in Australia);

• Cultural sensitivities in which some cultures/societies may still have arranged marriages;

Australian citizens, therefore, have the freedom to procreate with whomever they want, whenever they want and however they want.

When discussing procreation, one approach may be to draw on a rights-based approach. Problematically, however, it has been argued that while there is the right to choose to procreate, there is no absolute right to a child.[920] If there were such a right, then the state would have to ensure that every person who wished to have a child was provided with one. It is subsequently more appropriate to discuss procreation using an autonomy and freedoms approach.

Procreative autonomy and procreative freedom are often used interchangeably as they are inextricably linked. However, a distinction is made here between the two with procreative autonomy being the ability to make decisions about procreating[921] and procreative freedom being the ability to act on procreative decisions.[922] As donor conception is the act of creating a child through the use of donated gametes; procreative freedoms will be discussed primarily rather than procreative autonomy.

In the case of donor conception, if the child's welfare is held as paramount and certain conditions are required to meet that welfare, then these conditions alter a parent's autonomy and freedoms. As an example, where it is determined that the child has the right to access identifying information on the donor, the procreative autonomy and freedom of a parent will be curtailed. Such a situation occurs if the parents sought to utilise a donor who would remain

anonymous. This choice has now been adversely affected because they would be prevented from making that choice. In effect, they would be prevented from using an anonymous donor in order to protect the child's right to have access to the donor's identity. Currently, in Australian clinical practice of donor conception, anonymous gamete/embryo donations are prohibited to protect this right of the child.[887, 923] For an analysis of other factors affecting the welfare of the child, including a lack of access to identifying information on the donor, please see the publication *Conceptualising a Child-Centric Paradigm: Do We Have Freedom of Choice in Donor Conception Reproduction?* (Appendix 4).[839]

5.4.1 Current Procreative Freedoms

John Robertson, an ethicist who specialised in reproductive medicine, provided a broad definition of procreative autonomy, which he defined as the freedom to choose whether or not to bring a child into the world.[922] Applying a donor conception lens to this concept redefines procreative autonomy as the freedom to choose whether to bring a child into the world with the assistance of a gamete/embryo donor (a third party).

Legally that freedom can only occur provided donor conception or processes associated with it were not prohibited by law. Prohibition occurs in some countries such as Italy which prevents access to donor conception by same-sex couples and single women,[924] and Germany, which prohibits oocyte donation and surrogacy.[925] From an Australian perspective, any person meeting eligibility requirements stipulated by legislation, regulation and guidelines to receive treatment with donated gametes from an ART clinic has the procreative freedom to create a child using donor conception.

Some recipient parents have turned to donor sperm from private arrangements, including the sourcing of donors online.[926-929] These cases will be excluded from any further analysis or discussion as these private arrangements are not conducted within clinics and subsequently fall outside of legislation/regulation. Subsequently, private arrangements cannot be encompassed by the institutionalised paramountcy principle in the context of donor conception, but certainly, child welfare paramountcy is still applicable to private arrangements in other areas of law.

The outcome of having a child may have little to do with the autonomy of choice or freedom to act. Instead, it could potentially be situational circumstances such as not having a partner or biological in nature such as not being able to produce gametes capable of fertilisation and creating a viable embryo. In the case of a woman, it may also be the ability to carry that

embryo and resultant foetus to term. The freedom to procreate has not been infringed by law or regulation. Instead, it is an outcome of nature and or circumstance. Procreation is a biological function and not an automatic right.

The following statement has been made previously:

> "Donor conception is a means to an end, a choice that circumvents infertility." p370.[839]

What this means is that the condition that makes a person infertile is not treated in donor conception. For a male who has azoospermia (zero sperm count), or has a low sperm count, or poor-quality sperm, he is not treated so that he can produce progeny himself. Rather, another man is brought in as a donor/substitute to provide sperm. For a woman who may be of advanced age or has poor quality oocytes, they are not treated to improve the quality of their oocytes. Once again, another woman is brought in who then provides oocytes so that a pregnancy can be achieved. In all of these cases, the actual cause of infertility has not been treated and using the term 'fertility treatment' in these instances is a misnomer.

The non-treatment of the cause of infertility for those listed above is in contrast to those who use donor conception because they are socially infertile. In these situations, the reason that these people are unable to have a child is not that they are biologically infertile, but rather their social situation means that they are unable to have a child without assistance. For same-sex men or single men who are not biologically infertile, they will have to use surrogacy to have a child. Subsequently, they are socially infertile.[930] Similarly, single women or same-sex female couples may also be socially infertile and will require assistance through the use of donor sperm.[930] In these cases, they are also not receiving fertility treatment themselves to correct a biological infertility problem, but instead are using donor conception because their social situation impedes conceiving a child. It is worth noting that biological infertility may also afflict those who have social circumstances preventing the ability to have a child.

The introduction of ART in its many modalities of IVF, donor conception, ICSI, surrogacy or other various treatments has enabled countless couples and individuals to fulfil their dreams of becoming parents. In essence, ART had provided them with increased freedom to procreate. Procreative freedom in the context of this thesis is the ability to use donor conception in an attempt to have a child which may not have otherwise been possible due to biological and or social reasons. The use of a donor(s) means that the child will, therefore, not be biologically related to one or both parents.

5.4.2 The (Ir)Relevance of Genetic Connections

While donor conception does not treat infertility itself, what it does do is provide a genetic link, a genetic continuity, for one person when creating a child. The exception to this genetic continuity is embryo donation. Donor conception also allows a woman to carry a child and experience pregnancy which is a significant reason for some who chose donor conception, including oocyte donation.[931-934] The genetic link is another major deciding factor when parents choose to undertake specific forms of donor conception such as sperm and oocyte donation (but not embryo donation) over adoption.[846, 935]

The significance of this genetic link is supported empirically with the majority of parents who have surplus embryos created through IVF electing to discard them or donate them to research in preference to donating them to other people.[637-639, 936] Parents who decide to discard embryos likened the process of embryo donation to adoption.[636] This genetic link is both profound and emotionally important to them.

The concept of genetics and genetic inheritance is highlighted by parents choosing a donor that looks like them so that the child will 'pass' as theirs.[937] However, the genetic connection to the sperm or oocyte donor is often ignored or obsolete. For example, in the case when parents keep the child's conception a secret and withhold that information from the child. They have ignored this genetic connection but upheld the one with the raising parent who is biologically related. In effect, they have created a duality in which genetic connections are both important and unimportant. This relevance or irrelevance of genetic versus social connections is interchanged to fit the desires of the parents to justify their procreative decisions and freedoms.[938]

Genetics and the effect it can have on a person's appearance and the subsequent notion of family connectedness is significant. A genetic connection is also a reason why ICSI, an ART procedure used to treat some male infertility, is chosen in favour of donor insemination or even adoption.[939, 940] This decision to use ICSI is made even when the increased risk for adverse perinatal outcomes and that male children are also more likely to experience infertility themselves is known.[454, 941, 942] A deep sociological and biological desire to procreate induces parents to make decisions about the child that fertile parents do not typically have to make and which may affect the child's welfare.

5.4.3 Child Welfare Paramountcy vis-à-vis Procreative Freedoms

Procreative autonomy and procreative freedoms are not confined to just choosing donor conception as a fertility treatment modality. Once that decision has been made, the adults wishing to be parents then have the choice of which clinic to receive treatment in, which in turn dictates what state or country the treatment would be obtained. If this occurs outside their own state, then this is termed reproductive tourism.[943] This choice has implications for the legislation and regulation that may affect their treatment and what rights or privileges their child may experience later on, particularly concerning the access of information about the donor and siblings.[944-946] The potential parents may also have a choice about which donor to use as some clinics have donor catalogues.[947, 948] Depending on the jurisdiction, they may have a choice of using an anonymous donor or one whose identity may be known currently or at a later date.

Additionally, potential parents will have to decide whether or not they will inform the child of their donor conception status (disclosure). Parents of spontaneously conceived children will typically have freedom of choice in many areas of the child's life, including whether to disclose various family issues. Unlike families with spontaneously conceived children, families with donor-conceived children have to deal with additional complexities including the physical and mental health welfare issues outlined in the previous chapters as well as social welfare issues that have been the subject of considerable academic discourse.[8, 12, 30-32, 949-953] Debate, therefore, centres on the question of whether these parents have the same freedoms?

Placing prohibitions or constraints on procreative autonomy or freedoms in the spontaneous conception setting would be considered unethical. By extrapolation, it could be argued that it would also be unethical to apply prohibitions or constraints on donor conception. Nevertheless, applying the same rationale to an artificial construct that implements a third party for sperm or oocyte donation or third parties for embryo/double donation is untenable. Not only does the addition of third parties muddle the relationship between the recipient parents themselves but also between the child and their parents.[839] Furthermore, there are potential life-long adverse effects of being conceived with donated gametes,[5] as shown in the previous chapter.

Due to the state-sanctioned and funded donor conception treatments, in addition to altered health trajectories, a greater level of duty of care must be afforded to the donor-conceived by the state, their parents, the donor(s), and clinicians. Existing legal frameworks and legislation should already cater to this duty of care, and no further consideration should be required.

However, the risk of adversely impacting the welfare of the child as a consequence of these procreative freedoms warrants further analysis of these issues using the child welfare paramountcy principle. John McMillan succinctly argues:

> "However, in cases where assisted reproductive techniques are requested even though it is known that there is a significant risk of a poor health outcome or a breakdown in the family unit, then there is a question mark over whether this is an appropriate use of procreative autonomy." pp54-55.[954]

What McMillan is describing is that procreative autonomy, and by association, procreative freedom should not necessarily be unmitigated if the autonomy and freedom adversely impact the welfare of the child significantly. In the case of donor conception, 'poor health' as described by McMillan includes both poorer mental as well as physical health which was observed in the preceding chapters. However, what does the welfare of the child fully encapsulate? The next section will describe the child's welfare concerning donor-conception.

5.5 Are All Donor-Conceived Welfare Issues Created Equal?

The focus of this thesis has been on the quantifiable physical and mental health welfare outcomes for those people who are donor-conceived. However, their welfare issues are not confined to these quantifiable outcomes but also incorporate other psychosocial welfare issues which have been described by the author of this thesis in the publication *Conceptualising a Child-Centric Paradigm: Do We Have Freedom of Choice in Donor Conception Reproduction?* (see Appendix 4).[839]

This publication described seven welfare issues, which may affect DC people differently. These welfare issues were:

1) Deception of their origins;
2) Kinship separation;
3) Loss of identity;
4) Late discovery;
5) Incomplete medical histories;
6) Quantifiable physical health issues;
7) Consanguineous relationships.[aa]

[aa] Consanguineous relationships in the legal context are between a person and a genetic relative.[883] Such consanguineous relationships may be objectionable on moral and biological grounds. Furthermore, consanguineous relationships between a person and their ancestor/descendent, or between siblings, including half-siblings, are also prohibited in Australia by the *Marriage Act.*[919]

The quantifiable physical health outcomes have been presented in the preceding chapters. While the publication initially presented quantifiable physical health outcomes only, this issue should also be expanded to include mental health outcomes, and therefore it should be relabelled as simply quantifiable health issues. The purpose of listing the other six welfare issues is not to discuss them in any detail as they are adequately described in the publication. Instead, it is to highlight that a DC child's welfare is multifactorial, and the case of why the quantifiable physical and mental health outcomes are significant to the child welfare paramountcy principle will be presented.

Except for one welfare issue, the effect on the person can depend on many external factors.[839] These can include psychosocial components such as the family they were raised in, whether their donor conception origins were disclosed and whether the DC person has access to identifying and medical information about the donor which have been central to previous debates concerning the welfare of DC people.[8, 11, 12, 31, 37, 837, 838, 884-886] Subsequently, these other six welfare issues are termed 'psychosocial welfare issues'.

They also include the DC person themselves and whether they seek out information/contact, or it may include various cultural factors. Additionally, there may be institutionalised components such as the practice paradigm surrounding donor conception when they were conceived such as but not limited to whether anonymous or identity release donors were used, or the completeness and accessibility of records including familial health histories. The exception is quantifiable physical and mental health outcomes, as these numerous external factors can have a significant influence on the other welfare issues.

Regarding welfare issues that involve psychosocial factors, for example, there are a considerable number of studies that show that DC children, in particular, appear to be well adjusted and are flourishing in these family environments.[739, 740, 826, 827, 844, 955-964] Conversely, there are some studies and reports that show that some DC people are traumatised and unhappy with how donor conception has affected them.[37, 746, 830, 837, 838, 965] Furthermore, some DC adults have taken their issues with their respective jurisdictions to court for redress.[bb] Highlighting the issues faced by some DC adults is that in 2019, sixteen donor-conceived and surrogacy born adults travelled from around the world to the United Nations in Geneva under their own funding to attend the conference celebrating the 30th anniversary of the UNCRC and

[bb] Pratten v British Columbia, 2012; Rose and Another v Secretary of State for Health, Human Fertilisation and Embryology Authority, 2002; Adams v Registrar of Births Deaths and Marriages, 2014.

presented their stories and the adverse effects being donor-conceived had on them at a special workshop titled *Children in the age of biotechnology*.[966, 967]

What is interesting from the previously mentioned studies, reports and legal proceedings is that those showing good psychological adjustment were typically represented by children or young adolescents, while the latter reports of poor psychosocial and legal outcomes occurred in adults. This correlation is consistent with the findings of a systematic narrative review in which the importance of the genetic ties was noted in adolescents and adults.[968] This observation does not imply that children will always be unaffected by their conception, whereas adults will represent a change in this outcome. Instead, it would be more accurate to stipulate that the situation is complex and can be affected by many aspects occurring within the family environment.[969] Furthermore, in some instances a proportion of adults may spend more time dealing with their conception, particularly after having children of their own; and or, additionally, some may have found out in adulthood about their conception with reported increases in adverse outcomes for these late discoverees.[800, 801]

While this section has not presented information on each psychosocial welfare issues in-depth (for further analysis, please see Appendix 4), the purpose of presenting these issues is to highlight that any argument regarding psychosocial issues is contentious. There is both evidence and philosophical argument which can support either side of the debate.

In contrast to psychosocial outcomes, the issue of quantifiable physical and mental health is unarguably significant to the welfare paramountcy principle. It is problematic to argue that a DC person is not worse off than spontaneously conceived or autologous gamete conceived peers if the empirical data proves otherwise. Unlike psychosocial data, physical health outcome data is less prone to the external factors described above. Subsequently, if there are increased incidences of physical conditions or diseases occurring in the DC population, then this shows that they are adversely affected by the process. That is not to say the other six welfare issues are not significant to the DC person and the welfare paramountcy principle; rather, it is to say that quantifiable outcomes are more readily defensible.

Notwithstanding links between physical and mental health and potential bias of studies through self-selection, quantifiable health outcome data provide the most rigorous means of determining if the immediate and long-term welfare of DC people has been adversely affected. Furthermore, they provide a robust means of assessing the child welfare principle in donor conception and whether procreative freedoms should be constrained, which will be

determined in Chapter 6. The assessment of the DC person's welfare centres on whether DC people are being harmed.

5.6 Conclusion - Welfare Issues or Harms?

This chapter has investigated child welfare. In some instances, it can be argued that DC people are adversely affected by the paradigm and or by their actual mode of conception. Previously these issues have been described as 'welfare issues', but perhaps a more appropriate description would be 'harms' or 'potential harms'.

In an attempt to determine if the welfare issues constitute harm, it is pertinent to discuss the definition of harm. The Collins English dictionary describes 'harm' as:

> "physical or mental injury or damage."[970]

While the Merriam-Webster's online legal definition of 'harm' describes it as the:

> "loss of or damage to a person's right, property, or physical or mental well-being."[971]

The Australian Law Dictionary does not describe the term 'harm' but only references a 'harm principle' in Australian Law that is used in jurisprudence in which power or authority over someone against their will can only be done to prevent harm to others.[883] The plain English language definition and legal definition provided above accurately describes the adverse physical and mental health outcomes observed in DC neonates and adults, and therefore they would be accurately described as harm.

The Australian Law Dictionary definition further supports the principle that if DC people are harmed by being donor-conceived and the paradigm, that legally there are grounds to support restricting procreative freedoms if the actions of parents in exercising this freedom harm the child. Nevertheless, what constitutes harm in the context of the outcomes already described?

In the *Conceptualising a Child-Centric Paradigm* publication, the seven welfare issues were described as potential harms.[839] They are potential in as much that they will not affect each DC person equally. From an individual perspective, some individuals have not been adversely affected by being donor-conceived, whether physically, mentally or emotionally. These people have not been harmed. Those that have been adversely affected could potentially be classified as being harmed as is the collective group of DC people who have poorer health measures in terms of neonatal outcomes and self-reported adult health characteristics, both diagnosed and self-assessed.

For specific individual outcomes, it is imperative to recognise a difference between what may be statistically significant and what may be clinically significant as the two are not always the same. This difference can be particularly relevant in self-reported outcomes which may include data that is not discrete or dichotomous but may fit somewhere on the range of outcomes.[972] An example of such an outcome from the studies in this thesis is the outcome of mean gestational age in oocyte donation neonates which had a statistically significant mean difference of -0.3 weeks, in comparison to those conceived with autologous oocytes. It could be argued that such a difference is not clinically significant as 0.3 weeks is unlikely to affect the health outcomes of the child as they were still above 37 weeks of gestation. Another example, this time from the adult health survey, is evidence showing that DC adults had a significantly lower mean BMI of 25.3, which is still in the overweight category as was the spontaneously conceived people's mean BMI of 26.2. Therefore, the result, in this case, may not be clinically significant as the risk to health from being overweight is still the same.

Dichotomous outcomes that were significantly different, however, such as preterm delivery, are clinically significant as the neonate is now in the at-risk category. Additionally, outcomes of increased incidences of type 1 diabetes diagnoses, would also have clinical relevance. The majority of the adverse physical and mental health outcomes presented in this thesis are dichotomous, and their increased incidences of diagnosis are of clinical relevance and therefore constitute harm.

The psychosocial welfare issues or potential harms described above have been considerably debated in the literature,[8, 10, 12, 824, 839, 949, 950, 973] unlike the novel physical and mental health welfare issues/harms presented in chapters 2-4. The novelty is particularly noted with this thesis presenting the first published systematic review and meta-analyses of donor oocyte[1] and donor sperm[3, 4] neonatal outcomes, and the first published quantifiable physical health outcomes in an adult DC cohort.[5]

A framework and model for the analysis of the welfare issues, specifically the physical and mental outcomes described previously will, therefore, now be discussed and used to assess arguments for or against unconstrained procreative freedoms using donor conception.

5.6.1 Linking Procreative Freedoms, Child Welfare and DOHaD

Child welfare principles and that their welfare is paramount is a cornerstone of not only legislation concerning reproductive technologies but many other pieces of Australian legislation, guidelines and international conventions. Although this can be a very complex concept to address, the welfare of the child can be assessed using a simplified strategy by determining whether a child is worse off than their peers. In this instance, according to the findings of the studies, it appears that a cohort of DC people are in health terms, worse off than their spontaneously or autologous oocyte-conceived counterparts. However, it has yet to be verified whether they have been harmed.

It is this verification which can cause problems when assessing outcomes which involve psychosocial influences. The problem of verification is because there can be a rainbow of outcomes with evidence and theory alluding to both positive and negative consequences. Quantifiable physical and mental health outcomes provide a means of assessing the welfare principle in a more systematic and scientifically defensible way.

Procreative freedoms and specifically the ability to create a child through the use of donor conception can adversely affect the welfare of that child. This potential was highlighted through DOHaD and donor conception mechanisms of inducing epigenetic change that was associated with adverse neonatal and adulthood outcomes.

In the following chapter, a harms-based assessment will be implemented to analyse both the welfare of DC people and parental freedoms separately.

CHAPTER 6. FREEDOM AND HARMS

Given that in the previous chapter it was argued that poor physical and mental health outcomes could be construed as harms, this chapter will provide a synthesis and summary of the findings of the studies conducted (section 6.3) and their place within the DOHaD phenomenon (section 6.4). These findings will then be assessed against the child welfare paramountcy principle and parental procreative freedoms using a harms-based approach.

6.1 Introduction

A harms-based assessment of a DC person's welfare was chosen because it was considered to be preferable to alternative approaches, such as a rights-based assessment. A justification for this choice is presented in section 6.5. The assessment will then be used to determine if the welfare paramountcy principle is being upheld in Australia (section 6.6) and whether there is a case for parental procreative freedoms to be constrained (section 6.7). While this thesis focussed on the DC people themselves, broader implications for society as a whole as a result of these findings will also be discussed (section 6.7.1).

However, before harms are addressed, a significant ethical argument against child welfare paramountcy must be considered. This argument forwards the position that regardless of the outcomes for DC people, the alternative of not existing at all is worse and therefore, any adverse outcomes are simply the cost of existence.

6.2 It is Better to Exist

From the non-identity problem first put forward by Derek Parfit,[974] some may argue it is better to exist and be adversely affected or harmed than not to exist at all. This argument has been used in various contexts in discussions of donor conception outcomes.[975-979] This assertion can be used as an argument against the quantifiable physical and mental health welfare issues.

An argument sometimes used to counter the non-identity problem is that it could be argued that if the life that exists is so horrible, it would be better not to exist at all. This argument is the concept of 'wrongful life' or 'wrongful birth' which has been used legally in suing obstetricians, paediatricians or others whose actions or decisions may have harmed a child significantly.[980] This concept is distinct from the non-identity problem in subtle ways, and it is erroneous to use it as a counter to the non-identity problem in donor conception.[954]

Conception and existence as a specific person is a matter of chance. In spontaneous conceptions, on any given day, a different sperm may fertilise the egg resulting in a different person. There is no guarantee that the same sperm will fertilise the egg if at all. This alternative also does not consider timing and whether a day later will miss the woman's fertility window. Nor does it consider genetic recombination, which is the shuffling of DNA between chromosomes when creating gametes and also when a sperm fertilises an egg. It is a reason why not only siblings are so varied, but that genetic variability is a cornerstone of sexual reproduction. Alternatively, in IVF with donated gametes, the embryologist may choose a different donated oocyte or sperm to fertilise for IVF. In this instance, if donor conception were not used, the child would not exist. Furthermore, even when donor conception, including donor insemination, is used, the specific child created is highly dependent on chance.

The non-identity problem has been addressed and rejected by various academics. For instance, Weinberg posits that there is a distinction to be made between future people who will exist but are not yet born and just merely hypothetical people that possibly could be born but also have not.[981] What this means for Weinberg is that people who will not exist cannot be harmed by non-existence. The corollary is that those who will exist should not have their future and current interests influenced by their need to exist in the first instance. In analysing the work of Weinberg, Johns asserts in support of this concept:

> "But people who do exist can be, and are, harmed by the conditions of their conception, and have an interest in not being so harmed." p134.[982]

The statement by Johns goes to the heart of this thesis. Which is the question of whether DC people have different short and long-term health outcomes, and are harmed as a result? Reports from adults highlight that some suffer emotional and psychological traumas.[37, 746, 830, 837, 838, 965] Those authors who propose that the non-identity problem should prevail are applying an existential debt[cc] onto the donor-conceived. The imposition is that they should accept any adverse effects that befall them that is associated with their conception because otherwise, they would not exist.

McMillan addresses the non-identity problem by assessing some rival solutions. He presents the work of Kamm and Hanser who both assert that it can be wrong to create someone who is harmed even if the alternative is not to have existed.[985, 986] However, McMillan's position is that such a harms-based analysis is not an appropriate approach to address the non-identity

[cc] For discussion regarding existential debt and donor conception please refer to Rushbrooke[983] and Rose.[984]

issue. His conclusion is drawn from the postulation that a harms-based approach relies on decisions being made preconception when we cannot know what the likely outcomes of these decisions are.[954] Subsequently, he proposes the use of a rights-based approach. On face value, this approach is appealing because the welfare of DC people is often described in terms of rights (i.e. the right to know who the donor and kin are, as well as a right to know a familial medical history).[949, 950, 953, 987-994]

McMillan's rejection of the harms-based approach is problematic in donor conception even before the findings of this thesis emerged. Historically, evidence from similar fields could have been implemented in the analysis. Academic literature has highlighted psychological issues that adoptees were faced with, in the decades prior to donor conception becoming a mainstream treatment modality (the 1970s).[995-999] The similarities between adoption and donor conception were being drawn in the early period of adoption law reform debate,[18, 1000] and have continued in more recent times.[10, 752, 854, 898, 953, 1001] Furthermore, reports show that there are a proportion of DC people who have been traumatised by their parent's deception or withholding of information and their lack of knowledge of their kin and heritage.[37, 746, 830, 837, 838, 965] It has also been argued that a familial medical health history is vitally important to the welfare of DC people.[1002-1004] With the findings presented in this thesis of the quantifiable physical and mental health outcomes in addition to the aforementioned reports, the assessment of outcomes can be made preconception due to the evidence available.

An antithetical argument is that any adverse effects are only potential and that there is no guarantee that they will occur. However, many judgments and decisions in medicine, including preconception and perinatally, are based on risk and probability.

The non-identity problem is a substantial ethical argument which posits that it is better to exist and to suffer various adverse outcomes than not to exist at all. The concept also involves the possibility that if different actions are undertaken, the person would also not exist. However, the non-identity argument is not appropriate in donor conception because the DC person does not exist yet, and a non-existent person cannot be harmed by non-existence. Additionally, when they do exist, they will have an intrinsic interest in not being adversely affected by their conception. It is also known what the risks are to their health as befitting a harms-based approach. Evidence suggests that donor-conception may produce an at-risk group healthwise.

While the discussion in this section is not an exhaustive exposé, it does provide a rebuttal to the substantial ethical argument that is used against the welfare of DC people as a paramount concern. With the non-identity argument rebutted, it is appropriate that attention now is focussed on the interaction between the welfare outcomes (including DOHaD), the child welfare paramountcy principle and procreative freedoms.

6.3 Welfare Outcomes for Donor-Conceived People

In terms of the welfare outcomes for DC people, the studies included in this thesis started by exploring what was currently known in the literature through a systematic review and meta-analysis that investigated health outcomes from the neonate to adulthood. Interestingly, considerably more evidence was found on the outcomes for donor oocyte-conceived people than those conceived from the other treatment modalities of donor sperm and donor embryos even though the use of donor sperm predates donor oocyte/embryos by almost 100 years. This evidence was in the form of neonatal outcomes, as childhood and adulthood outcomes were absent from the donor oocyte/embryo literature.

Meta-analyses revealed that donor oocyte-conceived neonates were more likely than those conceived with autologous oocyte IVF to be born of low birthweight, very low birthweight, preterm delivery, and preterm delivery with low birthweight.[1] They were also more likely to be born at a lower mean gestational age and as a twin or a higher-order multiple.[1] These findings remained significant when controlling for singletons and were supported by systematic reviews conducted by other researchers who observed the same adverse outcomes as well as other outcomes, including small for gestational age and very preterm delivery.[275, 654-656]

IVF using autologous oocytes has also been associated with increased incidences of adverse perinatal outcomes in comparison to neonates conceived spontaneously.[58, 1005] Subsequently, the use of donor oocytes is correlated with a further worsening of outcomes over and above the already acknowledged adverse outcomes linked with autologous IVF.

Meta-analyses for donor sperm-conceived offspring was far more equivocal. Initial analysis suggested that donor sperm-conceived neonates were not at increased risk for being born of low birthweight, preterm delivery or with increased incidences of birth defects than spontaneously conceived neonates.[3] However, the review highlighted that very few studies had comparable outcomes that could be used in meta-analyses. There was also little in the way of childhood outcomes except for an increase in malformation rates at approximately five

years of age, and inconclusive data on IQ, learning difficulties and giftedness. Similar to donor oocyte outcomes, no data was available on the physical health of adult donor sperm-conceived people.

Subsequently, a perinatal study was conducted investigating the physical health outcomes in a population-based cohort in South Australia to increase knowledge in the area of donor sperm perinatal outcomes that were identified as being under-studied in the systematic review. The South Australian population-based study showed that those neonates who were conceived with donor sperm were more likely to be born with a lower mean gestational age and at an increased risk of being born preterm delivery with low birthweight.[2] Further outcome analysis was hampered by issues of statistical power and a low count of events for some outcomes, which could potentially be improved with a larger sample size that could be obtained from data pertaining to subsequent years.

This data was entered into the existing meta-analysis along with data from two further studies to improve the knowledge of donor sperm neonatal outcomes. This analysis showed that the initial conclusions were not consistent with the updated meta-analysis due to the lack of studies that were initially included and that the new meta-analysis showed that donor sperm-conceived neonates were more likely to be born of low birthweight and with increased incidences of birth defects.[4] Furthermore, these infants were more likely to be delivered via caesarean section, with forceps delivery, through induction of labour and that their mother was more likely to experience preeclampsia.[4]

The outcomes for donor sperm and donor oocyte-conceived neonates were different in that donor oocyte-conceived neonates were more likely to be born with a greater range of adverse outcomes. In comparison, donor sperm-conceived neonates were more likely to be born with birth defects. Nevertheless, those conceived with donor oocytes were not more likely to be born with birth defects which could potentially be associated with the better quality of the oocyte that is correlated with the relatively younger age of the donor and or poor quality oocytes failing to survive or fertilise after the freeze/thawing process.

There was a lack of studies and data investigating outcomes from donor embryos to make any conclusions. However, considering that mechanistically there are similarities for novel antigen induction of PE and PIH by the donated oocyte as well as the culture of the embryo in the laboratory, it would be plausible that the outcomes for donor embryos would be equivalent to donor oocyte outcomes. Notwithstanding, there is some evidence in the

literature to suggest that the outcomes can potentially be worse, particularly in terms of the incidence of maternal complications of pregnancy.[189, 667]

Limited evidence was available from the systematic review suggesting there may potentially be an increased risk for neonates conceived with donated gametes to be admitted to the NICU and with longer stays in the hospital. More recent studies support this suggestion.[572, 645, 646, 712]

With a dearth of studies investigating the physical health of adult DC people, the opportunity was taken to conduct the first exploratory study of the self-reported physical health of DC adults in comparison to spontaneously conceived adults. The study also provided an opportunity to investigate the self-reported mental health of DC adults in a quantitative manner that had not been done previously. After adjusting for false-discovery, DC adults were observed to self-report significantly higher incidences of being diagnosed by a medical health professional with a range of adverse physical and mental health outcomes including type 1 diabetes, thyroid disease, Hashimoto's disease, acute bronchitis, environmental allergies, sleep apnoea, depressive disorder, attention deficit disorder or attention deficit hyperactivity disorder, and autism or autism spectrum disorder. They were also more likely to self-report having undergone surgery to have ear tubes or grommets implanted. For non-diagnosed outcomes they were more likely to report experiencing panic attacks, recurrent nightmares, difficulty forming their identity, eating disorders, alcohol/drug dependency, learning difficulties, and have visited a mental health professional. They were also more likely to have been stressed in the week before the survey as determined by DASS-21 analysis.

The adult health survey is not without limitations, similar to previous studies of adult DC people, primarily due to the secrecy that surrounds donor conception. This secrecy results in the majority of DC people being unaware of their mode of conception.[747] Subsequently, the cohort is self-selecting and non-representative. The study is, therefore, best described as showing that a specific group of DC adults self-reported poorer health outcomes than a specific group of spontaneously conceived people. Extrapolation of results to the broader DC community should be done with caution. The purpose of the study was exploratory to determine if any data would suggest that further investigation was warranted. The answer is; yes.

Further studies should be conducted to see if these associations hold or are ameliorated. The increased incidences of adverse maternal complications associated with donor conception which are iatrogenically linked to the treatment and therefore part of the aetiological pathway

are correlated with increased risks for adverse perinatal outcomes and adverse adult physical and mental health outcomes. These findings are consistent with mechanisms and outcomes associated with DOHaD, making rejection of the findings due to limitations or confounding problematic.

6.4 DOHaD and Donor Conception

In Chapter 1, the phenomenon of DOHaD was outlined in addition to how donor conception provides mechanisms that may introduce changes, including epigenetic modifications, which may potentially lead to adverse perinatal outcomes, which in turn have been associated with adverse long-term health outcomes for adults.

In the classical DOHaD model, the most common correlations cited are between the adverse perinatal outcomes of preterm delivery and small for gestational age (as well as low birthweight) and the increased incidences of cardiovascular disease, obesity and type 2 diabetes.[1006] From the neonatal outcomes observed in the studies presented in this thesis of the systematic reviews and the combination of the population-based study of donor sperm-conceived neonates, it was found that DC neonates were significantly more likely to be born with a range of outcomes that would fit within the DOHaD concept. Notably, donor oocyte-conceived neonates were more likely to be born preterm and also of low birthweight and very low birthweight among other outcomes. While donor sperm-conceived neonates were more likely to be born of low birthweight.

Given these neonatal outcomes, it could be postulated that the adult DC population may potentially experience increased incidences of cardiovascular disease, obesity and type 2 diabetes. However, that was not the case. DC adults and primarily donor sperm-conceived adults were no worse than their spontaneously conceived peers on those three outcomes. Conversely, they were observed to have a statistically significant lower mean BMI.

These observations do not preclude the DC cohort from going on in the coming years to have an increased incidence of type 2 diabetes, and cardiovascular disease as the window for observing these may be in the future. Instead, it means that at this point in time at an average age of 32-33 years, the DC cohort was not adversely affected by the typical DOHaD long-term outcomes associated with their birth characteristics. Potential reasons for the lower observed mean BMI were outlined in the discussion of the physical health outcomes.

Adult DC people self-reported increased incidences of other adverse health outcomes in comparison to spontaneously conceived adults. An interesting finding of the diagnosed physical health outcomes of type 1 diabetes, thyroid disease, Hashimoto's disease, acute bronchitis, environmental allergies and sleep apnoea is that four of those six are immunological in nature. Type 1 diabetes is an autoimmune disorder in which the immune system has attacked the insulin-producing cells in the pancreas. Hashimoto's disease is an autoimmune disorder leading to hypothyroidism. The immunological nature of environmental allergies is mostly self-explanatory, while acute bronchitis is inflammation of the bronchial tubes. This proportion of physical health outcomes that have an immunological component is suggestive that perhaps there has been an immune system modification in these individuals.

The association of donor conception with an altered immunological profile in the offspring has been linked with ART treatments more generally. A recent study has shown an unadjusted increased risk for type 1 diabetes in ART children.[1007] Adjusting for confounders ameliorated the association except for frozen embryo transfer suggesting that cryopreservation may also be involved.

6.4.1 Preeclampsia, DOHaD and Offspring Outcomes

Considering that donor conception is associated with an increase in maternal hypertensive disorders and particularly preeclampsia for both donor oocyte,[654, 1008] and donor sperm,[181, 294] which is described as an immune-mediated disorder characterised by chronic inflammation;[1009] it is plausible that the altered maternal immune environment has also reprogrammed the immune system of the foetus and subsequent adult. This concept is supported by the conclusions from a review on PE and the long-term health outcomes for offspring.[220] Other studies have also been suggestive of such an altered immunological system with increased incidences of long-term infectious morbidity,[1010] childhood asthma,[228, 1011, 1012] atopic or allergic sensitisation,[230, 1013] and an increased pro-inflammatory profile,[1014] observed in offspring gestated under preeclamptic conditions.

Also supporting the concept that PE and in particular, the maternal immune system is a significant contributor to adverse neonatal outcomes and subsequently adulthood outcomes for DC people, is an observation from the donor oocyte-conceived systematic review. The outcome in question is the decreased incidence of low birthweight in those donor oocyte neonates that made it to term. These neonates were less likely to be affected by a PE gestation,

as the most effective treatment for PE is delivery[dd] in which the mother may be induced early,[1016] and PE is also associated with preterm delivery.[704] In these instances, in which a severe maternal immune response is not induced through the presence of a novel antigen (donor oocyte), perhaps the better-quality oocyte from a donor who is younger than the recipient mother,[520] may lead to improved outcomes. Supporting these correlations is evidence of PE being associated with SGA/IUGR,[210-215] and SGA/IUGR with altered immune systems in the offspring.[99-101] The issue then becomes about avoiding the incidences of PE and ameliorating the maternal immune response, which will be discussed in the recommendations presented in Chapter 7.

Mechanistically, PE may induce programming of the foetus through oxidative stress and epigenetic modification. PE is characterised by elevated oxidative stress,[1017] over that typically associated with a normal pregnancy.[1018, 1019] Oxidative stress is a significant driver of epigenetic modification,[1020] and has been argued to be part of the pathway leading to programming and altered outcomes through DOHaD.[1021, 1022]

In a review of the literature, it was argued that abnormal DNA methylation is the most important epigenetic modification associated with PE.[276] In an analysis of cord blood from foetuses experiencing a gestation complicated by PE, genome-scale hypomethylation (decreased DNA methylation) was observed, with the top pathway and network affected being involved in the inflammatory response as well as cellular function/maintenance, and respiratory disease.[1023] Inflammatory/immunological and respiratory disorders were the main statistically significant self-reported diagnoses observed in the adult physical health survey.

From a mental health aspect, PE is associated with SGA/IUGR due to placental insufficiency, with SGA/IUGR shown to adversely affect brain development in human infants,[1024] and animals.[134, 135] Animal models have also shown an adverse effect of PE on brain development in addition to the effects of SGA/IUGR.[1025-1027] While human studies have shown impaired cognitive function in children born from a PE gestation,[1028] and who have been argued to be an at-risk paediatric group for adverse neural development.[1029] The effect of PE on mental health continues into adulthood with a correlation with cognitive dysfunction and reduced memory,[1030] as well as increased psychological problems.[240]

[dd] Another common treatment for preeclampsia is the use of aspirin.[1015]

Preterm delivery which is also correlated with PE is another risk factor for adverse neurodevelopment and reduced brain volume.[1031] The direct effect of PE and SGA/IUGR/PD on the mental health of offspring appears straightforward, but other maternal mediators further complicate the situation.

It has been suggested that high maternal anxiety may also lead to increased incidences of adverse mental health outcomes in offspring.[1032] However, others suggest that there are both maternal and foetal factors which do include preterm delivery and low birthweight,[1033] and therefore maternal factors including stress or postnatal influences are not the only considerations for the pathway of PE outcomes.

In terms of epigenetic mechanisms for mental health, altered methylation of the glucocorticoid receptor and the corticotropin-releasing hormone-binding protein occurs as a result of PE,[1034] which may then adversely affect foetal brain development.[1035] Altered glucocorticoids levels perinatally (or the ability for glucocorticoids to bind to receptors), is associated with psychiatric disorders in later life with evidence in animal models and has been proposed as one mechanism for the DOHaD origins of psychiatric disorders in humans.[1036]

Another mechanism for altered neurodevelopment is inflammation. Interleukin-6 (IL-6), which is a pro-inflammatory cytokine is elevated in pregnancies complicated by PE.[1037, 1038] Elevated maternal IL-6 in the third trimester, independent of PE, has been correlated with altered behaviour in children,[1039] including autism,[1040] suggesting that inflammation can alter neurological development.

Kratimenos and Penn have coined the effect that the placenta has on neurodevelopment as 'neuroplacentology'.[1041] They showed in their review that placental disorders such as PE increase the risk for psychiatric disorders in adulthood,[1041] which is what was observed in the adult mental health survey. O'Donnell and Meaney in discussing the DOHaD origins of mental health, suggest that:

> "fetal development appears to establish a "meta-plastic" state that increases sensitivity to postnatal influences" p319.[831]

Therefore, their donor-conceived origins might influence the mental health of DC people. Additionally, other childhood and adulthood influences may exacerbate potential issues (to be discussed later).

6.4.2 Pregnancy-Induced Hypertension, DOHaD and Offspring Outcomes

While PE is a significant obstetric complication in terms of maternal and foetal mortality, the less serious complication of PIH is not without its links to donor conception and DOHaD. The increased incidence of PIH associated with the use of donor oocytes appears to be evident,[200, 289] while its links to donor sperm are somewhat more contentious.[184, 200] Considering that primipaternity and a shorter period of sexual cohabitation have previously been correlated with PIH,[1042, 1043] it would not be unreasonable to assume that the use of donor sperm may induce PIH.

Offspring born as a result of a pregnancy complicated by PIH are more likely to suffer from cardiovascular disease, type 2 diabetes and obesity, in much the same manner as observed for PE offspring. They are also more likely to experience behavioural problems,[309] and mental disorders.[310-312] There is less evidence in the literature on PIH outcomes for the offspring, which may be because PIH is less of an obstetric concern than PE.

Mechanistically, from a DOHaD perspective, there also appears to be little in the way of published evidence. However, it has been observed that offspring born following a pregnancy complicated by PIH (included in the broader hypertensive disorders of pregnancy category) have more epigenetic modifications which have been suggested to be a mediator for reduced gestational ages and birthweights.[313] Furthermore, another analysis of hypertensive disorders of pregnancy found that young male offspring had six differentially methylated DNA regions, of which three included genes related to vascular function.[1044] These results provide mechanisms for the increased cardiovascular risk observed by several authors.

The association between hypertensive disorders of pregnancy and adverse outcomes in the adult DC people included in this thesis is supported by the correlation between maternal complications and increased adverse physical and mental health outcomes observed in the spontaneously conceived cohort. The donor sperm-conceived cohort suffered from sample size issues after stratification, which reduced statistical power. However, increased frequencies of numerous adverse outcomes were observed in the donor sperm-conceived cohort.

6.4.3 Cryopreservation, DOHaD and Offspring Outcomes

Data on the effect of cryopreservation on offspring outcomes in all studies included in this thesis was inconclusive. The lack of studies investigating the long-term health outcomes of offspring conceived with cryopreserved sperm has been noted in recent years by other authors.[1045] The main evidence found in this thesis was obtained from individual studies included in the original systematic review. Some data suggested a possible increased risk for chromosomal anomalies and aneuploidies. However, without appropriate studies disentangling general sperm handling techniques in the laboratory from cryopreservation, this question will be challenging to answer.

Notwithstanding limitations from previously published studies and the results of this thesis in terms of the effect of cryopreservation, there are DOHaD mechanisms that should not be ignored. Increased levels of DNA fragmentation results from cryopreservation,[325, 326] as a direct result of oxidative stress.[339] Oxidative stress has been described as a significant driver of epigenetic modification that is involved in DOHaD and altered health trajectories.[1021, 1022]

Animal studies investigating the effect of ART techniques are suggestive that altered epigenetic disorders and alterations to imprinting genes can occur in the offspring,[1046, 1047] and that specifically, cryopreservation of sperm/oocytes may lead to altered methylation patterns.[396, 1048, 1049] Human studies on altered epigenetic profiles and methylation patterns appear to be reassuring with most showing no difference,[406, 408, 1050, 1051] however, as noted in Chapter 1, many of these studies only investigate a limited number of genes or regions and further studies are required.

6.4.4 Embryo Culture, DOHaD and Offspring Outcomes

The long-term health consequence of embryo culture on DC adults is unclear from the evidence of the adult health survey and the systematic review. The systematic review of donated oocyte/embryo outcomes did not include comparisons of culture conditions, while the sample size for those adults conceived with donated oocytes, embryos or surrogacy with donated gametes was too small for separate analysis. However, in general, the exclusion of these groups in the adult health survey did not change the significance of outcomes except for diagnosed depressive disorders and the surgical implantation of ear tubes grommets which were only significant when donor oocyte/embryo/surrogacy conceived people were included.

In the majority of those physical and mental health adult outcomes with significant findings, thirteen of nineteen (68.4%) had a lower *p* value, while three more had no change (15.8%).

Suggesting that for the majority of outcomes, the incidence of adverse events for donor oocyte/embryo/surrogacy conceived adults were greater than donor sperm-conceived adults.

Whether the outcomes observed for donor oocyte/embryo/surrogacy conceived people in these studies were altered by embryo culture is unclear. It is also unclear what influence embryo culture may have had in the outcomes for adult respondents who were donor sperm-conceived as the data could not be stratified for conceptions using IVF/ICSI with donor sperm. However, considering that culture media has been shown to alter the trajectories for BMI, body weight, and adiposity in human studies,[438, 439] as well as blood pressure and hypomethylation of imprinting control regions in animal studies,[1052, 1053] the possibility for embryo culture to have adversely affected the physical health of those DC people cannot be ruled out.

In terms of their mental health, the effect of embryo culture is inconclusive. One study suggests that the cognitive development of children is unaffected by the culture media,[1054] while another showed alterations in developmental problems.[444] Nonetheless, the effects of ART and embryo culture on the long-term health trajectories of DC people as a separate subset of ART offspring is an interesting area of research.

6.4.5 ICSI, DOHaD and Offspring Outcomes

In terms of perinatal outcomes, ICSI has been associated with an increase in birth defects.[446] An increased risk of birth defects was observed in donor sperm perinatal outcome meta-analysis,[4] but not donor oocyte.[1]

Similarly, to embryo culture, the effect of ICSI on the long-term health of DC adults is unclear. As described previously, the majority (70.6%) of respondents to the adult survey were born before ICSI was introduced, and subsequently, ICSI is unlikely to affect the outcomes significantly. During the early period of ICSI introduction, the use of donated gametes would have also been less prevalent than currently. If there were young ICSI DC respondents in the survey, we could compare published adverse outcomes associated with ICSI above those associated with IVF and those observed in the adult DC cohorts. Problematically from the perspective of the effect of ICSI specifically from the available evidence is that ICSI is typically grouped with IVF in outcome analyses.

Of relevance is the increased incidence of autism associated with ICSI, potentially contributing to the increased frequency of autism observed in the DC cohort. However, autism is also

associated with PE. Furthermore, the association between ICSI and autism in some studies has been recently criticised by Diop *et al.,* who argued that the analysis was restricted to ART children and that other studies have found no difference.[1055] The association between ICSI and autism appears to be less convincing than the association with PE, which also provides an inflammatory pathway. This inflammatory pathway is not only linked with neurological development and subsequently, autism, but also the majority of other adverse physical health outcomes. While PE is more likely to be associated with the adverse adult outcomes observed than ICSI, the effect of ICSI cannot be excluded.

6.4.6 Confounding, DOHaD and Offspring Outcomes

6.4.6.1 Multiplicity

Multiplicity has been described as a well-known confounder for adverse perinatal outcomes.[470, 471] Data from the systematic review showed that for oocyte donation, the significance of the adverse outcomes reported did not change when controlling for singletons. Consequently, oocyte donation is an independent risk factor to multiplicity in IVF modalities.[1] The case of donor sperm outcomes is less clear, and further data is required to analyse singleton outcomes appropriately. Compounding the issue is the use of ovulation induction treatment regimes which is also associated with adverse perinatal outcomes.[2] The adverse adult physical and mental health outcomes were also associated with an increase in the rate of twins in the DC cohorts.[5]

6.4.6.2 Maternal Age

Advanced maternal age is associated with adverse perinatal outcomes.[515] For donor oocyte treatments the effects of advanced maternal age are less of a concern as most of the adverse outcomes have been correlated with poor quality oocytes, and the use of donated oocytes from younger donors is correlated with improved outcomes over autologous oocytes.[530] In the donor oocyte systematic review, 97.6% of birthweight data was appropriately controlled for maternal age and was therefore not affected.[1] Meanwhile, for other outcomes, the influence of maternal age was not clear. In the case of donor sperm outcomes, the effect of maternal age was also unclear. However, some studies had appropriately controlled for maternal age, including the population-based perinatal study published from this thesis.[2] In the adult health survey, no data was collected on the ages of the respondent's mothers when they gave birth, and therefore no inference could be made.

6.4.6.3 Parity

Both nulliparous and grand multiparas are associated with adverse perinatal outcomes.[533] In the systematic review of donor oocyte outcomes, 97.6% of birthweight data was appropriately controlled for parity as it was for maternal age and was therefore not affected.[1] However, as for maternal age, the effect of parity on other outcomes was unclear. In terms of donor sperm outcomes, the effect of parity could not be deduced. Parity was also appropriately controlled for in some studies, including the population-based perinatal study.[2] In the adult health survey, no data was collected on whether the respondent was first born or had older siblings, and therefore no inferences could be made on the effect of parity on the adult DC cohort.

6.4.6.4 Obesity

The most common maternal condition associated with both infertility and adverse perinatal outcomes is obesity.[540] The effect of obesity on outcomes was not able to be determined from the systematic review, the population-based perinatal study, and was not collected as part of the adulthood study.

6.4.6.5 Socioeconomic Status

The effect of socioeconomic status (SES) on outcomes is debatable; however, evidence has suggested that when controlling for SES, IVF was independently associated with adverse perinatal outcomes.[561] The population-based perinatal study published from this thesis controlled for SES,[2] while the systematic review and adult health survey did not capture this data. Considering that the use of ART is associated with a higher SES,[562] including in Australia,[563, 564] and that SES has generally been associated positively with health,[1056, 1057] it is unlikely that an increased SES will result in adverse outcomes.

6.4.5.6 Confounding is Part of the Aetiological Pathway

Further research of confounding in the outcomes presented would assist in the understanding of donor conception outcomes. In terms of the long-term health of DC people and using a survey to capture data on confounding of the mother such as their obesity and specific details of the parental SES at the time is problematic and prone to considerable errors including the respondent 'guessing' what the information may be.

Even though multiplicity, advanced maternal age, parity, obesity and the use of ART technologies, in general, are potential significant confounders, it does not diminish the outcomes from the perspective that there is still a subset of people conceived with ART that have adverse perinatal outcomes and poorer long-term health trajectories. Except for

multiplicity which can be improved through single embryo transfers and reduced reliance on ovulation induction treatments, the other confounders will always be present in those parents wishing to undertake donor-conception and therefore part of the aetiological pathway.

6.4.7 Donor Origins of Health and Disease

From the evidence presented in this thesis, it appears as though the increased incidences of adverse neonatal and adulthood outcomes may be more strongly linked with the origin of the gametes and their novel antigen nature. A lack of evidence on the effects of cryopreservation on human gametes means that no conclusion can be drawn on its long-term consequences. There is, however, some data and mechanisms that were presented in Chapter 1, which suggests cryopreservation may be problematic and therefore, should still be a concern.

For neonatal outcomes from donor oocyte/embryos and IVF/ICSI with donor sperm, they may also be adversely affected by the culture conditions used in the IVF modality. These culture conditions have been increasingly linked with altered epigenetic profiles and increased imprinting disorders.[420, 429, 1058, 1059] Subsequently, maternal complications of pregnancy, including PE and PIH, should be considered as significant risk factors for the long-term health of DC people under the DOHaD phenomenon. Furthermore, ICSI using autologous gametes has been correlated with an increased risk of birth defects,[446] and therefore is also a significant risk factor for the health of DC people considering its current popularity.[445]

In light of the findings of the studies included in this thesis in combination with evidence in the literature, the developmental origins of health and disease acronym, DOHaD, is co-opted for the purposes of this thesis to stand for 'Donor Origins of Health and Disease'. While the health trajectories of DC people on balance have been altered, the question is - have they been harmed significantly to warrant constraining procreative freedoms and a revision of the paradigm? Furthermore, has their welfare been treated as paramount? As a means to answer these questions, a harms-based approach will be used.

6.5 Harms Based Approach

It is appropriate now to return to the harms-based approach described by McMillan.[954] Problematically, mental health issues may be associated with circumstances and emotions surrounding the psychosocial welfare issues of deception of origins, kinship separation, loss of identity, late discovery, incomplete medical histories and the possibility for consanguineous relationships.[839] These stressors may combine with O'Donnell and Meaney's meta-plastic

state of mental health[831] in which DC people may be more sensitive to these postnatal influences to drive their mental health further down the path of adverse events than what may be already occurring through the influence of epigenetic changes associated with PE and PIH. Therefore, adverse mental health in DC adults may have separate aetiologies which also interact with each other synergistically to worsen the outcome.

Evidence from this thesis shows that some DC people are adversely affected perinatally and in adulthood by their mode of conception regardless of disclosure. It is posited that these adverse effects do constitute being harmed.

Additional health concerns are a DC person's ability to obtain a timely diagnosis and appropriate treatment which is adversely impacted by a lack of knowledge of their familial medical health history.[949, 987] Furthermore, the medical profession as a general rule would be unaware of the potential increased risks for both mental and physical adverse health outcomes associated with being donor-conceived as that is novel information presented in this thesis. The lack of knowledge of the person's conception so that they can discuss this as a possible risk factor for their health with their medical health professional is also problematic as their autonomy over their health has been diminished. Donor-conceived people are being harmed by non-disclosure, lack of access to familial medical histories and also by being conceived with donated gametes.

Knowledge about these potential physical and mental harms is central to the argument by ethicist John McMillan who described that a harms-based approach was not necessarily the best way to address the issue of non-identity as decisions are required preconception when the parents are unaware of what the outcome will be.[954] However, he also stated that if there was a significant risk of inducing poor health, then the use of procreative autonomy could be questioned,[954] as is being done here.

With the knowledge presented in this thesis, parents would be able to make a more educated decision about whether to proceed with donor conception if they are aware of the increased risks to the potential child's physical and mental health as well as the mother's own health with the increased risk of PE. Without such information, they do not retain full autonomy over their decisions. Such information is routinely provided for expected risks of trisomy 21 (Down's syndrome) and other disorders, and therefore the information relevant to the risk associated with donor conception should also be disclosed. The risks of harm preconception

are now known. Subsequently, the evidence required by McMillan to address the non-identity problem has been provided.

The identification of various harms that may befall an individual born as a result of donor conception is central to this thesis and essential in assessing the child welfare paramountcy principle.

6.6 Is the Welfare of Donor-Conceived People Being Treated as Paramount?

Chapter 5 established the legal principle of child welfare paramountcy in Australia. It also established that DC children are not excluded but rather are highlighted as requiring special consideration. This special consideration was underscored in the South Australian *Assisted Reproductive Treatment Act,* which also made it a fundamental principle in the operation of the Act.[1060] This welfare principle does not cease when childhood ends but also extends to their welfare as an adult and following on from the DOHaD phenomenon should also extend prior to their birth as their welfare is impacted by decisions about the use of donated gametes/embryos.

For any jurisdiction that enshrines the child welfare principle as paramount, they first must assess what welfare outcomes are currently being experienced. Then they should compare those outcomes to some form of standard. In this instance, the standard would be those who have been conceived spontaneously for those conceived with donated sperm (or autologous oocytes for those people conceived with donated oocytes/embryos). It is not feasible to claim that the welfare of the child is being treated as paramount if little consideration is made as to what their welfare currently is and how it compares to others.

From the Australian perspective, there have been steps made concerning the improvement of the welfare of DC people. These include the national prohibition of the use of anonymous donations through the NHMRC guidelines,[893] and the introduction of retrospective legislation enabling Victorian DC people to access identifying information, which also gave the same rights to donors.[1061]

The changes occurring in Australia have primarily focused on the psychosocial welfare issue of the right to know who a DC person's donor is, and in some instances who their other DC siblings are. Little effort has been made in considering the physical health welfare issues for

DC people except for discussions concerning the access to a familial medical health history, which has been raised in various inquiries and legislative reviews.[37, 837, 838, 885, 886]

The lack of consideration for physical health outcomes as presented in this thesis is perhaps an area that legislators simply did not or could not possibly begin to comprehend. Nor has the long-term mental health outcomes outside of those associated with the deception of origins, kinship separation, late discovery, identity formation issues and consanguinity been considered. The findings presented in this thesis thus provide new information that has not been previously available. Additionally, the DOHaD phenomenon, as well as knowledge that ART treatments may produce altered long-term health trajectories, are far more recent developments. However, as new knowledge comes to light, legislators need to adapt legislation and regulation by incorporating such data.

Australian jurisdictions have failed to investigate all potential welfare issues thoroughly. Some jurisdictions have provided avenues for experts and members of the public to have input by allowing them to voice their concerns through inquiries and reviews.[37, 837, 838, 884-886] However, these do not constitute the rigorous scientific approach needed to fully address the question of whether the DC person's welfare is being treated as paramount.

There has been little jurisdictional involvement in ensuring follow up studies of their DC citizens to determine how they are faring, especially long-term. The Australia and New Zealand Assisted Reproduction Database (ANZARD) is capturing ART outcomes from ART clinics, including donor conceptions. However, data regarding those who were spontaneously conceived is not captured for comparison.[ee] While the ANZARD data was referenced in the South Australian,[837] and Western Australian reviews,[886] it was not mentioned in the Federal Senate, Victorian, New South Wales or Tasmanian inquiries.[37, 838, 884, 885] Reference to the short and long-term health of DC people were discussed in both the Western Australian and South Australian reviews.[837, 886] In particular, the South Australian review recommended that the health outcomes of DC people be researched and then used to inform policy to uphold the child welfare paramountcy principle:

> "The Minister should, pursuant to sections 9 and 20 of the Assisted Reproductive Treatment Act 1988 (SA), issue regulations, conditions of registration, or directives from time-to-time, informed

[ee] ANZARD is a data collection initiative of the National Perinatal Epidemiology and Statistics Unit (NPESU) that was created in conjunction with the Fertility Society of Australia (FSA), and the ART clinics around Australia and New Zealand. ANZARD collects ART treatment and neonatal outcome data from ART clinics in Australia. It does not collect information on donor numbers, nor does it collect data on neonatal outcomes of spontaneously conceived Australians and New Zealanders. Annual ANZARD reports are available at: https://npesu.unsw.edu.au/data-collection/australian-new-zealand-assisted-reproduction-database-anzard (last accessed: July 13, 2020).

> by research on the short and long term outcomes for people born as a result of A.R.T., that may set the bounds of A.R.T. practice necessary to uphold the principle of the paramountcy of the welfare of the child." pxxxiii.[837]

These reviews were relatively recent, and no implementation of independent research or ANZARD data has yet been used to inform policy regarding the welfare of the child. Notably, both reviews were independent reviews commissioned by the respective governments and conducted by the same person. Therefore, it is not surprising that the findings of one review are mirrored in the second regarding the use of data to help inform policy.

The short and long-term health outcomes, both physical and mental which are extraneous to the traditional considerations of disclosure, identification of the biological parent (donor), identity formation, familial medical health history and consanguinity have until now been poorly researched and largely ignored. The paramountcy principle is, therefore a paradox; a principle that is ethical, but which has carried little weight in practice. Until more research is conducted, and those research findings are used to influence the paradigm through not only policy but also clinical practice, donor conception will remain paradoxical to the concept of child welfare paramountcy.

From the findings presented in this thesis, the paramountcy principle is not being appropriately upheld in South Australia as part of the operation of the Act, let alone elsewhere in Australia as a principle under various pieces of legislation, regulation or international convention. In short, the welfare of DC people has not been treated as paramount.

The implications of research findings should not be confined to policy and practice paradigms but should also be available to recipient parents so that they are fully informed and can maintain their procreative autonomy. However, this raises the question of how should the findings of this thesis impact parental procreative freedoms.

6.7 Conclusion - Harms v Procreative Freedoms

The first step in addressing the question of whether parents should have unmitigated procreative freedoms is to acknowledge that potential harms can occur from the implementation of past and current donor conception paradigms. These potential harms include not only the findings presented in this thesis of increased frequencies of adverse physical and mental health outcomes in adult DC people as well as adverse perinatal outcomes, but also the issues of deception of their origins, kinship separation, loss of identity, late discovery, lack of a familial medical history and consanguinity.[839] The second step is to revise the paradigm by shifting the focus from a parent-centric to a child-centric paradigm.[839] In essence, the child welfare paramountcy principle needs to be not only adopted but also implemented by all jurisdictions. Application of this principle inadvertently reduces the procreative freedoms of parents as it may adversely affect their choice. Such as the choice to not disclose to the child, their origins.

It is hereby argued that constraining these freedoms, in effect promotes child welfare paramountcy. The implementation of child welfare paramountcy is not necessarily a zero-sum game in which increased rights and welfare of the child only negatively influences the autonomy, freedoms and beneficence of parents, but can also have the potential to improve them in other ways.

The current paradigm impinges on a parent's autonomy and ability to make fully informed decisions by not providing vital information to the prospective parent before they choose to undergo donor conception. While the increased incidence of preeclampsia has been well established, the knowledge of the increased risk of adverse perinatal outcomes associated with donor conception is relatively new. The systematic reviews and meta-analyses presented in this thesis were published in 2016, 2017 and 2018, and were the first systematic reviews and meta-analyses published in the academic literature on donor conception perinatal outcomes.

It typically takes time before such information is more widely known. It is also unknown if any ART clinics have started disseminating this knowledge to their patients of potential adverse outcomes in the perinatal period associated with donor conception as a treatment modality. Some ART clinics are informing patients of the increased risks for preeclampsia associated with the use of donated gametes which has been known for far longer as is visible on some ART clinic websites.[1062, 1063] Although whether this is occurring uniformly and or as

part of the consultation procedure is unknown. The increased risk is provided by the Australian Government Department of Health as part of their *Pregnancy Care Guidelines*,[1064] and is also freely available on their website,[1065] and therefore should be known by all ART clinics in Australia. ART clinics certainly would not be informing their patients of the increased risk for poorer long-term health outcomes for any child they conceive with donated gametes as these outcomes were investigated for the first time as part of this thesis.

The constraining of unmitigated procreative freedoms does not necessarily preclude the use of donor conception. Rather, a constraint could encapsulate how the practice paradigm is conducted specifically and the choices available. Another perspective to consider is that the provision of information about the increased incidences of hypertensive disorders of pregnancy including PE, the increased risk to the mother's own health as well as that of the child both in the short and long-term enables procreative freedom and autonomy rather than restricting it. Procreative freedoms are not only about when, who with, and how to have a child but also about not having a child.[922] In a context, more people would be familiar with; it would be widely regarded that contraception has improved procreative freedoms rather than hampered them. In this way, too, having information that would assist the parent to avoid adverse outcomes for the health of themselves and their child could be viewed as improving their procreative freedom.

Harms or adverse health outcomes to the DC person are not confined to just specific conditions but can have further far-reaching implications, including life expectancy. For example, preterm delivery, as observed in donor oocyte-conceived neonates, is associated with significantly increased all-cause mortality in adulthood.[1066] Type 1 diabetes which was observed in the adult DC cohort to have higher incidences than the spontaneously conceived cohort has been associated with a decreased life expectancy of 14.2 life-years for men and 17.7 life-years for women.[1067] Further reductions in life-expectancy are associated with mental disorders,[1068-1070] which were observed in the adult DC cohort. These mental disorders in an analysis of over 7.3 million people, resulted in a reduction of life-expectancy between 5.42 years to 14.84 years.[1069] The reduction in life-expectancy associated with mental disorders has also been correlated with the physical health of these people through the *Global Burden of Disease Study,* which showed that they might die from physical health disorders such as cardiovascular disease, diabetes, cancer and respiratory disease in addition to suicide associated with their mental disorder.[1071]

The practice paradigm which is associated with increased incidences of preeclampsia primarily but also pregnancy-induced hypertension is correlated with an increase in adverse health outcomes for DC people driven through the DOHaD phenomenon and underlying mechanisms including epigenetic modification. The influence of cryopreservation and or embryo culture cannot be ruled out until further studies have been conducted. It was determined that DC people had been physically and mentally harmed when analysed using a harms-based assessment of these altered health trajectories. These harms were associated with factors surrounding their conception. Consequently, the welfare of DC people has not been treated as paramount.

Currently, the practice paradigm of donor conception and lack of knowledge of outcomes for people conceived is adversely affecting the DC person's welfare due to current procreative freedoms. Recommendations pertaining to revising the paradigm to substantively improve the DC person's welfare and constraining procreative freedoms will be discussed in Chapter 7.

6.7.1 Other Considerations

Due to the adverse neonatal outcomes experienced by DC people which are correlated with increased adulthood morbidity and mortality,[60-62] including the poorer long-term physical and mental health outcomes observed in the adult DC health survey, donor conception is associated with an increased health care burden for the individual and society.

Not only is there a substantial immediate and long-term healthcare burden resulting from being born preterm delivery or of low birthweight, but there is also the financial burden that is associated with increased healthcare. For example, in the United States, neonates born preterm delivery on average cost the healthcare insurers USD 76,153, low birthweight costs USD 114,437, and those born at 24 weeks USD 603,778.[1072] For those pregnancies complicated with preeclampsia or hypertension, they also represent combined maternal, and infant increased costs of USD 28,603. Mental disorders, as observed in the adult health survey, are reportedly top of the list for costly conditions in the US with direct costs of USD 201 billion in 2013.[1073]

Indirectly, mental disorders have been argued to be associated with:

> "poverty, unemployment, productivity losses, low educational level, social exclusion and inequality, gender inequity, and violence" p381.[1074]

In effect, increased procreative freedoms through the use of donor conception treatment modalities are correlated with extra economic burdens to the state that extends past the

initial ART treatments, and into the perinatal period, which are then extended into adulthood. The added adult healthcare burden is observed through DOHaD studies and the results of the studies presented in this thesis. These increased health care and economic burdens are irrespective of any confounding reasons as to why DC people fare worse than their spontaneously or autologous oocyte-conceived peers.

The risks of PE for the child's health and welfare has been a clear focus of this thesis. However, the implications for the mother are also worthy of mention, as these are also significant. Preeclampsia, as a leading cause of maternal mortality is well-known.[1075, 1076] What is perhaps less well known are other long-term health consequences for the mother experiencing a PE complicated pregnancy. The mother is then also more likely to develop conditions such as cardiovascular disease,[1077-1079] stroke,[1079, 1080] chronic hypertension,[1081] cerebral vascular disease,[1082] dementia,[1083] postpartum psychiatric episodes,[1084] kidney disease,[1085-1087] diabetes,[1081, 1088, 1089] and death.[1079, 1090] The maternal post-partum cardiovascular association is increased for infants born SGA,[1091-1094] and PD,[1093, 1095] thereby highlighting a link between poor maternal cardiovascular health and foetal growth. Preeclampsia is a severe condition in the longitudinal sense from the perspective of both the child and the mother.

An opportunity exists to revise the paradigm that may not only potentially improve the short and long-term health trajectories of DC people and their mothers but also reduce the healthcare burden to the individual, their family and the state. In the following and final chapter of this thesis, revision of the donor conception paradigm will be considered, and recommendations for altered policy and practice proposed.

CHAPTER 7. RECOMMENDATIONS, PARADIGM REVISION AND CONCLUSIONS

In this thesis, the findings of the empirical studies and the policy analysis have shown that the welfare of DC people has not consistently been treated as paramount, and the procreative freedom exercised by parents has adversely affected the welfare of some children. From the perspective of the findings, these welfare issues include adverse perinatal outcomes such as low birthweight, preterm delivery and birth defects (depending on the donor conception treatment modality), and some altered health outcomes in adulthood with increased incidences of self-reported physical and mental health conditions.

7.1 Introduction

It is apparent from the findings of this thesis that the paradigm of donor conception needs to be revised to strengthen child welfare paramountcy. In this chapter, recommendations will be presented to improve the welfare outcomes of DC people through changes to the practice, policy, education and parental freedoms. Further research will be outlined that will aid in the improvement of the knowledge of donor conception outcomes, followed by concluding remarks pertaining to the findings of the thesis.

The use of ART treatment modalities and technologies provide modifiable factors that can potentially improve the outcomes for the donor-conceived. Advanced maternal age or older mothers, parity, obesity and infertility are all un-modifiable factors from the treatment perspective. These confounders are endemic to the patients, and therefore, recommendations will be restricted to modifiable factors within the practice and the paradigm.

7.2 Recommendations

One modifiable factor that is being widely used to reduce the issue of multiplicity is the use of elective single embryo transfer, which can be applied to IVF treatments, including donor oocyte/embryos and IVF or ICSI with donor sperm. Single embryo transfers should be the preferred treatment modality where appropriate. Multiplicity in donor sperm insemination conceived cohorts is associated with ovulation induction treatments.[708, 709] Some of these medications, such as clomiphene citrate, have also been associated with an increased risk for adverse perinatal health, increased hospitalisation and birth defects.[708, 712, 713, 715, 716] In terms of donor sperm conceptions, the ovulation induction regime needs to be carefully monitored to try and reduce multiplicity.

Another modifiable factor is the use of ICSI. Except for its use to treat male fertility factor, its use with donated gametes does not improve the cumulative live birth rate compared to standard IVF,[1096] and therefore unwarranted on live birth grounds. Its use in donor conception is somewhat driven by other factors, including using less sperm per treatment. Subsequently, its use in donor conception should be reduced based on the child welfare paramountcy principle to reduce the incidence of birth defects.

Perhaps most importantly and critically for donor conception outcomes is the pregnancy complications of PE, which is an immune-mediated response. For donor sperm treatments, a simple potential methodology is evident from the ample literature highlighting the increased incidence of PE with new fathers and the decreased risk associated with sexual cohabitation, particularly in nulliparous women.[202, 204] These outcomes are consistent with the immune maladaptation hypothesis for PE concerning novel donor sperm antigens and poor immune tolerance.[1097] Human spermatozoa are known to express both human leukocyte antigen (HLA) classes I and II,[1098] with the HLA complex well known for its regulation of the immune system. A properly functioning immune system and immune response are vital for a successful and healthy pregnancy.[1099] The problem occurs when the immune system maladapts.

Additionally, a study highlighted that those women undergoing donor sperm treatment who had received multiple treatments with sperm from the same donor had a reduced risk for PE.[181] The multiple treatments have in effect induced tolerance in the immune system. It is therefore advisable that a series of immune system 'tolerance inducing' treatments with sperm from the same donor be undertaken during the woman's infertile window of her menstrual cycle to enable the immune system to desensitise to the novel antigen. Further research should be conducted to determine the optimum number of tolerance inducing treatments required to desensitise the woman's immune system and reduce the incidence of PE.

For donor oocytes and embryos, the situation has some similarities. The number of HLA class II mismatches between the oocyte donor and recipient mother has been associated with an increased incidence of PE.[1100] HLA class II molecules have been implicated in the regulation of Natural Killer cells,[1101] with uterine Natural Killer cells being involved in placentation and subsequently preeclampsia.[1102] Specifically for oocyte donation pregnancies, mothers have an increased risk for developing HLA antibodies specific to the foetus.[1103] It has been argued that in oocyte donation pregnancies in comparison to natural conceptions (and by extrapolation

autologous oocytes), that the immunoregulation is different and is likely to be implicated in the pathophysiology of PE.[1104, 1105]

It has also been suggested that tissue type matching of HLA and killer immunoglobulin-like receptor[ff] variants between oocyte donors and recipient mothers could potentially be conducted to help reduce the potential for preeclamptic pregnancies.[1106, 1107] The results presented in this thesis is suggestive that such a methodology is worthy of investigation.

Currently, there exist some treatments that are used to reduce the incidences of PE, such as aspirin,[1108] vitamin D,[1109] calcium,[1110] low-molecular-weight heparin[1111] and folic acid.[1112] However, these methodologies do not treat the cause, which is the novel nature of the antigen, whereas the recommendations provided above attempt to treat the cause. Instead, these treatments involving medications or supplements have the potential for side-effects.

Problematically, the use of donor gametes/embryos increases the risks not only for the child to have poorer health, but also the mother due to PE. A reduction in the incidence of PE would significantly improve both outcomes. Not only is a healthy child a significant desire of any parent, let alone those choosing donor conception methodologies, but the recommendations may improve their odds of achieving this.

Increased procreative freedoms which have incorporated the use of ART have raised concerns of associated increased risks for altered health trajectories for those conceived with ART including IVF and ICSI,[57, 671, 941, 1113, 1114] and now also donated gametes/embryos from the evidence presented in this thesis. By providing prospective parents with an increased ability to have a child through the introduction of ART, some people have been created who are more likely to have poorer health in adulthood, both physically and mentally than their spontaneously conceived peers. While ameliorating the pain of one person or a couple of people is beneficence, it has negatively impacted the most vulnerable person, the child. These adverse outcomes thereby conflict with the child welfare paramountcy principle.

In Chapter 6, it was argued that procreative freedoms should not be unmitigated but constrained such that the welfare of the child is held as the primary consideration. The findings of the systematic reviews, perinatal study and adult health study support constraining procreative freedoms by showing that there are increased risks to both the

[ff] Uterine Natural Killer cells expressing killer immunoglobulin-like receptor bind to HLA molecules on the invading trophoblast during placentation and inhibitory killer immunoglobulin-like receptors have been implicated in preeclampsia.[1106]

physical and mental health of people conceived with donated gametes in both the short and long-term. Eight recommendations are now presented to improve the outcomes for DC people.

7.2.1 Eight Key Recommendations for Improving Welfare Outcomes

Improvements to child welfare can be made using the following recommendations:

1) Donor sperm treatments should be conducted with a period of immune system tolerance treatments without the possibility of pregnancy in an attempt to reduce preeclampsia.
2) Donor oocyte/embryo treatments should involve HLA and killer immunoglobulin-like receptor matching between the oocyte donor and recipient mother in an attempt to reduce preeclampsia.
3) Clinicians, ART clinics, fertility nurses and ART counsellors should counsel and fully inform their patients of the increased risks for the short and long-term physical and mental health of their child.
4) Clinicians, ART clinics, fertility nurses and ART counsellors should counsel and fully inform their patients of the increased risks for hypertensive disorders of pregnancy including PE associated with the use of donated gametes/embryos and the correlated short and long-term health consequences for the mother. This counselling should also extend to the risks associated with multiplicity.
5) Donor conception treatments should endeavour to reduce the risk of multiplicity by using elective single embryo transfers in the case of donor oocyte/embryo treatments and reduced use of, and or careful monitoring of ovulation induction in the case of donor sperm treatments.
6) ICSI should be reserved for only male factor infertility treatments in donor conception.
7) Parents should inform their child of their origins from an early age to improve medical diagnosis and psychosocial welfare outcomes.
8) Jurisdictions must uphold the welfare paramountcy principle by investigating the welfare of people conceived with donated gametes and use that information to help inform policy.

With the implementation of these recommendations, it is possible to alter the health and welfare trajectories of DC people. Improvements in physical and mental health outcomes reduce the level of harm befalling those who are adversely affected but also takes a step towards honouring the child welfare paramountcy principle. In order to improve outcomes

through the above recommendations, changes to the paradigm are required to support their implementation.

7.2.2 Revision of the Paradigm

Implementing these recommendations to create change is not an easy task. Historically, change to the donor conception paradigm has been ongoing for decades ever since the first legislation was enacted in the 1980s and is still currently undergoing change. A multipronged approach should be implemented to assist with the revision of the paradigm.

7.2.2.1 Education of Health Professionals

Health professionals need to be educated that donor conception creates an at-risk group to assist in the care of their patients. Specifically, ART clinicians must be aware that the use of donated gametes is associated with increased risks for hypertensive disorders of pregnancy, including preeclampsia, as well as adverse perinatal and adult outcomes for the offspring.[1, 4, 5, 181, 275, 656] Accordingly, this would allow them to counsel patients of the increased risks and also implement specific treatment methodologies to reduce the incidence of preeclampsia as included in the eight key recommendations.

Obstetricians also have to be educated on the increased risk of preeclampsia, pregnancy-induced hypertension and adverse perinatal outcomes associated with the use of donated gametes.[181, 182, 185, 275, 656] They also need to be aware of the increased risk for induction of labour, forceps delivery and caesarean section associated with donor sperm conceptions as observed in the meta-analysis presented in this thesis. These increased risks have direct implications for the management and treatment of the mother during pregnancy and during delivery.

General practitioners, physicians and mental health professionals need to be educated on the evidence that DC people are an at-risk group for increased incidences of adverse physical and mental health outcomes.[1, 4, 5, 656] Furthermore, they also need to be educated on the increased risks for those DC people who were born from a gestation complicated by PE to experience adverse physical and mental health outcomes.[220, 842, 1115, 1116] From the parental perspective, these medical professionals also need to be aware that mothers that have had a pregnancy complicated by preeclampsia are also at increased risk of long-term adverse physical and mental health outcomes.[702, 1115, 1117-1119] This knowledge can potentially be critical for the care and treatment of their patients.

ART counsellors and fertility nurses should also be educated on these increased risks and assist in the dissemination of information to the patients prior to undergoing donor conception treatments.

While some health professionals may be aware of some of these risks, there is a need to educate them on new information, including the findings of this thesis. The education of health professionals is complex and multifactorial. For new health professionals, the information could be introduced as part of their university studies in which DOHaD (including donor and ART origins) and its implications for the health of people must be introduced as part of their education. For existing health professionals, the dissemination of information to them is more complicated. Some evidence suggests that online continuing medical education can improve the knowledge of health professionals,[1120, 1121] however, workshops/seminars, lectures and manuals/literature may be equally effective.[1122, 1123] More modern online methodologies being used for education with some success have included the use of apps on smartphones/tablets.[1122] For those health professionals that have the ability to do so, attendance at specific conferences can also assist with new knowledge acquisition.[1124]

The education of clinicians and guidance for clinical practice is also currently being provided by the Australian Government's Department of Health, through the *Clinical Practice Guidelines: Pregnancy Care.* These guidelines describe that clinicians should be identifying women with risk factors for PE by stating:

> "Identifying women with risk factors for or clinical signs of pre-eclampsia allows timely provision of advice on prevention and symptoms that may indicate a need for additional care."p150.[1064]

As part of the Australian Government's identification of risks for PE, they have included the use of donated gametes:

> "assisted reproductive technology: in contrast to the findings on prevalence above, systematic reviews suggested that risk was increased in women receiving donor oocytes (OR 4.34; 95%CI 3.10 to 6.06; *P*<0.0001) (Blazquez et al 2016; Masoudian et al 2016) or sperm (OR 1.63; 95%CI 1.36 to 1.95) (Gonzalez-Comadran et al 2014)"p152.[1064]

Furthermore, the guidelines highlight the long-term health risks to the mother resulting from a pregnancy complicated by PE and that those health professionals such as obstetricians, GPs, and midwives should be aware of these risks. However, the guidelines do not describe the increased risks to the health of children resulting from pregnancies complicated by PE even though these risks are known.[220, 1115, 1125]

ART counsellors in Australia must follow the *Guidelines for Professional Standards of Practice Infertility Counselling* provided by the Australian and New Zealand Infertility Counsellors Association (ANZICA) which is the peak body for ART counsellors in Australia and New Zealand.[1126] Both the Department of Health's pregnancy care and ANZICA's counsellor guidelines can be updated and disseminated to all Australian ART clinicians/counsellors in addition to education at various symposiums and conferences held by the Fertility Society of Australia and attended by ART clinicians and counsellors. Further dissemination of information to and counselling of parents is also vitally important in the revision of the paradigm.

7.2.2.2 Counselling of Parents

Parents should, as part of their treatment, be seeking all information concerning outcomes and potential risks associated with that treatment modality. It is also an obligation on the clinician, fertility nurses, ART clinic and ART counsellors that they provide such information so that the parents can maintain autonomy over their procreative freedoms. However, counselling to parents by ART clinicians, fertility nurses and counsellors of the increased risks to the welfare of the DC person is only achievable after these professionals are first educated about these increased risks as described above.

Specifically, Australian ART counsellors have a significant role in disseminating information to their patients under the guidelines specified by ANZICA. The goal of ANZICA, as stated on their website, is:

> "It is essential that counsellors have a voice in the field of Reproductive Technology both as advocates for the clients and for the potential unborn child."[1127]

This statement highlights that ART counsellors in Australia play a crucial role in advocating for the welfare of the child under the paramountcy principle.

Furthermore, the ANZICA guidelines stipulate:

> "assist with the clarification of the potential impact of the proposed treatment (particularly psychosocial)" p6
> "identify any risk factors for the patients e.g. mental health history" p6
> "provide supplementary information and resources as appropriate" p6
> "Adjusting to the medical realities of a "high risk" pregnancy, the ante-natal and post-natal implications, for the mother and the babies" p8
> "Current guidelines and research and information to assist to tell donor offspring about the story of their conception and advice re available resources." p15.[1126]

These ANZICA guidelines provide clear references to the dissemination of information to their patients regarding risks to the mother and child that includes not only disclosure but also

their medical welfare. These guidelines are supported by the NHMRC guidelines, which also describe that parents using donor conception should be counselled on:

> "any potential short or long-term physical and psychosocial implications for the person who would be born, the individual or couple, acknowledging that these may be uncertain" p31.
> "the currently available published data on morbidity, and short and long-term outcomes for persons born through ART, including for future generations" p31.
> "the potential significance of the biological connection, the right of persons born to know the details of their genetic origins, and the benefits of early disclosure" p35.[887]

The dissemination and discussion of risks to the mother is also expressly described in the Department of Health's pregnancy care guidelines:

> "It is important that women are given information about the symptoms of pre-eclampsia from early pregnancy." p154.[1064]

The Department of Health in that statement describes that the woman should be counselled on preeclampsia early in their pregnancy. Problematically, from a donor conception perspective, the increased risk has been implicated through their choice of donor gametes/embryos. Considering that PE is such a significant contributor to both maternal and foetal morbidity and mortality in both the short and long-term, these risks should arguably be disclosed before conception. Two pieces of national guidelines provided by the Australian government and one guideline provided by the peak governing body associated with fertility treatment in Australia, therefore, stipulate that parents should be counselled on disclosure and the risks to the health of the child and the woman receiving the treatment. This counselling would also form part of an altered practice paradigm.

7.2.2.3 Alteration of the Practice Paradigm

As described in the eight key recommendations, techniques should be implemented that potentially reduce the incidences of preeclampsia and therefore, subsequent associated adverse health outcomes perinatally and long-term. If these were implemented as a standard practice rather than as an add-on that occurs with some fertility treatments,[1128] then the welfare paramountcy principle would be appropriately implemented. Many add-ons are claimed to be costly and ineffective,[1129] however, if these preeclampsia avoidance techniques are shown to be successful, the long-term costs that they potentially could save for the individual and society are substantial.

Findings from this thesis were unable to determine the effect that cryopreservation and embryo culture had on the outcomes investigated. However, considering that there have been significant concerns raised regarding their impact on the health of those conceived with these

technologies,[427, 1130, 1131] it is imperative that further research be conducted to improve the understanding of their implications. As described in the previous section on counselling of parents, the ANZICA guidelines[1126] in addition to the NHMRC guidelines,[887] specify that parents should be counselled on the benefits of disclosure of the child's mode of conception as part of the practice paradigm, which can have further implications.

7.2.2.4 Disclosure

The discussion of disclosure in this section will not be restricted to the parents disclosing to the child that they are donor-conceived. It will also include discussion concerning disclosure to their obstetrician that their pregnancy involved a conception with donated gametes/embryos, and also to general practitioners and other health professionals that the DC person was conceived with donated gametes/embryos.

In the immediate obstetric sense of carrying a DC baby to term, the obstetrician should be made aware of the fact the mother is carrying a DC baby. This disclosure will enable the obstetrician not only to be hypervigilant to the increased risk for maternal disorders of pregnancy including preeclampsia and pregnancy-induced hypertension but also the increased risk for preterm delivery, low birthweight and birth defects. Disclosure to the obstetrician is critical for patient management of both the mother and baby.

Parental freedoms and choice, such as withholding information from the child may have seemed appropriate for the parent's agenda. However, they are not appropriate from a child welfare paramountcy perspective.[1132] A systematic review has highlighted that the majority of DC people have not had their conception disclosed to them.[747] Although currently it is recommended that parents disclose to their child that they are donor-conceived.[878, 887, 1126]

Historically, donor conception was used by heterosexual couples; however, single mothers and same-sex couples are now the dominant family type utilising donor conception.[1133, 1134] There has also been an observed increase in disclosure rates in these family types compared to heterosexual families.[750, 1135]

Evidence has suggested that the stigma associated with infertility is one reason why parents may not disclose.[1136, 1137] Another potential reason is the inability to access information, particularly for those parents who have conceived using an anonymous donor.[1138] Without information or the ability to access information, the parents may be reluctant to disclose. Assisting parents in disclosing to the child their origins have been paradigm shifts that have created more open systems where more information may be made available. For example, the

prohibition of anonymous donors in countries such as Australia,[887] the Netherlands,[1139] New Zealand,[1140] Sweden,[1141] and the UK,[502] has enabled parents to disclose to their child, knowing that the information will be available if the child seeks it. Elsewhere, the use of anonymous donors has also been decreasing,[1142] which has assisted the parents in being able to disclose.

Regardless of parental reasons, studies of DC adults have highlighted that some are distressed and traumatised by their parent's procreative freedom including their lack of early disclosure, which has adversely affected them emotionally and physically.[746, 830, 837, 838, 965, 1143] Further assistance is already provided in the Australian context through ART counsellors providing information to the parents during their counselling sessions prior to undergoing donor conception treatment of the need to disclose to the child as well as advice on how to disclose.[1126]

Not only should disclosure occur as a matter of principle, but the disclosure should occur early in childhood, preferably before adolescence.[1144] Early disclosure has been shown to produce less trauma to the DC person than disclosure in adolescence or adulthood.[800, 844, 1145] External to the psychosocial welfare issues associated with the disclosure of donor conception are those that are pertinent to the findings of this thesis. These issues are the physical and mental health outcomes that are particularly relevant to the health profession.

Whether disclosure to a general practitioner or other health professionals about a DC person's conception status occurs from the parents or the DC person themselves is not important. What is important is that the general practitioner or health professional is made aware of the person's donor conception status to identify them as being in an at-risk group. With the findings from this thesis known, in addition to access to the donor's familial medical health history, the ability for quick diagnosis and appropriate treatment can be improved.[949, 987, 1002-1004] The disclosure of the use of donor conception and also any incidence of preeclampsia to health professionals is also significant for the mother's long-term physical and mental health.[220, 1090, 1117, 1118, 1146]

The disclosure of a person's donor conception status has the potential to improve not only the welfare of the DC person but also the mother and is, therefore, in the best interests of all parties. As described, disclosure can be influenced by the stigma associated with infertility.[1136, 1137] Stigma is a component of the culture surrounding infertility and donor conception, which also needs to be addressed.

7.2.2.5 Culture Change

While culture change can refer to numerous areas, in this context, the issue of stigma in society as a form of culture, will be specifically addressed. Infertility has historically been and continues to be associated with significant stigma,[1147-1150] including the receiving of ART treatments such as donor conception.[1136, 1137, 1151, 1152] This situation has been improving over the years with a reduction in infertility and ART treatment stigma.[1153, 1154] However, as the majority of parents are still not disclosing, even though disclosure rates are increasing,[747] it would appear that further destigmatisation is warranted. While this may not result in all parents disclosing as some may choose to withhold the information for other reasons, destigmatisation can be viewed as beneficent to all parties.

Reducing the stigma associated with infertility and the receiving of ART treatments is an effect of normalisation. This normalisation has been suggested to be achievable through conversation,[1155, 1156] public education campaigns,[1157, 1158], non-judgemental environments in healthcare,[1159] online support groups[1155, 1160, 1161] and media stories.[1155] Stories, in general, have been empirically linked to the reduction of stigma in abortion,[1162] and therefore, could be a crucial component in reducing the stigma of infertility. The use of online support groups has also been used by DC people to help reduce the stigma they feel with being donor-conceived.[828] Reducing stigma can, therefore, be achieved through numerous avenues.

Another avenue which was described by Cook and Dickens specified that law (and therefore policy), has a significant role to play in the reduction of stigma in reproductive health and infertility.[1163] Policy change is not only a potential source for the reduction of stigma, but it can also significantly revise the paradigm to encapsulate child welfare paramountcy properly.

7.2.2.6 Policy Change

Policy change can be a long and complicated process that can span many decades. An example of such a process is the legislative changes that occurred in Victoria that culminated in world-first legislation awarding DC people and donors retrospective access to identifying information on each other.[1061] The Victorian experience subsequently provides an excellent example of how policy change can be created.

Allan described the process as involving many factors, including:
1) Various Victorian inquiries starting in the 1980s prior to the introduction of the states first donor conception legislation;
2) Further Federal and state inquiries over the decades;

3) Submission to the inquiries by various interested parties, particularly those from the donor conception triad of DC people, parents and donors;
4) Lobbying by members of the triad, specifically DC people and parents;
5) Media campaigns instigated by DC people;
6) Introduction of a private members bill to the Victorian parliament, and finally;
7) The introduction of a bill by the government of the day in 2015, which was passed in 2016.[1164]
As can be seen from the steps listed above, the Victorian experience has been a long and ongoing process over 30+ years that has required input from numerous parties. Policy change is, therefore, not a simple process within the context of donor conception in Australia.

At the forefront of these inquiries in Australia is the lobbying and media campaigns of DC people themselves and parents to instigate legislative and regulatory change.[31, 37, 838, 884, 885] Furthermore, they can be pivotal in getting inquiries started. For example, the Federal Senate inquiry was instigated by the Donor Conception Support Group of Australia[gg] who successfully petitioned the Federal government to conduct an inquiry.[31]

Alternatively, another means of instigating policy change is for the interested party to undertake court proceedings to challenge the legislation. Successful challenges have been previously conducted by DC people to challenge donor anonymity in the UK[1165] and by parents to reduce discrimination in the access to ART treatments in Australia.[1166-1169]

More simplified means of creating policy change are occurring in the states of South Australia and Western Australia, which have conducted reviews of their legislation as stipulated in their existing donor conception legislation.[837, 886] As part of these reviews, all interested parties including DC people, parents, donors and others can make submissions to the review. The recommendations of these reviews are yet to be fully implemented. However, South Australia is in the process of creating a donor conception register,[1170, 1171] which was one of the recommendations of the South Australian review. These reviews also suggested that research be conducted into the short and long-term health outcomes for DC people.[837, 886] Future research will be essential to the process of paradigm revision that has been outlined.

[gg] The DCSG was a self-funded organisation run by volunteers that started in 1993. Membership was made up of "people considering or using donor sperm, egg or embryo, those who already have children conceived on donor programs, adult donor offspring and donors, as well as social workers, clinic staff, researchers and other interested people." The DCSG has sinced dissolved. p708[31]

Suggestions for not only the investigation of short and long-term health outcomes but other areas of donor conception will now be discussed.

7.2.3 Future Research Suggestions

This thesis has presented significant findings regarding the welfare outcomes for DC people. It has also highlighted significant gaps in the literature and illuminated further areas of study that require investigation.

Returning to the information obtained from the systematic reviews, increased numbers of studies investigating perinatal outcomes of donor sperm conception in comparison to those who are spontaneously conceived are required. These studies should follow a similar systematic approach as presented in the population-based study of donor sperm perinatal outcomes from South Australia that were presented, in preference to those that investigate few outcomes and which fail to account for appropriate confounding. Population-based studies would improve the rigour and reduce bias in the studies. These studies should then be added to the existing systematic review and meta-analysis to improve the knowledge of the perinatal outcomes associated with donor sperm conception and determine whether the current findings of the meta-analysis are supported or refuted.

The systematic reviews showed that a dearth of studies had been conducted on the outcomes occurring from embryo donation (double donation). Subsequently, further studies are required to enable meta-analysis to be conducted in a manner similar to the meta-analysis of donor oocyte outcomes. This meta-analysis would allow the determination of whether the addition of donor sperm, altered the outcomes further than those observed in donor oocytes.

Also highlighted from the systematic reviews was the lack of quantifiable health data in childhood. Instead, there has been considerable research conducted on child-parent interaction and family function in DC families.[824] Cohort studies of childhood health outcomes would improve this situation substantively; however, data-linkage studies which can connect clinic treatment data, perinatal data and childhood health data would be the most rigorous option. Data-linkage was used in the population-based donor sperm perinatal study conducted from South Australian data. This information could then be further linked with health data that is collected on children throughout their childhood.

The self-reported adult health study of donor sperm-conceived people conducted as part of this thesis was the first that has been published. It was an exploratory study which addressed

the question of whether there was any evidence that DC people had altered health trajectories. Subsequently, because of both its exploratory nature, and that it is the first of its kind, further studies are required to ascertain whether the findings apply to the broader DC community. Considering that the online DC community is continually expanding, a similar study with an increased sample size could potentially be conducted to see if the results are different. As all studies involving DC adults are biased through self-selection and non-disclosure, data-linkage studies would be preferable to remove bias in that area.

Investigations into the effect of cryopreservation on DC people health outcomes in this thesis were inconclusive. However, the potential negative impact resulting from cryopreservation is still a concern. In terms of sperm cryopreservation, the most appropriate study that would address this question is to examine the use of fresh and cryopreserved sperm use in artificial insemination with the woman's partner's sperm. Preferably this study would be done with couples that have sexually cohabitated for a significant period to reduce the incidence of PE. Such a study would reduce potential confounding from novel sperm antigens. The effect of oocyte/embryo cryopreservation has been an issue that is currently being investigated by various researchers with some suggesting improved perinatal outcomes of higher birthweights (but still within the normal birthweight category)[1172-1174] and reduced incidence of SGA.[1174] Research in the area of oocyte cryopreservation outcomes needs to continue.

This thesis highlighted the significant burden of PE and its association with perinatal and adulthood outcomes in DC people. It was recommended that future donor conception treatment regimens implement practices which aim to reduce PE such as donor sperm tolerance treatments and oocyte donor HLA and killer immunoglobulin-like receptor matching. Therefore, studies are required to determine if such strategies are successful in reducing the incidences of PE. Furthermore, data should also be collected on obstetric and perinatal outcomes to determine if the adverse outcomes are ameliorated through the implementation of these strategies. Longitudinal studies would be required to determine if adult health outcomes have improved as a result.

Irrespective of whether the incidence of PE can be reduced through the implementation of the first two recommendations, it would be pertinent to study any differences in the long-term health of those people conceived with donated gametes from pregnancies that were uncomplicated. Such a study would enable the investigation of the influence of other treatment modality factors that may also affect long-term health trajectories. These studies would help address concerns associated with laboratory manipulation and embryo culture.

The culture of embryos and its health effects is currently an area that has already been receiving attention as part of a broader investigation into the effects of ART treatment modalities.[443, 738, 1059]

Finally, studies have highlighted that those offspring gestated under preeclamptic conditions have altered epigenetic profiles. It would therefore be of considerable interest to determine in any study that has shown adverse health outcomes in a DC cohort if those adversely affected people had altered epigenetic profiles in comparison to the control or comparison cohort that is being used. Such a study would assist in answering the question of whether adverse health outcomes in DC people were correlated with altered epigenetic profiles, which would be consistent with the DOHaD phenomenon and provide a mechanism explaining why these altered trajectories are occurring.

The aforementioned studies would assist in future research aims. However, returning to the original research aims of this thesis, a determination of whether they were achieved will now be made.

7.2.4 Achievement of the Thesis Research Aims

Specifically, concerning the research aims presented in Chapter 1 (section 1.3.1):

1. The primary aim of the research was to obtain quantifiable physical and mental health data on DC people for two stages of life:
a) perinatally (physical health outcomes);
b) adulthood (physical and mental health outcomes).

This aim was achieved by presenting data on donor sperm, oocyte and embryo outcomes in the perinatal period compared to an appropriate comparison group. Self-reported physical and mental health outcomes of adult DC people were presented in comparison to spontaneously conceived adults.

2. Determine if the quantifiable health of DC people is altered when compared to their appropriate comparator group.

This aim was achieved with data presented showing that a significantly increased incidence of adverse outcomes was observed for donor oocyte and donor sperm neonates. Data on donor embryo outcomes were inconclusive. Self-reports of diagnosed and own experience outcomes for adult DC people highlighted that a small proportion of the total number of health outcomes

analysed was significantly different from the self-reports from spontaneously conceived adults.

3. Determine if adult DC people have health outcomes that have been potentially influenced by their mode of conception and which are implicated in the DOHaD phenomenon.

This aim was achieved through the correlation between the increased incidences of hypertensive disorders of pregnancy, particularly preeclampsia, which are associated with the use of donated gametes/embryos and the increased incidences of adverse outcomes both perinatally and long-term. Preeclampsia is a significant source of epigenetic change and implicated in DOHaD in the literature, as described in Chapter 1.

4. Assess health outcome data within the donor conception paradigm to determine if the welfare of DC people is appropriately considered in Australia.

This aim was achieved through the analysis of the altered health outcomes in the context of the ethico-legal principle of child welfare paramountcy in Australia. This analysis showed that the welfare of DC people is not being treated as paramount.

With the research aims achieved, this thesis will now present the final conclusion.

7.3 Conclusion

Eight recommendations were made that may improve the welfare outcomes for DC people. The first two pertain directly to the crux of this thesis and the question of whether the health outcomes of people conceived with donated gametes/embryos are different from those conceived spontaneously or through autologous oocytes. Preeclampsia is a significant health care burden with severe implications for both the mother and child during pregnancy but also long-term. This burden is also passed on to future generations with those gestated under preeclamptic conditions more likely to have a child also gestated under preeclamptic conditions[241-246] creating a cycle of increased burden and adverse long-term physical and mental health. An opportunity exists to implement modifiable factors that may reduce the incidence of preeclampsia. However, this potentially impacts an adult's procreative freedoms.

Adults currently have freedom of choice in procreation using donor conception. This freedom does not fit precisely within Robertson's broad freedom definition[922] but is already partially constrained to fit within the legislation, regulation and the person's biological ability. Returning to the argument by Bromham and Lilford is the claim that laws and principles that

benefit one party can impinge on the autonomy and beneficence to another, which may be an injustice.[916] In the case of donor conception, laws and principles that uphold child welfare paramountcy by ameliorating the potential harms can potentially be viewed as reducing the procreative autonomy and freedom of the parents. However, this is juxtaposed against the decreased healthcare burden to the child, parents and society, that procreative freedom constraint would bring, which is beneficence. While some parental freedoms would be reduced, others would be increased, including the ability to give critical information to their child. This information is essential for a child's development, wellbeing and health diagnoses.

It has been observed that unmitigated procreative freedoms have the potential to adversely affect the physical and mental welfare of the most vulnerable, the child. As the welfare of the child has been institutionalised as being paramount, the procreative freedoms should be constrained to cater to this paramountcy principle. This constraint should not be taken as meaning that parents cannot use donor conception at all, instead, when donor conception is used, various treatment modalities and specific social environments (such as disclosure) should be implemented that places the welfare interests of the child first rather than the interests of the parent and or donor. This revision of parental freedoms and the paradigm is essential when the state has been involved in the donor conception process by providing services and funds. Such a position is supported by Hall and Gillam who argued:

> "But reproductive liberty doesn't automatically extend to unfettered ART access."
> and
> "Where the state has an active role in bringing children into being, it would fail future children by not acting to ensure their well-being."[1175]

Improvements to outcomes achievable through paradigm revision are not confined to the long-term health and welfare interests of the donor-conceived and the mother, but also may provide significant economic savings to the individual and the state. The improved physical and mental health outcomes for the DC person would be associated with improved productivity and a lower health care burden in terms of both resources and direct costs. In the previous chapter (section 6.7.1 'Other Considerations'), some of the direct extra costs associated with increased incidences of preterm delivery, low birthweight, preeclampsia and mental health were outlined. Long-term extra health care costs are also relevant to the mother experiencing a preeclamptic pregnancy due to their altered health trajectories associated with preeclampsia.[1176] If jurisdictions fully embrace and implement the child

welfare paramountcy principle, substantial economic savings can be made in addition to welfare outcomes to the child and mother.

7.3.1 Final Remarks

This thesis provides a significant original contribution to knowledge by presenting:
1) The first systematic reviews on donor sperm, oocyte and embryo neonatal outcomes.
2) The first population-based analysis of South Australian donor sperm neonatal outcomes.
3) The first exploratory study of the physical and mental health of adult donor-conceived people.
4) Evidence that donor oocyte-conceived neonates are more likely to be born with an increased risk for low birthweight, very low birthweight, preterm delivery, preterm delivery with low birthweight, as a twin or higher-order multiple and at a lower mean gestational age than those conceived with IVF using autologous oocytes. They were also less likely to be born at term with low birthweight. However, they were not significantly different in terms of their mean birthweight or the incidences of birth defects.
5) Evidence that donor sperm-conceived neonates are more likely to be born with an increased risk for low birthweight, birth defects, to be delivered via caesarean section, with forceps delivery, through induction of labour and that their mother was more likely to experience preeclampsia than those conceived spontaneously. However, they were not significantly different in terms of their mean birthweight, mean gestational age, the incidences of low birthweight, preterm delivery, very preterm delivery, small for gestational age, large for gestational age and perinatal mortality.
6) Evidence that a specific cohort of donor-conceived adults self-reported increased incidences of being diagnosed with type 1 diabetes, thyroid disease, Hashimoto's disease, acute bronchitis, environmental allergies, sleep apnoea, depressive disorder, attention deficit disorder or attention deficit hyperactivity disorder, and autism or autism spectrum disorder than those conceived spontaneously. They were also more likely to report having undergone surgery to have ear tubes or grommets implanted. However, they were not significantly more likely to self-report being diagnosed with the majority of physical health outcomes analysed.
7) Evidence that a specific cohort of donor-conceived adults self-reported experiencing greater incidences of the following in comparison to those conceived spontaneously; panic attacks, recurrent nightmares, having difficulty forming their identity, having an eating disorder, alcohol/drug dependency, learning difficulties, and had visited a mental health

professional. However, they were not significantly different in terms of being diagnosed with an anxiety disorder, bipolar disorder or to self-report greater incidences of insomnia.
8) Evidence that a specific cohort of donor-conceived adults self-reported being more stressed as determined by DASS-21 analysis than those conceived spontaneously.

What is clear from the findings of this thesis is that we are only starting to understand the implications of our origins and how the environment concerning our conception, gestation and development can have far-reaching consequences for not only the health of the person conceived but the health of future generations. Whether looking at perinatal outcomes or those in adulthood, there is evidence supporting the Donor Origins of Health and Disease.

This thesis has highlighted that the well-intentioned child welfare paramountcy principle is a paradox in the field of donor conception. It has also highlighted that by enabling greater procreative freedoms to parents that there is also a possibility that some DC people will have adverse health outcomes both when they are born and in adulthood which are associated with their mode of conception and which can potentially be passed on to future generations. By opening the lid of ART treatments, we may have inadvertently opened Pandora's box.

APPENDICES

Appendix 1 Systematic Reviews Publications

Appendix 1.1 Systematic Review of Donor Oocyte Offspring Outcomes

See next page

D H Adams, R A Clark, M J Davies, S de Lacey. A Meta-Analysis of Neonatal Health Outcomes From Oocyte Donation. J Dev Orig Health Dis. 2016 Jun;7(3):257-272.
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REVIEW

A meta-analysis of neonatal health outcomes from oocyte donation

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Donated oocytes are a treatment modality for female infertility which is also associated with increased risks of preeclampsia. Subsequently it is important to evaluate if there is concomitant increased risks for adverse neonatal events in donated oocyte neonates. A structured search of the literature using PubMed, EMBASE and Cochrane Reviews was performed to investigate the perinatal health outcomes of offspring conceived from donor oocytes compared with autologous oocytes. Meta-analysis was performed on comparable outcomes data. Twenty-eight studies were eligible and included in the review, and of these, 23 were included in a meta-analysis. Donor oocyte neonates are at increased risk of being born with low birth weight (<2500 g) [risk ratio (RR): 1.18, 95% confidence interval (CI): 1.14–1.22, *P*-value (*P*) < 0.00001], very low birth weight (<1500 g) (RR: 1.24, CI: 1.15–1.35, *P* < 0.00001), preterm (<37 weeks) (RR: 1.26, CI: 1.23–1.30, *P* < 0.00001), of lower gestational age (mean difference −0.3 weeks, CI: −0.35 weeks to −0.25 weeks, *P* < 0.00001), and preterm with low birth weight (RR: 1.24, CI: 1.19–1.29, *P* < 0.00001), when compared with autologous oocyte neonates. Conversely, low birth weight outcomes were improved in term donor oocyte neonates (RR: 0.86, CI: 0.8–0.93, *P* = 0.0003). These negative outcomes remained significant when controlling for multiple deliveries. The donor oocyte risk rates are higher than those found in general ART outcomes, are important considerations for the counselling of infertile patients and may also influence the long term health of the offspring.

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Key words: donor conception, meta-analysis, neonate, oocyte, outcome

Introduction

The use of donor oocytes is an increasingly common strategy for the treatment of female infertility. The manipulation of gametes and culture of embryos, however, have the potential to negatively influence embryological development and perinatal outcomes compared to normally conceived children.[1] Moreover, Assisted Reproductive Technologies (ART) perinatal outcomes are worse than those observed from spontaneous conceptions with increased incidences of birth defects (BD), preterm delivery (PD), lower birth weights and mortality.[2–7] Additionally, poor neonatal outcomes have been linked with increased incidences of morbidity and mortality in later life in the general population,[8–10] and phenotypically normal ART offspring have also been linked to increased epigenetic changes throughout their genome.[11]

With adverse perinatal outcomes from the ART population already established, there is an opportunity to consider the pattern of outcomes within specific exposure groups to identify opportunities for intervention and to inform patient decision making. Donor oocyte conceptions form one such sub-group and has a novel characteristic within the ART population. The woman receiving treatment will be gestating an embryo derived from another woman's oocyte which potentially represents an immunological challenge to the mother.

The incidence of preeclampsia is increased when donated oocytes are used in infertility treatments.[12–14] Preeclampsia is argued to be an immune response[15,16] that can alter placentation[17,18] and is a leading cause of foetal and maternal morbidity and mortality.[19] Notably, the immune mechanism of preeclampsia is associated with factors such as intra uterine growth retardation (IUGR) and PD known to adversely affect the health of the child.[20,21] Individuals born following preeclampsia in their gestation have an increased risk of hypertension,[22–24] endothelial dysfunction,[25] higher body mass index (BMI),[26] epilepsy,[27] increased hospitalization due to disease,[28] and stroke.[29] Preeclampsia has also been associated with an increased risk of an autism spectrum disorder in offspring.[30] Millis found that the placenta suffered from altered methylation due to preeclampsia and that infants also had altered methylation of insulin-like growth factor 2,[31] which is associated with metabolic diseases in later life.[32] Since the use of donor oocytes is associated with preeclampsia, it is reasonable to consider whether there is a concomitant increased risk for poor neonatal outcomes that is elevated above those found in ART offspring conceived with autologous oocytes.

Accordingly, there is a need to review and summarize the literature related to conceptions after oocyte donation to provide a knowledge base to inform reproductive technology

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practitioners and patients. The aims of this review were to summarize the published literature on neonatal outcomes such as birth weight, gestational age, and BD, for conceptions after oocyte donation in comparison to those conceived from autologous oocytes and spontaneous conceptions.

Methods

Literature search

A computerized literature search was conducted on articles published up to November 2012 in the online databases PubMed, EMBASE and Cochrane Reviews to identify studies containing data on neonatal health outcomes from donor oocytes.

The literature search comprised a three-stage process. First, relevant articles known to the authors were used to identify keywords along with a search of the U.S. National Library of Medicine MeSH (medical subject headings) database to identify appropriate search headings. Second, MeSH terms and other identified keywords were used to search the online databases. Search results were then analysed to determine specificity and to refine search terms, and filtered based on human not animal studies. Finally, the references of articles fitting the criteria were examined and online searches were implemented to find related articles.

Two main search categories were created and were termed 'Techniques', these were: oocyte donation and reproductive techniques. The term 'reproductive techniques' was chosen as a catch-all phrase. Two descriptors of human and donor were chosen to filter out animal studies and autologous treatments (own gametes). Three further qualifiers were implemented to each of the two techniques plus descriptor searches to refine the results. These qualifiers were: outcome*, morbidity, and adverse effects. The * wildcard was implemented to cover studies whose keywords implemented outcomes *v.* outcome. Search terms are also presented in Supplementary Table 1 for reference.

Eligibility and selection

Article selection and eligibility was performed by D.H.A. and verified by S.de L. according to the following PICOS criteria: *Participants*; cohorts of neonates that had neonatal health data presented in a study. *Interventions*; the treatment group must be comprised of a cohort of neonates conceived through fertility treatment of their parents with donated oocytes. The treatment group data must be appropriately segregated from comparison group data and not subsumed into larger combined data sets. *Comparators*; comparison cohorts could include offspring conceived through fertility treatment with autologous oocytes or general population data of spontaneous conceptions. *Outcomes*; studies to be included must report neonatal health outcomes such as (but not restricted to), birth weights, PD and BD (as determined by the publishing authors). Studies that only focused on live-birth rates or were case studies of single or few outcomes were excluded. *Study design;* only those observational case-controlled studies that used a treatment-cohort and comparison-cohort, or those studies involving a treatment-cohort that was compared to published, or public health data for that specific region and within 10 years of the study were included in the review. This was to remove any natural variation occurring between populations and between given time points. Published articles were restricted to the English language to allow for careful analysis of the study to ensure accurate data extraction as terminology and reporting methods varied considerably. There was no time restriction posed on publication dates, however, EMBASE would only allow a search from 1980. Database search results were downloaded into Endnote then analysed by their titles and abstracts. Some articles were initially included as they could not be excluded based on their titles or abstracts, and were subsequently excluded following a full review of the text article (Fig. 1). Any disagreement was resolved via discussion.

Data extraction

The following data were recorded by D.H.A. from the eligible studies: citation data, country, comparison type (autologous cohort, published data), number of offspring in treatment/comparison group, if cryopreservation of oocytes was used, and specific neonatal health outcomes. Data were recorded onto a specially designed data extraction form. Specific health outcomes included birth weights, chromosomal or congenital malformations (BD), PD/gestational age, IUGR, and singletons *v.* multiple births (Table 1). Maternal age and parity were also extracted to assess confounding where applicable. Multiple birth is a known predictor of increased adverse outcomes[33,34] and was therefore a confounder to the analysis unless the data were stratified and extracted where presented. Oocyte cryopreservation is also a potential confounder as its effects on neonatal outcomes are poorly characterized, and therefore data were extracted where possible.

Data referring to previously published data or general population databases, but that did not record the actual outcome data, were not included in meta-analysis. No authors were contacted for missing or obscure data.

Meta-analysis

Meta-analyses of dichotomous outcomes data of low birth weight (LBW), very low birth weight (VLBW), PD and BD were performed according to Mantel-Haenszel methods, using a fixed effects model, risk ratios, 95% confidence intervals, and assessment of statistical heterogeneity using Cochrane's Q test and I^2 statistic. Continuous mean birth weight and gestational age data were analysed by inverse variance with fixed effects and 95% confidence intervals to determine the mean difference. Heterogeneity of data were determined by the I^2 value and is considered significant when $I^2 > 65\%$. Sensitivity analysis of studies that presented overlapping data were performed by conducting separate meta-analysis with those studies removed

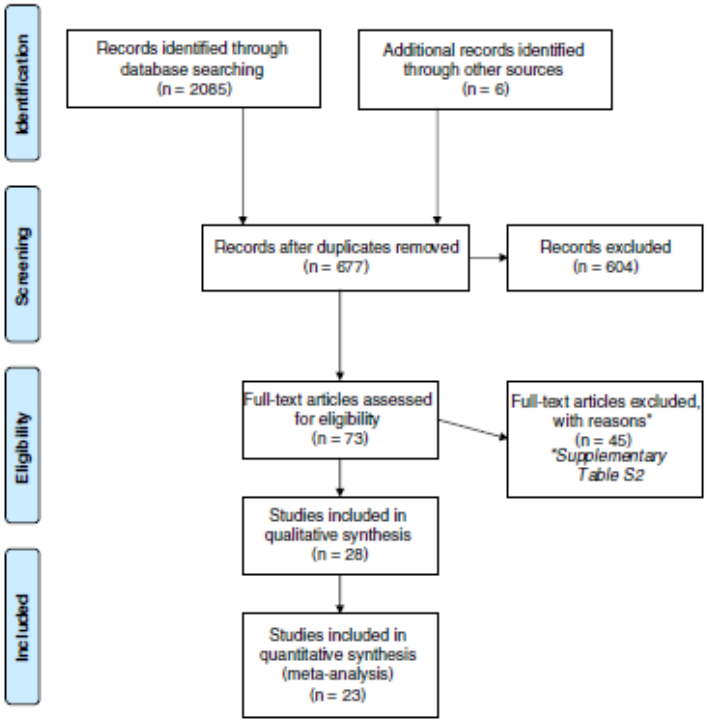


Fig. 1. PRISMA flowchart for identifying studies for inclusion in the review.

to determine any influence on data. All analyses were performed using Review Manager (RevMan) Version 5.2.8 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2012). Publication bias was assessed by visual analysis of funnel plots constructed in RevMan for asymmetry.

Risk of bias in individual studies

Included studies were assessed for methodological quality and the risk of bias using a modification of the Joanna Briggs Institute Meta Analysis Statistics Assessment and Review Instrument (JBI-MAStARI), with critical appraisal criteria for comparable cohort/case control studies.[35] Studies were assessed on the following criteria; Are patients in cohorts representative of patients typically receiving fertility treatment (for example, do they only include patients who may have been treated for ovarian cancer)? Are the patients at a similar point in the course of their condition/illness (do they describe how many times the patient had received treatment)? Has bias been minimized in relation to selection of cases and of comparators? Were singleton *v.* multiple births identified and strategies to deal with them stated? (If singleton *v.* multiples was described but all of the outcome data relevant to the review was not stratified then = No); Are other confounding factors identified and strategies to deal with them stated? Was cryopreservation of oocytes or the use of fresh oocytes adequately described, and were they appropriately stratified if both were included? Are outcomes assessed using objective criteria? Were outcomes measured in a reliable way? Was appropriate statistical analysis used?

Results

Searching of the three databases yielded 2085 articles with another six identified by hand-searching references lists. Duplicate removal reduced potential articles to 677. After screening the article titles and abstracts, 73 full-text publications were reviewed leaving a total of 28 studies to be included in the review and, of these, 23 were included in a meta-analysis (Fig. 1).

A summary of the characteristics and outcomes of all studies included in this review is presented in Table 1. Studies removed and the reasons for exclusion are presented in Supplementary Table S1.

There was a large amount of heterogeneity in the presentation of published outcomes. Subsequently, meta-analysis was only performed for outcomes that presented comparable statistical outcomes. The five studies not included in meta-analysis did not present comparable outcome data and have been summarized in the text.

Table 1. *Donor oocyte offspring health outcomes*

Study	Donation treatment(s) and sample size	Comparison and sample size	Frozen or fresh	Specific results
Gibbons *et al.*[36] United States	Oocyte 10,176	Autologous oocyte 49,252	Fresh	BW 3236 ± 652.7 *v.* 3240.1 ± 607.4 g LBW OR 1.21 *v.* 1 VLBW OR 1.28 *v.* 1 Gestational age 37.4 ± 2.4 *v.* 37.7 ± 2.2
Zegers-Hochschild *et al.*[37] South and Central America	Oocyte 73	Autologous oocyte 90	Not Specified	Singleton BW 2980 ± 446 *v.* 3170 ± 517 g Tw BW 2390 ± 577 *v.* 2057 ± 572 g ($P < 0.05$) Mult BW 1658 ± 452 *v.* 1365 ± 465 g ($P = 0.05$) Singleton GA 37.6 *v.* 38.5 (not significant) Tw GA 36.3 *v.* 34.7 (not significant)
Krieg *et al.*[38] United States	Oocyte 71 (pregnancies)	Autologous oocyte 108 (pregnancies)	Not Specified	BW 2835.6 ± 693.52 *v.* 3081.6 ± 674.29 g ($P = 0.02$) GA 37.0 (3.00 S.D.) *v.* 38.1 (2.61 S.D.) weeks ($P = 0.01$) Not significant when adjusted for multiple gestations IUGR OR 1.35 (0.67–2.72)
Söderström-Anttila *et al.*[39] Finland and Sweden	Oocyte 61 (67.2% S, 32.8% Mult)	Autologous oocyte 126 (54% S, 46% Mult)	Both	BW singletons 3338 ± 740 *v.* 3475 ± 630 g LBW singletons 10 *v.* 7% PD singletons 13 *v.* 7% SGA singletons 5 *v.* 6% Singletons in hospital (>7days) 36 *v.* 13 ($P < 0.01$) BW multiples 2216 ± 689 *v.* 2582 ± 556 g ($P < 0.05$) LBW multiples 50 *v.* 39% PD multiples 30 *v.* 48% SGA multiples 40 *v.* 24% Multiples admitted to ICU 60 *v.* 24 ($P < 0.01$)
Porreco *et al.*[40] United States	Embryo/oocyte 35 (pregnancies)	Autologous oocyte 32 (pregnancies)	Not Specified	BW 2446 ± 784 *v.* 2442 ± 687 g GA all births 36.9 ± 2.8 *v.* 37.2 ± 2.6 GA multiples 35.4 ± 2.6 *v.* 35.8 ± 3.2 PD 39 *v.* 29%
Friedman *et al.*[41] United States	Oocyte 22	Autologous oocyte 22	Unclear	BW 2924 ± 703 *v.* 2374 ± 822 g ($P < 0.005$) GA 35 (29–41) *v.* 38 (35–42) ($P < 0.01$)
Nelson and Lawlor[60] United Kingdom	Oocyte Total 144,018 donor plus own	Autologous oocyte Included in N of 144,018	Fresh	LBW donor 1 *v.* own 0.42 (0.26–0.68) ($P < 0.001$) PD donor 1 *v.* own 0.41 (0.26–0.64) ($P < 0.001$)
Kalra *et al.*[42] United States	Oocyte Fresh 5595 Frozen 3072	Autologous oocyte Fresh 20,916 Frozen 10,906	Both	LBW fresh 11.5 *v.* 10% LBW frozen 11.3 *v.* 7.2% PD fresh 19.3 *v.* 16% PD frozen 20.7 *v.* 15.8% PD LBW fresh 32.7 *v.* 34.1% PD LBW frozen 33.1 *v.* 23.8% Term LBW fresh 2.2 *v.* 2.5% Term LBW frozen 1.7 *v.* 1.2%
Sunderam *et al.*[43] United States	Oocyte 2995	Autologous oocyte 18,603	Fresh	LBW 12 *v.* 9.3% ($P < 0.01$) VLBW 2.6 *v.* 1.9% ($P < 0.01$) PD 17 *v.* 13.4% ($P < 0.01$) PD LBW 9.3 *v.* 6.7% ($P < 0.01$) PD VLBW 2.5 *v.* 1.9% ($P < 0.01$) Term LBW 2.7 *v.* 2.7% ($P < 0.01$) Term VLBW (0.1 *v.* 0%)

Wright *et al.*[44] United States	Oocyte 2864	Autologous oocyte 17,642	Fresh	LBW 11 *v.* 9.5% ($P<0.01$) VLBW 2 *v.* 1.7% PD 16.9 *v.* 13.4% ($P<0.01$) PD LBW 9 *v.* 6.9% Term LBW 2.1 *v.* 2.7% ($P<0.01$)
Thapar *et al.*[61] United Kingdom	Oocyte 146	Autologous oocyte 378	Not Specified	LBW singletons 13.6 *v.* 6.7% LBW all deliveries 23.4 *v.* 14.7%
Wright *et al.* [45] United States	Oocyte 2772	Autologous oocyte 17,230	Fresh	LBW 10.4 *v.* 9.5% ($P<0.01$) VLBW 1.9 *v.* 1.8% PD 16.2 *v.* 13.4% ($P<0.01$) PD LBW 8.3 *v.* 6.9% Term LBW 2.1 *v.* 2.5% ($P<0.01$)
Wright *et al.*[46] United States	Oocyte 2507	Autologous oocyte 16,082	Fresh	LBW 11.2 *v.* 9.3% ($P<0.01$) VLBW 2.3 *v.* 1.9% PD 17.6 *v.* 13.4% ($P<0.01$) PD LBW 9.1 *v.* 6.9% ($P<0.01$) Term LBW 2.1 *v.* 2.4% ($P<0.01$)
Wright *et al.*[47] United States	Oocyte 2199	Autologous oocyte 14,615	Fresh	LBW 10.7 *v.* 9.3% ($P<0.01$) VLBW 2.1 *v.* 1.9% PD 16.3 *v.* 13.3% ($P<0.01$) PD LBW 9 *v.* 7% ($P<0.01$) Term LBW 1.8 *v.* 2.3% ($P<0.01$)
Schieve *et al.*[48] United States	Oocyte 6432 (total) 899 (1996) 1019 (1997) 1250 (1998) 1459 (1999) 1805 (2000)	Autologous oocyte 47,586 (total) 6943 (1996) 8119 (1997) 9578 (1998) 10,511 (1999) 12,435 (2000)	Fresh	LBW 15.2 *v.* 13.7% (1996), 13 *v.* 13.5% (1997), 13.1 *v.* 12% (1998) 10 *v.* 9.9% (1999), 10.6 *v.* 9.1% (2000) VLBW 3.1 *v.* 2.2% (1996), 3.8 *v.* 3.1% (1997), 2 *v.* 2.1% (1998) 1.9 *v.* 1.8% (1999), 2.3 *v.* 1.9% (2000) PD 18.5 *v.* 13% (1996), 17.3 *v.* 12.7% (1997), 18.2 *v.* 13.1% (1998) 15.2 *v.* 12.2% (1999), 16.2 *v.* 13.1% (2000) PD LBW 8.8 *v.* 6.7% (1996), 8.1 *v.* 6.5% (1997), 8.9 *v.* 6.7% (1998) 7.5 *v.* 6.2% (1999), 8.2 *v.* 6.4% (2000) Term LBW 6.3 *v.* 6.9% (1996), 5 *v.* 6.7% (1997), 4.1 *v.* 5.2% (1998) 2.6 *v.* 3.7% (1999), 2.4 *v.* 2.5% (2000)
Sheffer-Mimouni *et al.*[62] Israel	Oocyte 134	General population Published data	Not Specified	PD 14.9 *v.* 7% ConMal 2.2% *v.* gen pop (no difference)
Corradetti *et al.*[63] Italy	Oocyte 14	Autologous oocyte 28	Unclear	IUGR 21.4 *v.* 7.1% ($P<0.011$)
Pados *et al.*[64] Europe, Lebanon and South America	Oocyte 60	Autologous oocyte and General population Published data	Both	IUGR 11.5% (donor) *v.* 17% (own) *v.* 3–7% (gen pop)
SART and ASRM[49] United States	Oocyte 2458 (56.5% S, 37.5% Tw, 6% Mult)	Autologous oocyte 17,677 (61.0% S, 31.8% Tw, 7.1% Mult)	Fresh	BD 1.9 *v.* 1.6%
SART and ASRM[50] United States	Oocyte 1849 (59.7% S, 35.6% Tw, 4.7% Mult)	Autologous oocyte 14,314 (61.0% S, 31.8% Tw, 7.1% Mult)	Fresh	BD 1.3 *v.* 1.8%
SART and ASRM[51] United States	Oocyte 1743 (58.9% S, 35.8% Tw, 5.3% Mult)	Autologous oocyte 11,342 (63.4% S, 29.6% Tw, 7% Mult)	Fresh	BD 0.6 *v.* 0.7%

Table 1. *Continued*

Study	Donation treatment(s) and sample size	Comparison and sample size	Frozen or fresh	Specific results
SART and ASRM[52] United States	Oocyte 1239 (61.8% S, 32.3% Tw, 5.9% Mult)	Autologous oocyte 6513 (63.7% S, 28.3% Tw, 6.5% Mult)	Fresh	BD 2.1 *v.* 2.7%
SART and ASRM[53] United States	Oocyte 1018 (59.6% S, 35% Tw, 5.4% Mult)	Autologous oocyte 7034 (65.9% S, 27.5% Tw, 5.8% Mult)	Fresh	BD 1.8 *v.* 2.3%
AFS and SART[54] United States	Oocyte 735 (62.9% S, 31.5% Tw, 4.1% Mult)	Autologous oocyte 5798 (67.3% S, 26% Tw, 6.2% Mult)	Fresh	BD 1.7 *v.* 1.9%
SART and AFS[55] United States	Oocyte 372 (66.8% S, 27.6% Tw, 5.6% Mult)	Autologous oocyte 3930 (70% S, 25% Tw, 4.8% Mult)	Fresh	BD 2.1 *v.* 1.5%
MRI *et al.*[58] United States	Oocyte 167 (45.8% S, 40.2% Tw, 14% Mult)	Autologous oocyte 3110 (52.8% S, 37.1% Tw, 10.1% Mult)	Fresh	ConMal 0.56 *v.* 1.22% ChAb 0 *v.* 0.7%
MRI *et al.*[57] United States	Oocyte 112 (47.3% S, 44.6% Tw, 8.1% Mult)	Autologous oocyte 2876 (50.8% S, 39.5% Tw, 9.7% Mult)	Fresh	ConMal 2.7 *v.* 0.9% ChAb 2.7 *v.* 1.2%
MRI *et al.*[56] United States	Oocyte 50 (46% S, 48% Tw, 6% Mult)	Autologous oocyte 2133 (56.9% S, 33.4% Tw, 9.7% Mult)	Fresh	ConMal 0 *v.* 0.84% ChAb 0 *v.* 0.75%

BW, birth weight; LBW, low birth weight <2500 g; VLBW, very low birth weight <1500 g; ConMal, congenital malformation; ChAb, chromosomal abnormalities; BD, birth defects; IUGR, intra-uterine growth retardation; PD, preterm delivery (<37 weeks); GA, gestational age (weeks); SGA, small for gestational age; S, singleton; Tw, twin; Mult, multiple (triplets or greater); OR, odds ratio; gen pop, general population.

Health outcomes for neonates conceived via donated oocytes. Sample sizes represented by statements such as 'published data' refers to the study citing data published elsewhere. Data are presented as donor *v.* control, *P* value for significance is only provided where $P<0.05$. Comparison groups are autologous cohorts unless otherwise noted. General population refers to data obtained from spontaneous conceptions that have either been presented in 'published data' by other authors, or were part of a comparison cohort with specific data presented in the study.

Oocyte donation outcomes

A total of 28 studies investigating the health outcomes of people conceived via donated oocytes met the criteria for inclusion, 23 of which were included in the meta-analysis.[36–59] The remaining five studies were used in a qualitative analysis.[60–64] Two studies reported on comparisons to spontaneous conceptions but the data did not allow for meta-analysis. Subsequently all meta-analysis were comparisons against neonates conceived with autologous oocytes. From these studies a total of 201,628 neonatal health outcomes from donor oocytes and 432,361 from autologous oocytes have been analysed.

The actual number of offspring is overestimated due to the overlap of some studies[36,43–45] in relation to the data they obtained from the Society for Assisted Reproductive Technology databases covering the same years. We did not have access to the raw data and therefore the exact number cannot be ascertained, however, a sensitivity analysis was conducted to determine if it affected the meta-analysis outcomes (described later). The majority of the studies represented national data obtained from multicentres (71.4%), of which most were from the United States of America [data from Society for Assisted Reproductive Technology (SART) and Centers for Disease Control and Prevention (CDC)], while the single largest study was from a national study in the United Kingdom with data collected by the HFEA (Human Fertilisation and Embryology Authority). There is no consensus in the types of outcomes data these studies collected.

Cryopreservation data were recorded in some studies, however, the data were either poorly stratified, or in some instances was cryopreserved embryos created from donated oocytes and therefore could not be used in a meta-analysis. Consequently we do not report on the effects of cryopreservation on donated oocyte outcomes, however, we have left references to which studies noted cryopreservation in Table 1. Subsequently data will include both fresh and cryopreserved outcomes unless otherwise specified.

Oocyte donation birth weights

One of the most common outcomes reported was birth weights, which also included the categories of LBW < 2500 g, VLBW < 1500 g and IUGR or small for gestation age.

Ten studies reported a significant reduction in either the birth weights ($P = 0.02$),[38] or increased incidences of low birth weight category births (($P < 0.001$),[60] ($P < 0.01$)[43–47]), IUGR ($P < 0.011$),[63] or increased odds ratios for low (1.21 *v.* 1)[36] or very low birth weights (1.28 *v.* 1)[36] of children conceived from donated oocytes when compared to those conceived from autologous oocytes. A further study found a similar significance but only in multiples and not singletons ($P < 0.05$).[39] Another two studies reported a higher incidence of LBW for donor oocyte neonates, but did not conduct statistical analysis on the outcome.[42,61] The four studies reporting no significant difference in birth weights or higher birth weights in donor oocyte neonates were associated with the smallest sample sizes,[37,39–41] while studies reporting significant differences were associated with large multicentre national cohorts.[36,42–47,60]

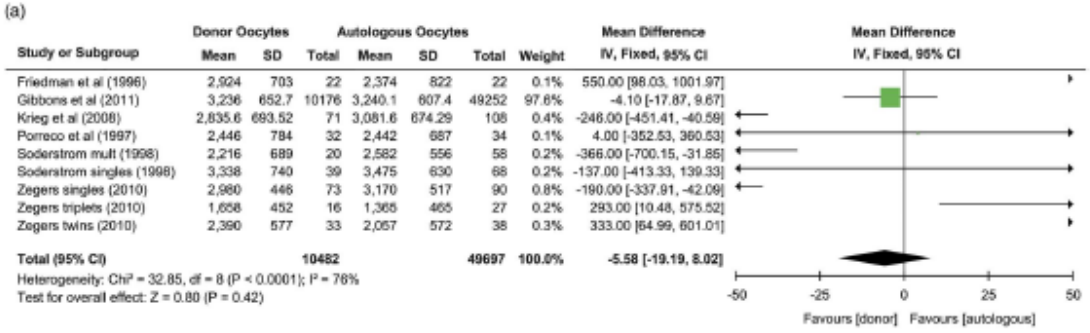
Meta-analysis of mean birth weights showed that donor oocyte neonates (singleton and multiple deliveries) had a lower mean difference but was not statistically different to control cohorts (autologous oocytes) (mean difference −5.58 g, CI: −19.19 to −8.02 g, $P = 0.42$, $I^2 = 76\%$) (Fig. 2a). When multiple deliveries were excluded, the outcome was relatively unchanged (mean difference −4.91 g, CI: −18.63 to −8.81 g, $P = 0.48$, $I^2 = 26\%$), even though heterogeneity was improved. These data are extensively influenced by the publication of Gibbons *et al.* who used a 3-year data set from U.S. national data obtained by the SART.[36] Donor oocyte neonates were at an increased risk ratio (RR: 1.18, CI: 1.14–1.22, $P < 0.00001$, $I^2 = 36\%$) observed for being born <2500 g (LBW) when compared to autologous oocytes (Fig. 2b). Schieve *et al.* stratified the data into years and subsequently each year was treated as a separate study to match the data from other studies that also reported on annual CDC and SART data (the Gibbons *et al.* data from the continuous data analysis of mean birth weights could not be similarly stratified as it was pooled data). Similarly to LBW, the risk of being born below 1500 g (VLBW) was increased for those conceived from donor oocytes compared to autologous oocytes (RR: 1.24, CI: 1.15–1.35, $P < 0.00001$, $I^2 = 32\%$) (Fig. 2c). VLBW was the only outcome measure that was of fresh donor oocytes only. These birth weight outcomes were for all neonates irrespective of whether they were born preterm (<37 weeks), at term (37–42 weeks), or post term (>42 weeks).

The data reported by Gibbons *et al.*[36] and Kalra *et al.*[42] covered SART data from 2004 to 2006, which overlapped with the SART data (same years) reported by Wright *et al.*[44,45] and Sunderam *et al.*,[43] however, outcome measures and numbers differed. Subsequently, they were included in the review and meta-analysis. To determine if the inclusion of Gibbons *et al.* and Kalra *et al.* adversely affected the meta-analysis, a sensitivity analysis was performed whereby they were removed from the meta-analysis. The outcomes for donor oocyte neonates was similar irrespective of the exclusion or inclusion of Gibbons *et al.* and Kalra *et al.* with LBW (excluded RR: 1.14, CI: 1.09–1.19, $P < 0.00001$, $I^2 = 31\%$), (included RR: 1.18, CI: 1.14–1.22, $P < 0.00001$, $I^2 = 36\%$), and VLBW (excluded RR: 1.23, CI: 1.12–1.36, $P < 0.0001$, $I^2 = 39\%$), (included RR: 1.24, CI: 1.15–1.35, $P < 0.00001$, $I^2 = 32\%$).

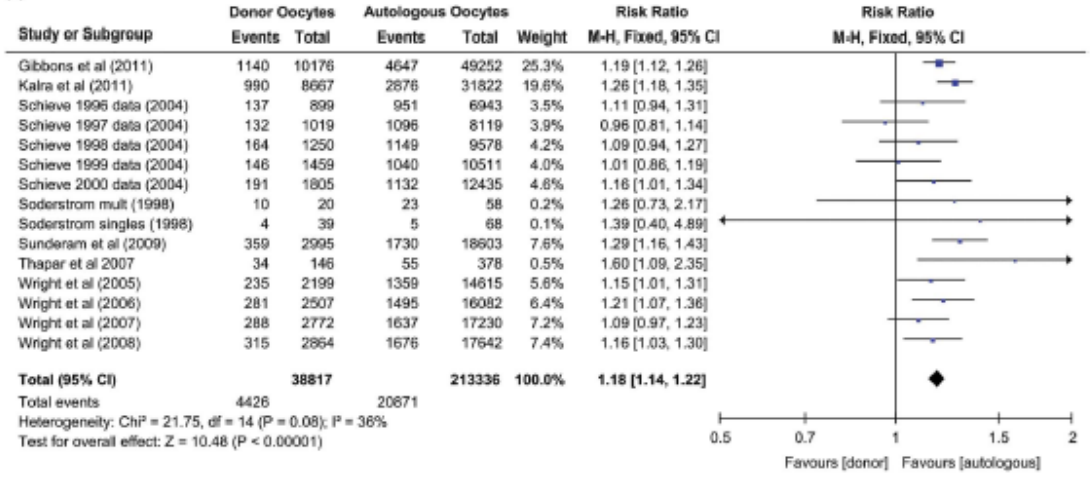
Oocyte donation PD

A total of 10 studies reported on the incidences of being born prematurely (PD < 37 weeks).[40,42–48,60,62] Of these ten studies, six reported that neonates conceived of donor oocytes were significantly more likely to be born PD ($P < 0.001$),[60] ($P < 0.01$).[43–47] Kalra *et al.* and Schieve *et al.* did not statistically analyse the donor *v.* autologous oocyte results.[42,48] Porreco *et al.* reported a higher percentage of donor oocyte neonates

(a)



(b)



(c)

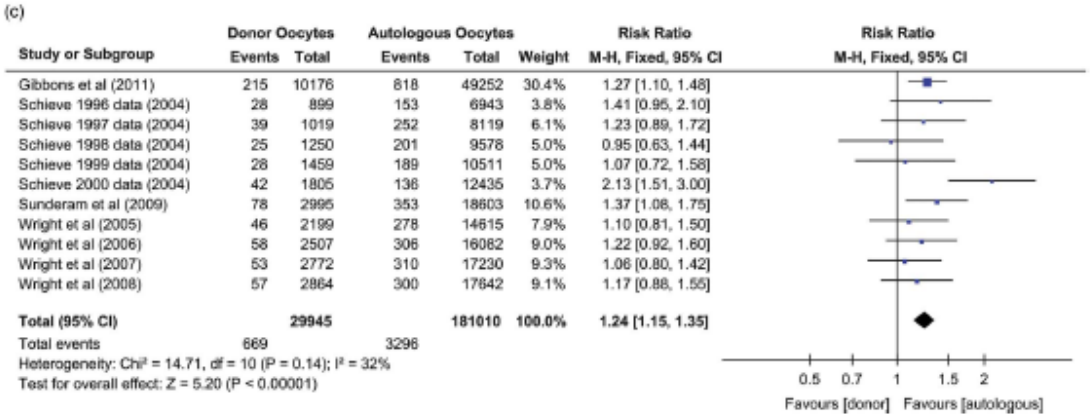


Fig. 2. Forest plots of birth weight outcomes of neonates from donor oocytes *v.* autologous oocytes; (*a*) mean differences of birth weights, (*b*) risk ratio for being born of low birth weight <2500 g, (*c*) risk ratio for being born of very low birth weight <1500 g.

born PD, but it was not statistically significant (*P* value not reported).[40] Meta-analysis showed a significant increased risk of being born PD as a result of using donor rather than autologous oocytes (RR: 1.26, CI: 1.23–1.30, $P<0.00001$, $I^2 = 0\%$) (Fig. 3a). Five studies investigated gestational age in absolute terms (age in weeks) with two finding that donor oocytes were

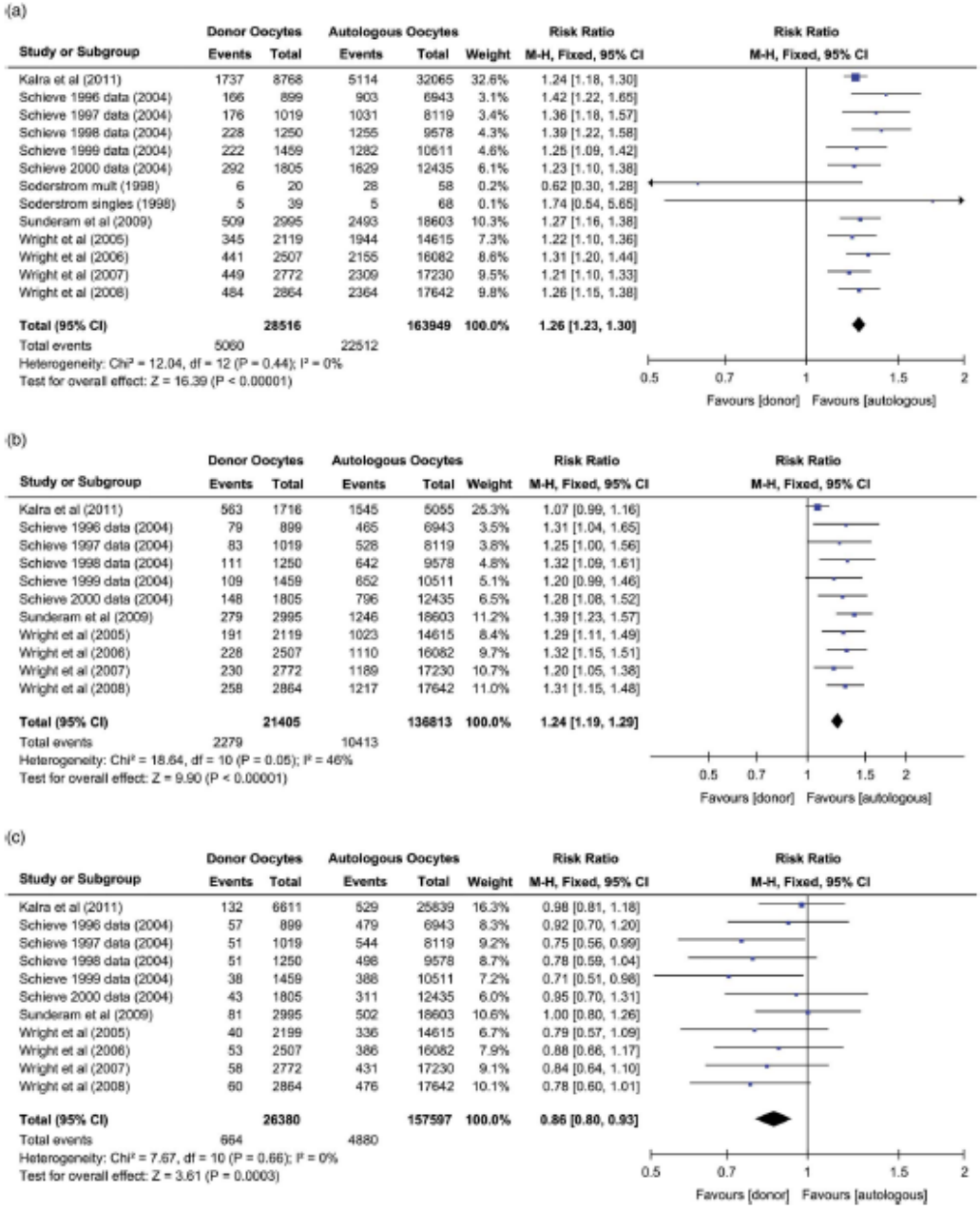


Fig. 3. Forest plots of preterm and term delivery outcomes of neonates from donor oocytes *v.* autologous oocytes; (*a*) risk ratio for being born preterm (<37 weeks), (*b*) risk ratio for being born preterm and of low birth weight, (*c*) risk ratio of being born term and low birth weight.

more likely to be born at a lower gestational age ($P < 0.01$),[38,41] while the other three ($P = 0.563$),[36] (*P* value not reported),[37,40] found no difference when compared with autologous oocyte gestations. The Krieg *et al.* gestational age data were also associated with a lower birth weight. By contrast, Zegers-Hochschild *et al.* found no significant difference in singleton or twin

gestational ages (*P* value not reported).[37] Additionally, Porreco *et al.* found no difference between groups in respect to birth weights, gestational age (including singleton *v.* multiple delivery analysis) and PD.[40] Meta-analysis of the continuous data on gestational age showed that donor oocytes were born significantly earlier by 0.3 weeks when compared to autologous oocytes (mean difference −0.3 weeks, CI: −0.35 to −0.25 weeks, $P < 0.00001$, $I^2 = 40\%$) (Zegers-Hochschild *et al.*[37] was excluded due to lack of standard deviation data).

Oocyte donation birth weight with PD

Seven studies correlated the birth weight results with the incidences of the neonates being born prematurely.[42–48] Of these, three found a significant correlation in donor oocyte neonates when compared with autologous oocyte neonates being born PD and LBW ($P < 0.01$).[43,46,47] One study also showed an association of PD with being born VLBW ($P < 0.01$).[43] Schieve *et al.* did not perform statistical analysis of donor *v.* autologous oocytes; however, in every year of data there was a higher percentage of donor oocyte neonates born PD with LBW (8.8 *v.* 6.7% (1996), 8.1 *v.* 6.5% (1997), 8.9 *v.* 6.7% (1998), 7.5 *v.* 6.2% (1999), 8.2 *v.* 6.4% (2000)).[48] The other two studies found no significant difference. Meta-analysis of the incidence of PD with LBW in donor oocytes showed a significant increased risk compared with autologous oocytes (RR: 1.24, CI: 1.19–1.29, $P < 0.00001$, $I^2 = 46\%$) (Fig. 3b).

Seven studies correlated the birth weight results with the incidences of the neonates being born at term.[42–48] For those born at term with donated oocytes there was a decreased risk of LBW (RR: 0.86, CI: 0.8–0.93, $P = 0.0003$, $I^2 = 0\%$) (Fig. 3c).

Oocyte donation BD

The reporting of BD was absent from recent analysis of donor oocyte outcomes but were presented in earlier studies by Medical Research International (MRI) *et al.*[56–58] Additionally, data collected by the SART from clinics in the United States from 1990 to 1997 reported on congenital malformations and BD,[49–53] and Sheffer-Mimouni *et al.*[62] reported on congenital malformations.[62] The MRI and SART data did not include statistical analysis but rather reported percentages of incidences in which a higher percentage of BD was observed in 3 of the 10 years (see Table 1). Sheffer-Mimouni *et al.* found no significant difference to the general population in Israel (statistics not reported).[62] Meta-analysis of BD showed no increased risk ratio for fresh donor *v.* fresh autologous oocytes, although a non-significant tendency to a lower risk was observed (RR: 0.89, CI: 0.75–1.05, $P = 0.15$, $I^2 = 48\%$) (Fig. 4). The data set from the BD meta-analysis contained the incidences of twin and multiple (triplets or higher order) birth occurrences. Donor oocyte neonates were more likely to be born as a twin or from higher order deliveries (RR: 1.1, CI: 1.07–1.13, $P < 0.00001$, $I^2 = 31\%$), in the cohorts included in the BD meta-analysis.

Oocyte donation other outcomes

Söderström-Anttila *et al.* also investigated the length of time neonates stayed in hospital before going home and the incidences of them being admitted to the intensive care unit (ICU).[39] The authors found a significant increase in the length of stay in the hospital of donor oocyte singleton neonates ($P < 0.01$), as well as an increase in the incidence of admissions to the ICU for donor oocyte multiple birth neonates ($P < 0.01$), when compared to autologous multiple birth oocytes.[39]

Effect of multiplicity on outcomes

Multiple births is a well known confounder for negative neonatal outcomes. Subsequently we assessed the risk ratios for the occurrences of multiple deliveries for the studies included in this review. As shown above, there was an increased risk

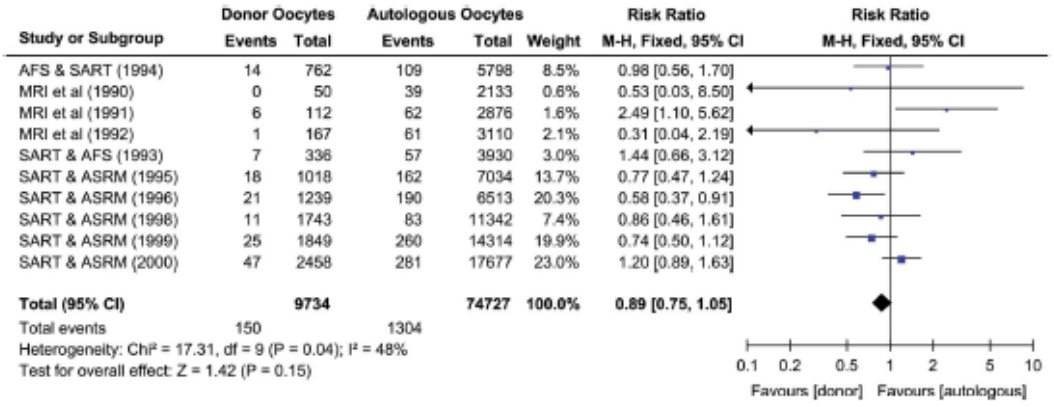


Fig. 4. Forest plots of birth defect risk ratios of neonates from donor oocytes *v.* autologous oocytes.

of multiple deliveries as a result of using donor rather than autologous oocytes (RR: 1.1, CI: 1.07–1.13, $P<0.00001$, $I^2 = 31\%$), in the studies used for BD meta-analysis. The studies showing increased multiplicity were typically those published before 2000 and since that time there has been a greater awareness of the need to reduce the number of embryos implanted. For example the ASRM guidelines which described the maximum number of embryos to be implanted were introduced in 1998 but have been adjusted down over the course of the period since with resultant multiple pregnancies decreasing dramatically during that time.[59] Therefore it was important to determine whether the increased risk ratios observed in the outcomes reported above would still hold in an analysis of singleton outcomes.

Mean birth weights remained lower but still not significant for donor oocyte neonates when compared to autologous oocyte neonates (Singleton mean difference; −4.91 g, CI: −18.63 to −8.81 g, $P = 0.48$, $I^2 = 26\%$ *v.* All births mean difference −5.58 g, CI: −19.19 to −8.02 g, $P = 0.42$, $I^2 = 76\%$). The risk of being born of LBW as a result of using donor oocytes compared with autologous oocytes remained significant (Singleton RR: 1.17, CI: 1.12–1.23, $P<0.00001$, $I^2 = 59\%$ *v.* All births RR: 1.18, CI: 1.14–1.22, $P<0.00001$, $I^2 = 36\%$), as did being born of VLBW (Singleton RR: 1.31, CI: 1.11–1.54, $P = 0.001$, $I^2 = 65\%$ *v.* All births RR: 1.24, CI: 1.15–1.35, $P<0.00001$, $I^2 = 32\%$), PD (Singleton RR: 1.27, CI: 1.22–1.32, $P<0.00001$, $I^2 = 5\%$ *v.* All births RR: 1.26, CI: 1.23–1.30, $P<0.00001$, $I^2 = 0\%$), as well as PD and LBW (Singleton RR: 1.17, CI: 1.10–1.24, $P<0.00001$, $I^2 = 42\%$ *v.* All births RR: 1.24, CI: 1.19–1.29, $P<0.00001$, $I^2 = 46\%$). Additionally the association of decreased risk of donor oocyte neonates being born at term of LBW also remained in the meta-analysis of singletons (Singleton RR: 0.86, CI: 0.77–0.96, $P = 0.007$, $I^2 = 2\%$ *v.* All births RR: 0.86, CI: 0.8–0.93, $P = 0.0003$, $I^2 = 0\%$). Controlling for multiple births in the meta-analysis of outcomes did not alter the increased risk of poor neonatal outcomes for donor oocyte neonate singletons when compared with autologous oocyte singletons.

Risk of bias

There was variation in the methodological quality of the studies included (Table 2). In general, the reporting of the length of time the woman had been receiving treatment (number of previous attempts) was poorly documented and even when such data were presented it was not stratified into donor *v.* autologous treatments. This lack of stratification also occurred frequently in the reporting of other confounders such as maternal age, parity, BMI, reasons for infertility and other demographic data. Singleton *v.* multiple deliveries was poorly stratified into donor *v.* autologous treatments in many of the studies.

Maternal age and parity data where reported are presented in Table 3. Mean birth weight meta-analysis incorporated 97.6% of weighted data adjusted and controlled for maternal ages and parity.[36] Of those studies reporting maternal ages and low birth weight, the associations were conflicting. Gibbons *et al.* adjusted for maternal age and found no correlation with maternal age,[36] whereas the higher maternal ages of the donor oocyte cohort reported by Sunderam *et al.* were associated with increased risk of low birth weight and very low birth weight.[43] The single study reporting maternal age data in relation to PD, found donor oocyte cohort maternal ages to be proportionally higher compared to the autologous oocyte cohort and was associated with PD and PD with low birth weight.[43] Maternal age and parity data of included studies investigating BD were not reported.

Studies reporting outcomes such as birth weights, LBW, VLBW, GA and PD were deemed to be reporting objective criteria. However, those only reporting BD (or what was classified as congenital malformations) were more subjective in nature as BD can potentially be missed in the neonatal period. Five of the studies stated that the reporting of BD outcomes was poor and therefore the data set did not contain all BD data.[51–54] The study by Pados *et al.* did not have a comparison cohort but only referred to previously published work, which was limited,[64] while Corradetti *et al.* did not adequately describe the selection of comparators.[63]

Funnel plot analysis showed publication bias in oocyte donation health outcome meta-analysis for fresh oocyte BD, while birth weights were too heterogeneous. Outcome measures LBW, VLBW, PD, PD with LBW, and term with LBW were symmetrical. Funnel plot analysis of singleton outcomes showed that birth weight data again was too heterogeneous, and that LBW, PD, and term with LBW were symmetrical, while VLBW and PD with LBW were asymmetrical showing the presence of reporting bias.

Limitations of study

This review was limited by the restriction to three databases, limited hand-searching and the restriction to the English language. Methodological quality and reporting details in earlier publications was generally lower than later studies, which prevented the inclusion of some studies in meta-analysis.

From the data retrieved via this review, the lack of statistical analysis in some of these studies is a concern as is the ability for the studies to capture accurate data when self-reporting is involved. The AFS and SART[54], and SART and ASRM[51–53], reported that the incidence of BD were low but that 'more stringent requirements for follow-up and reporting' (P1126, P19, P703, P395, respectively) were to be implemented in subsequent years.[51–54] This suggests that the ability to accurately capture this data could be improved. Furthermore, in 2000 they suggested that there were still limitations on the data for birth outcomes,[49] thereby suggesting that the incidences of BD in all groups may be underreported.

The reporting of multiple deliveries was inconsistent and not all data were appropriately stratified for analysis of singleton *v.*

Table 2. *Critical appraisal and risk of bias of included studies*

Study	Criterion								
	Representative patients	Similar point in condition	Minimized case selection bias	Singleton *v.* multiples	Other confounders	Cryopreservation	Objective criteria	Reliable outcomes	Appropriate statistics
Gibbons *et al.*[36]	Yes	Unclear[a]	Yes	No[a]	Yes	Yes	Yes	Yes	Yes
Zegers-Hochschild *et al.*[37]	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	Yes
Krieg *et al.*[38]	Yes	Unclear	Yes	No[a]	Yes	No	Yes	Yes	Yes
Söderström-Anttila *et al.*[39]	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Porreco *et al.*[40]	Yes	Unclear	Yes	No	No	No	Yes	Yes	Yes
Friedman *et al.*[41]	Yes	Unclear	Yes	No	Yes	No	Yes	Yes	Yes
Nelson and Lawlor[60]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Kalra *et al.*[42]	Yes	Unclear[a]	Yes	Yes	No[a]	Yes	Yes	Yes	No[b]
Sunderam *et al.*[43]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Wright *et al.*[44]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Thapar *et al.*[61]	Yes	Unclear	Yes	Yes	No[a]	No	Yes	Yes	Yes
Wright *et al.*[45]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Wright *et al.*[46]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Wright *et al.*[47]	Yes	Unclear[a]	Yes	No	No[a]	Yes	Yes	Yes	Yes
Schieve *et al.*[48]	Yes	Unclear	Yes	Yes	No[a]	Yes	Yes	Yes	No[b]
Sheffer-Mimouni *et al.*[62]	Yes	Unclear	Yes	Yes	No[a]	No	Yes	Yes	No[b]
Corradetti *et al.*[63]	Yes	Unclear	Unclear	No	No	No	Yes	Yes	Yes
Pados *et al.*[64]	Yes	Unclear	No[c]	No[a]	No[a]	No	Yes	Yes	No
SART and ASRM[49]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and ASRM[50]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and ASRM[51]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and ASRM[52]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and ASRM[53]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
AFS and SART[54]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
SART and AFS[55]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No
MRI *et al.*[58]	Yes	Unclear	Yes	No[a]	No	No	Yes	No	No
MRI *et al.*[57]	Yes	Unclear	Yes	No[a]	No	No	Yes	No	No
MRI *et al.*[56]	Yes	Unclear	Yes	No[a]	No[a]	No	Yes	No	No

[a] Data presented but not stratified donor *v.* autologous, or not used in an analysis.
[b] Statistics used appropriately but did not analyse donor *v.* autologous.
[c] Comparison group was used but was published data not comparison cohort.

Table 3. *Maternal age and parity reporting of included studies*

Study	Maternal age details	Parity details
Gibbons *et al.*[36]	Data adjusted for maternal age	Data adjusted for parity
Zegers-Hochschild *et al.*[37]	(14% ⩽ 34 years, 25.1% 35–39 years, 60.9% ⩾ 40 years) *v.* (50% ⩽ 34 years, 34.6% 35–39 years, 15.4% ⩾ 40 years)	
Krieg *et al.*[38]	(42.7 ± 4.4 years) *v.* (41.3 ± 1.84 years)	(0.32 ± 0.528) *v.* (0.35 ± 0.569)
Söderström-Anttila *et al.*[39]	(33.5 ± 4.7 years) *v.* (33.4 ± 3.7 years)	84 *v.* 69% nulliparous
Porreco *et al.*[40]	(38.8 years (range 27–50)) *v.* (38.7 years (range 34–44))	89 *v.* 78% nulliparous
Sunderam *et al.*[43]	(12% < 35 years, 11.7% 35–37 years, 17.3% 38–40 years, 16.2% 40–42 years, 42.8% > 42 years) *v.* (56.3% < 35 years, 25.1% 35–37 years, 14.3% 38–40 years, 3.5% 40–42 years, 0.8% > 42 years)[a]	
Thapar *et al.*[61]	(37.88 ± 5.89 years) *v.* (34.14 ± 3.53 years)	
Corradetti *et al.*[63]	(range 32–50 years) *v.* (range 30–46 years)	

Only those studies reporting maternal age and parity are listed.
[a]A function of live birth delivery rates.

multiple birth outcomes. While rates of multiples were broken down in some studies, in some of these instances the outcome data were pooled rather than stratified and therefore meta-analysis could not be performed in a stratified manner for those studies, thereby reducing the number of studies available for meta-analysis of singleton data. However, when meta-analysis of the singleton data were performed, similar risk ratios for negative outcomes were observed suggesting that multiple birth confounding data did not significantly influence the analysis on outcomes.

Methodological quality and reporting of outcomes in a systematic way generally improved over time, with later studies better addressing the donor *v.* autologous outcomes question. Consistency in reporting, with increased analysis of confounders such as multiple deliveries, maternal age, parity and cryopreservation, can be improved.

Discussion

This review has demonstrated that donor oocyte neonates, when compared with autologous oocyte neonates, are at increased risk of being born of low birth weight, very low birth weight, preterm, preterm with low birth weight, and have a lower gestational age. The incidences of low birth weight were not increased, rather they were decreased when donor oocyte neonates were born at normal gestation. These correlations also occurred when controlling for multiple deliveries. However, singleton very low birth weight and PD with low birth weight analysis showed the presence of some reporting bias and more data is required to clarify these outcomes in singletons. The majority of comparison group data and all of meta-analysis comparison data were of autologous oocytes, of which only two studies of small sample size reported spontaneous conception data as a comparison.[62,64] The use of autologous oocyte neonates as the comparison cohort rather than spontaneous conceptions is a more appropriate comparison as the manipulation of oocytes may influence neonatal outcomes and therefore strengthens the review findings.

Meta-analysis showed no increase in the incidences of BD occurring as a result of using donor *v.* autologous oocytes, but rather a non-significant decrease was observed. While several studies (particularly those involving SART data) reported on the incidences of multiple deliveries, the incidences of BD was not appropriately stratified by plurality to determine if the BD were occurring in the multiple deliveries, and subsequently could only be used to determine the risk ratio for all births as a result of using donated or autologous oocytes. The use of donor oocytes was correlated with multiple deliveries in the studies used for BD meta-analysis. While this is a known confounder, a lower risk of BD was observed. This would be consistent with oocytes being donated by women younger than the recipients and in whom lower incidences occur of poor quality oocytes such as those with aneuploidy.[65,66] In comparison to ART outcomes in general, the incidences of BD in donor oocyte neonates are less (ART birth defects RR: 1.32, CI: 1.24–1.42, $P = 0.000$, $I^2 = 47\%$).[3]

The results of this review suggest that the incidences of BD and or congenital malformations are not adversely affected by the use of fresh donor oocytes and that data should be collected on the BD incidences from neonates conceived with cryopreserved donor oocytes. This is pertinent considering that oocyte cryopreservation often involves the use of genotoxic cryoprotectants,[67] with some researchers reporting increased incidences of DNA damage.[68,69]

There was only one study investigating length of hospital stays and admissions to neonatal intensive care units (NICU)

for those neonates conceived with donor rather than autologous oocytes. The increased length of hospital stay and NICU admissions found by Söderström-Anttila *et al.* (including in singletons), has been corroborated since the review census date. Malchau *et al.* reported a significant increase in the percentage of donor oocyte singleton neonates entering NICU (24.2 *v.* 7.6%, $P < 0.0001$), and an increase in their length of stay (2.5 ± 7.5 *v.* 0.9 ± 5.8 days, $P = 0.002$).[70] Further investigation in this area is therefore warranted.

Additionally, others have reported increased negative neonatal outcomes following oocyte donation when compared to autologous oocytes of low birth weight, very low birth weight, PD, very PD, small for gestational age, and very small for gestational age;[2] and PD, and low birth weight[70] since the literature search was completed and support the findings of this review.

Patients undergoing treatment for infertility require accurate information, not only about the expected pregnancy and take home baby rates of the treatment, but also about the expected health of their infant and how this might be affected by the procedure. Clinicians involved in interventions for the treatment of infertility have an obligation to provide this information, to the best of their ability, in counselling couples about treatment choices.

Increased incidences of low birth weight, very low birth weight, lower gestational age, PD, PD with low birth weight, and preeclampsia that are correlated with the use of donor oocytes constitute obstetric risks that will pose a challenge for obstetricians in their provision of care. Preliminary evidence suggestive of increased NICU admissions associated with donor oocytes are also of concern. While low birth weight can be avoided in donor oocyte conceptions when the fetus reaches normal gestation, it is unclear if this is clinically possible or advisable, considering the correlation with preeclampsia. It could possibly be viewed that preeclampsia represents a far greater risk to mother and fetus than low birth weight and PD outcomes. Therefore preeclampsia would warrant the primary consideration of the obstetrician. Patients should be counselled on the gestational/perinatal risks so that they are fully informed of potential outcomes and therefore maintain full autonomy over their reproductive choices.

The results of this review also highlight other areas that require further investigation. Studies that specifically stratify and isolate negative neonatal outcomes as a direct consequence of preeclampsia rather than just as a correlation will help ascertain if the increased incidences are primarily the result of a significant immunological challenge or if a more minor immunological response can also produce these outcomes. Finally, studies are required that investigate the longitudinal outcomes into childhood and adulthood to determine if these negative neonatal outcomes resulting from their conception with donated oocytes also negatively impact their long term health as currently there are no such studies.

Due to poor neonatal outcomes of low birth weights and preterm deliveries being associated with increased incidences of morbidity and mortality in later life,[8–10] the donor oocyte cohort represent a significant health care burden for the individual and society. This is irrespective of any reasons as to why this cohort fares worse than autologous oocyte neonates or spontaneously conceived neonates.

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Conflicts of Interest

None.

Supplementary material

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Appendix 1.2 Systematic Review of Donor Sperm Offspring Outcomes

See next page

D H Adams, R A Clark, M J Davies, S de Lacey. A Meta-Analysis of Sperm Donation Offspring Health Outcomes. J Dev Orig Health Dis. 2017 Feb;8(1):44-55.
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REVIEW

A meta-analysis of sperm donation offspring health outcomes

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Although the use of donor sperm as a treatment modality for male infertility has become common place, the health outcomes for those conceived has been poorly studied. A structured search of the literature using PubMed, EMBASE and Cochrane Reviews was performed to investigate the health outcomes of offspring conceived from donor sperm. Eight studies were eligible and included in the review, and of these, three were included in a meta-analysis. Meta-analysis of clinical outcomes showed that donor sperm neonates are not at increased risk of being born of low birth weight (<2500 g), preterm (<37 weeks) or with increased incidences of birth defects, than spontaneously conceived neonates.

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Key words: Donor conception, meta-analysis, neonate, outcome, sperm

Introduction

The use of donor sperm as a treatment for male infertility has been used for well over a century with the first documented case occurring in 1884.[1] The introduction and increased use of intracytoplasmic sperm injection[2,3] has meant that donor sperm is not necessarily required as a treatment for male infertility in certain cases, and has therefore decreased demand for donated semen in this area. However, its use has been increasing due to reproductive choice by women in same sex relationships, or by single mothers without a male partner.[4–6] Sperm donation and neonatal outcomes are therefore still relevant today.

Mechanistically, there is little reason to suggest that fertilization with donor sperm and subsequent outcomes would be different to naturally conceived outcomes. Whilst one introduces semen from a donor by means of a medical procedure, the latter involves intercourse between the woman and a male sexual partner. However, there are two factors which differentiate sperm donation from natural conception and that have the potential to introduce negative outcomes for the former. The first is that the incidence of preeclampsia is higher in donor conceived pregnancies and the second is that there is the use of cryopreservation procedures in storing donated sperm.

The incidence of preeclampsia is increased in donor sperm recipients when compared with spontaneously conceived pregnancies.[7–11] As a leading cause of fetal and maternal morbidity and mortality, and one which is associated with increased incidences of intrauterine growth retardation (IUGR) and preterm delivery (PD),[12,13] preeclampsia represents a significant burden to the woman, her partner and the health care system. This burden is also further highlighted in the adult life of a person born where preeclampsia was present. This person has been shown to have an increased risk of hypertension,[14–16] endothelial dysfunction,[17] higher body mass index (BMI),[18] epilepsy,[19] increased hospitalization due to disease,[20] stroke[21] and autism spectrum disorder.[22]

Preeclampsia is considered a maternally mediated immune response.[23,24] This is supported, indirectly, by data from sperm donor recipients, where the incidence of preeclampsia reduced as the woman underwent subsequent inseminations with sperm from the same donor.[25] As those couples that are trying to conceive naturally are likely to have had intercourse several times before conception occurs, the maternal immune system has adapted to the partner's sperm and is less likely to induce preeclampsia in that population. Because the use of donor sperm is associated with preeclampsia, it is important to investigate whether there are increased risks for other poor neonatal outcomes when compared with spontaneous conceptions. In addition to the risk of preeclampsia described above, emerging evidence is suggestive of potential risks to health from sperm cryopreservation.

The technique of cryopreserving sperm was initially introduced for practical reasons of storage and shipment, and later became an important component of the donor conception practice to ensure appropriate screening of donors for genetic[26–28] and communicable diseases such as HIV.[29] This improvement is not without its own problems. As cryopreservation has been shown to cause DNA fragmentation,[30,31] and adversely affect morphology, motility and viability[32] in sperm. DNA fragmentation can also be induced through the mere handling of sperm in the laboratory.[33] For cryopreserved sperm, DNA fragmentation is typically mediated via oxidative stress,[34] as a direct result of cryopreservation.[35] With the potential to induce DNA changes through the manipulation of sperm, it is important to monitor how

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cryopreservation may impact on the health of donor conceived people.

As described above, the use of donor sperm has been in practice for a long time. A literature search of online databases in a non-systematic approach by the authors found few studies that investigated these outcomes in a case-controlled manner. It would appear from this investigation and the lack of published studies that the practices of donor insemination and intercourse have been assumed by some to be the same and therefore neonatal outcomes have also been presumed to mirror natural conception. Subsequently, offspring health outcomes have not been thoroughly investigated. Due to the modern practice of cryopreservation and subsequent knowledge of the incidence of preeclampsia in donor sperm pregnancies, we felt that these outcomes warranted a current systematic and structured review of the literature.

Furthermore, with evidence showing that neonates conceived with donated oocytes have significantly increased risks of being born of low birth weight (LBW) (<2500 g), very low birth weight (VLBW) (<1500 g), PD (<37 weeks), of lower gestational age (GA) and PD with LBW,[36] it is therefore important to consider whether neonates conceived with donated sperm are also at increased risk of these negative outcomes. This concern is not limited to the perinatal period, but also adulthood as poorer neonatal outcomes are associated with increased incidences of adult morbidity and mortality.[37–39]

The purpose of this review was to summarize the published literature on neonatal outcomes such as birth weight (BW), PD and birth defects (BD), for conceptions after sperm donation. We aimed to elucidate whether the outcomes were altered when compared with a comparison cohort of spontaneously conceived neonates. Furthermore, the study would also include health outcomes reported from child and adult cohorts to determine any longitudinal effects. In addition, we aimed to investigate whether sperm cryopreservation influenced reported outcomes.

Methods

Literature search

A computerized literature search was conducted on articles published up to November 2012 in the online databases PubMed, EMBASE and Cochrane Reviews to identify studies containing data on neonatal health outcomes from donor sperm.

The literature search comprised a three-stage process. First, relevant articles known to the authors were used to identify keywords along with a search of the U.S. National Library of Medicine MeSH (medical subject headings) database to identify appropriate search headings. Second, MeSH terms and other identified keywords were used to search the online databases. Search results were then analyzed to determine specificity and to refine search terms, and filtered based on human not animal studies. Finally, the references of articles fitting the criteria were examined and online searches were implemented to find related articles.

Two main search categories were created and were termed 'Techniques', these were: artificial insemination and reproductive techniques. Artificial insemination was used in preference to sperm or semen donation as it had a long history of being used to describe the technique in the literature and other search terms and descriptors were designed to cover any of those publications not covered by the term artificial insemination. The term 'reproductive techniques' was chosen as a catch-all phrase. Two descriptors of human and donor were chosen to filter out animal studies and autologous treatments (own gametes). Three further qualifiers were implemented to each of the two techniques plus descriptor searches to refine the results. These qualifiers were: outcome*, morbidity and adverse effects. The * wildcard was implemented to cover studies whose keywords implemented outcomes *v.* outcome. Search terms are also presented in Supplementary Table 1 for reference.

Eligibility and selection

Article selection and eligibility was performed by D.H.A. and verified by S.d.L. according to the following PICOS criteria.

Participants

Cohorts of neonates that had neonatal health data presented in a study. Studies that incorporated offspring of older ages (children and adults) were also included.

Interventions

The treatment group must be comprised of a cohort of offspring conceived through fertility treatment of their parents with donated sperm. This could include both intrauterine insemination or in vitro fertilization (IVF) with donor sperm. The treatment group data must be appropriately segregated from comparison group data and not subsumed into larger combined data sets.

Comparators

Comparison cohorts could include offspring conceived through artificial insemination with their partner's sperm or general population data of spontaneous conceptions.

Outcomes

Studies to be included must report neonatal health outcomes such as (but not restricted to), BWs, PD and BD (as determined by the publishing authors). Health outcomes of older offspring were also included if published. Studies that only focussed on live-birth rates or were case studies of single or few outcomes were excluded.

Study design

Only those observational case-controlled studies that used a treatment-cohort and comparison-cohort, or those studies

involving a treatment-cohort that was compared with published, or public health data for that specific region and within 10 years of the study were included in the review. This was to remove any natural variation occurring between populations and between given time points.

Published articles were restricted to the English language to allow for careful analysis of the study to ensure accurate data extraction as terminology and reporting methods varied considerably. There was no time restriction posed on publication dates, however, EMBASE would only allow a search from 1980. Database search results were downloaded into Endnote then analyzed by their titles and abstracts. Some articles were initially included as they could not be excluded based on their titles or abstracts, and were subsequently excluded following a full review of the text article (Fig. 1). Any disagreement was resolved via discussion.

Data extraction

The following data were recorded by D.H.A. from the eligible studies: citation data, country, comparison type (partner's sperm, spontaneous conception, published data), number of offspring in treatment/comparison group, if cryopreservation of sperm was used, specific neonatal health outcomes. Data were recorded onto a specially designed data extraction form. Specific health outcomes were included, but were not restricted to BWs, chromosomal or congenital malformations (BD), PD/GA, IUGR, and singletons *v.* multiple births (Table 1). Maternal age and parity were also extracted to assess confounding where applicable. Multiple birth is a known predictor of increased adverse outcomes[40,41] and was therefore a confounder to the analysis unless the data were stratified and extracted where presented.

Data referring to previously published data or general population databases, but that did not record the actual outcome data, were not included in meta-analysis. No authors were contacted for missing or obscure data.

Meta-analysis

Meta-analyses of dichotomous outcomes data of LBW, PD and BD were performed according to Mantel–Haenszel methods, using a fixed effects model, risk ratios (RR), 95% confidence intervals (CI) and assessment of statistical heterogeneity using Cochrane's Q-test and I^2 statistic. Heterogeneity of data were determined by the I^2 value and is considered significant when $I^2 > 65\%$. All analyses were performed using Review Manager (RevMan) Version 5.2.8 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2012). Publication bias was assessed by visual analysis of funnel plots constructed in RevMan for asymmetry.

Risk of bias in individual studies

Included studies were assessed for methodological quality and the risk of bias using a modification of the Joanna Briggs Institute Meta Analysis Statistics Assessment and Review Instrument, with nine critical appraisal criteria for comparable cohort/case control studies.[42] Studies were assessed on the following criteria; are patients in cohorts representative of patients typically receiving fertility treatment (e.g. do they only include patients who may have been treated for ovarian cancer)? Are the patients at a similar point in the course of their condition/illness (do they describe how many times the patient had received treatment)? Has bias been minimized in relation to selection of cases and of comparators? Were singleton *v.* multiple births identified and strategies to deal with them stated? (If singleton *v.* multiples described but all of the outcome data relevant to the review was not stratified then = No); are other confounding factors identified and strategies to deal with them stated? Was cryopreservation of sperm or the use of fresh sperm adequately described, and were they appropriately stratified if both were included? Are outcomes assessed using objective criteria? Were outcomes measured in a reliable way? Was appropriate statistical analysis used?

Results

Searching of the three databases yielded 1911 articles with another 12 identified by hand-searching references lists. Duplicate removal reduced potential articles to 582. After screening the article titles and abstracts, 80 full-text publications were reviewed leaving a total of eight studies to be included in the review and, of these, three were included in a meta-analysis (Fig. 1).

A summary of the characteristics and outcomes of all studies included in this review is presented in Table 1.

There was a large amount of heterogeneity in the presentation of published outcomes. Subsequently, meta-analysis was only performed for outcomes that presented comparable statistical outcomes. The five studies not included in meta-analysis did not present comparable outcome data and have been summarized in the text.

Sperm donation

A total of eight studies investigating the health outcomes of people conceived via donated sperm met the criteria for inclusion.[9,43–49] From these studies a total of 24,699 health outcomes have been analyzed from sperm donation births and 423,763 from spontaneous conceptions. All donor sperm outcomes are from intrauterine inseminations unless otherwise stated.

Impacts of sperm donation on BWs

The most common parameter measured in all studies was BW with the exception of Forse *et al.*[49] Notably, BWs were reported in different formats and subsequently meta-analysis could not be conducted due to a lack of comparable data. Although Davies *et al.*[47] reported BWs, these were not stratified as a separate outcome of donor insemination, but rather as a combined outcome for all Assisted Reproductive Technology (ART)

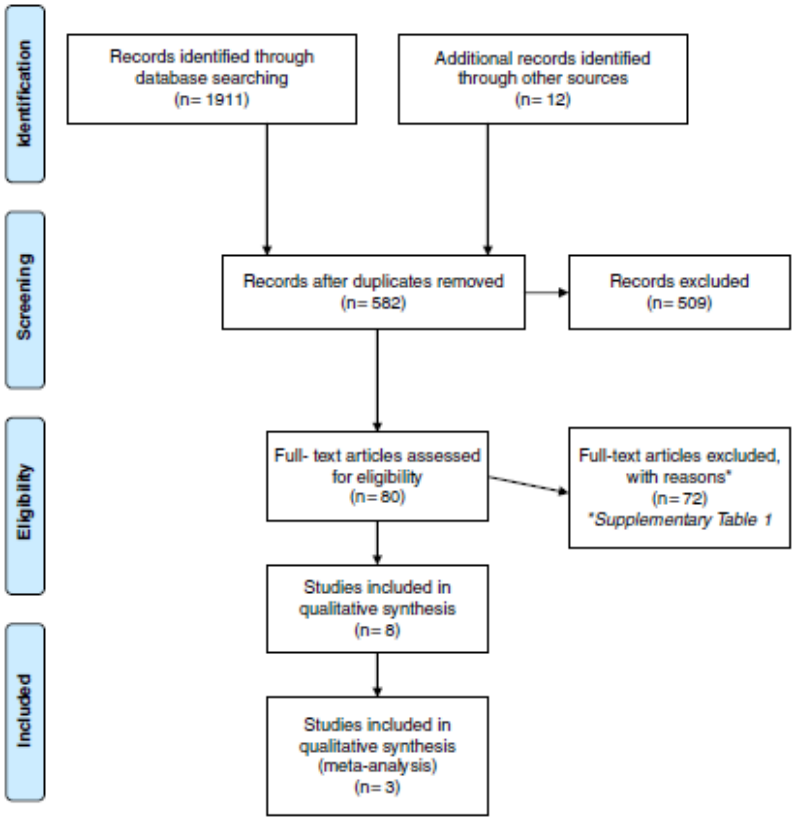

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart for identifying studies for inclusion in the review.

procedures. Of the remaining six studies, none reported a statistically significant difference in BWs between donor sperm (treatment) and spontaneous conceptions in the general population (comparison) (see Table 1). Problematically, the study by Lansac *et al.*[48] compared the BWs of singleton donor sperm conceived neonates to all births including multiples of spontaneously conceived neonates. BW data from these studies were not controlled for GA.

Thapar *et al.*[43] showed a higher incidence of LBW of singleton donated sperm IVF neonates when compared to homologous IVF treatments but no difference to the spontaneous conceptions of the general population (general population data were not reported). The incidence of LBW were higher for donor sperm IVF neonates (19.6%), in comparison with homologous IVF (14.7%), and the spontaneous conceptions (8%) in the same cohorts. Gaudoin *et al.*[44] also found a higher incidence of LBW in donor sperm neonates (11.4%), when compared with the general population (7.1%), but lower than that achieved when the partner's sperm was used (22.7%). Hoy *et al.*[9] reported no significantly increased risk of LBW (7.3 *v.* 6.8%, RR: 1.1), even though the actual frequency was greater. Conversely, a lower frequency of 4.7% LBW for donor sperm neonates when compared with 6.2% for spontaneous conceptions was reported by Lansac *et al.*[48] LBW data from these studies were not controlled for GA. Meta-analysis of comparable data showed that the RR for LBW was not statistically significant (RR: 1.04, CI: 0.86–1.25, $P = 0.71$, $I^2 = 0\%$) (Fig. 2a).

Impacts of sperm donation on PD

Of the three studies reporting PD outcomes, all of them reported no increase in the rates of PD, rather the incidences were reduced (5.7 *v.* 6.9%;[44] 6.4 *v.* 6.6%;[9] 4.8*v.* 5.9%[48]). Meta-analysis of the above studies (Lansac *et al.* was excluded due to lack of comparable cohort data), showed no significant change to PD outcomes (RR: 0.91, CI: 0.75–1.12, $P = 0.38$, $I^2 = 0\%$) (Fig. 2b).

Impacts of sperm donation on BDs

A significant increased incidence of BD between neonates conceived via sperm donation *v.* the comparison cohorts

Table 1. *Health outcomes for offspring conceived via sperm donation*

Study and country	Donation treatment and sample size	Comparison and sample size	Frozen or fresh	Age of children studied	Specific results
Thapar *et al.*[43] United Kingdom	Sperm 170	Homologous IVF 378 General population	Not specified	5–9 years	LBW (all births) 19.6% sperm *v.* 14.7% homologous IVF *v.* 8% general population LBW (singletons) 8% sperm *v.* 6.7% homologous IVF (gen pop singleton LBW not specified)
	AID as IVF (IVF-D)	Published data			
Gaudoin *et al.*[44] United Kingdom	Sperm 35	Partners sperm 97 General population 109,302 General population	Not specified	Neonates	BW 3149 ± 233 g (donor) *v.* 2921 ± 165 g (partner) *v.* 3301 ± 4 g (comparison) LBW 11.4% (donor) *v.* 22.7% (partner) *v.* 7.1% (general population) PD 5.7% (donor) *v.* 15.5% (partner) *v.* 6.9% (general population) LBW 7.3 *v.* 6.8%, RR 1.1
Hoy *et al.*[9] Australia	Sperm 1603	7516	Frozen	Neonates	BD 3.6% *v.* 3.2%, RR 1.1 Perinatal death 1.2% *v.* 1.1%, RR 1.4 ChAb 0.4% *v.* 0.2%, RR 2.5 PD 6.4% *v.* 6.6%, RR 1
Amuzu *et al.*[45] USA	Sperm 481	General population Published data	Both	3 months–15 years (average 5 years)	BW (7.5 lb ± 1.3) and birth length (20.1 inch ± 1.2) same as general population Major anomalies (2.9% at birth, 6.2% at time of study *v.* 2 and 5%) ChAb 0.2% *v.* not specified Developmental milestones same as general population Learning disabilities 5.8% *v.* not specified Gifted and talented programme 10.5% *v.* not specified
Iizuka *et al.*[46] Japan	Sperm 54	General population Published data	Both (frozen = 9)	$n = 40 \geqslant 2.5$ years (oldest 11.8 years)	BW and length better in AID
Davies *et al.*[47] Australia	Sperm 428	General population 293,314	Not specified	$n = 14 \leqslant 2.5$ years Neonates	IQ of donor sperm children higher range than controls (better) BD 8.4 *v.* 5.7%, OR 1.51 (adjusted OR 1.37)
Lansac *et al.*[48] France	Sperm (AID) 18,128 AID as IVF (IVF-D) 3405	General population 13,631	Frozen	Neonates	BW 3281 ± 491 g ($n = 8943$) *v.* 3300 ± 600 g ($n = 13,631$) LBW 4.7% (singleton) *v.* 6.2% (national register of natural conceptions) Malformations (1.9% AID, no significant difference to general population, not specified) Malformations (2.74% IVF-D *v.* 2.99% husband sperm, no significant difference) PD 4.8% (singleton) *v.* 5.9% (National Register of Natural Conceptions) ChAb 0.25% *v.* 0.2% (Paris $P < 0.05$) *v.* not specified (Strasbourg et Marsailles, no significant difference)
Forse *et al.*[49] Canada	Sperm 395	General population Published data	Not specified	Neonates	ChAb 0.75% *v.* 0.15%

AID, artificial insemination by donor; BW, birth weight, LBW, low birth weight <2500 g, ChAb, chromosomal abnormalities, BD, birth defects, IQ, intelligence quotient, IVF = in vitro fertilization; PD, preterm delivery (<37 weeks), RR, risk ratio, OR, odds ratio.
Sample sizes represented by statements such as 'published data' refers to the study citing data published elsewhere. Comparison data are presented as donor *v.* comparison group, *P*-value for significance is only provided where $P < 0.05$. General population refers to data obtained from spontaneous conceptions that have either been presented in 'published data' by other authors, or were part of a comparison cohort with specific data presented in the study.

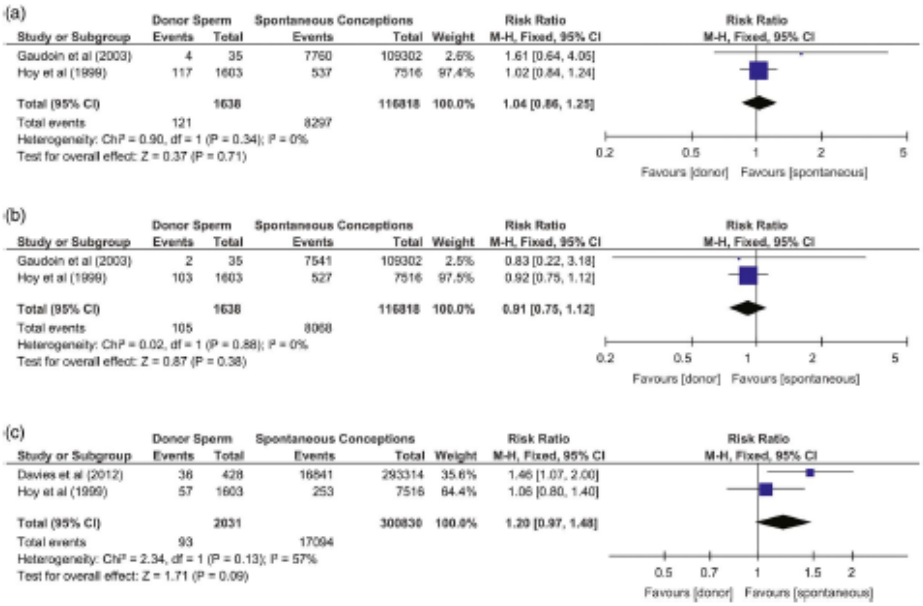

Fig. 2. Forrest plots of sperm donation outcomes; (*a*) risk ratio for being born of low birth weight (<2500 g), (*b*) risk ratio for being born preterm delivery (<37 weeks), (*c*) risk ratio for incidences of birth defects, neonates from donor sperm offspring *v.* spontaneous conceptions.

[8.4 *v.* 5.7%, odds ratio (OR) 1.5, 95% CI 1.08–2.11], was reported.[47] However, when this was adjusted for confounders such as maternal age, parity, fetal sex, year of birth, maternal race or ethnic group, maternal country of birth, maternal conditions in pregnancy, maternal smoking during pregnancy, socioeconomic status, and maternal and paternal occupation the association was attenuated and subsequently non-significant (OR: 1.37, 95% CI: 0.98–1.92). Amuzu *et al.*[45] reported no significant difference in malformation rates in neonates to those found in the general population even though their incidence was 45% higher than the general population (2.9 *v.* 2%). Although not as large, this trend was also evident in the older children they studied (longitudinal), whereby the incidences of malformations were 24% higher (6.2 *v.* 5%). Hoy *et al.*[9] reported no significant difference in BD rates (3.6 *v.* 3.2%, RR 1.1), and Lansac *et al.* also reported no significant differences in malformation rates between sperm donor neonates and the general population. However, the data for the general population was not reported by Lansac *et al.*[48] Meta-analysis showed a non-significant increased incidence of BD (RR: 1.20, CI: 0.97–1.48, $P = 0.09$, $I^2 = 57\%$) (Fig. 2c).

Of the four studies investigating chromosomal abnormalities, two found a higher incidence of occurrence which was restricted to aneuploidies.[9,49] However, Thapar *et al.*[43] found no increase in chromosomal abnormalities and that the chance of this occurring was correlated to both the maternal age as well as the donor age. Comparable chromosomal abnormality data were not available for meta-analysis.

Impacts of sperm donation on other outcomes

The only study to investigate the intelligence quotient (IQ) outcomes of these children found that those conceived via donor sperm had a higher IQ[47] than the general population.[50] A further study reported that 10.5% of donor sperm children were in gifted and talented programs while 5.8% had learning disabilities, however, no general population comparison data were provided by the authors.[45]

Effects of cryopreservation on outcomes

Cryopreservation was only recorded in two studies.[9,48] Both of which only used cryopreserved sperm in their donor sperm cohorts. A further three studies used cryopreserved data due to the mandatory use of cryopreserved sperm in their respective jurisdictions but did not report it as such (see discussion for further information).[43,44,47] Subsequently, all three studies used in meta-analyses (two could not be included in meta-analyses due to lack of comparable data), involved the use of cryopreserved sperm; one from self-reporting and two from cryopreservation mandated jurisdictions. Of the studies using cryopreserved sperm, the outcomes that were statistically significant from comparison groups was an increased RR of 2.5 for aneuploidies,[9] increased OR of 1.73 (CI: 0.26–11.69) for LBW,[44] increased OR of 1.51 (CI: 1.08–2.11) for BD which was subsequently non-significant (1.37, CI: 0.98–1.92) when adjusting for confounders,[47] and an increased incidence of chromosomal anomalies ($P < 0.05$).[48] A further study

reported a higher percentage of LBW neonates in the cryopreserved sperm donation cohort when compared to the general population but did not conduct statistical analysis of the data.[43] Contrastingly, BD were not affected in the study by Hoy *et al.*, and the malformation rate was the same as comparison groups in the study by Lansac *et al.* As there was insufficient studies and data to conduct meta-analyses of outcomes from cryopreserved sperm *v.* fresh sperm, the effect of cryopreservation on neonatal outcomes requires elucidation through further studies.

Effects of multiplicity on outcomes

The incidences of multiple births were either poorly recorded in several of the studies or were not stratified from other data to allow for appropriate comparisons. Subsequently, meta-analysis of multiplicity could not be conducted on these studies. However, the three studies that provided the majority of data for neonatal health outcome meta-analysis had appropriate multiplicity data or were appropriately controlled.[9,44,47] Three further studies provided data on the incidences of multiplicity in the sperm donation cohorts,[43,45,48] but did not provide comparison cohort data from natural conceptions (general population). Rather, only multiplicity data were provided for homologous IVF[43] and IVF-D (IVF with frozen donated sperm).[48]

As Hoy *et al.* did not control for multiplicity, no conclusion can be drawn on the confounding effects of multiplicity when interpreting sperm donor effects on LBW, PD or BD outcomes.

Risk of bias

There was variation in the methodological quality of the studies included (Table 2). In general, the length of time the woman had been receiving treatment (number of previous attempts) was not documented. Data of other confounders such as maternal age, BMI, reasons for infertility and other demographic data were poorly reported. Or in the instance where these confounders were reported well, they were not stratified into sperm donation *v.* spontaneous conception cohorts.[47] Multiplicity was reported in only half of the studies, but a lack of comparison data meant that meta-analysis of the rates of multiplicity could not be performed. Studies reporting outcomes such as BWs, LBW, and PD were deemed to be reporting objective criteria, although BWs and LBWs were not controlled for GA. However, those reporting BD (or what was classified as malformations) were more subjective in nature as BD is a general category that it is not typically well defined. Additionally, BDs can potentially be missed in the neonatal period with the reporting of BDs in reproductive technology cohorts historically being described as needing to be 'more stringent' by the American Fertility Society, Society for Assisted Reproductive Technology, and the American Society for Reproductive Medicine.[51–54] By contrast Davies *et al.*,[47] were more objective in reporting BD using the British Paediatric Association modification of the International Classification of Diseases (9th Revision), in addition to when chromosomal abnormalities and congenital cerebral palsy were reported.[9,45,48,49] Studies by Thapar *et al.*, Amuzu *et al.*, Iizuka *et al.*, and Forse *et al.*, used general population data as a comparison cohort but only referred to previously published information and did not provide data for comparison.[43,45,46,48]

Funnel plot analysis showed publication bias in sperm donation health outcome meta-analysis for PD. Maternal age and parity data were not consistently reported or adjusted for in the studies included. Those studies that reported this data are presented in Table 3.

Limitations to this study

This review was limited by the restriction to three databases, limited hand-searching and the restriction to the English language. It was also limited due to the lack of studies meeting the inclusion criteria. There was a lack of consensus in the types of outcomes and how they were reported in these studies which prevented the inclusion of some studies in meta-analysis.

The reporting of multiple deliveries was inconsistent and data were rarely appropriately stratified for analysis of singleton *v.* multiple birth outcomes. While rates of multiples were reported in some studies, the outcome data were pooled rather than stratified and therefore meta-analysis could not be performed in a stratified manner for those studies. Only two studies restricted data to singleton outcomes,[44,47] one of which appropriately adjusted for multiple confounders.[47]

Consistency in reporting, with increased analysis of confounders such as multiple deliveries, maternal age, parity, and cryopreservation can be improved. There was a distinct lack of sperm donation outcomes in the reporting of other annual ART reports such as the 'Assisted reproductive technology surveillance–United States' reports that are produced by the Centers for Disease Control and Prevention (CDC), or early reports published by the Society for Assisted Reproductive Technology and the American Society for Reproductive Medicine, which includes comprehensive data (such as oocyte donation outcomes) for all other areas of reproductive technology treatments.

Discussion

This review has demonstrated that donor sperm neonates, when compared to spontaneously conceived neonates, are not at increased risk of being born of LBW (<2500 g), PD (<37 weeks), or with increased incidences of BD. There was also little to suggest any correlation with IQ or learning disabilities. In contrast to donor oocyte neonatal outcome data,[36] the limited amount of data on perinatal outcomes after donor insemination suggests that this group has been understudied.

While individual studies reported donor sperm neonates were not born of significantly lower mean BW, there was one report of increased BWs and body length in the sperm

Table 2. *Critical appraisal and risk of bias of included studies*

	Criteria								
Study	Representative patients	Similar point in condition	Minimized case selection bias	Singleton *v.* multiples	Other confounders	Cryo-preservation	Objective criteria	Reliable outcomes	Appropriate statistics
Thapar *et al.*[43]	Yes	Unclear	Yes	Yes	No	No	Yes	Yes	No
Gaudoin *et al.*[44]	Yes	Unclear	Yes	Yes	Yes	No	Yes	Yes	Yes
Hoy *et al.*[9]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes[d]	Yes	Yes
Amuzu *et al.*[45]	Yes	No	Yes[a]	No	No	No	Yes[d]	No	No[b]
Iizuka *et al.*[46]	Yes	Unclear	No[a]	No	Yes	No	Yes	Yes	No
Davies *et al.*[47]	Yes	Unclear	Yes	Yes	Yes	No[c]	Yes	Yes	Yes
Lansac *et al.*[48]	Yes	Unclear	Yes[a]	No	Yes	Yes	Yes[d]	No	No[b]
Forse *et al.*[49]	Yes	Unclear	Yes[a]	No	No	No	Yes[d]	Yes	No

[a]Comparison group was published data not a comparison cohort.
[b]Statistics used appropriately, but did not provide details of results in analysis to comparison group.
[c]Although cryopreservation was not recorded by, it is known through other means that cryopreservation was mandated during the period of those studies.
[d]Includes both objective and subjective data.

Table 3. *Maternal age and parity reporting of included studies*

Study	Maternal age details	Parity details
Thapar *et al.*[43]	33.88 ± 3.82 years (donor) *v.* 34.14± 3.53 years (homologous IVF) *v.* unknown (general population)	
Gaudoin *et al.*[44]	33.1 (31.9–34.3 95% CI, donor) *v.* 32.4 (31.6–33.1, partner) *v.* 25.9 (25.9–25.9, general population)	All nulliparous
Hoy *et al.*[9]	16% ⩾ 35 years *v.* 10% ⩾ 35 years	53.4 *v.* 40.5% primiparous
Amuzu *et al.*[45]	29.3 ± 4.2 years *v.* unknown	
Iizuka *et al.*[46]	30.1 ± 2.7 years *v.* unknown	
Davies *et al.*[47]	(2.2% 20–24 years, 22.2% 25–29 years, 44.4% 30–34 years, 26.2% 35–39 years, 5.1% ⩾ 40 years) *v.* (20.8% 20–24 years, 37.7% 25–29 years, 29.4% 30–34 years, 10.5% 35–39 years, 1.7% ⩾ 40 years)[a]	65.3% *v.* 37.5% nulliparous
Lansac *et al.*[48]	[b]	
Forse *et al.*[49]	28.9 years[c]	

[a]Maternal age and parity data are from larger assisted conception cohort that also includes donor sperm outcomes.
[b]No maternal age data of sperm donor outcomes *v.* comparison, rather maternal age data were presented within sperm donation outcomes stratified as healthy infants *v.* malformed infants.
[c]Used comparison data for population with same maternal age distribution.

donation neonates,[46] which requires consideration. While the authors postulated that this may be attributed to the environment of the Tokyo metropolitan and surrounding areas of the 1960s, it is plausible that the effect was confounded as the parents of the donor sperm conceived neonates were reported to have higher education levels than comparators, and therefore perhaps able to access a range of resources, including energy and protein dense diets, which can influence fetal development. Additionally in regard to mean BWs, another study compared singleton donor sperm conceived neonates to all births (including multiples) of spontaneously conceived neonates,[48] which may adversely affect the data as typically multiple births result in lower BWs[55,56] and therefore any effect may be missed.

A higher incidence of elective early caesarean section deliveries observed in cohorts of women that have used various forms of ART,[57,58] could also adversely affect outcome measures leading to reduced BWs reported for the donor sperm conceived neonates. These incidences would not be apparent from PD data analysis which is of delivery prior to 37 weeks, as elective caesarean is typically not performed before 37 weeks.

Meta-analysis of BD showed no significant increased incidences as a result of using donor sperm. However, there were some reports including chromosomal abnormalities that had conflicting outcomes. The increases in aneuploidy reported in two studies could potentially be explained by higher maternal and donor ages rather than as a function of the donor conception procedure itself.[9,49] This was supported by another study which correlated malformation rates with maternal age but not with donor age.[48]

The use of cryopreserved sperm raises the possibility of increased negative outcomes due to increased oxidative stress.[35] Oxidative stress can lead to DNA changes[34] and is therefore of considerable interest in regard to offspring outcomes. While not specifying the use of cryopreserved sperm, three studies were conducted in jurisdictions which introduced mandatory cryopreservation following the transmission of HIV to recipient mothers,[29] prior to the start of those study's inclusion periods.[59,60] Mandatory use of cryopreserved sperm was not brought in to other jurisdictions[61,62] until after the inclusion periods of those respective studies.[45,49] Subsequently there was only one study where the use of cryopreserved or fresh sperm was not reported and the use of which could not be elucidated through mandated protocols in the appropriate jurisdiction.[49]

Reports in some studies of increased incidences of BD,[47] and chromosomal aneuploidies/anomalies,[9,48] could potentially be attributed to the use of cryopreserved sperm. However, one study found no difference in BD in their cryopreserved cohort.[9] While one of the studies that reported chromosomal aneuploidies/anomalies only found a difference in one comparison cohort and not two other comparison cohorts.[48] Additionally, in another study, after adjusting for multiple confounders, the OR for increased BD[47] was attenuated and subsequently non-significant, however, the authors caution that the adjusted data for the sperm donation cohort was limited by a small sample size. The effect that cryopreservation induced DNA damage/fragmentation may have on offspring outcomes therefore remains somewhat unclear and requires additional studies as well as elucidation via longitudinal studies. Due to the fact that cryopreservation of donor sperm is mandated in several jurisdictions, the ability to be able to determine the influence of sperm cryopreservation on offspring outcomes would be difficult to ascertain in donor sperm offspring cohorts and therefore may be better achieved through the analysis of cryopreserved and fresh outcomes from artificial inseminations using partner sperm.

It was reported in the only study investigating IQ outcomes, that children conceived with donor sperm had higher IQs *v.* comparators.[46] IQ is a function of both nature and nurture, genetics and environment.[63] Given that it was reported by the authors that the recipient parents of the children with higher IQs had higher levels of education themselves (college education), and the fact that in the earlier period of artificial insemination by donor (AID) practice the majority of sperm donors were recruited from students at universities including medical students,[64–66] which was also stated by the authors as the recruiting pool of donors for their study; this result is not surprising and may be due to confounding by either genetic or social factors related to IQ. Recruitment of donors by fertility clinics has changed over time with this earlier period of recruitment being before the advent of internet advertisement which some clinics currently employ.[67,68] Earlier methods of recruitment often but not exclusively relied on advertisements in university student newspapers,[64,65,69] or even personal approaches by doctors to medical students.[60,65]

Learning difficulties of 5.8% were reported in one of the donor sperm children cohorts.[45] The American Academy of Pediatrics describe that 'learning disabilities are complex'.[70] Subsequently, there can be considerable variability in reported prevalence between geographic locations due to inconsistencies in identification procedures,[71] however, some estimate that the prevalence in children in the United States is in the vicinity of 5[72] or 6.5%[73] in a comparable time-period to the study in the review. Therefore, the figure of 5.8% reported could be considered as being within the reported frequency in the general population. Assessing gifted and talented students is additionally very complex with little consensus in how to define the group and with subsequent prevalence thereby ranging from 1 to 15–20%,[74] the figure reported in one study of 10.5%,[45], without corresponding comparison cohort data are therefore impossible to interpret. Subsequently, there is little evidence to suggest that the use of donor sperm has any effect on IQ or learning abilities of children outside of those effects that are attributable to genetic or environmental factors that are normally present in all families.

Although meta-analysis data showing increased incidences of negative outcomes in donor oocyte neonates of LBW, VLBW, PD, PD with LBW and lower GA have been reported recently,[36] there is little evidence to suggest that the outcomes for donor sperm neonates are equally affected. However, oocyte neonate outcomes have been more rigorously studied and reported in a systematic manner than donor sperm outcomes allowing for greater confidence in the data and subsequent analysis.

The lack of increased risks for negative outcomes compared with those observed in spontaneous conceptions is perceived as reassuring to both clinicians and their patients. Reports of increased incidences of preeclampsia that occur in donor conceived cohorts (not a focus of this review), are typically associated with poor neonatal outcomes such as IUGR and PD. Yet, these outcomes were not significantly elevated in the studies included in this review. Interestingly, each study reporting PD outcomes showed a non-significant decreased frequency. The dearth of multiple case-controlled studies to provide robust meta-analysis of outcomes however means that the results should be treated with caution. Considering the

length of time that sperm donation has been used in a clinical setting for the treatment of male infertility, the lack of multiple case-controlled studies was surprising.

What is clear is that there is little evidence on the health outcomes not only in the neonatal period, but also in childhood; and a paucity of data on adult donor sperm offspring. There are some reports emerging of outcomes in the adult population, however the data are combined with other ART data,[75] and as such more studies need to be conducted on health outcomes for donor sperm neonates, children and adults.

As poor neonatal outcomes are associated with increased incidences of morbidity and mortality in later life,[37–39] the types of outcomes represented in this review are significant for the long-term health of those conceived with donor sperm. Studies showed that there was not an increased risk of being born of lower mean BW or born of LBW (<2500 g). In addition, the lack of increased incidences of PD is also suggestive that long-term health outcomes for donor sperm offspring may not be as adversely impacted as those offspring conceived from donor oocytes. Although some reports suggest that there could be increased incidences of BD which may be associated with cryopreservation, this requires confirmation or rejection with further studies.

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Conflicts of Interest

None.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S2040174416000489

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Appendix 1.3 PRISMA Checklist for Reporting of Systematic Reviews

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Appendix 1.4 Systematic Review Data Extraction Form

Study Citation (Author and year)	Country	Donation Treatment(s) and Sample Size (N)	Comparison Cohort and Sample Size (N)	Cryo/Fresh	Ages of Cohorts	Specific Results

Appendix 1.5 Systematic Review Confounding Data Extraction Form

Study Citation (Author and year)	Country	Maternal Age	Parity	Multiplicity (Singletons/Twins/Multiples)

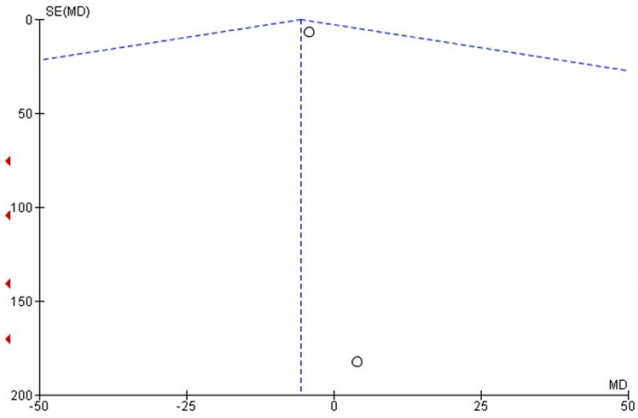
Appendix 1.6 Table of Systematic Review Excluded Studies and the Reasons for their Exclusion

Study Citation	Reason for exclusion
Abdalla *et al.* (1998) [1177]	No appropriate controls and only includes aggregate data.
Adesiyun (2011) [1178]	No appropriate controls and outcome is not allocated to donor or autologous.
Allen *et al.* (2006) [1179]	Review.
Andersen *et al.* (2008) [1180]	No appropriate controls and no perinatal health studies.
Applegarth *et al.* (1995) [1181]	No appropriate controls and perinatal data is not numerical.
Barratt and Cooke (1989) [1182]	Letter to the editor and no data presented.
Beckett and Serhal (1994) [1183]	Letter to the editor and no data presented.
Bensdorp *et al.* (2007) [1184]	Review.
Botchan *et al.* (2001) [1185]	No appropriate controls.
British Fertility Society (2011) [1186]	Conference programme.
Brzyski (2001) [1187]	Review.
Bustillo and Yee (1999) [1188]	Duplicate reference appearing in another format.
Centola *et al.* (2000) [1189]	No appropriate controls and no perinatal health studies.
Chong and Taymor (1975) [1190]	No appropriate controls.
Clarke *et al.* (1997) [1191]	No appropriate controls.
Clayton and Kovacs (1982) [1192]	Controls were outdated by 20 years and study involved selection of families to include (possible bias).
Cobo *et al.* (2008) [1193]	No perinatal health studies.
de Mouzon *et al.* (2010) [1194]	No appropriate controls and no perinatal health studies.
Doyle (1999) [1195]	No appropriate controls and no perinatal health studies.
Dyer and Kruger (2012) [1196]	No appropriate controls and no perinatal health studies.
ESHRE Capri Workshop Group (2007) [1197]	No donor gametes.
Esteves (2002) [1198]	Editorial comment, no data.
European IVF-Monitoring Programme for ESHRE et al. (2006) [1199]	No perinatal health studies.
Formigli *et al.* (1990) [1200]	No appropriate controls and no perinatal health studies.
Glezerman (1981) [1201]	No appropriate controls and no perinatal health studies.
Guerif *et al.* (2002) [1202]	No appropriate controls and no perinatal health studies.
Guerif *et al.* (2004) [1203]	No appropriate controls and no perinatal health studies.
Gunby *et al.* (2005) [1204]	Only showed aggregate perinatal health data, not separated into donor v control.

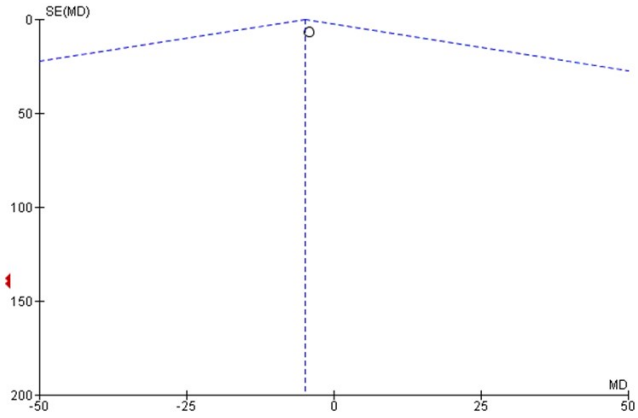
Gunby *et al.* (2006) [1205]	Only showed aggregate perinatal health data, not separated into donor v control.
Gunby *et al.* (2007) [1206]	Only showed aggregate perinatal health data, not separated into donor v control.
Gunby *et al.* (2008) [1207]	Only showed aggregate perinatal health data, not separated into donor v control.
Gunby *et al.* (2009) [1208]	Only showed aggregate perinatal health data, not separated into donor v control.
Gunby *et al.* (2010) [1209]	Only showed aggregate perinatal health data, not separated into donor v control.
Gunby *et al.* (2011) [1210]	Only showed aggregate perinatal health data, not separated into donor v control.
Hayashi *et al.* (2012) [469]	Use of donor gametes is unclear.
Hedges and Saunders (1993) [1211]	No donor gametes.
Horne *et al.* (1998) [1212]	No appropriate controls and no perinatal health studies.
Kahn *et al.* (2012) [1213]	Inappropriate controls.
Katzorke *et al.* (1981) [1214]	Inappropriate controls.
Kovacs (1996) [1215]	Review.
Lambert (2003) [1216]	Review.
Lansac and Royere (2001) [1217]	Review.
Ledward *et al.* (1985) [1218]	No appropriate controls and no perinatal health studies.
Liu *et al.* (2011) [1219]	Don't provide source of their control data.
Medical Research International *et al.* (1989) [1220]	Only contains aggregate perinatal data.
Mochimaru *et al.* (1980) [1221]	Don't provide source of their control data.
Morris and Sauer (1993) [1222]	Review.
Newill (1976) [1223]	Inappropriate controls.
Patel *et al.* (2003) [1224]	Single case study.
Ramsay (1995) [1225]	Letter to the editor and no data presented.
Raoul-Duval *et al.* (1992) [1226]	No specific perinatal data just generalisations from a parent self-filled questionnaire.
Raoul-Duval et al. (1994) [1227]	No appropriate controls and perinatal data is only preliminary.
Remohi *et al.* (1997) [1228]	Inappropriate controls.
Robinson *et al.* (1989) [1229]	Letter to the editor and no data presented.
Sauer and Kavic (2006) [1230]	Review.
Sauer *et al.* (1996) [1231]	Only involved advanced maternal age - confounding.
Shaw and Sauer (1995) [1232]	Inappropriate controls.
Society for Assisted Reproductive Technology and ASRM (2002a) [1233]	No appropriate controls and no perinatal health studies.
Society for Assisted Reproductive Technology and ASRM (2002b) [1234]	No appropriate controls and no perinatal health studies.

Society for Assisted Reproductive Technology and ASRM (2004) [1235]	No appropriate controls and no perinatal health studies.
Society for Assisted Reproductive Technology and ASRM (2007) [1236]	No appropriate controls and no perinatal health studies.
Soderstrom-Anttila (2001) [1237]	Review.
Soderstrom-Anttila *et al.* (1998a) [1238]	Data already reported in authors other paper.
Soderstrom-Anttila *et al.* (2001) [1239]	Review.
Steinberger and Smith (1973) [1240]	No perinatal health studies.
Steiner and Paulson (2006) [1241]	Review.
Talebi Chahvar *et al.* (2011) [1242]	Do not present data.
Thepot *et al.* (1996) [1243]	Data is reported in publication by Lansac et al. (1997) as part of a larger cohort.
van Balen (1998) [1244]	No donor gametes.
Virro and Shewchuk (1984) [1245]	Inappropriate controls.
Wright *et al.* (2003) [1246]	No perinatal health studies.
Wright *et al.* (2004) [1247]	No perinatal health studies.
Yaron *et al.* (1998) [1248]	Inappropriate controls.

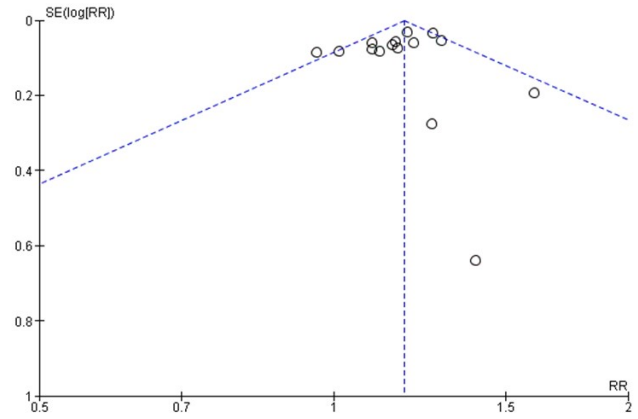
Appendix 1.7 Funnel Plots of Donor Oocyte Meta-Analysis



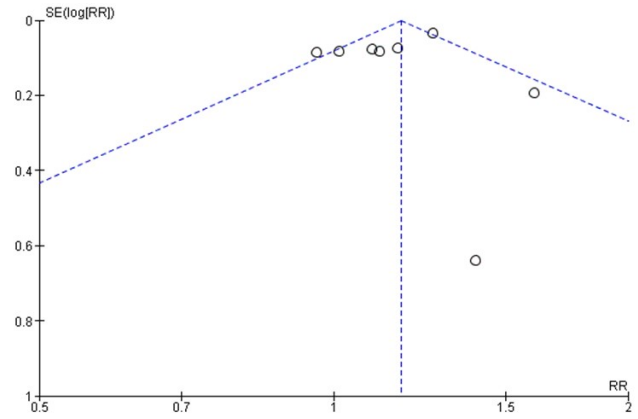
Mean BW – singletons and multiples



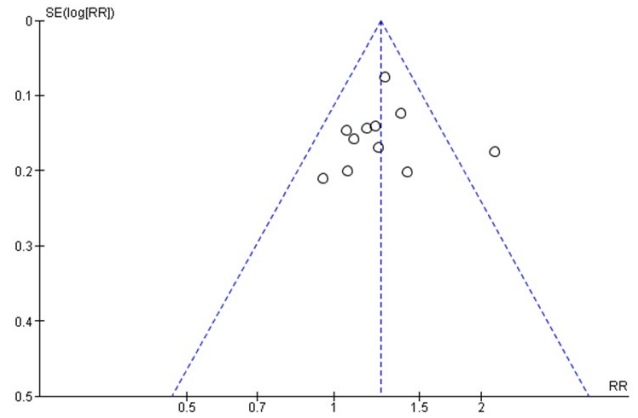
Mean BW – singletons only



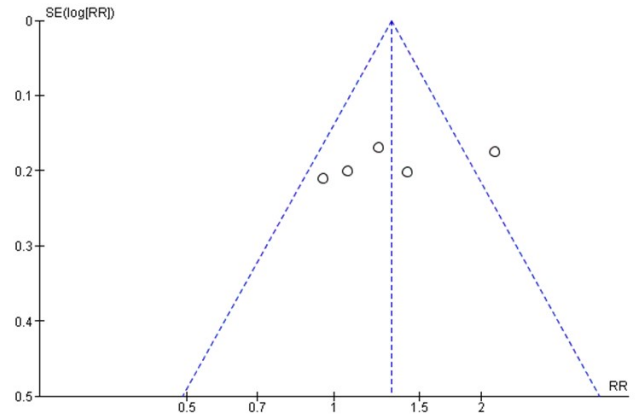
LBW – singletons and multiples



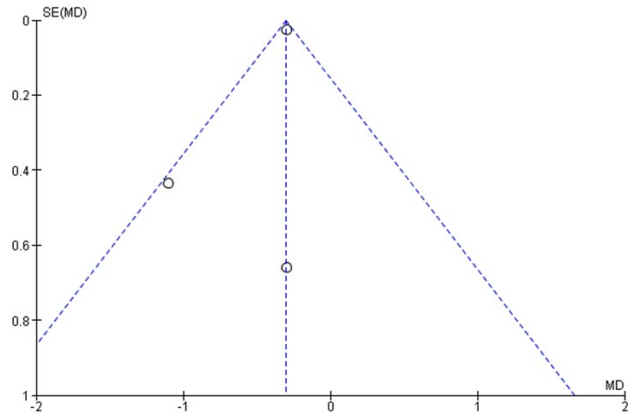
LBW – singletons only



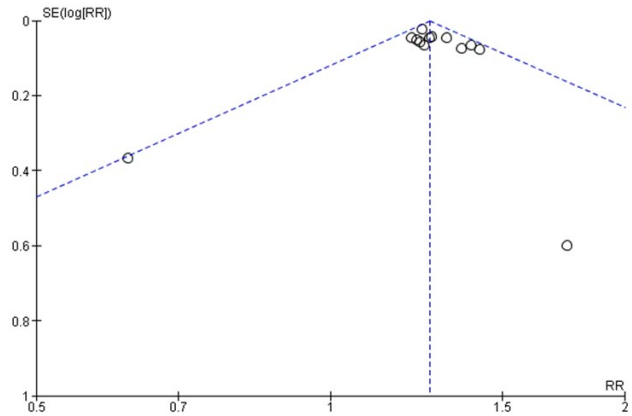
VLBW – singletons and multiples



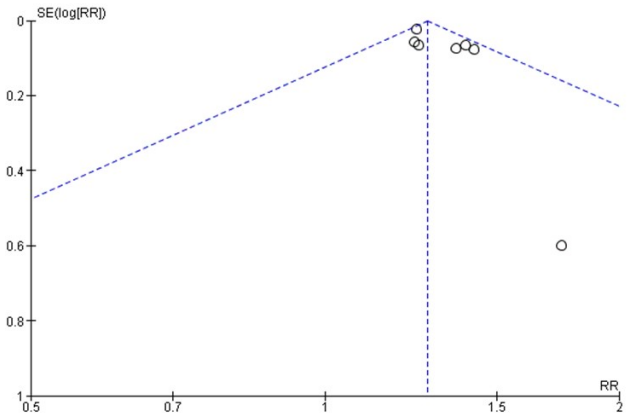
VLBW – singletons only



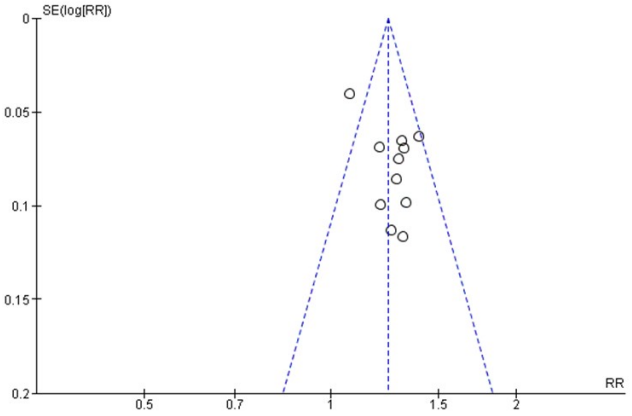
GA – singletons and multiples



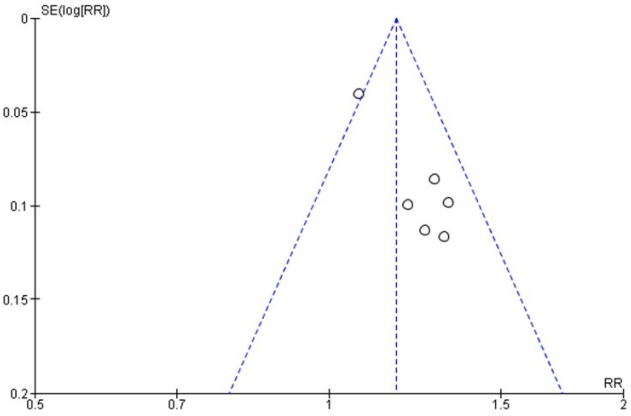
PD – singletons and multiples



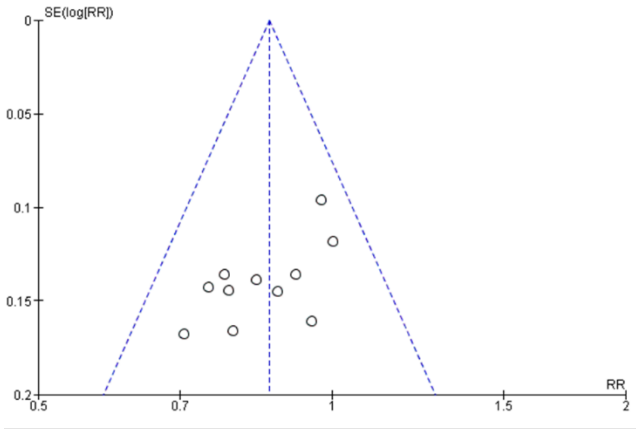
PD – singletons only



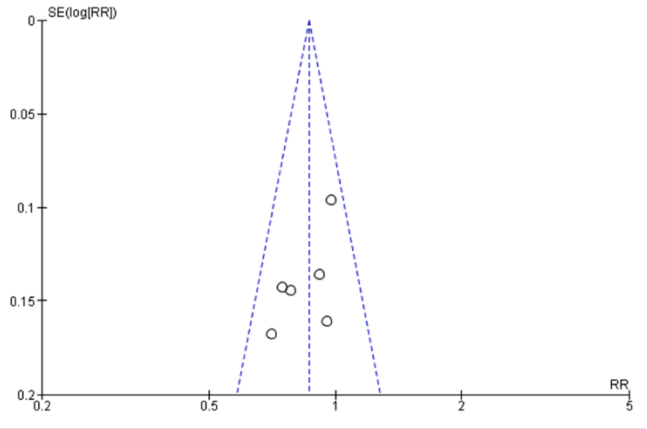
PD with LBW – singletons and multiples



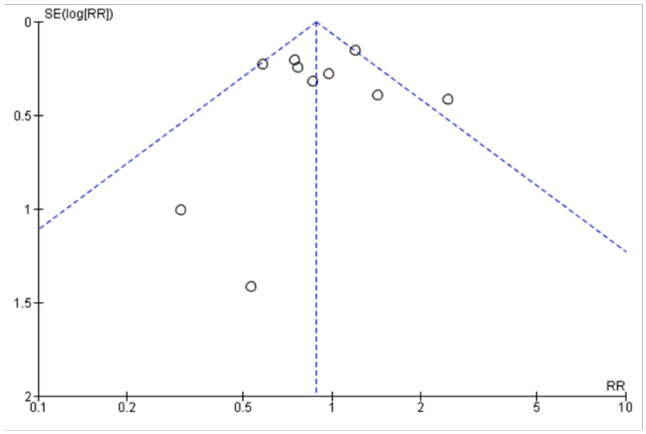
PD with LBW – singletons only



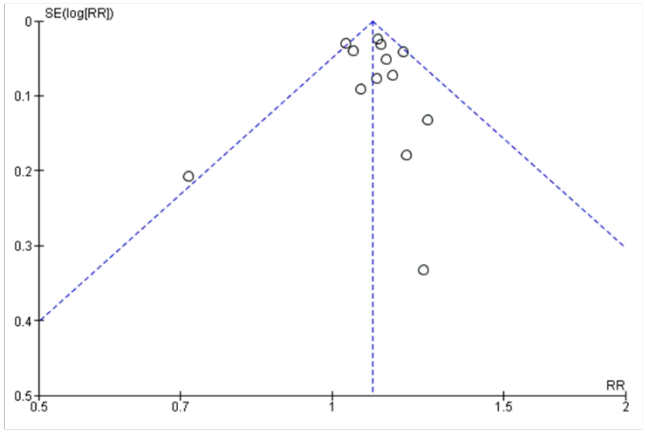
Term delivery with LBW – singletons and multiples



Term delivery with LBW – singletons only

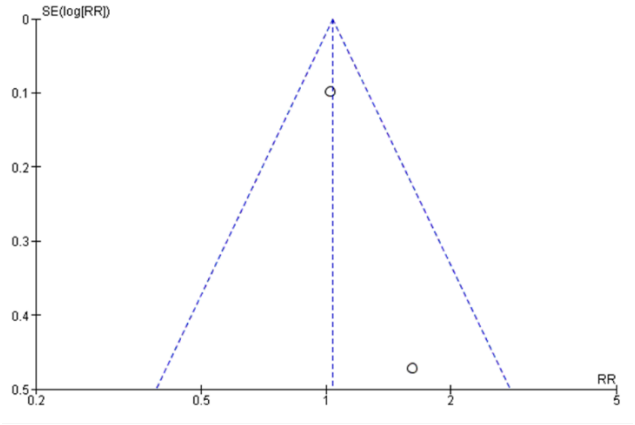


BD – singletons and multiples

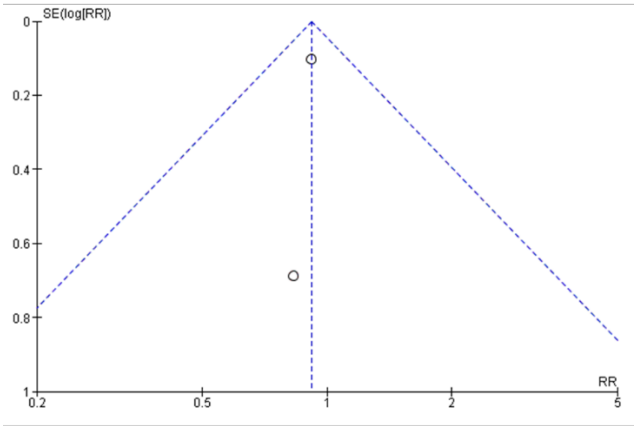


Multiplicity

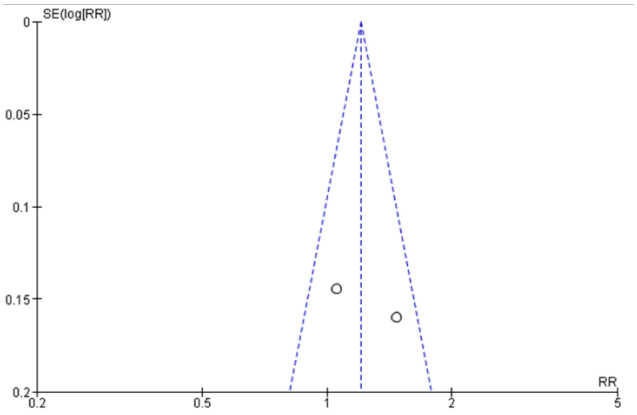
Appendix 1.8 Funnel Plots of Donor Sperm Meta-Analysis



LBW



PD



BD

Appendix 1.9 A Small Selection of Social Media Advertisements Recruiting Gamete Donors

FIRST EGG BANK
July 31, 2019 ·

Are you from 18 to 36 years old? Do you have at least one own healthy child?
You can give health and hope to the couples without children. First Egg Bank is thankful to all our egg donors for their kind heart and clearly mind, we appreciate people who understand that helping to another will make them stronger and better
Read more - https://bit.ly/2J0UIBY and contact us if necessary!
info@first-egg-bank.com
+1 929 999 2034 ... See More

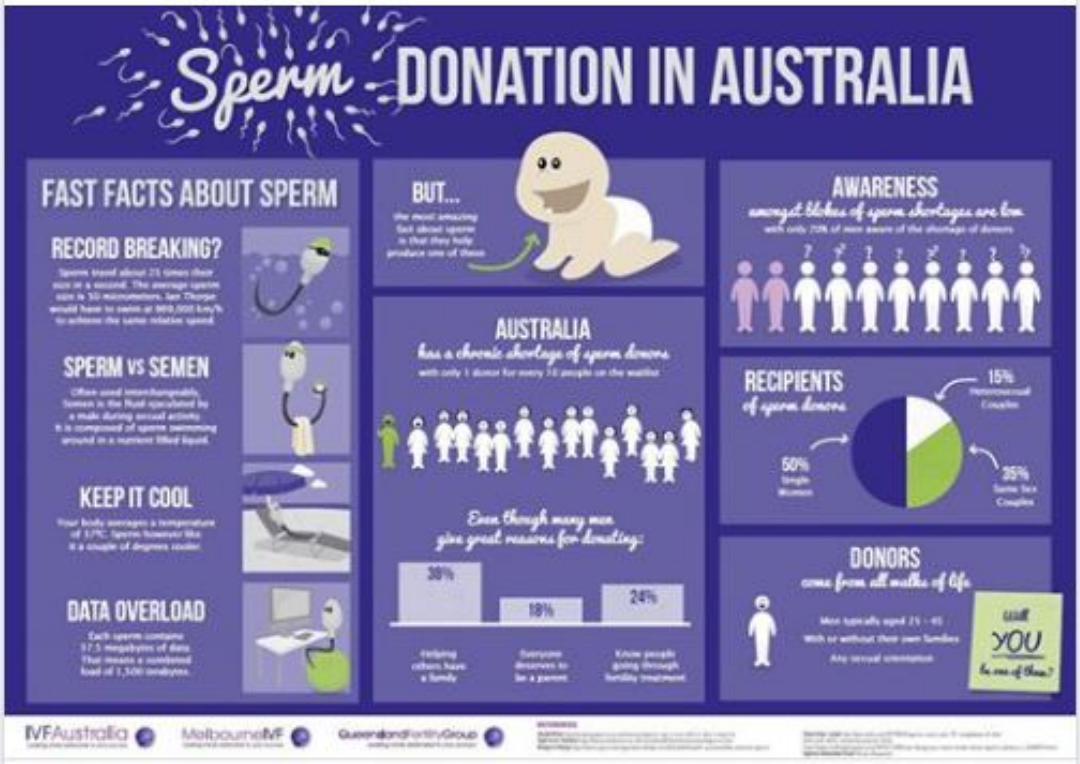
Seattle Sperm Donor
June 20, 2019 ·

Seattle Sperm Donor updated their business hours.

Contact Us

IVFAustralia
March 7, 2019 ·

From facts to stats, check out the cheat sheet for sperm donation in Australia.



Fertility Associates
Sponsored ·

Every day at Fertility Associates we see women hoping to have a baby of their own and who, after working through all the options, need the help of an... See More

FERTILITYASSOCIATES.CO.NZ
Egg Donors Needed
LEARN MORE

Australia Needs Sperm Donors
March 20, 2013 ·

Free health check-ups for all sperm donors! We'll provide a number of free tests and screens for you, and if you're fit for the job you can then receive approx $100 per donation as reimbursement. Most men who donate average between 10 and 20 donations. Click here for more details on what's in it for you http://qfg.com.au/australia-needs-sperm-donors

Appendix 2 Additional Information Relating to Sperm Donation Outcomes

Appendix 2.1 Publication: Sperm Donation Perinatal Outcomes in an Australian Population Cohort

See next page

Damian Adams, Renae Fernandez, Vivienne Moore, Kristyn Willson, Alice Rumbold, Sheryl de Lacey, Wendy Scheil, Michael Davies. Sperm Donation Perinatal Outcomes in an Australian Population Cohort. J Obstet Gynaecol Res. 2017 Dec;43(12):1830-1839.
doi: 10.1111/jog.13449. Epub 2017 Aug 17.

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doi:10.1111/jog.13449 J. Obstet. Gynaecol. Res. Vol. 43, No. 12: 1830–1839, December 2017

Sperm donation perinatal outcomes in an Australian population cohort

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Abstract

Aim: To compare perinatal outcomes for neonates conceived with donated sperm with those for neonates conceived spontaneously in an Australian population cohort.

Methods: Perinatal outcomes for all births in South Australia for the period January 1986–December 2002 were linked with assisted reproductive treatment records to determine those conceived from donated sperm. Birth outcome measures were analyzed using Student's *t*-test and logistic regression using generalized estimating equations to determine statistical significance.

Results: Donor sperm neonates were not significantly different from their spontaneously conceived counterparts in terms of mean birthweight, low birthweight, preterm delivery, small for gestational age, or large for gestational age. They were, however, significantly more likely to be born at lower mean gestational age ($P = 0.012$), and to have preterm delivery with low birthweight ($P = 0.008$), when controlling for maternal age, parity, ethnicity, socioeconomic quartile and baby's sex. These associations were not apparent when singletons and twins were considered separately.

Conclusion: There was some evidence of compromised perinatal outcomes for donor sperm neonates compared with their spontaneously conceived counterparts, which appeared to be partly attributable to multiplicity.

Key words: donor conception, infant, insemination artificial, population, spermatozoa.

Introduction

Pregnancy rates achieved through the use of donor sperm have been reported extensively,[1–8] but pregnancy is not the only important outcome to account for in clinical practice. The health of the child born is also of significant importance. Given that poor perinatal outcomes have been linked with poor adult health through the fetal origins of adult disease hypothesis,[9] the health of the newborn can potentially influence the health trajectory of the person in adulthood. Thus the perinatal outcomes for neonates conceived with donated sperm provide crucial evidence not only of the efficacy of the treatment to produce a live birth, but also its potential impact on the health of the person perinatally as well as in the long term.

A systematic review comparing perinatal outcomes among donor sperm neonates with those conceived spontaneously found that studies published up until November 2012 were not only scarce, but inadequate for a comprehensive meta-analysis, due to a lack of studies with an appropriate comparison group.[10]

The review did not find any evidence of increased or decreased prevalence of low-birthweight (LBW < 2500 g), preterm delivery (PD < 37 weeks), or birth defects (BD) in the donor sperm-conceived group compared with

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spontaneous conceptions.[10] The lack of available studies for meta-analysis, however, means that caution must be exercised when interpreting these findings. Individual studies included in the review, however, raised concerns about the possibility of increased chromosomal abnormalities in donor sperm neonates, which was potentially linked with the use of cryopreserved sperm. Furthermore, given that only three outcome categories could be meta-analyzed, any future studies should address a greater variety of outcome measures.

We have previously observed an increase in the risk of birth defects among singletons born from donor sperm that was attenuated after adjustment for maternal factors (unadjusted odds ratio [OR], 1.51; 95 %CI: 1.08–2.11; adjusted OR, 1.37; 95%CI: 0.98–1.92).[11] This observation raises the question as to whether there are accompanying, but less severe, adverse outcomes associated with donor sperm.

The use of donor sperm does provide mechanisms through which perinatal outcomes may be adversely affected. First, since the advent of the AIDS (HIV) epidemic in the 1980s, donor sperm has been exclusively cryopreserved in many Western jurisdictions.[10,12] Cryopreservation of sperm introduces oxidative stress, which increases DNA fragmentation rates.[13–15] Children conceived with oxidative stress-induced DNA-damaged sperm are at increased risk of childhood morbidity.[16,17]

Second, donor sperm represents an immunological challenge to the woman that may lead to increased occurrence of pre-eclampsia (PE).[18–22] PE represents a significant morbidity and mortality burden to not only the mother, but also to the fetus.[23–25] In the perinatal period, PE leads to increased occurrence of PD,[26] and even when controlling for PD it has been associated with an increased risk of being born small for gestational age (SGA), or the neonate having respiratory distress syndrome, apnea, asphyxia, peri- or intra-ventricular hemorrhage, and increased neonatal intensive care unit admissions.[27] Maternal PE is also associated with poorer health outcomes when the child reaches adolescence and adulthood such as increased incidences of cardiovascular disease,[23] hypertension,[28] stroke,[29] lower hip bone mass density,[30] and higher body mass index.[31]

In contrast to donor sperm-related perinatal outcomes, donor oocyte perinatal outcomes have been more thoroughly investigated. Meta-analysis within a systematic review has shown that donor oocyte neonates in comparison with autologous oocyte neonates (autologous *in vitro* fertilization [IVF]) are at significantly increased risk of being born LBW (no. studies in meta-analysis, 15), very LBW (VLBW <1500 g, n = 11), PD (n = 13), PD with LBW (n = 11), and of lower gestational age (n = 3).[32] They were also at decreased risk of being born at term and LBW (n = 11).[32] Additionally, a further systematic review and meta-analysis by Jeve *et al.*, concluded that donor oocyte neonates were at increased risk of being born SGA (n = 6), PD (n = 9), are more likely to be delivered by cesarean section (n = 6), and were more likely to have mothers with hypertensive disorders (n = 10), including PE (N = 4), when compared with autologous oocyte neonates.[33] The number of studies that were included in the donor oocyte meta-analyses is larger than the number included in the donor sperm meta-analysis, thereby highlighting the need for further well designed donor sperm perinatal studies.

It is therefore both pertinent and imperative that further studies are conducted on the perinatal outcomes of donor sperm-conceived neonates in comparison with spontaneously conceived neonates. Population-based studies will not only increase knowledge of any impact on offspring of donor sperm use, but also increase confidence in the analysis of the effects of the sperm donation treatment on perinatal outcomes. Such information is valuable to clinicians to allow them to fully inform their patients on the potential health outcomes for any child conceived using donated sperm.

Methods

Ethics approval for this study was obtained from the Flinders University Social and Behavioural Research Ethics Committee and is in accordance with the Declaration of Helsinki (as revised in Tokyo 2004). Consent from the participants was not required by the ethics committee because data were already recorded in a database. Approval for access to the perinatal data was provided by the University of Adelaide, Flinders University, and the South Australian Department of Health Ethics Committees.

Study design

In South Australia all births are recorded in the South Australian Perinatal Statistics Collection (SAPSC) as required by law, enabling a population-wide retrospective cohort study. The collection was linked to clinical data for those conceived through assisted reproductive technology (ART), including conceptions from donor sperm. The perinatal outcomes of neonates conceived using donor sperm were compared with that of spontaneously conceived neonates.

Setting

All births in South Australia occurring between January 1986 and December 2002 that were recorded in the SAPSC were included. During this period of time South Australia had a population of 1.35 million people in 1986,[34] expanding to 1.52 million by 2002.[35] Approximately 17 000 births were recorded annually during this period. Due to the practice paradigm of that period, all donor sperm-conceived neonates were from cryopreserved sperm.

The reporting of all births (live and stillbirth; SB), for outcomes of at least 20 weeks' gestation or with birthweight ≥400 g, is mandatory. A standardized notification form is used to provide consistency in reporting. Furthermore, it is also mandatory in South Australia to report medical terminations of pregnancy. Those occurring at 20 weeks of gestation or later are included in the SAPSC. The SAPSC also contains data on potential confounders such as maternal sociodemographic variables (age, ethnicity, socioeconomic status) and maternal pre-existing medical conditions (hypertension, diabetes, asthma, and epilepsy), in addition to those occurring during pregnancy (pregnancy-induced hypertension [PIH], and gestational diabetes).

Participants

The participants were all neonates born in the State of South Australia between January 1986 and December 2002. Those neonates conceived through alternative ART modalities that are not donor sperm such as donor oocytes, donor embryos, various forms of IVF, and intracytoplasmic sperm injection (ICSI), however, were excluded. Donor sperm neonates include those from standard donor insemination programs and those in which IVF had previously failed, but did not include gamete intra-fallopian transfer with donor sperm, or IVF with donor sperm.

Outcome variables

Birthweight and gestational age were analyzed as continuous variables. Several dichotomous outcomes were also considered: PD (< 37 weeks), very PD (VPD; <32 weeks), post-term delivery (PostD; >41 weeks), LBW (<2500 g), very LBW (VLBW; <1500 g), PD with LBW, term delivery (TD) with LBW, Apgar score <7 at 5 min (5'AS < 7), SGA (birthweight < 10th percentile),[36] large for gestational age (LGA; birthweight > 90th percentile),[36] neonatal death (death within the 28 days following birth), and SB.

Statistical analysis

Continuous variables that were normally distributed were summarized using means and standard deviation, and then subjected to two-tailed, Student's t-test to determine if differences according to mode of conception were statistically significant. For dichotomous outcomes, chi-squared tests were used to assess differences, and logistic regression analysis using generalized estimating equations was undertaken to produce OR and 95%CI. Results were deemed to be significant for $P < 0.05$. All statistical analysis was conducted using Stata V.14. (StataCorp, College Station, Texas, USA).

Higher order multiples of triplets and above were excluded from the spontaneously conceived cohort ($n = 384$), because there were no higher order multiples present in the donor sperm cohort. Thus analysis was restricted to singletons and twins. Births recorded to mothers under 20 years of age were excluded from the study because only one such case of a mother receiving donor insemination treatment was recorded. Babies of indeterminate or unknown sex ($n = 309$) were excluded from the spontaneously conceived cohort because there were none in the donor sperm cohort. Data on the zygosity of twins were not available.

Effect estimates were adjusted for the following *a priori* confounders of maternal age (categorized in 5-year age groups): parity, socioeconomic disadvantage on the basis of the postal code of the mother's residence (according to the Socio-economic Indexes for Areas (SEIFA)[37]), maternal race or ethnic group and fetal sex. Using the change in estimate approach,[38] maternal conditions of pre-existing hypertension, PIH, pre-existing diabetes, gestational diabetes, epilepsy, asthma, and anemia were included in the fully adjusted model if their inclusion produced > ±10 % change in the main effect estimate. PIH was the term used in the SAPSC for the period of the study, but is now known as hypertensive disorders of pregnancy. Analyses were conducted for all births, then stratified by multiplicity. All OR account for clustering within mother, i.e. births resulting from multiple gestations or serial pregnancies to the same woman, which cannot be treated as independent observations in statistical analyses.

During the study period a proportion of artificial insemination with donor sperm treatments were performed with ovulation induction (OI). To assess any impact of OI, birth outcomes for OI cycles were compared with those for natural cycles within the cohort.

Further adjustment for maternal conditions in pregnancy (pre-existing hypertension, PIH, pre-existing diabetes, gestational diabetes, epilepsy, asthma, anemia), did not produce any change in the effect estimates and are therefore not presented. Due to sparse data, OR could not be calculated for the outcomes of VPD, PostD, VLBW, TD with LBW, and 5'AS < 7 in any stratified groups, or for SGA and LGA in twins, but the data were included for reference.

Results

All births from January 1986 to December 2002 totaled 299 424, of which there were 297 756 live births (including 939 neonatal deaths) and 1668 SB. Characteristics of these births according to mode of conception and birth outcome are listed in Table 1.

With regard to live births, mothers of donor sperm-conceived neonates were in general older than their counterparts who conceived spontaneously. There were greater percentages of births from donor sperm in all maternal age groups >30 years. Mothers receiving donor sperm were significantly more likely to be primigravid ($P < 0.001$), and nulliparous ($P < 0.001$). No statistically significant differences were observed between spontaneous and donor sperm births for socioeconomic status as analyzed by quartiles, but mothers using donor sperm were more likely to be Caucasian ($P = 0.001$).

A higher percentage of neonates from donor sperm were male, while a higher percentage of spontaneously conceived neonates were female, although these differences were non-significant. A significantly higher proportion of neonates from donor sperm were twins ($P < 0.001$). Mothers of neonates from donor sperm were significantly more likely to have PIH as well as pre-existing diabetes (both $P = 0.027$) compared with their spontaneously conceiving maternal counterparts. The occurrence of PIH was not significantly elevated among women with donor sperm-conceived twin deliveries ($P = 0.116$), but was significantly elevated among those with donor sperm-conceived singleton deliveries ($P = 0.007$; data not shown).

Table 1 Characteristics of live births and stillbirths by mode of conception

	Live births				*P*-value	Stillbirths				*P*-value
	Spontaneous $n = 297280$		Donor $n = 476$			Spontaneous $n = 1664$		Donor $n = 4$		
Age (years), n (%)					<0.001					0.090
20–24	62186	(20.9)	21	(4.4)		386	(23.2)	0	(0.0)	
25–29	112494	(37.8)	141	(29.6)		571	(25.9)	1	(25.0)	
30–34	87145	(29.3)	198	(41.6)		431	(25.9)	2	(50.0)	
35–39	30632	(10.3)	107	(22.5)		221	(13.3)	0	(0.0)	
40+	4813	(1.6)	9	(1.9)		55	(3.3)	1	(25.0)	
Primigravid, n (%)	84947	(28.6)	194	(40.8)	<0.001	501	(30.1)	2	(50.0)	0.387
Parity, n (%)					<0.001					0.369
0	111696	(37.6)	257	(54.0)		699	(42.0)	2	(50.0)	
1	107488	(36.2)	175	(36.8)		460	(27.6)	2	(50.0)	
2+	78096	(26.3)	44	(9.2)		505	(30.4)	0	(0.0)	
Socioeconomic quartile, n (%)					0.113					0.762
Lowest	69521	(23.4)	120	(25.2)		448	(26.9)	0	(0.0)	
Low-middle	78739	(26.5)	103	(21.6)		485	(29.2)	2	(50.0)	
Middle-high	74694	(25.1)	126	(26.5)		409	(24.6)	1	(25.0)	
Highest	73410	(24.7)	127	(26.7)		295	(17.3)	1	(25.0)	
Caucasian, n (%)	277744	(93.4)	462	(97.1)	0.001	1493	(89.7)	4	(100.0)	0.499
Sex ratio (M:F)	0.93		1.03		0.314	0.92		3		0.280
Twin gestation, n (%)	7018	(2.4)	43	(9.0)	<0.001	144	(8.7)	1	(25.0)	0.246
Maternal conditions, n (%)										
Pre-existing hypertension	3280	(1.1)	8	(1.7)	0.228	62	(3.7)	0	(0.0)	0.694
PIH	26064	(8.8)	64	(13.5)	<0.001	158	(9.5)	1	(25.0)	0.292
Pre-existing diabetes	869	(0.3)	4	(0.8)	0.027	17	(1.0)	0	(0.0)	0.839
Gestational diabetes	3322	(1.1)	5	(1.1)	0.889	19	(1.1)	0	(0.0)	0.830
Epilepsy	1566	(0.5)	0	(0.0)	0.112	18	(1.1)	0	(0.0)	0.834
Asthma	12538	(4.2)	18	(3.8)	0.636	90	(5.4)	0	(0.0)	0.633
Anemia	17864	(6.0)	34	(7.1)	0.298	148	(8.9)	0	(0.0)	0.532

PIH, pregnancy-induced hypertension.

Table 2 Stillbirth and neonatal death

	Singletons		*P*	Twins		*P*-value
	Spontaneous *n* = 291 782	Donor *n* = 436		Spontaneous *n* = 7162	Donor *n* = 44	
Stillbirth, n (%)	1520 (0.5)	3 (0.7)	0.626	144 (2.0)	1 (2.3)	0.900
Neonatal death, n (%)	806 (0.3)	0 (0.0)	0.272	133 (1.9)	0 (0.0)	0.362

Data for SB and neonatal death, are presented in Table 2 . There was no significant difference between births conceived with donor sperm and those conceived spontaneously for risk of SB. Twins in both conception groups had higher proportions of SB compared with singletons (2.3% vs 0.7% donor sperm; 2.0% vs 0.5% spontaneously conceived). No neonatal deaths occurred among neonates conceived via donor sperm, whereas the prevalence of neonatal death among spontaneously conceived neonates was 0.3% for singletons and 1.9% for twins.

Perinatal outcomes of all live births, then stratified into singletons and twins, are presented in Table 3. Birthweight showed no statistically significant difference between conception groups overall and when singletons and twins were considered separately. Donor sperm-conceived neonates were more likely to be born at a lower gestational age than spontaneously conceived neonates (mean difference, −0.25 weeks; 95%CI: −0.45 to −0.06, $P = 0.012$). When singletons and twins were considered separately, however this was no longer statistically significant (singletons mean difference, −0.13 weeks; 95%CI: −0.31 to 0.05; twins mean difference, 0.51 weeks; 95%CI: −0.34 to 1.36).

Overall, donor sperm-conceived neonates were more likely to be born PD with LBW compared with spontaneously conceived neonates (7.1% vs 3.8%; OR, 1.74; 95% CI: 1.16–2.61, $P = 0.008$). When singletons and twins were considered separately, the differences were no longer statistically significant for singletons (4.2% vs 3.0%; OR, 1.37; 95%CI: 0.84–2.23), or twins (37.2% vs 37.2%; OR, 0.95; 95%CI: 0.42–2.13).

When PD was considered as a separate outcome, donor sperm neonates had a non-significant increased risk in comparison with spontaneously conceived neonates (9.5% vs 6.5%; OR, 1.34; 95%CI: 0.92–1.93), but no differences were observed for singletons (5.5% vs 5.5%; OR, 0.97; 95%CI: 0.63–1.50), or twins (48.8% vs 47.9%; OR, 1.19; 95%CI: 0.50–2.82) when considered separately. Similarly, LBW showed a non-significant increased risk for donor sperm neonates in comparison with spontaneously conceived neonates overall (8.2% vs 5.7%; OR, 1.34; 95%CI: 0.92–1.94). Differences, however, were not significant for singletons (5.1% vs 4.7%; OR, 1.07; 95%CI: 0.69–1.66) or twins (39.5% vs 49.2%; OR, 0.62; 95%CI 0.27–1.39) considered separately.

Donor sperm-conceived neonates had a non-significant lower risk of being born SGA compared with their spontaneously conceived counterparts (8.8% vs 10.1%; OR, 0.82; 95%CI: 0.59–1.15). Similar results were observed when singletons were considered separately (9.2% vs 10.2%; OR, 0.84; 95%CI: 0.59–1.20). There was no difference in the odds of LGA between donor sperm and spontaneously conceived neonates in the combined analysis (9.7% vs 9.9%; OR, 1.02; 95%CI: 0.74–1.42), or among singletons alone (10.2% vs 9.9%; OR, 1.06; 95%CI: 0.76–1.49).

The effect of OI on perinatal outcomes among donor sperm conceptions is presented in Table 4. OI was associated with twin pregnancy (10.0% vs 2.1%, $P < 0.001$). Among all donor sperm births, OI was associated with a lower mean birthweight ($P = 0.033$), lower mean gestational age ($P = 0.025$), and increased occurrence of PD ($P = 0.011$), and PD with LBW ($P = 0.021$). When singletons and twins were considered separately, the only association that persisted was lower mean gestational age for OI twins when compared with natural cycle twins ($P = 0.038$).

Discussion

This study represents a comprehensive analysis of perinatal outcomes of neonates conceived with cryopreserved donated sperm in a population. Despite the potential for adverse perinatal outcomes due to the increased occurrence of PE and oxidative stress-induced DNA fragmentation reported elsewhere,[13–31] significantly increased adverse outcomes were generally not observed in this cohort. There were, however, two exceptions. For all donor sperm births, mean gestational age was significantly lower and the likelihood of PD combined with LBW was significantly higher compared with spontaneously conceived births, after adjusting for maternal age, parity, ethnicity, socioeconomic quartile and sex of the neonate. These were no longer significant when singletons and twins were analyzed separately. Given the effect of stratifying by multiplicity on the number of events (≤24 events) in each group

Table 3 Perinatal outcomes

		All births		P-value	Singletons		P-value	Twins		P-value
		Spontaneous	Donor		Spontaneous	Donor		Spontaneous	Donor	
All	*n*	297 280	476		290 262	433		7018	43	
Birthweight (g)†	Mean ± SD	3377 ± 573	3312 ± 604	0.242	3400 ± 552	3392 ± 554	0.912	2430 ± 609	2510 ± 492	0.247
	Mean diff (95%CI)	0 (−)	−35 (−93,23)		0 (−)	3 (−51,58)		0 (−)	107 (−74288)	
Gestation (weeks)	Mean ± SD	39.1 ± 1.9	38.9 ± 1.9	0.012	39.2 ± 1.8	39.1 ± 1.7	0.169	35.8 ± 3.1	36.4 ± 2.0	0.243
	Mean diff (95%CI)	0 (−)	−0.25 (−0.45,−0.06)		0 (−)	−0.13 (−0.31,0.05)		0 (−)	0.51 (−0.34,1.36)	
PD	n (%)	19 265 (6.5)	45 (9.5)	0.125	15 901 (5.5)	24 (5.5)	0.903	3364 (47.9)	21 (48.8)	0.688
	OR (95%CI)	1 (−)	1.34 (0.92,1.93)		1 (−)	0.97 (0.63,1.50)		1 (−)	1.19 (0.50,2.82)	
VPD‡	n (%)	3027 (1.0)	6 (1.3)	0.599	2448 (0.8)	5 (1.2)	0.479	579 (8.3)	1 (2.3)	0.158
	OR (95%CI)	—	—		—	—		—	—	
PostD‡	n (%)	4858 (1.6)	3 (0.6)	0.084	4856 (1.7)	3 (0.7)	0.112	2 (0.03)	0 (0)	0.912
	OR (95%CI)	—	—		—	—		—	—	
LBW†	n (%)	16 986 (5.7)	39 (8.2)	0.129	13 530 (4.7)	22 (5.1)	0.768	3456 (49.2)	17 (39.5)	0.243
	OR (95%CI)	1 (−)	1.34 (0.92,1.94)		1 (−)	1.07 (0.69,1.66)		1 (−)	0.62 (0.27,1.39)	
VLBW†‡	n (%)	2710 (0.9)	6 (1.3)	0.424	2160 (0.7)	4 (0.9)	0.664	550 (7.8)	2 (4.7)	0.438
	OR (95%CI)	—	—		—	—		—	—	
PD with LBW†	n (%)	11 370 (3.8)	34 (7.1)	0.008	8761 (3.0)	18 (4.2)	0.208	2609 (37.2)	16 (37.2)	0.892
	OR (95%CI)	1 (−)	1.74 (1.16,2.61)		1 (−)	1.37 (0.84,2.23)		1 (−)	0.95 (0.42,2.13)	
TD with LBW†‡	n (%)	5603 (1.9)	5 (1.1)	0.181	4756 (1.6)	4 (0.9)	0.242	847 (12.1)	1 (2.3)	0.050
	OR (95%CI)	—	—		—	—		—	—	
SGA†‡	n (%)	30 126 (10.1)	42 (8.8)	0.259	29 464 (10.2)	40 (9.2)	0.341	662 (9.4)	2 (4.7)	0.284
	OR (95%CI)	1 (−)	0.82 (0.59,1.15)		1 (−)	0.84 (0.59,1.20)		—	—	
LGA†‡	n (%)	29 442 (9.9)	46 (9.7)	0.893	28 753 (9.9)	44 (10.2)	0.712	689 (9.8)	2 (4.7)	0.256
	OR (95%CI)	1 (−)	1.02 (0.74,1.42)		1 (−)	1.06 (0.76,1.49)		—	—	
5′ AS < 7‡	n (%)	4340 (1.5)	5 (1.1)	0.457	4119 (1.4)	5 (1.2)	0.642	221 (3.1)	0 (0)	0.237
	OR (95%CI)	—	—		—	—		—	—	

OR account for clustering within mother, i.e. births resulting from multiple gestations or serial pregnancies to the same woman, which cannot be treated as independent observations in statistical analyses, and are adjusted for maternal age, parity, ethnicity, socioeconomic quartile and baby's sex. †Twenty-four spontaneously conceived births were missing birthweight information. ‡Chi-squared *P*-values. OR and 95%CI could not be calculated due to sparse data. 5′ AS < 7, Apgar score <7 at 5 min; LBW, low birthweight (<2500 g); LGA, large for gestational age (>90th percentile)[36]; PD, preterm delivery (<37 weeks' gestation); postD, post-term delivery (>41 weeks); SGA, small for gestational age (<10th percentile)[37]; TD, term delivery; VLBW, very LBW (<1500 g); VPD, very PD (<32 weeks).

Table 4 Perinatal outcomes: Natural cycle vs OI

		All DI births			DI singletons			DI twins		
		Natural cycle	OI cycle	*P*	Natural cycle	OI cycle	*P*	Natural cycle	OI cycle	*P*
Total	n	326	155		312	125		14	30	
Birthweight (g)†	Mean ± SD	3352 ± 587	3226 ± 631	0.033	3387 ± 572	3404 ± 506	0.763	2600 ± 362	2466 ± 544	0.409
Gestation (weeks)†	Mean ± SD	39.0 ± 1.8	38.6 ± 2.1	0.025	39.1 ± 1.8	39.2 ± 1.6	0.544	37.3 ± 1.6	35.9 ± 2.1	0.038
PD†	n (%)	23 (7.2)	22 (14.4)	0.011	17 (5.5)	7 (5.7)	0.953	6 (42.9)	15 (51.7)	0.586
VPD†	n (%)	4 (1.2)	2 (1.3)	0.950	4 (1.3)	1 (0.8)	0.667	0 (0.0)	1 (3.5)	0.482
PostD†	n (%)	2 (0.6)	1 (0.7)	0.965	2 (0.7)	1 (0.8)	0.857	0 (0.0)	0 (0.0)	—
LBW†	n (%)	21 (6.5)	18 (11.8)	0.051	16 (5.2)	6 (4.8)	0.864	5 (35.7)	12 (41.4)	0.722
VLBW†	n (%)	4 (1.2)	2 (1.3)	0.950	4 (1.3)	0 (0.0)	0.203	0 (0.0)	2 (6.9)	0.314
PD with LBW†	n (%)	17 (5.3)	17 (11.1)	0.021	13 (4.2)	5 (4.0)	0.934	4 (28.6)	12 (41.4)	0.416
TD with LBW†	n (%)	4 (1.2)	1 (0.7)	0.559	3 (1.0)	1 (0.8)	0.872	1 (7.1)	0 (0.0)	0.145
SGA†	n (%)	30 (9.3)	12 (7.8)	0.604	29 (9.4)	11 (8.9)	0.867	1 (7.1)	1 (3.5)	0.590
LGA†	n (%)	32 (9.9)	14 (9.2)	0.794	31 (10.0)	13 (10.5)	0.888	1 (7.1)	1 (3.5)	0.590
5′ AS < 7†	n (%)	4 (1.2)	1 (0.7)	0.559	4 (1.3)	1 (0.8)	0.667	0 (0.0)	0 (0.0)	—
Stillbirth	n (%)	3 (0.9)	1 (0.7)	0.761	3 (1.0)	0 (0.0)	0.273	0 (0.0)	1 (3.3)	0.490
Neonatal death	n (%)	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—	0 (0.0)	0 (0.0)	—

Excludes terminations ($n = 1$); †Live births only; 5′AS < 7, Apgar score <7 at 5 min; DI, donor insemination; LBW, low birthweight (<2500 g); LGA, large for gestational age (>90th percentile)[36]; OI, ovulation induction; PD, preterm delivery (<37 weeks' gestation); postD, post-term delivery (>41 weeks); SGA, small for gestational age (<10th percentile)[36]; TD, term delivery; VLBW, very LBW (<1500 g); VPD, very PD (<32 weeks).

(singletons/twins), for the outcomes; PD, LBW, and PD with LBW, these results should be treated with caution, because a larger study from more recent births in South Australia may strengthen or weaken any association.

Of the maternal covariates, there is one pregnancy observation that may potentially contribute to the observed lower mean gestational age and increase in PD with LBW. Mothers receiving donor insemination had significantly higher prevalence of PIH, which is supported by the Salha *et al.* study.[21] In an analysis of PIH and PE, Villar *et al.* concluded that the conditions were related.[39] Data on the incidence of PE, however, were not available from the SAPSC to confirm whether this was also elevated in the donor sperm cohort, as has been reported elsewhere.[18–22] Given that PE has been associated with PD and fetal growth restriction,[40] which is a function of LBW, an increased incidence of PE could possibly explain the lower mean gestational age and increased incidence of PD with LBW observed in the donor sperm cohort.

Neonates conceived with donated sperm were more likely to be twins than those conceived spontaneously. This was associated with the use of OI as part of the donor insemination program. Overall, OI was associated with a number of adverse perinatal outcomes, but stratification by multiplicity showed that this reflected the elevated occurrence of twins and the only direct effect was a reduced gestational age in twins. OI was also a treatment modality for women with irregular cycles elsewhere in Australia, as part of donor inseminations programs during that period.[20]

The stimulant used for OI could adversely influence perinatal outcomes. For example, clomiphene citrate, a commonly used stimulant, has been associated with higher incidences of LBW,[41,42] PD,[42] and SGA neonates.[41] We did not have sufficient statistical power, however, to analyze outcomes associated with specific drugs.

The absence of adverse perinatal outcomes in donor sperm conceptions suggests that DNA damage may be minimized during cryopreservation of donor semen. Several factors may be influencing this finding.

The extent of DNA damage induced by cryopreservation is influenced by the quality of the sperm,[43,44] and, considering that one of the criteria for acceptance as a semen donor is good-quality sperm, it would be unsurprising if DNA damage in cryopreserved donor sperm was less than that for cryopreserved sperm from other men. A donor spermatozoa with DNA damage probably has a low likelihood of fertilizing an oocyte following artificial insemination, given that sperm DNA damage contributes to infertility in men.[45] Also, sperm with elevated levels of DNA damage has been associated with reduced pregnancy rates in IVF and ICSI.[46] Furthermore, the oocyte is able to repair small amounts of DNA damage introduced by the spermatozoa.[47]

Thus the combination of good-quality sperm from fertile donors, with natural selection of the fittest sperm through artificial insemination rather than specific sperm selected in IVF/ICSI treatment modalities, the oocyte's ability to repair small amounts of DNA damage, and the reduced likelihood of an abnormal embryo achieving implantation,[48] may potentially explain the absence of substantial differences in perinatal outcomes in the donor sperm cohort. The size of the donor sperm cohort, however, means that we cannot rule out the possibility of modest differences that were not detectable as statistically significant. This possibility will be investigated when more recent donor sperm conceptions can be added to the cohort.

The adverse perinatal outcomes observed in donor oocyte neonates,[32,33] were not mirrored in this donor sperm cohort with the exceptions of lower mean gestational age and PD with LBW. Hypothetically, donor oocyte perinatal outcomes could be worse than those observed for donor sperm neonates because a donor oocyte represents a significant immunological challenge. Novel oocyte antigens are not something a mother would naturally be exposed to, unlike novel sperm antigens, even though both result in increased incidences of PE. More studies are required, however, to confirm or refute the postulation that donor sperm neonates fare better than their donor oocyte counterparts.

These results may be reassuring to clinicians in the counseling of their patients as to the perinatal risks associated with using donated semen. Furthermore, the lack of adverse perinatal outcomes may also be reassuring for any adult person conceived with donated sperm in regard to their probability of developing adult-onset diseases such as heart disease and type-2 diabetes mellitus. Due to the sample size of the donor sperm cohort from January 1986 to December 2002, the inclusion of data from subsequent years would be of great benefit to improve statistical power and the reliability of the results observed.

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Disclosure

The authors declare no conflicts of interest.

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Appendix 2.2 Publication: Update On: A Meta-Analysis of Sperm Donation Offspring Health Outcomes - 2018 Update

See next page

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Letter to the Editor

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Update on: a meta-analysis of sperm donation offspring health outcomes – 2018 update

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Dear Editor,

In 2017 our team published a meta-analysis on the health outcomes of offspring conceived from donor sperm.[1] At the time of this review, there were only eight studies that were eligible for inclusion, and only three qualified for meta-analysis,[2–4] and only two studies provided data for each outcome analysis. Our review demonstrated the paucity of studies investigating the perinatal outcomes of sperm donation.

After identifying this gap in research, we undertook a population study comparing the perinatal outcomes for neonates conceived with donor sperm and those conceived spontaneously in the state of South Australia.[5] Furthermore, since the census date of the meta-analysis a further two studies have been published that also meet the criteria of our original review,[6,7] and we believed it was important that we add these three studies (two by other authors and one by ourselves), to our meta-analysis to see if the original findings were either supported or refuted.

The original findings showed that; donor sperm neonates in comparison to naturally conceived neonates were not at increased risk of being born of low birth weight [risk ratio (RR): 1.04, 95% confidence interval (CI): 0.86–1.25, *P*-value (*P*) = 0.71, I^2 = 0%]; preterm (RR: 0.91, CI: 0.75–1.12, *P* = 0.38, I^2 = 0%); or with increased incidences of birth defects (RR: 1.20, CI: 0.97–1.48, *P* = 0.09, I^2 = 57%).[1]

The addition of the new studies allowed not only for an increase in the number of studies included in the meta-analysis conducted above but also for a larger range of perinatal outcomes. All data extraction and analysis followed the method described in our original review. The studies that were included in each meta-analysis are listed as reference numbers in superscript after each meta-analysis.

The updated meta-analysis has demonstrated that, in comparison to naturally conceived neonates, donor sperm neonates were at increased risk of being born of low birth weight (RR: 1.17, CI: 1.03–1.33, *P* = 0.02, I^2 = 52%),[3–7] and with increased incidences of birth defects (RR: 1.30, CI: 1.05–1.59, *P* = 0.01, I^2 = 72%) (Fig. 1).[2,4,6] However, they were not at increased risk of being born preterm (RR: 1.05, CI: 0.91–1.21, *P* = 0.47, I^2 = 52%),[3–5,7] very preterm (<32 weeks) (RR: 1.17, CI: 0.75–1.81, *P* = 0.49, I^2 = 0%),[5,7] very low birth weight (<1500 g) (RR: 1.22, CI: 0.76–1.97, *P* = 0.4, I^2 = 0%),[5,7] small for gestational age (birth weight <10th percentile) (RR: 1.19, CI: 0.99–1.42, *P* = 0.06, I^2 = 82%),[5,7] large for gestational age (birth weight > 90th percentile) (RR: 1.04, CI: 0.86–1.38, *P* = 0.71, I^2 = 0%),[5,7] with altered perinatal mortality (RR: 0.93, CI: 0.59–1.45, *P* = 0.74, I^2 = 0%),[5,7] of lower mean birth weight (mean difference −12.5 g, CI: −32.03 to 7.02 g, *P* = 0.21, I^2 = 0%),[3,5–7] or of lower mean gestational age (mean difference −0.02 weeks, CI: −0.10 to 0.05 weeks, *P* = 0.55, I^2 = 12%).[5,7]

Of the newly included studies, one appropriately stratified data into singletons *v.* multiple deliveries,[5] whereas another only analysed singletons[7] to remove confounding from multiple births. All three studies reported maternal ages, two of which adjusted for maternal age,[5,7] whereas the other had no significant difference between maternal ages of those conceiving with donor sperm *v.* spontaneous conception.[6] Parity was appropriately adjusted for in two of the newly included studies.[5,7]

Caution should be taken when interpreting these results. Due to the heterogeneity present in some analysis, bias observed through funnel plot analysis, and the low number of studies included in some meta-analysis, more studies investigating perinatal outcomes in donor sperm-conceived neonates in comparison to spontaneously conceived counterparts in a systematic manner is required to improve our understanding of the effects of using donor sperm in assisted reproduction. Furthermore, the use of specific ovarian stimulation drugs such as clomiphene citrate during fertility treatment (including intrauterine insemination with donor sperm), is associated with increased incidences of poor neonatal outcomes.[7,8]

Results showed that there was an increased risk of low birth weight, but not a concomitant increased risk of preterm delivery. We did not conduct a meta-analysis of data for obstetric

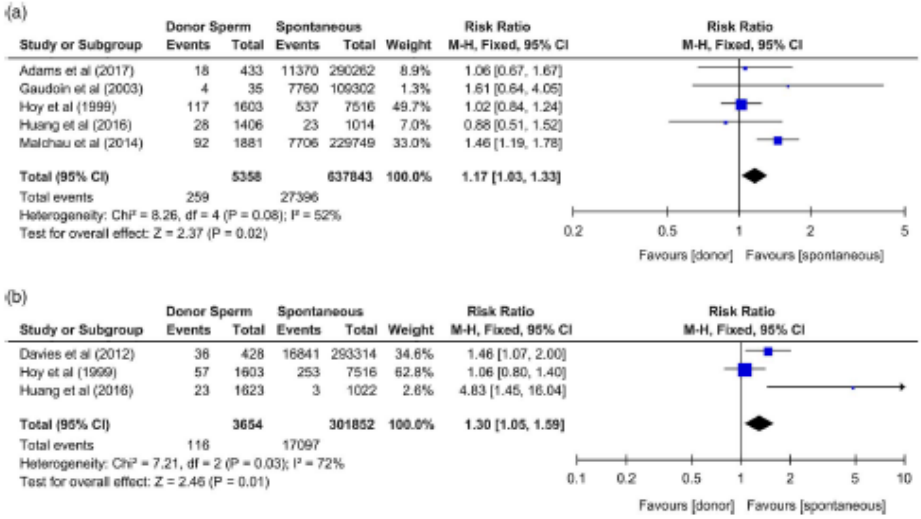

Fig. 1. Forest plots of sperm donation outcomes. (*a*) Risk ratio for being born of low birth weight (<2500 g); (*b*) risk ratio for incidences of birth defects, neonates from donor sperm offspring *v.* spontaneous conceptions. CI, confidence interval.

outcomes, only neonatal outcomes, and therefore cannot comment on any correlation with early obstetric intervention or delivery methods such as caesarean section. However, some studies did report higher incidences of caesarean section,[4,6,7] induction of labour[4,7] and forceps delivery,[4,6] in their donor sperm-conceived cohort which may have potentially been associated with those low birth weight incidences. These reported obstetric intervention increases nonetheless did not adversely affect the continuous outcome measures of mean gestational age or mean birth weight.

The addition of these three studies has improved the meta-analysis of perinatal outcomes for donor-conceived neonates in comparison to those conceived spontaneously. This updated meta-analysis has shown an increase in the risk of donor sperm-conceived neonates being born of low birth weight and with an increased risk of being born with birth defects. This increased risk presents concerns for clinicians and patients when deciding to use a sperm donor. It also shows that previous notions that donor sperm-conceived neonates are no different to their spontaneously conceived peers may have been premature. Whether such altered risk is a result of increased incidences of preeclampsia in the donor sperm cohort,[9] the use of sperm cryopreservation techniques inducing DNA damage,[10] ovarian stimulation drugs,[7,8] obstetric intervention or a combination thereof, is unclear.

Acknowledgements. D.A. is supported by an Australian Government Research Training Program Scholarship.

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Appendix 2.3 STROBE Checklist

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Appendix 2.4 South Australian Donor Sperm Conceived Perinatal Study Ethical Approval

Dear Damian,

Your ethics application was considered by the Executive of the Social and Behavioural Research Ethics Committee (SBREC) at Flinders University and was granted approval. Your ethics approval notice can be found below.

APPROVAL NOTICE (Negligible Risk)

Principal Researcher:	Mr Damian Adams
Email:	
Project Title:	Sperm Donation Perinatal Outcomes in an Australian Population Cohort

Project No.:	**7277**	Approval Date:	26 April 2016	Approval Expiry Date:	**28 February 2018**

The above proposed project fulfills the criteria for negligible risk research under chapter 2.1 (Risk and Benefit) of the *National Statement on Ethical Conduct in Human Research (March 2007)* and has been **approved** by the Executive out of session on the basis of the information contained in the application and its attachments.

RESPONSIBILITIES OF RESEARCHERS AND SUPERVISORS

1. **Participant Documentation**
   Please note that it is the responsibility of researchers and supervisors, in the case of student projects, to ensure that:

   - all participant documents are checked for spelling, grammatical, numbering and formatting errors. The Committee does not accept any responsibility for the above mentioned errors.

- the Flinders University logo is included on all participant documentation (e.g., letters of Introduction, information Sheets, consent forms, debriefing information and questionnaires – with the exception of purchased research tools) and the current Flinders University letterhead is included in the header of all letters of introduction. The Flinders University international logo/letterhead should be used and documentation should contain international dialling codes for all telephone and fax numbers listed for all research to be conducted overseas.

- the SBREC contact details, listed below, are included in the footer of all letters of introduction and information sheets.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project Number 'INSERT PROJECT No. here following approval'). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone on 8201 3116, by fax on 8201 2035 or by email human.researchethics@flinders.edu.au.

2. Annual Progress / Final Reports

In order to comply with the monitoring requirements of the *National Statement on Ethical Conduct in Human Research (March 2007)* an annual progress report must be submitted each year on the **26 April** (approval anniversary date) for the duration of the ethics approval using the report template available from the Managing Your Ethics Approval SBREC web page. *Please retain this notice for reference when completing annual progress or final reports.*If the project is completed *before* ethics approval has expired please ensure a final report is submitted immediately. If ethics approval for your project expires please submit either (1) a final report; or (2) an extension of time request and an annual report.

Student Projects

The SBREC recommends that current ethics approval is maintained until a student's thesis has been submitted, reviewed and approved. This is to protect the student in the event that reviewers recommend some changes that may include the collection of additional participant data.

Your first report is due on **26 April 2017** or on completion of the project, whichever is the earliest.

3. Modifications to Project

Modifications to the project must not proceed until approval has been obtained from the Ethics Committee. Such proposed changes / modifications include:

- change of project title;

- change to research team (e.g., additions, removals, principal researcher or supervisor change);

- changes to research objectives;

- changes to research protocol;

- changes to participant recruitment methods;

- changes / additions to source(s) of participants;

- changes of procedures used to seek informed consent;

- changes to reimbursements provided to participants;

- changes / additions to information and/or documentation to be provided to potential participants;

- changes to research tools (e.g., questionnaire, interview questions, focus group questions);

- extensions of time.

To notify the Committee of any proposed modifications to the project please submit a Modification Request Form available from the Managing Your Ethics Approval SBREC web page. Download the form from the website every time a new modification request is submitted to ensure that the most recent form is used. Please note that extension of time requests should be submitted prior to the Ethics Approval Expiry Date listed on this notice.

Change of Contact Details

Please ensure that you notify the Committee if either your mailing or email address changes to ensure that correspondence relating to this project can be sent to you. A modification request is not required to change your contact details.

4. Adverse Events and/or Complaints

Researchers should advise the Executive Officer of the Ethics Committee on 08 8201-3116 or human.researchethics@flinders.edu.au immediately if:

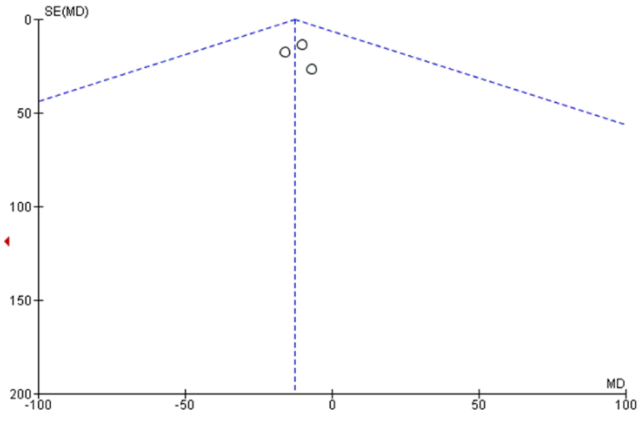
- any complaints regarding the research are received;

- a serious or unexpected adverse event occurs that effects participants;

- an unforseen event occurs that may affect the ethical acceptability of the project.

Kind regards
Andrea

Appendix 2.5 Funnel Plots of Updated Donor Sperm Meta-Analysis



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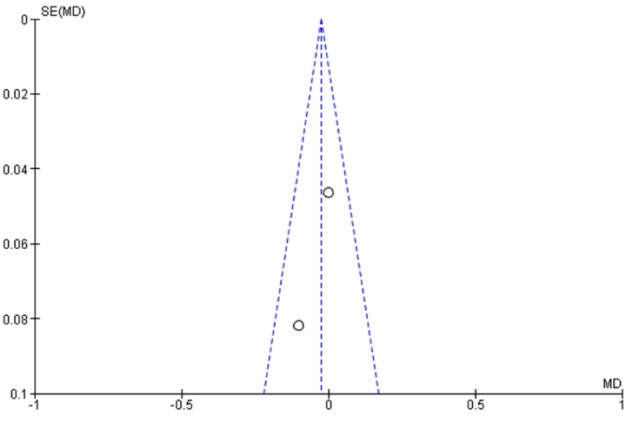

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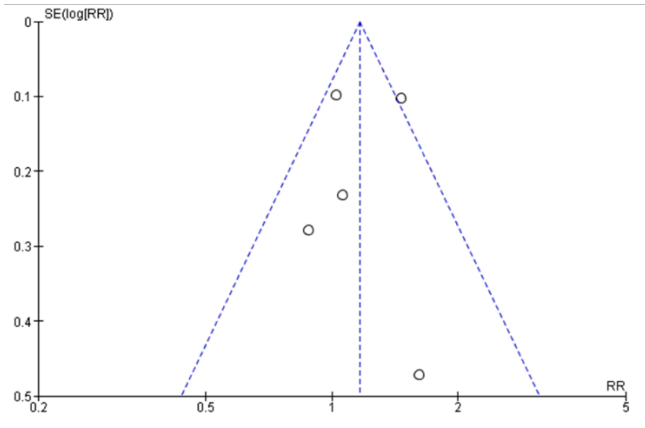

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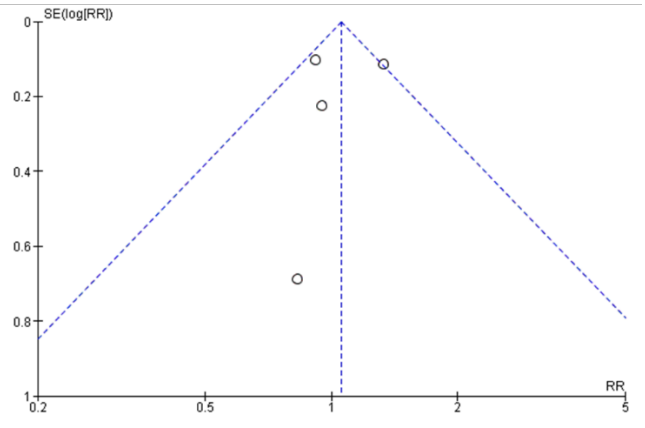

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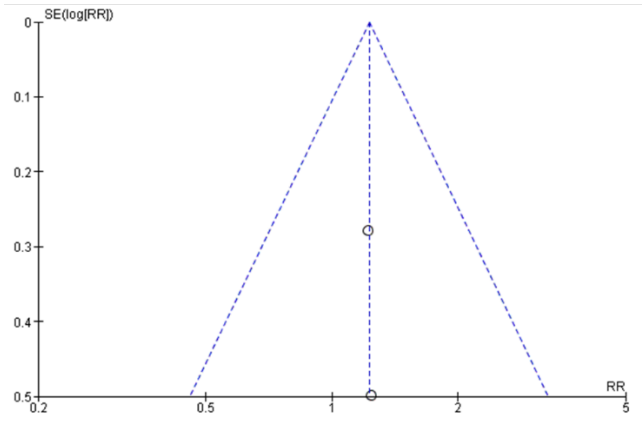
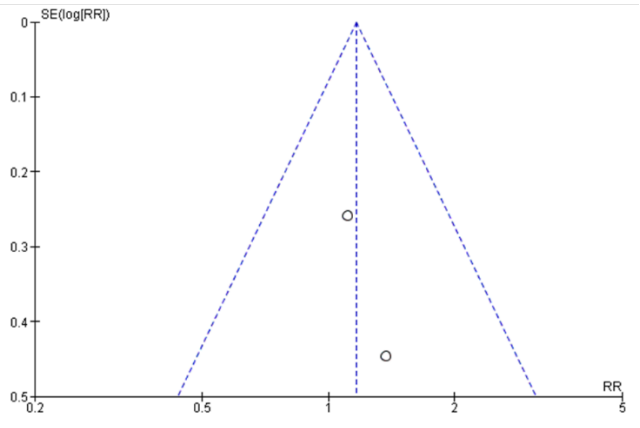


VLBW



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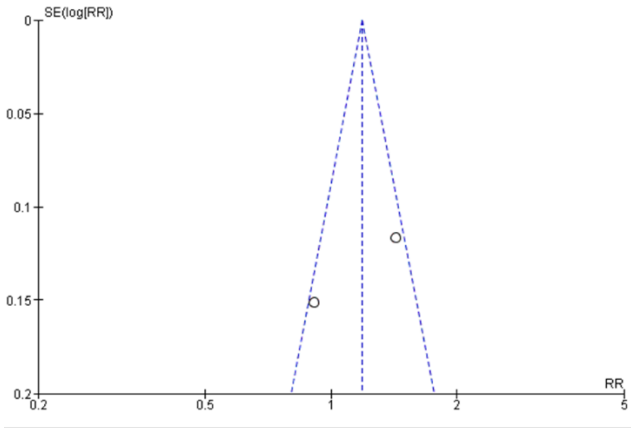

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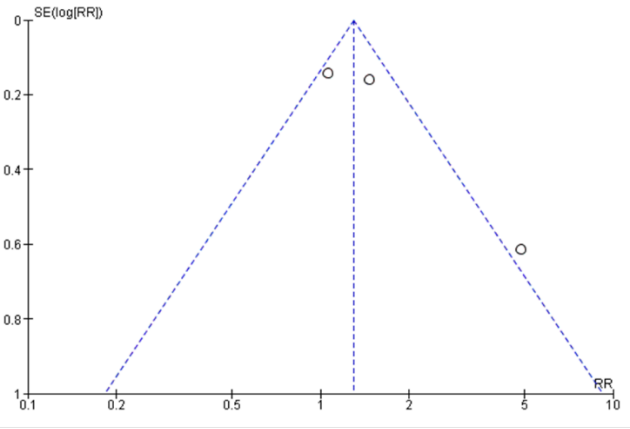

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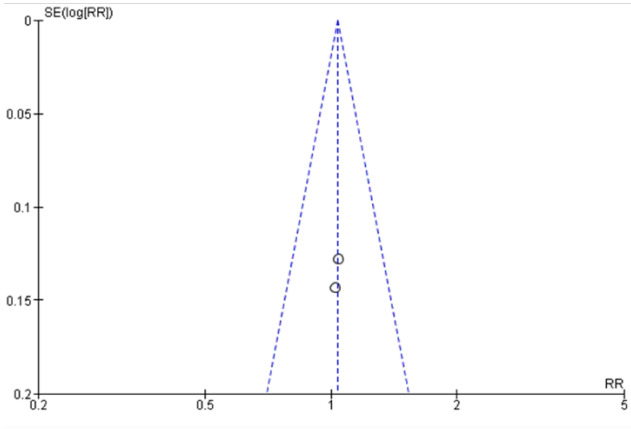

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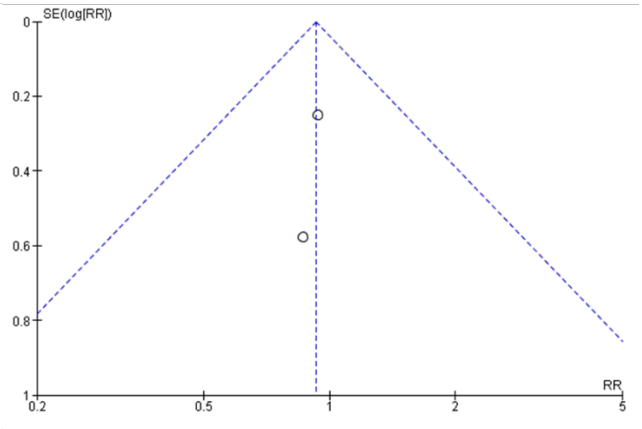
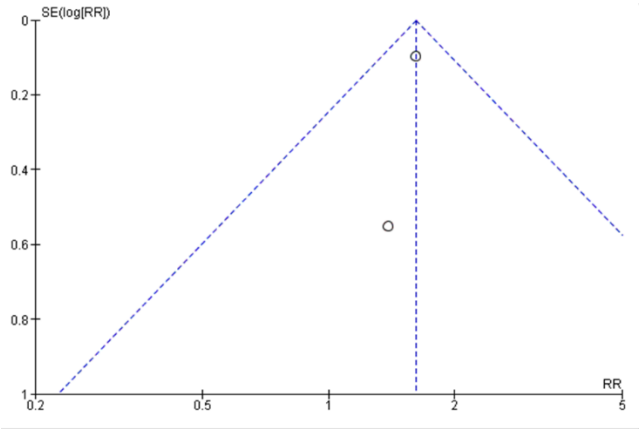


Perinatal mortality



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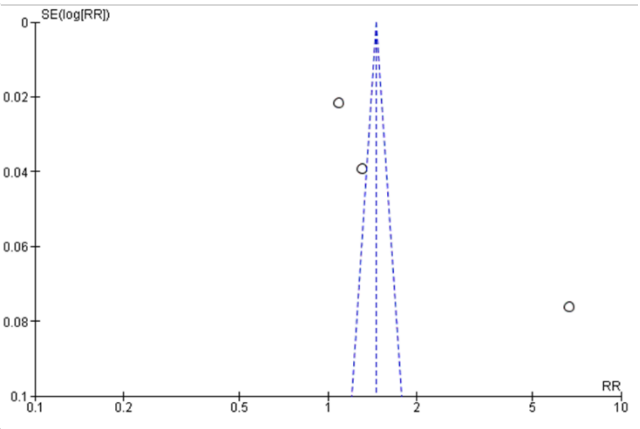
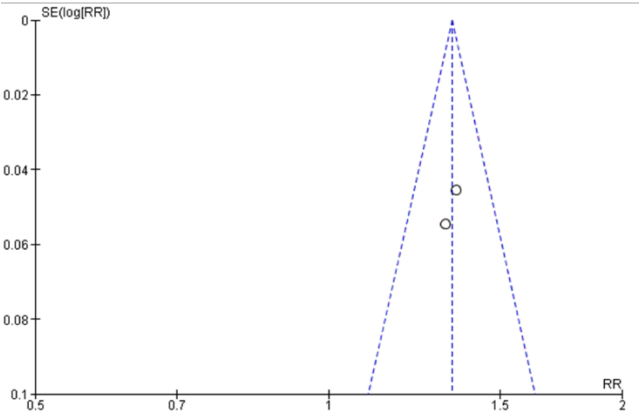
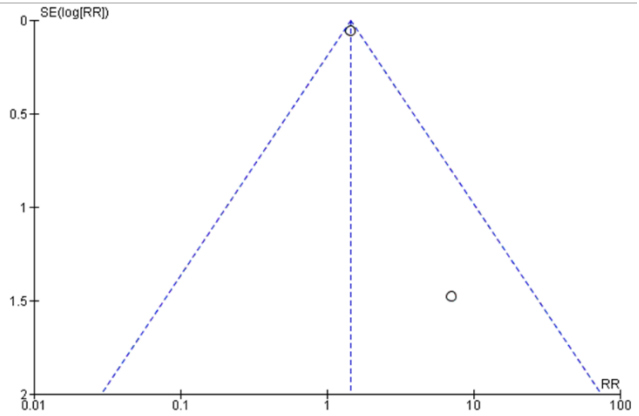


Caesarean section



Induction of labour



Forceps delivery

Appendix 3 Additional Information Relating to the Adult Health Survey

Appendix 3.1 Publication: Self-Reported Physical Health Status of Donor Sperm-Conceived Adults

See next page

Damian H Adams, Adam Gerace, Michael J Davies, Sheryl de Lacey. Self-reported physical health status of donor sperm-conceived adults. J Dev Orig Health Dis. 2020 Aug 28;1-14. doi: 10.1017/S204017442000080X. Online ahead of print.

Journal of Developmental Origins of Health and Disease

www.cambridge.org/doh

Original Article

Cite this article: Adams Damian H., Gerace Adam, Davies Michael J., and de Lacey Sheryl. Self-reported physical health status of donor sperm-conceived adults. *Journal of Developmental Origins of Health and Disease* doi: 10.1017/S204017442000080X

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Keywords:
Donor conception; health survey; online; outcome; self-reported

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CAMBRIDGE UNIVERSITY PRESS

Self-reported physical health status of donor sperm-conceived adults

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Abstract

Donor-conceived neonates have poorer birth outcomes, including low birth weight and preterm delivery that are associated with poorer long-term health in adulthood through the developmental origins of health and disease (DOHaD) theory. The aim of this study was to conduct the first investigation of the adult health outcomes of donor-conceived people. An online health survey was completed by 272 donor sperm-conceived adults and 877 spontaneously conceived adults from around the world. Donor and spontaneously conceived groups were matched for age, sex, height, smoking, alcohol consumption, exercise, own fertility and maternal smoking. Donor sperm-conceived adults had significantly higher reports of being diagnosed with type 1 diabetes ($P = 0.031$), thyroid disease ($P = 0.031$), acute bronchitis ($P = 0.008$), environmental allergies ($P = 0.046$), sleep apnoea ($P = 0.037$) and having ear tubes/grommets surgically implanted ($P = 0.046$). This is the first study to investigate the health outcomes of adult donor sperm-conceived people. Donor sperm-conceived adults self-reported elevated frequencies of various health conditions. The outcomes are consistent with birth defect data from donor sperm treatment and are consistent with the DOHaD linking perturbed early growth and chronic disease in adulthood.

Introduction

There is increasing interest and concern regarding the health of people conceived by assisted reproductive technologies. Studies have shown that in vitro fertilisation (IVF) singleton neonates are statistically more likely to suffer a range of adverse perinatal outcomes compared to spontaneously conceived neonates, including low birth weight (LBW = < 2500 g), very LBW (VLBW = < 1500 g), small for gestational age (SGA = < 10th percentile for weight), preterm delivery (PD = < 37 weeks), very PD (VPD = < 32 weeks), and have higher incidences of congenital abnormalities (including heart defects) and perinatal mortality.[1–8] The developmental origins of health and disease (DOHaD) theory[9] posits that poor perinatal outcomes of PD, LBW and SGA are associated with poorer health outcomes in adulthood.[10–14] Subsequently, the increased incidences of poor perinatal outcomes have become a cause for concern for the long-term health of people conceived with IVF and other assisted reproductive technologies.[15–19]

A subset IVF treatment modality, donated oocytes, has been shown in systematic reviews to be associated with LBW, VLBW, PD, SGA and of lower gestational age, when compared to neonates conceived with autologous oocytes.[20–24] While oocyte donation, perinatal outcomes appear from those reviews to be conclusively poorer than their autologous oocyte IVF counterparts, the perinatal outcomes from sperm donation are less clear with very few systematic reviews or meta-analysis investigating these outcomes. One recent meta-analysis showed that sperm donation neonates were significantly more likely to be born of LBW and with more birth defects than those conceived spontaneously.[25] However, an earlier review (non-systematic and without meta-analysis) suggested that the perinatal outcomes were comparable to those spontaneously conceived.[26] Uncertainty remains due to the lack of systematic reviews and meta-analysis, as well as the low number of studies that met the inclusion criteria and were then able to be included in the meta-analysis of donor sperm perinatal outcomes.[25] The long-term health of donor-conceived people continues to be of concern and therefore warrants further investigation.

Only one oocyte donation systematic review investigated longitudinal physical health outcomes into childhood or adulthood in addition to perinatal outcomes; however, the included studies only reported perinatal outcomes, not longitudinal outcomes.[24] The sperm donation systematic review found three studies investigating outcomes into childhood and no studies investigating adulthood outcomes.[27] Since the sperm donation review, another study that investigated the health outcomes for school-aged children conceived with donor sperm found that the healthcare outcomes did not differ from spontaneously conceived children except for a small

healthcare needs increase.[28] To date, there are still no studies investigating adulthood outcomes. Consequently, donor-conceived adults represent a population that has not been studied in terms of their physical health outcomes.

This paper presents the first study investigating the self-reported health outcomes of donor sperm-conceived adults compared to spontaneously conceived adults to determine if mode of conception has affected their long-term health through the DOHaD phenomenon. Furthermore, this study focuses only on the physical health outcomes reported in the survey, while mental health outcomes will be presented in a subsequent publication.

Methods

Participants

Adults (individuals aged 18 years and over) who were either donor conceived or spontaneously conceived from around the world and who could understand English and had access to the internet were eligible to participate.

Problematically, low disclosure rates from parents to the donor conceived, described hereafter, make the recruitment of subjects for an unbiased analysis of their health in a laboratory/clinic difficult. While donor conception practice has seen more openness and an increasing disclosure rate (informing the child of their mode of conception), a 2016 systematic review found that most donor-conceived children are still not aware of their donor conception status.[29] More recent data still show that most parents are not disclosing to children,[30] except for solo mothers by choice.[31] Furthermore, there is a dearth of data on disclosure rates amongst adult donor-conceived people. Nonetheless, a small study from Australia found that only 11% were aware of their donor conception status.[32] While recruitment of a true cross section of the donor-conceived community is not possible, opportunities exist to recruit donor-conceived participants through internet groups of self-identified donor-conceived people. These groups are typically in the form of support and networking groups that use social media platforms and are subsequently recruited through those platforms. In the absence of population sampling frames, innovative use of these platforms provides early, and potentially valuable data, for future investigation.

Respondents were recruited from a variety of sources. Donor-conceived adults were primarily recruited through advertisements placed on social media. Specifically, groups that only contained donor-conceived people were targeted on Facebook (Worldwide Donor Conceived People Network; We Are Donor Conceived; RUDC), and email lists (PCVAI – People Conceived Via Artificial Insemination); while groups that contained donor-conceived people as well as other people such as recipient parents and donors were also targeted on Facebook [Donor Conceived Offspring, Siblings, Parents (sperm or egg); DNA for the Donor Conceived; TangledWebs]. Advertisements were placed on behalf of the researchers by group administrators. Organisations involved in donor conception placed the survey advertisement on their websites, newsletters and social media pages (VARTA – Victorian Assisted Reproductive Treatment Authority; Donor Children online registry; Donor Conception Network – United Kingdom; Donor Conception Support Group – Australia; FIOM – Netherlands; VANISH – Victorian Adoption Network for Information and Self Help). The advertisement was also placed on the Flinders University Facebook page, as well as the Flinders University research studies webpage (https://www.flinders.edu.au/research/research-study). Finally, respondents were also recruited via the survey recruitment website Prolific (https://prolific.ac/).

The advertisement requested that respondents pass on the survey link to others they knew who may be interested in completing the questionnaire (snowball sampling); and specifically, in the case of donor-conceived participants, that, if possible, they forward on the survey to a spontaneously conceived adult who was similar in age and location.

Measures

The questionnaire was completed anonymously on the SurveyMonkey website and was live for four months between the start of December 2017 and the end of March 2018. Questions were developed based on known DOHaD adult health outcomes associated with the perinatal outcomes of donor conception,[21–25] as well as other questions developed by the authors using their experience to cover a wide range of physical and mental health outcomes. The questions covered the following categories: demographics, information regarding birth (such as whether participants were donor conceived), general health [including outcomes such as body mass index (BMI), exercise levels and alcohol usage], cardiovascular, chromosomal and genetic, dermatological, EENT (ears/eyes/nose/throat), endocrinological, gastrointestinal, immunological, musculoskeletal, neurological, oncological, reproductive, respiratory, urogenital and mental health questions (mental health outcomes are described in the companion article). Only questions concerning the respondents' age, sex, birth status (donor or spontaneously conceived) and whether they had received fertility treatment themselves were compulsory. All other questions were voluntary. Health outcomes that were not continuous variables (e.g., weight, height, age, etc.) or descriptive (e.g., free text input),were binary and required a 'yes' or 'no' response. Participants were asked to only report 'yes' to health conditions for which they had been diagnosed by a health professional such as a general practitioner or specialist. Those unsure were advised to answer 'no'. For each health outcome category listed above, respondents were given the option of responding in a free text box to describe any other condition or illness that they may have been diagnosed with to cover conditions or illnesses that may have been inadvertently omitted.

Statistical analyses

While all donor-conceived people regardless of the treatment modality used in their conception, whether they were conceived with donor sperm, oocyte, embryo or surrogacy using donated gametes were able to participate in the survey, this was restricted to the analysis of donor sperm outcomes in comparison to those conceived spontaneously due to the low sample size of each of the other groups. Statistical analysis was conducted using SPSS V25. (IBM Corporation, New York, USA). All analysis was comparisons between the donor sperm-conceived group and those spontaneously conceived. Further stratification of the cohorts was performed to analyse the effect of sex, maternal complications and country of birth (Australia), on outcomes. Australia was implemented as a country of birth stratification as Australians represented the largest cohort in both donor sperm and spontaneously conceived individuals. Continuous variables were summarised using mean values and standard deviation, and then subjected to two-tailed, Student's *t*-test to determine significance. Binomial outcomes are presented with the number of 'yes' responses as a function and percentage of the total number of

responses received for each question and are analysed using two-tailed Pearson's chi-squared analysis. When cross tabulation resulted in > 20% of cells having an expected count less than 5 in a 2 × 2 table, two-tailed Fisher's exact test was used to test significance, and for cross tabulation larger than 2 × 2, likelihood ratios were implemented. If free text input outcomes had 20 responses or greater for the donor-conceived adults, then these outcomes were subjected to quantitative content analysis. The free text responses were coded and grouped into categories according to themes. These were then combined where appropriate to reduce the groups down to three or four main categories which were then subjected to a right-tailed chi-squared distribution analysis.

In large health studies that implement multiple comparisons, it is inevitable that some analysis will be statistically significant ($P < 0.05$), due to sampling variability. To correct for false positives associated with multiple comparisons, the Benjamini–Hochberg procedure was implemented on the health outcome responses using a false discovery rate at alpha 0.05 level.[33] The Benjamini–Hochberg procedure has been used widely as a false discovery rate adjustment when analysing multiple comparisons.[34] False discovery rate has been recommended in the literature over other commonly used multiple comparison controls such as the Bonferroni adjustment for health studies.[35] Quantitative content analysis data were not subjected to Benjamini–Hochberg correction as these results were grouped by the authors post hoc rather than a specific question that the respondents answered. Results were deemed to be significant if $P < 0.05$.

The spontaneously conceived group provides the basis for comparison to those who were conceived with donated sperm. Subsequently, it was important to verify how representative of the general population this group was in terms of condition frequencies. The spontaneously conceived group was stratified and restricted to Australia for country of birth as they represented the largest cohort of spontaneously conceived adults. These were compared to comparable data obtained from the Australian Bureau of Statistics, National Health Survey (ABS NHS), dated 2017–2018 as this corresponds to the date of our survey. Furthermore, as the worldwide spontaneous group contains a wide variety of cultures and ethnicities, the worldwide spontaneous group was also compared to comparable data from the Centres for Disease Control and Prevention, National Health and Nutrition Examination Survey (CDC NHANES), from the same period (2017–2018).

Results

The final sample consisted of 1149 respondents. By mode of conception, the number of respondents was as follows: spontaneous ($n = 877$) and donor sperm conceived ($n = 272$).

The average time spent completing the questionnaire was 10 min, 17 s, with a completion rate of 78%. Response rates cannot be calculated as the number of people viewing the advertisement is unknown, nor is the number of donor-conceived people worldwide known.

Characteristics of respondents

The characteristics of the two respondent groups are shown in Table 1. No significant differences were observed between the donor sperm-conceived group and those conceived spontaneously in terms of mean age (years), sex (female/male/other as designated by the respondent), mean height, current smoking status, alcohol consumption, amount and level of exercise per week [both low/moderate (example was walking), and high/strenuous (example was running)] and whether they had received fertility treatment themselves. However, donor sperm adults had a lower current mean weight ($P = 0.035$) and lower BMI ($P = 0.023$). Furthermore, donor sperm-conceived adults had significant differences in educational outcomes with higher levels of education ($P < 0.001$), more specifically post-graduate degrees, than spontaneously conceived adults. Donor sperm adults reported lower incidences of being a former smoker (sperm $P = 0.032$) and were more likely to be currently using prescribed medications ($P = 0.002$) and be using recreational/illicit drugs ($P = 0.047$).

In terms of their birth and gestational characteristics, donor sperm-conceived adults reported significantly higher incidences of being born as a twin ($P = 0.004$), and whose mothers had higher incidences of maternal complications ($P = 0.001$). However, no significant differences were reported in the incidences of maternal smoking during pregnancy.

The top five countries of birth and countries of current residence by the number of respondents are shown in Table 2. All other countries had $N < 10$ for country of birth or residence (Supplementary Table S1). There is considerable variation in percentage of respondents between spontaneous and donor sperm-conceived groups in both countries of birth and residence for those countries represented with larger numbers of respondents (Australia, Belgium, the Netherlands, the United Kingdom and the United States of America). Australia and the United Kingdom had higher proportions of spontaneously conceived respondents than donor sperm-conceived respondents, while Belgium, the Netherlands and the United States of America had higher proportions of donor sperm-conceived respondents than those spontaneously conceived.

Cardiovascular outcomes

Donor sperm-conceived adults did not report any significantly different incidences of diagnosed cardiovascular outcomes of congenital heart disease, cardiovascular disease (including heart attack, stroke, angina, cardiomyopathy, cerebrovascular disease, arteriosclerosis, atherosclerosis, rheumatic heart disease, peripheral arterial disease, aneurysm and deep vein thrombosis), bleeding disorders (such as haemophilia), heart murmur, palpitations, high blood pressure [over 140/90, either or both reading(s) could be higher], low blood pressure [below 90/60, either or both reading(s) could be lower], anaemia, poor peripheral circulation [leading to white/blue fingers and or toes (such as Raynaud's syndrome)], high cholesterol, aneurysms, phlebitis, varicose veins, heart defects requiring surgery or other conditions as reported by the respondent when compared to spontaneously conceived adults (Supplementary Table S2).

Chromosomal and genetic outcomes

No significant differences were observed between the self-reported incidences of chromosomal or genetic abnormalities of the donor sperm-conceived group and their spontaneously conceived peers (Supplementary Table S3).

Dermatological outcomes

Donor sperm-conceived adults did not report significant differences in the incidences of the diagnosed skin conditions of eczema, psoriasis, urticaria (hives) or other conditions not covered

Table 1. Characteristics of respondents

	Spontaneous	Donor sperm conceived	
	N Total [877]	*N* Total [272]	*P*
Age, mean (SD)	33.2 (12.5)	32.6 (10.3)	0.395
Sex, %			
Female	80.8	86.0	0.074*
Male	18.8	14.0	
Other	0.3	0	
Multiplicity of own birth, %			
Singleton	98.5	95.2	**0.004***
Twin	1.0	4.4	
Multiple (3 or more)	0.5	0.4	
Mother had maternal complications, %			
Yes	12.6	17.3	**0.001#**
No	75.0	63.1	
Do not know	12.4	19.6	
Mother smoked during pregnancy, %			
Yes	16.0	15.1	0.598#
No	79.0	81.2	
Do not know	5.0	3.7	
Highest level of education attained, %			
Less than high school	2.5	2.6	**< 0.001#**
High school degree or equivalent	27.1	16.5	
Vocational qualifications	11.4	8.1	
University/college undergraduate degree	39.0	41.2	
University/college postgraduate degree	20	31.6	
Height, mean cm (SD)	168.8 (9.2)	169.0 (9.3)	0.724
Weight, mean kg (SD)	74.7 (18.6)	72.0 (17.4)	**0.035**
BMI, mean (SD)	26.2 (6.4)	25.2 (6.0)	**0.023**
Currently smoke, %	7.9	9.4	0.455
Former smoker, %	30.0	22.9	**0.032**
Alcoholic drinks consumed per week			
0–1	62.7	60.3	0.758#
2–4	20.8	23.7	
4–10	13.0	12.1	
10+	3.5	3.9	
Low/moderate exercise per week, mean (SD)	4.7 (5.0)	4.9 (4.3)	0.720
High/strenuous exercise per week, mean (SD)	1.4 (1.9)	1.3 (1.6)	0.546
Prescribed medications, %	39.1	49.8	**0.002**
Recreational/illicit drugs, %	6.8	10.5	**0.047**
Fertility treatment themselves, %	6.7	3.9	0.094

[ ], total respondents.
P value using Students two tailed TTEST versus spontaneously conceived unless specified by alternative test below.
#Pearson's chi-squared (two-tailed) *P* value versus spontaneously conceived. Chi-squared results are based on total chi-squared table results of all outcomes and not individual outcome groupings (i.e., all of the all donor conceived outcomes versus all spontaneously conceived outcomes).
*Likelihood ratio *P* value versus spontaneously conceived people used instead of Fisher's exact test for when > 20% of cells in chi-squared table have expected values less than 5 in tables larger than 2 × 2.
Note, percentages may not equal 100% due to rounding.

by those classifications in comparison to spontaneously conceived adults (Supplementary Table S4). However, as the 'other' category had greater than 20 respondents for the donor sperm-conceived group, the free text inputs were subjected to quantitative content analysis using the following four categories: acne, colouring, infections and ungrouped conditions. Acne included other conditions such as hormonal cysts, hidradenitis suppurativa and eccrine hidrocystoma. Colouring included conditions that change the colour of the skin such as rosacea, dermatitis, pityriasis rosea, Henoch–Schonlein purpura and vitiligo. Infections included conditions involving bacterial, viral or fungal infections of the skin such as impetigo, cellulitis, shingles and tinea versicolour.

Table 2. Country of birth and residency (top 5 countries by number of participants)

	Spontaneous				Donor sperm conceived			
	Birth, N	Birth, %	Residence, N	Residence, %	Birth, N	Birth, %	Residence, N	Residence, %
Australia	372	46.3	490	55.9	78	30.7	85	31.3
Belgium	23	2.9	21	2.4	16	6.3	19	7.0
The Netherlands	89	11.1	70	8.0	57	22.4	59	21.7
The United Kingdom	190	23.7	186	21.2	16	6.3	17	6.3
The United States of America	86	10.7	90	10.3	77	30.3	84	30.9

Descriptive table of countries of birth and current residence.

Table 3. Significant physical health outcomes

	Spontaneous		Donor sperm conceived			
	N (Total)	%	*N* (Total)	%	*P*	BH *P*
Type 1 diabetes	3 (842)	0.4	7 (253)	2.8	0.002^	**0.031**
Acute bronchitis	111 (844)	13.2	57 (254)	22.4	< 0.001	**0.008**
Thyroid disease	33 (840)	3.9	22 (253)	8.7	0.002	**0.031**
Sleep apnoea	23 (843)	2.7	17 (252)	6.7	0.003	**0.037**
Ear tubes/grommets	51 (830)	6.1	28 (247)	11.3	0.006	**0.046**
Allergic to anything	297 (826)	36.0	113 (248)	45.6	0.006	**0.046**

Pearson's chi-squared (two-tailed) *P* value versus spontaneously conceived people.
BH, Benjamini-Hochberg procedure adjusted *P* value versus spontaneously conceived people.
^Fisher's exact test (two-tailed) *P* value versus spontaneously conceived people used instead of Pearson's chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Ungrouped conditions included all other responses that could not be grouped into the previous three categories. Quantitative content analysis revealed no differences between sperm donor conceived to those conceived spontaneously on any of the skin conditions.

EENT outcomes

Donor sperm-conceived adults, when compared to those conceived spontaneously, reported significantly higher incidences of having ear tubes/grommets surgically implanted (11.3% v 6.1%, $P = 0.046$) (Table 3). However, they did not report significant differences in terms of being diagnosed with eye disorders, hearing loss, total deafness, nasal allergies/hay fever, tinnitus, Meniere's disease or other non-classified conditions. Furthermore, they also did not report significant differences in having corrective glasses/lenses, eye surgery or their tonsils or adenoids surgically removed (Supplementary Table S5).

Endocrinological outcomes

The donor sperm-conceived group when compared to those conceived spontaneously reported significantly higher incidences of type 1 diabetes (2.8% v 0.4%, $P = 0.031$) and thyroid disease diagnoses (8.7% v 3.9%, $P = 0.031$) (Table 3). No significant differences were observed for the reported diagnoses of type 2 diabetes, pancreatitis, adrenal disorders, pituitary disorders or other non-classified disorders (Supplementary Table S6).

Gastrointestinal outcomes

Donor sperm-conceived adults did not report significant differences in the incidences of being diagnosed with liver disease, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), ulcers, coeliac disease, appendicitis, gall bladder problems, gastro-esophageal reflux disease or other non-classified disorders in comparison to spontaneously conceived adults (Supplementary Table S7).

Immunological outcomes

There was a significant increase in the reported incidence of being allergic to anything (45.6% v 36.0%, $P = 0.046$), for donor sperm-conceived adults in comparison to spontaneously conceived adults (Table 3). Respondents were able to input text on specific allergies. These responses were categorised into four categories for quantitative content analysis: environmental allergies, ingested allergies, medication allergies and ungrouped allergies. Environmental allergies included contact allergies such as animals, plants, pollen, cosmetics, mould and latex. Ingested allergies included food type allergies (medication excluded). Medication allergies incorporated all types of medications such as antibiotics (can be ingested, topical or intravenous). Ungrouped allergies were all other allergies not covered by the above categories such as insect bites and stings. Donor sperm-conceived adults were significantly more likely to be allergic to environmental allergens (29.4% v 16.7%, $P < 0.001$), but not to ingested, medication or ungrouped allergens (Supplementary Table S8). There were no significant differences observed between groups for the diagnosed immunological outcomes of arthritis, rheumatoid arthritis, spleen problems, gout, lupus, ankylosing spondylitis, connective tissue disorders, chronic infectious disease or other non-classified immunological disorders (Supplementary Table S8).

Musculoskeletal outcomes

The donor sperm-conceived group did not report significant differences for the diagnosed musculoskeletal outcomes of joint problems, osteoporosis, scoliosis, growth disorder, muscular dystrophy or other non-classified musculoskeletal disorders when compared to those spontaneously conceived (Supplementary Table S9).

Neurological outcomes

No significant differences were observed between the self-reported incidences of the diagnosed neurological outcomes of epilepsy/seizures, tremors, migraines, multiple sclerosis, vertigo, cerebral palsy, fibromyalgia, Parkinson's disease or other non-classified neurological outcomes of the donor sperm-conceived group and those spontaneously conceived (Supplementary Table S10).

Oncological outcomes

Donor sperm-conceived adults were not statistically more or less likely than those conceived spontaneously to have had various forms of cancer. They reported no differences in terms of diagnosed blood, skin, bowel, breast (female only and all sexes combined), prostate (males only), bone, brain, lung/tracheal, pancreatic or other malignancies (Supplementary Table S11).

Reproductive outcomes

Female donor sperm-conceived adults in comparison to females conceived spontaneously did not report significant differences in the diagnosed incidences of ovarian cysts, endometriosis, menstrual problems, polycystic ovary syndrome, infertility or other non-classified reproductive disorders. They also reported no significant difference in pregnancy rates and parity (Supplementary Table S12).

Male donor sperm-conceived adults in comparison to males conceived spontaneously also reported no significant differences in their reproductive outcomes of testicular problems, prostate problems, low sperm count/quality, infertility or other non-classified reproductive disorders (Supplementary Table S13).

Respiratory outcomes

The donor sperm-conceived groups in comparison to spontaneously conceived adults were significantly more likely to report incidences of acute bronchitis (22.4% v 13.2%, $P = 0.008$) and sleep apnoea (6.7% v 2.7%, $P = 0.037$) (Table 3). There were no significant differences observed between the donor-conceived groups and spontaneously conceived adults for the outcomes of asthma, chronic obstructive pulmonary disease (COPD), pneumonia or other non-classified respiratory disorders (Supplementary Table S14).

Urogenital outcomes

Donor sperm-conceived adults were not statistically more or less likely than those conceived spontaneously to report incidences of diagnosed kidney disease, kidney stones, bladder disease, urogenital defects or other non-classified urogenital disorders (Supplementary Table S15).

Effect of sex

With both cohorts having a greater than 80% proportion of females in the sample, the rates of reported diagnoses were analysed by sex to determine if there were significant differences between the sexes. Females and males in both donor sperm and spontaneously conceived groups were well matched in terms of mean age, multiplicity, maternal complications, maternal smoking, education levels and smoking (both currently and formerly) (Supplementary Table S16). Males were significantly heavier ($P < 0.001$), and taller ($P < 0.001$), than their female counterparts, as is typical for male versus female populations. However, no significant difference was observed in their BMI. Both donor sperm and spontaneously conceived males were more likely to report higher levels of alcohol consumption (sperm $P = 0.016$; spontaneous $P < 0.001$), but lower levels of prescribed medication use (sperm $P = 0.001$; spontaneous $P < 0.001$). Spontaneously conceived males, but not donor sperm-conceived males, reported higher amounts of exercise (low/moderate $P = 0.009$; high/strenuous $P = 0.012$), recreational/illicit drug use ($P = 0.013$) and lower incidences of receiving fertility treatment themselves ($P = 0.001$) than their spontaneously conceived female counterparts.

In terms of the physical health outcomes, spontaneously conceived males reported significantly reduced incidences of being diagnosed with low blood pressure ($P = 0.002$), anaemia ($P < 0.001$), varicose veins ($P = 0.001$), urticaria ($P = 0.001$), nasal allergies/hay fever ($P = 0.001$), tonsillectomy ($P = 0.019$), irritable bowel syndrome (IBS) ($P = 0.007$), gall bladder problems ($P = 0.038$), migraines ($P = 0.001$), asthma ($P = 0.003$), acute bronchitis ($P = 0.007$) and pneumonia ($P = 0.041$) than spontaneously conceived females (Table 4). Both donor sperm and spontaneously conceived males reported lower diagnoses than females in terms of being allergic to anything (sperm $P < 0.001$; spontaneous $P = 0.004$); however, content analysis of type of allergy showed only spontaneously conceived males reported a significantly reduced diagnosis of medication allergies ($P < 0.001$) (data not shown). Donor sperm-conceived females were also significantly more likely to report having corrective glasses/lenses ($P = 0.005$) than male donor sperm-conceived adults.

Effect of maternal complications

Maternal complications are a well-known confounder of neonatal outcomes and have been linked to long-term health trajectories. Subsequently, it was pertinent to stratify data based on maternal complications to determine if these had an effect on health outcomes in the cohorts. Those respondents who reported that they did not know if their mother experienced maternal complications were excluded from the analysis. In terms of respondent characteristics, mean age was lower in both cohorts for those respondents whose mother experienced maternal complications (sperm $P = 0.020$; spontaneous $P < 0.001$) than those whose mother did not experience maternal complications (Supplementary Table S17). Donor sperm-conceived adults whose mother had maternal complications were more likely to be a former smoker ($P = 0.017$), while spontaneously conceived adults whose mother experienced maternal complications were more likely to be female ($P < 0.003$), and to be shorter in mean height ($P < 0.001$). All other respondent characteristics were not statistically different.

Spontaneously conceived adults whose mother experienced maternal complications were significantly more likely than those whose mother did not experience maternal complications to report being diagnosed with eczema ($P < 0.001$), psoriasis ($P = 0.019$),

Table 4. Significant physical health outcomes by sex

	Female		Male			
	N (Total)	%	*N* (Total)	%	*P*	BH *P*
Spontaneous						
Low blood pressure	114 (660)	17.3	9 (159)	5.7	< 0.001	**0.002**
Anaemia	219 (660)	33.2	8 (160)	5.0	< 0.001	**< 0.001**
Varicose veins	61 (660)	9.2	1 (160)	0.6	< 0.001	**0.001**
Urticaria	73 (669)	10.9	2 (160)	1.3	< 0.001	**0.001**
Nasal allergies/hay fever	285 (671)	42.5	41 (159)	25.8	< 0.001	**0.001**
Tonsillectomy	119 (670)	17.8	13 (158)	8.2	0.003	**0.019**
IBS	100 (679)	14.7	8 (161)	5.0	0.001	**0.007**
Gall bladder	45 (678)	6.6	2 (161)	1.2	0.007	**0.038**
Allergic to anything	258 (665)	38.8	38 (159)	23.9	< 0.001	**0.004**
Migraines	207 (675)	30.7	24 (159)	15.1	< 0.001	**0.001**
Asthma	190 (680)	27.9	23 (160)	14.4	< 0.001	**0.003**
Acute bronchitis	103 (680)	15.1	8 (162)	4.9	0.001	**0.007**
Pneumonia	88 (675)	13.0	9 (161)	5.6	0.008	**0.041**
Donor sperm conceived						
Corrective glasses/lenses	137 (216)	63.4	9 (33)	27.3	< 0.001	**0.005**
Allergic to anything	99 (214)	46.3	0 (34)	0	< 0.001	**< 0.001**

Pearson's chi-squared (two-tailed) *P* value females versus males.
BH, Benjamini–Hochberg procedure adjusted *P* value females versus males.

nasal allergies/hay fever ($P = 0.019$), migraines ($P < 0.001$), blood cancers ($P = 0.026$) and acute bronchitis ($P = 0.011$) (Table 5). While female spontaneously conceived adults resulting from a pregnancy involving maternal complications were more likely to report being diagnosed with menstrual problems ($P = 0.004$) but were less likely to have been pregnant themselves ($P = 0.033$). No significant differences were observed in the donor sperm-conceived cohort.

Effect of country of birth

The criteria for diagnosis of various health conditions and the ability to access medical health care can vary between countries. Restricting outcomes to a subset of respondents based on their country of birth allows us to determine whether there is bias in the comparison cohort and whether there is an effect on outcomes based on country of birth. The largest proportions of spontaneously conceived adults were born in Australia (42.4%) as well as the largest proportion of donor sperm conceived (28.6%) and therefore Australians were used for analysis.

Donor sperm-conceived Australians differed significantly from their spontaneously conceived compatriots in terms of having a lower mean age ($P < 0.001$) and whose mother had experienced maternal complications ($P = 0.002$) (Supplementary Table S18). They were, however, not significantly different in all other characteristics. Furthermore, Australian donor sperm-conceived adults were statistically not different to Australian spontaneously conceived adults for all physical health outcomes surveyed (data not shown).

Validation of comparison group

Frequencies of comparable reference data, ABS NHS and CDC NHANES, against spontaneously conceived Australian and worldwide cohorts respectively are shown in Table 6. Australian born spontaneously conceived adults represent 42.4% of all spontaneously conceived respondents and were largely representative in terms of frequencies of conditions to the whole worldwide spontaneously conceived frequencies with exceptions of low blood pressure, eczema and nasal allergies/hay fever.

Comparison of condition frequencies included those who were comparable, but also that in numerous instances, the survey respondents had either lower or higher frequencies than those of the reference data. Worldwide spontaneously conceived respondents reported lower frequencies of currently smoking and taking prescribed medications, and lower or same frequencies of conditions than the CDC NHANES reference data in 24 of 27 categories. Higher frequencies of female infertility and asthma were reported by the worldwide spontaneously conceived adults than observed in the CDC NHANES data. Australian spontaneously conceived respondents self-reported lower frequencies in 2 of 2 characteristics and 12 of 29 conditions than those observed in the ABS NHS data. They also reported higher frequencies in 17 of 29 conditions.

Discussion

This study is the first of its kind to compare the self-reported health outcomes of adult donor sperm-conceived people and spontaneously conceived people. Results revealed that, for most health

Table 5. Significant physical health outcomes by maternal complications

	Spontaneous					
	Yes *N* (Total)	%	No *N* (Total)	%	*P*	BH *P*
Eczema	42 (103)	40.8	131 (626)	20.9	< 0.001	**<0.001**
Psoriasis	14 (103)	13.6	34 (623)	5.5	0.002	**0.019**
Nasal Allergies/hay fever	55 (103)	53.4	233 (625)	37.3	0.002	**0.019**
Menstrual problems	43 (93)	46.2	132 (491)	26.9	< 0.001	**0.004**
Pregnancy	38 (93)	40.9	277 (487)	56.9	0.004	**0.033**
Migraines	49 (104)	47.1	161 (628)	25.6	< 0.001	**< 0.001**
Blood cancers	3 (104)	2.9	0 (629)	0	0.003^	**0.026**
Acute bronchitis	25 (106)	23.6	75 (634)	11.8	0.001	**0.011**

Pearson's chi-squared (two-tailed) *P* value versus spontaneously conceived people.
BH, Benjamini-Hochberg procedure adjusted *P* value versus spontaneously conceived people.
^Fisher's exact test (two-tailed) *P* value versus spontaneously conceived people used instead of Pearson's chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table 6. Spontaneous cohort comparisons

	Spontaneous (all countries)	CDC NHANES	Spontaneous (Australia)	ABS NHS
	%	%	%	%
Characteristics				
Currently smoke	7.9	49.6	5.4	15.1
Former smoker	30.0	–	28.9	29.2
Prescribed medications	39.1	73.5	44.0	–
Cardiovascular				
Cardiovascular disease	2.2	4.8[a]	1.8	6.2
Heart murmur	5.6	–	6.3	1.6
High blood pressure	10.5	34.7	12.7	13.6
Low blood pressure	15.0	–	21.4	1.2
High cholesterol	8.8	32.4	11.5	7.8
Varicose veins	7.5	–	9.2	1.7
Chromosomal and genetics				
Chromosomal and genetic abnormality	2.4	–	3.2	0.4[b]
Dermatology				
Eczema	24.0	–	29.1	0.6
Psoriasis	6.4	–	8.8	3.1
EENT				
Deafness and hearing loss (total)	6.0	–	6.4	12.9
Nasal allergies/hay fever	39.3	–	45.6	21.6
Endocrinological				
Diabetes [types 1 and 2 (total)]	2.9	10.0	2.0	6.2
Thyroid disease	3.9	11.8[c]	4.9	5.0
Gastrointestinal				
Liver disease	1.5	5.3[d]	1.4	–
Ulcers	3.1	–	2.9	3.2
Gall bladder	5.6	11.5[e]	5.5	0.4[f]

(*Continued*)

Table 6. (*Continued*)

	Spontaneous (all countries)	CDC NHANES	Spontaneous (Australia)	ABS NHS
	%	%	%	%
Immunological				
Arthritis	7.8	30.4	8.5	18.3
Rheumatoid arthritis	2.2	–	1.8	2.5
Gout	1.2	6.1	1.5	3.0[g]
Allergic to anything	36.0	–	35.8	13.2
Ingested allergy	9.9	–	8.2	6.4
Medication allergy	13.4	–	16.8	5.6
Musculoskeletal				
Osteoporosis	1.1	12.9	1.5	5.0
Neurological				
Epilepsy	3.1	–	3.2	0.7
Migraines	27.8	–	29.8	7.6
Oncological				
Blood cancers	0.4	0.4	0.6	–
Skin cancers	1.8	2.4	2.0	0.7
Bowel cancer	0	0.8	0	–
Breast cancer (all sexes)	0.6	1.6	1.2	–
Prostate cancer (males only)	0	1.7	0	–
Bone cancer	0	0	0	–
Brain cancer	0	0.1	0	–
Lung/tracheal cancer	0	0.4	0	–
Pancreatic cancer	0	0	0	–
Other cancers	2.2	3.5	2.3	1.6[h]
Reproductive (female)				
Female infertility	8.9	6.7	8.2	–
Pregnancy (females)	51.7	85.1	46.9	–
Respiratory				
Asthma	25.3	14.9	28.6	11.5
COPD	0.5	5.3	0	3.0
Urogenital				
Kidney disease	0.7	–	0.6	1.2
Kidney stones	3.3	9.9	3.4	–

CDC NHANES, Centres for Disease Control and Prevention, National Health and Nutrition Examination Survey, 2017–2018 data (USA), all ages; ABS NHS, Australian Bureau of Statistics, National Health Survey, 2017–2018, ages 18 and over.
[a]Coronary heart disease as designated by CDC.
[b]Chromosomal abnormalities but also includes congenital malformations and deformations.
[c]Thyroid disease but also includes other thyroid problems.
[d]Liver condition including disease.
[e]Gall bladder surgery.
[f]Gallstones.
[g]Includes gout and other soft tissue disorders.
[h]Australian cancers other than skin and benign neoplasms or neoplasms of unknown nature.

outcomes, there was no statistically significant difference between donor sperm conceived and spontaneously conceived groups. However, donor sperm-conceived adults self-reported higher incidences of being diagnosed by a medical health professional with the following conditions: type 1 diabetes, thyroid disease, environmental allergies, acute bronchitis, sleep apnoea and having ear tubes/grommets surgically implanted.

Demographically, spontaneously conceived and donor sperm-conceived groups were not significantly different in terms of mean age, sex, mean height, current smoking status, alcohol

consumption, exercise regimes, whether their mother had smoked during pregnancy and whether they had received fertility treatment themselves. Donor sperm-conceived adults were more likely, however, to have been born as a twin, and their mothers were more likely to have experienced complications during pregnancy. They were also more likely to have a lower BMI and had completed a higher level of education but were also more likely to be using prescribed medications and recreational/illicit drugs. Donor sperm adults had a lower current mean weight and were less likely to have been a former smoker. Many of these findings are supported by previous studies.

Higher reported incidences of twins observed have been associated previously with both donor sperm[36,37] and donor oocyte treatments.[38–42] Similarly, higher maternal complications during pregnancy have also been previously associated with the use of donor sperm,[36,43] donor oocytes[23,44,45] and pregnancies involving twins/multiples.[46,47] Fertility treatment is typically associated with higher socioeconomic status of parents also and related factors,[48] even in jurisdictions where fertility treatment is covered through the public medical system with no self-payment,[49] or jurisdictions that have mandated insurance coverage.[50] This higher socioeconomic status of families seeking fertility treatment may potentially be associated with the higher education outcomes, lower BMI, weight and lower incidences of smoking observed in the donor sperm-conceived cohort. The increased incidences of taking prescribed medications may be linked with the increased incidences of self-reported medically diagnosed conditions observed.

With a high proportion of female respondents, the data were stratified to analyse the effect of sex on outcomes. In all instances of significant differences between the sexes in terms of physical health outcomes, females reported significantly higher incidences of being diagnosed with a range of conditions including low blood pressure, anaemia, varicose veins, urticaria, nasal allergies/hay fever, tonsillectomy, IBS, gall bladder problems, migraines, asthma, acute bronchitis, pneumonia, being allergic to anything and wearing corrective glasses/lenses. However, the majority of those differences were observed in the spontaneously conceived cohort. Considering that the donor sperm-conceived males' sample size was $N = 38$, the analysis lost power to detect many of the differences even though there was variation in the frequencies reported. Those differences that were initially observed between donor sperm-conceived females and males were no longer significant after controlling for false-discovery utilising the Benjamini–Hochberg procedure. Nonetheless, the increased incidence of various conditions that were observed in females appears to be supported by the significant increase in the use of prescribed medications by both spontaneously and donor sperm-conceived females.

The DOHaD theory typically associates poor perinatal outcomes such as LBW, PD and SGA with cardiovascular disease,[51,52] hypertension,[12,53] type 2 diabetes[54,55] and obesity.[56,57] Evidence shows that donor-conceived neonates also experience similar poor perinatal outcomes.[20–25] However, those common adult outcomes of cardiovascular disease (including hypertension and other cardiovascular outcomes) and type 2 diabetes were not observed in the responses of the donor-conceived adults in this study. Furthermore, not only did the donor sperm-conceived group not have a significant increase in bodyweight or BMI as suggested through the DOHaD theory but actually reported a significantly lower BMI. Considering that the mean age of the donor sperm-conceived respondents in this survey was 32.6 years of age, which is relatively young from a population study perspective, it is problematic to assume that they will or will not go on to develop age-related illnesses such as cardiovascular disease later in life. Furthermore, outcomes such as lower BMI, weight, incidences of previously smoking and increased post-graduate education levels observed in the donor sperm-conceived cohort may potentially be linked to the socioeconomic status of the individual as fertility treatments have been typically associated with higher socioeconomic status of parents.[58] Caution should therefore be taken in extrapolating the findings of this study to age-related conditions in the context of DOHaD as well as those outcomes that could be influenced by socioeconomic factors. Nevertheless, these observations provide a reference point for further investigations.

For those medical conditions observed in the donor sperm-conceived cohort that are not supported by previous studies investigating longitudinal effects of LBW, PD and SGA, these conditions may instead be potentially associated with other pregnancy or birth characteristics that can also be classified under DOHaD. Alternatively, or in addition to, they may be influenced by the fertility treatment methodology itself. For example, preeclampsia is a known maternal complication of donor oocyte,[20,59–61] and donor sperm modalities,[43,62,63] and has been associated with a variety of diseases in later life.[64–67] These diseases have included those involving cardiovascular, immune, endocrine, respiratory, nervous, urogenital, digestive and musculoskeletal systems, as well as metabolic, mental, nervous and blood disorders among others. The use of donor sperm, now but not always historically, involves the use of manual handling and cryopreservation which can cause DNA fragmentation,[68,69] through oxidative stress,[70] and can also adversely affect sperm morphology, motility and viability.[71] The long-term health consequences of manual handling and cryopreservation-induced DNA damage on resultant offspring are poorly understood but have been associated with increased incidences of poorer outcomes such as epigenetic disorders, DNA methylation and morbidity in animal studies.[72–74]

As a method to determine if maternal complications such as preeclampsia had an effect on health outcomes in the cohorts, the data were stratified into those who reported that their mother had maternal complications and those whose mother did not. As was the case with analysis of sex differences, the sample size for those reporting maternal complications in the donor sperm-conceived cohort of $N = 47$ reduced the power to detect differences in the donor sperm cohort. All differences in the donor sperm-conceived cohort were no longer significant after adjusting for false-discovery using the Benjamini–Hochberg procedure. While no inference can be made regarding the impact of maternal complications on the increased incidences of diagnosed health conditions in the donor sperm-conceived cohort, the concept that maternal complications may potentially be associated with poorer long-term health outcomes was supported by data from the spontaneously conceived cohort which showed increased incidences of being diagnosed with eczema, psoriasis, nasal allergies/hay fever, migraines, blood cancers, acute bronchitis and menstrual problems (females). Females were also less likely to have experienced a pregnancy. The survey question of whether the respondents' mother experienced maternal complications is potentially subject to recall bias on behalf of the respondent. However, for those who did not know for certain, they were instructed to answer that they did not know and were subsequently excluded from the maternal complication analysis. Notwithstanding, the possibility remains for recall bias in this regard and therefore may have affected the outcomes

even though the increased incidences of maternal complications in the donor sperm-conceived group are consistent with published studies.

The sample size obtained for this study was larger than several previous studies investigating donor-conceived people,[75–79] but smaller than some others.[80–82] However, unlike the present study, the larger previous studies all involved children and or adolescents in addition to adults, rather than adults alone. Using an online questionnaire, therefore, proved to be an acceptable form of participant recruitment to access a reasonable sample size of adults who were donor conceived from around the world.

While this is the first study to investigate the self-reported health outcomes of adult donor-conceived people, there are limitations. A limitation of the study was sample bias due to the respondents self-reporting health conditions. We attempted to reduce reporting bias by asking that respondents only answer 'yes' to those conditions to which they had been diagnosed by a medical health professional. Considering that few physical health significant differences were observed between the groups, this approach appeared to be somewhat successful. Furthermore, statistical procedures were implemented to control for the false discovery rate.

The primary recruitment sources for donor-conceived participants were from social media support groups and online donor conception groups, thereby making them a self-identified sample. Subsequently, it could be postulated that this pool represents a subset of donor-conceived adults who may potentially be having some form of difficulty dealing with their conception status or are perhaps looking for assistance in obtaining information about, and or connecting with their biological (donor) parent.[76,83] The mental health of participants in this survey was also captured as part of the survey. While the results are yet to be published, mental and physical health can be both directly and indirectly associated,[84] and subsequently, mental health outcomes should be considered when interpreting the physical health outcomes in relation to the support groups that some of the donor sperm-conceived adults were recruited from. Since the majority of donor-conceived adults were not aware of their conception status,[29] it was not possible to get a representative cross section of this population cohort. The same sample bias problem has been repeatedly reported by other researchers investigating various outcomes in donor-conceived offspring[77,79,85,86] and will continue to be an issue while non-disclosure of a person's conception status still exists. Nonetheless, caution should be taken in extrapolating the results to all donor sperm-conceived adults and those conceived with other modalities such as donated oocytes, embryos and surrogacy using donated gametes that may also differ.

The countries in which individuals are conceived, raised and live in may affect their ability to access health care and subsequently their long-term health trajectories. Additionally, diagnosis may vary between countries. While the majority of respondents in this survey were conceived in western countries (87.4% of respondents were born in just five countries), with excellent health care availability, an analysis was still conducted by restricting outcomes to the largest country of birth cohort, Australia. Differences initially observed from chi-squared analysis were no longer significant after adjustment using the Benjamini–Hochberg procedure to remove false discoveries. Thereby highlighting that the differences observed in the global analysis is biased by the remaining countries including those with excellent health care such as the United States of America, the United Kingdom, Belgium, the Netherlands, New Zealand, Canada etc. However, as was found in previous stratification analysis, statistical power was reduced primarily due to the smaller sample size in the donor sperm-conceived cohort and subsequently it is difficult to determine if Australian donor sperm-conceived adults are equally healthy as their spontaneously conceived peers.

Validation of the comparison group (spontaneously conceived) is difficult due to the reference data. By and large, the whole (worldwide) spontaneously conceived cohort is healthier than those in the CDC NHANES data. The CDC states that the NHANES data are oversampled for Hispanic, non-Hispanic black and Asians, making it non-representative of the USA population, but it also provides greater multi-ethnicity which is perhaps better in terms of the spontaneously conceived respondents in our survey which had a variety of individuals from all over the world including some Asian countries. However, the CDC also states that they oversampled non-Hispanic whites below 185% poverty guidelines and non-Hispanic whites over 80 years of age. Whereas, there was only 1 respondent in the spontaneously conceived group who was over the age of 80. In effect, the CDC NHANES data are likely to have bias towards age-related conditions as well as poor access to health treatment due to poverty, making the data biased towards poorer health outcomes which is consistent with the healthier frequencies observed in the spontaneously conceived respondents.

Australian validation data from the ABS NHS showed a mix of better and poorer health outcomes in the Australian spontaneously conceived group. The Australians provided roughly 2 out of every 5 worldwide spontaneously conceived respondents and their data were generally consistent with the worldwide cohort. ABS NHS data include a bias towards young people with 28.3% of participants between the ages of 0–19 years, whereas respondents in this survey were all over the age of 18 years. Of those conditions that Australian spontaneously conceived respondents reported of having large differences in frequencies including eczema, nasal allergies/hay fever, allergic to anything, medication allergy, asthma, migraines and low blood pressure, the majority have associations with the immune system. Both reference data sets are representative for the dates that they are collected and that they are both surveys of the population and therefore subject to the same recall bias issues that the respondents in our survey are. Differences between the reference data sets and the spontaneously conceived cohort are not surprising due to age (NHANES and NHS), and poverty (NHANES), biases present in the reference data.

While this study is not without its limitations, it does represent valuable outcomes from a subset of adults conceived with reproductive technologies not previously studied. Moreover, the self-reports are consistent with the increased incidences of birth defects associated with donor sperm treatment.[25]

This study highlights that there is a group of people conceived through reproductive medicine that self-reported worse adulthood health outcomes than their spontaneously conceived peers. Confounding of multiplicity and maternal complications, which can include preeclampsia, can be directly associated with the fertility treatment that their mother received. These confounders are therefore intrinsically linked with the treatment modality, and consequently, dismissal of outcomes simply by appealing to confounding is problematic. Multiplicity is iatrogenically induced through ovulation induction which is sometimes used in donor insemination or also through multiple embryo transfer and therefore preventable. Several of the findings run contrary to those that would be expected from typical DOHaD outcomes associated with LBWs and PD, albeit that these may alter with age due to the relatively young age of the sample, but nonetheless may also be

associated with other DOHaD maternal/perinatal characteristics such as preeclampsia and therefore require further investigation.

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Author contributions. All authors contributed to the conceptualisation and design of the study. D.A. had correspondence with the administrators and organisations involved in the advertising of the study. D.A. managed the collection of data and provided initial data analysis with input from A.G., M.D. and S.deL. Data were critically assessed and interpreted by all authors. D.A. wrote the first draft of the manuscript. All authors provided critical revision of the paper and approved the final version.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the Australian ethical standards and guidelines of The National Statement on Ethical Conduct in Human Research (2007) in accordance with the National Health and Medical Research Council Act (1992), and with the Helsinki Declaration of 1975, as revised in 2008. This study has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Approval number: 7827).

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Appendix 3.2 Ethical Approval

Dear Damian,

Your ethics application was considered at the last meeting of the Social and Behavioural Research Ethics Committee (SBREC) at Flinders University and was granted approval. Your ethics approval notice can be found below.

APPROVAL NOTICE

Project No.:	**7827**		
Project Title:	Self-Reported Health Status of Donor Conceived Adults		
Principal Researcher:	Mr Damian Adams		
Email:			
Approval Date:	4 December 2017	Ethics Approval Expiry Date:	**30 June 2021**

The above proposed project has been **approved** on the basis of the information contained in the application and its attachments.

RESPONSIBILITIES OF RESEARCHERS AND SUPERVISORS

1. Participant Documentation

Please note that it is the responsibility of researchers and supervisors, in the case of student projects, to ensure that:

- all participant documents are checked for spelling, grammatical, numbering and formatting errors. The Committee does not accept any responsibility for the above mentioned errors.
- the Flinders University logo is included on all participant documentation (e.g., letters of Introduction, information Sheets, consent forms, debriefing information and questionnaires – with the exception of purchased research tools) and the current Flinders University letterhead is included in the header of all letters of introduction. The Flinders University international logo/letterhead should be used and documentation should contain international dialling codes for all telephone and fax numbers listed for all research to be conducted overseas.
- the SBREC contact details, listed below, are included in the footer of all letters of introduction and information sheets.

This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project Number 'INSERT PROJECT No. here following approval'). For more information regarding

ethical approval of the project the Executive Officer of the Committee can be contacted by telephone on 8201 3116, by fax on 8201 2035 or by email human.researchethics@flinders.edu.au.

2. Annual Progress / Final Reports

In order to comply with the monitoring requirements of the *National Statement on Ethical Conduct in Human Research (March 2007)* an annual progress report must be submitted each year on the **4 December** (approval anniversary date) for the duration of the ethics approval using the report template available from the Managing Your Ethics Approval SBREC web page. *Please retain this notice for reference when completing annual progress or final reports.*

If the project is completed *before* ethics approval has expired please ensure a final report is submitted immediately. If ethics approval for your project expires please submit either (1) a final report; or (2) an extension of time request and an annual report.

Student Projects

The SBREC recommends that current ethics approval is maintained until a student's thesis has been submitted, reviewed and approved. This is to protect the student in the event that reviewers recommend some changes that may include the collection of additional participant data.

Your first report is due on **4 December 2018** or on completion of the project, whichever is the earliest.

3. Modifications to Project

Modifications to the project must not proceed until approval has been obtained from the Ethics Committee. Such proposed changes / modifications include:

- change of project title;
- change to research team (e.g., additions, removals, principal researcher or supervisor change);
- changes to research objectives;
- changes to research protocol;
- changes to participant recruitment methods;
- changes / additions to source(s) of participants;
- changes of procedures used to seek informed consent;
- changes to reimbursements provided to participants;
- changes / additions to information and/or documentation to be provided to potential participants;
- changes to research tools (e.g., questionnaire, interview questions, focus group questions);
- extensions of time.

To notify the Committee of any proposed modifications to the project please submit a Modification Request Form available from the Managing Your Ethics Approval SBREC web page. Download the form from the website every time a new modification request is submitted to ensure that the most recent form is used. Please note that extension of time requests should be submitted prior to the Ethics Approval Expiry Date listed on this notice.

Change of Contact Details

Please ensure that you notify the Committee if either your mailing or email address changes to ensure that correspondence relating to this project can be sent to you. A modification request is not required to change your contact details.

4. Adverse Events and/or Complaints

Researchers should advise the Executive Officer of the Ethics Committee on 08 8201-3116 or human.researchethics@flinders.edu.au immediately if:

- any complaints regarding the research are received;
- a serious or unexpected adverse event occurs that effects participants;
- an unforseen event occurs that may affect the ethical acceptability of the project.

Kind regards
Andrea

Appendix 3.3 Advertisement Wording for Online Support Groups

Dear Member,

Please find below a link to a study being conducted by researchers at Flinders University, South Australia, examining the health of adult donor conceived people and naturally conceived adults. The survey will take approximately 15 minutes to complete and comprises mainly of questions seeking yes/no answers to various health conditions that have been diagnosed by health professionals. There is also a section consisting of questions regarding mental health at the end of the survey. Your responses will remain anonymous and no identifying information will be requested. If you are interested in participating, you may click on the link at the bottom of this message which will take you to an introductory page and then a participant information sheet which provides further details about the survey before deciding whether you wish to participate. Please feel free to share the details of the survey and the link with anyone you feel may be interested in participating.

https://www.surveymonkey.com/r/VWCFLR2

Appendix 3.4 Advertisement Wording for Flinders University's 'Participate in Research Studies' Webpage

Title: Self-Reported Health Status of Adults

Information: Participation will involve answering an online survey examining the self-reported health status of adults. Specifically, we are comparing the health status of naturally conceived people to those who are donor conceived. You do not need to be donor-conceived to participate – we are looking for both donor-conceived and naturally conceived adults to participate.

The survey will take approximately 15 minutes to complete and comprises mainly of questions seeking yes/no answers to various health conditions that have been diagnosed by health professionals. There is also a section consisting of questions regarding mental health at the end of the survey.

https://www.surveymonkey.com/r/VWCFLR2

Email

Participants required:

Gender – male and female

Age – 18+

Other criteria – nil

Participant benefits – the assistance of research into the health outcomes of those conceived with donated gametes

Participants required until – ongoing.

Appendix 3.5 Advertisement Wording for the Prolific Survey Recruitment Website

"Dear .....,

Please find below a link to a study being conducted by researchers at Flinders University, South Australia, examining the health of adults. It is a study which will compare the self-reported health status of naturally conceived individuals to those who were conceived with donated gametes/embryos. You do not need to be donor-conceived to participate – we are looking for both donor-conceived and naturally conceived adults to participate. The survey will take approximately 15 minutes to complete and comprises mainly of questions seeking yes/no answers to various health conditions that have been diagnosed by health professionals. There is also a section consisting of questions regarding mental health at the end of the survey. Your responses will remain anonymous and no identifying information will be requested. If you are interested in participating, you may click on the link at the bottom of this message which will take you to an introductory page and then a participant information sheet which provides further details about the survey before deciding whether you wish to participate."

https://www.surveymonkey.com/r/VWCFLR2

Appendix 3.6 Online Resources Used for Construction of the Adult Health Questionnaire

The following resources were located through a Google search and Google Image search using the terms "Medical Health Questionnaires" and "Medical History Questionnaires". The aim was to find examples of the types and specific questions that are typically asked to gain an insight into the health history of a person. The resources were all accessed on October 25, 2015.

University of Nebraska-Lincoln, Confidential Medical History Form.
https://health.unl.edu/forms/ConfidentialMedicalHistoryForm.pdf

University of California, Education Abroad Program, Confidential Health History Form
http://eap.ucop.edu/Documents/_forms/1112/Health_Confidential_History_Form.pdf

Aetna, Health Insurance, Group Medical Questionnaire
http://www.aetna.com/employer/small_group/data/Group_Med_Ques.pdf

LaSalle University, Division of Student Affairs, Counselling and Health Services, Student Health Centre Health History Form 2015-2016
http://studentaffairs.lasalle.edu/health/files/2015/03/Health-History-Form-1516.pdf

MIT Medical, Patient Health History
https://medical.mit.edu/sites/default/files/patienthealthhx_EN.pdf

Risksavers, Second Injury Fund Employee Questionnaire
http://www.louisianacomp.com/Second%20Injury%20Fund%20Questionnaire%20Revised%202009.pdf

Drake University, Drake University Medical History Form
https://www.drake.edu/media/departmentsoffices/healthcenter/documents/pdf/Student_Health_Records.pdf

PADI, Recreational Scuba Training Council, Medical Statement
www.padi.com/scuba-diving/documents/padi-courses/medical-form/

Yumpu Documents, Medical History Questionnaire
https://www.yumpu.com/en/document/view/45987876/medical-history-questionnaire

American Academy of Health and Fitness, Medical History Questionnaire

www.aahf.info/pdf/Medical_Questionnaire.doc

Lafayette College, Recreation Services, Individual Fitness and Medical History Questionnaire

http://recreation.lafayette.edu/files/2010/02/Individual-Fitness-Medical-History-Questionaire.pdf

Appendix 3.7 Adult Health Survey as Appearing on SurveyMonkey

1. Introduction Page

Hello,
I'd like to introduce Damian Adams to you. Damian is a PhD candidate in the College of Nursing and Health Sciences at Flinders University.
https://www.flinders.edu.au/college-nursing-health-sciences

Damian is carrying out research for publication and the production of a doctoral thesis on the subject of donor conception and child/adult welfare. This particular survey addresses the question of the self-reported health status of donor conceived adults. You do not have to be donor-conceived to complete this survey – we are interested in self-reported health of donor and non-donor conceived people.

Damian will invite you to assist with this project by agreeing to complete an online survey that is completely voluntary, and in which you will remain anonymous.

If you have any enquiries or concerns regarding this project please contact me at the address shown below,
by telephone on:
or e-mail:

Yours sincerely
Professor Sheryl de Lacey
College of Nursing and Health Sciences
Flinders University
GPO Box 2100
Adelaide
South Australia, 5001

2. Participant Information Page

Title: Self-Reported Health Status of Donor Conceived Adults.

Researcher:
Mr Damian Adams
College of Nursing and Health Sciences
Flinders University

Supervisor(s):
Prof Sheryl de Lacey
College of Nursing and Health Sciences
Flinders University
Ph:
Dr Adam Gerace
College of Nursing and Health Sciences
Flinders University
Ph:
Prof Michael Davies
Robinson Research Institute
Adelaide University
Ph:

Description of the study:
This study is part of the project entitled 'Child welfare paramountcy: the donor conception paradox'. This project will investigate the current self-reported health status of adults. This project is supported by Flinders University College of Nursing and Health Sciences.

Purpose of the study:
There have previously been studies investigating the health outcomes of donor conceived babies and children however there have been no studies investigating the long term health of the donor conceived into adult-hood. This project aims to examine differences and similarities between the self-reported health status of donor conceived adults and adults who were conceived naturally.

What will I be asked to do?
You are invited to complete an anonymous online survey about your health status. To assist with data analysis we will start off by asking some demographic questions as well as ascertaining if you are donor conceived or conceived naturally. Then we will ask a range of questions regarding physical and mental health conditions, which are for the majority of questions simple yes or no checkboxes. Finally, you will be asked a series of questions about how you are currently feeling.

We also invite participants who are donor-conceived to consider sending the survey off to a friend who is of a similar age so that we may have a large enough sample for comparison. This can be done by cutting and pasting the link to this survey and sending to friends, or by sharing the original message you received regarding this survey (e.g. from a Facebook group).

Survey Monkey link:
https://www.surveymonkey.com/r/VWCFLR2

Participation is entirely voluntary. The survey will take about 15 minutes to complete.

Will I be identifiable by being involved in this study?
We do not need your name and you will be anonymous. Once the survey has been completed the only information kept will be demographics and the percentage of people responding to a question in a certain way. There is no possible way for any person to be identifiable from the information provided in the survey. Any comments made by you personally in the survey cannot be linked directly to you.

What benefit will I gain from being involved in this study?
While individual participants will not gain direct benefit by participating, the sharing of health status information will provide the basis for the first ever study into health outcomes in adult donor conceived people. No studies to date have been conducted on the physical health of adult donor conceived people and it is vitally important to determine differences and similarities compared to non-donor conceived people. Understanding how reproductive technologies influence the long term health trajectories of people can contribute to improved reproductive technology methodologies as well as the targeting of health resources to assist those conceived with those technologies.

Are there any risks or discomforts if I am involved?

We anticipate few risks from your involvement in this study; however given the personal nature of the questions, some participants could experience emotional discomfort. If in the unlikely event that you experience discomfort while completing the survey or have concerns regarding your health, you should close the browser window and speak with your general practitioner/family doctor or contact support or counselling that are available in your region such as BeyondBlue in Australia, Anxiety and Depression Association of America, or Depression UK in the United Kingdom. Furthermore, if after completing the survey, participation has brought up any concerns or issues, you should contact these same organisations.

How do I agree to participate?

Participation is entirely voluntary. By clicking on the "I agree to participate" button at the start of the survey you have indicated your willingness to be involved. You must be 18 years of age or older to participate.

You can exit the survey at any stage. However, once completed it will not be possible to withdraw your data as all data is non-identifiable. There are some questions that are mandatory to progress through the survey (such as whether you were donor conceived or conceived naturally).

How will I receive feedback?

On project completion outcomes of the project will be published in a peer reviewed scientific journal and at scientific conferences. Once published outcomes will be posted in the social media groups where the survey was first advertised and also via the organisations that advertised it. Alternatively they can also be obtained by contacting the researcher.

Thank you for taking the time to read this information sheet and we hope that you will accept our invitation to be involved.

*This research project has been approved by the Flinders University Social and Behavioural Research Ethics Committee (Project number **INSERT PROJECT No. here following approval**). For more information regarding ethical approval of the project the Executive Officer of the Committee can be contacted by telephone on 8201 3116, by fax on 8201 2035 or by email human.researchethics@flinders.edu.au*

3. Agreement to Participate

This page allows you to give your consent to participate in the survey if you choose to do so. Please make sure that you have read and understood the Participant Information Page and Introduction Page before providing your consent. If you have any concerns or questions please return to the Information Page and use the contact information to contact the researcher.

* 1. Agreement to Participate

- ◯ I Agree to Participate and Confirm that I am Over 18 Years of Age
- ◯ I Do Not Agree to Participate and or I am Under 18 Years of Age

4. General Questions

* 1. What is your age (years)?

2. In what country do you live?

* 3. What sex are you?

- Female
- Male
- Other

4. What is the highest level of education you have completed?

- Less than high school degree
- High school degree or equivalent (secondary school)
- Vocational qualifications
- University/College Undergraduate (tertiary - eg. Bachelor or Diploma)
- University/College Postgraduate (eg Masters, PhD)

5. Details About Your Birth

1. In what country were you born?

* 2. How were you conceived?

- ◯ Naturally conceived
- ◯ Donor sperm
- ◯ Donor egg
- ◯ Donor embryo
- ◯ Surrogacy (including donor embryo/egg/sperm)

3. Were you born as a:

- ◯ Singleton (only baby from that pregnancy)
- ◯ Twin
- ◯ Multiple (3 or more)

4. Did your mother have any complications during the pregnancy with you such as gestational diabetes, preeclampsia, hypertension (high blood pressure) etc?

- ◯ Yes
- ◯ No
- ◯ Don't know

5. Did your mother smoke during the pregnancy?

- ◯ Yes
- ◯ No
- ◯ Don't know

6. General Health

These questions are about your current status

1. Height

Numerical value (eg '185' for cm or '5.11' for feet)

Centimeters or Feet (please type cm or ft)

2. Weight

Numerical value (eg '78' for kg or '153' for lbs)

Kilograms or Pounds (please type kg or lbs)

3. Do you smoke (cigarettes, tobacco, cigars)?

- Yes
- No

4. If you do not currently smoke, have you smoked previously?

- Yes
- No

5. How many alcoholic drinks do you have per week?*(One alcoholic drink would approximately be one glass of wine or beer or a shot of spirit)*

- 0-1
- 2-4
- 4-10
- 10+

6. How many times per week do you undertake low or moderate exercise such as walking?

7. How many times per week do you undertake high or strenuous exercise such as running?

8. Are you currently taking any prescribed medications?

- Yes
- No

If you answered yes, please specify which medications.

9. Do you currently take any recreational/illicit drugs such as marijuana, cocaine, ecstasy, methamphetamine, LSD, heroin etc?

- Yes
- No

* 10. Have you required fertility treatment yourself such as IVF or donor gametes due to your own infertility?

- ◯ Yes
- ◯ No

7. Respiratory Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Asthma	○	○
Chronic obstructive pulmonary disease (including emphysema and chronic (long term) bronchitis)	○	○
Acute bronchitis (short term)	○	○
Sleep apnea	○	○
Pneumonia	○	○

2. Have you been diagnosed with any other respiratory disease/disorders?

○ Yes

○ No

If you answered yes, please specify.

8. Gastrointestinal Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Liver disease (such as cirrhosis, hemochromatosis, fatty liver disease)	○	○
Irritable bowel syndrome (IBS)	○	○
Irritable bowel disease (IBD including Crohn's disease, ulcerative colitis)	○	○
Ulcers (stomach/gastric and or duodenal)	○	○
Coeliac	○	○
Appendicitis	○	○
Gall bladder problems	○	○
Gastroesophageal reflux disease (GERD - acid reflux, heartburn)	○	○

2. Have you been diagnosed with any other gastrointestinal disease/disorders?

○ Yes

○ No

If you answered yes, please specify.

9. Endocrine Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Diabetes type 1	○	○
Diabetes type 2	○	○
Pancreatitis	○	○
Adrenal disorders (such as Addison's disease, Cushing's syndrome, congenital adrenal hyperplasia, pituitary tumours, pheochromocytoma, paraganglioma)	○	○
Thyroid disease (such as hyper or hypo, goiter, nodules, thyroiditis)	○	○
Pituitary disorders	○	○

2. Have you been diagnosed with any other endocrine disease/disorders?

○ Yes

○ No

If you answered yes, please specify.

10. Neurological Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Epilepsy or other convulsions/seizures	○	○
Tremors	○	○
Migraines	○	○
Multiple sclerosis (MS)	○	○
Vertigo (dizziness)	○	○
Cerebral palsy	○	○
Fibromyalgia	○	○
Parkinson's disease	○	○

2. Have you been diagnosed with any other neurological disease/disorders?

○ Yes

○ No

If you answered yes, please specify.

11. Chromosomal and Genetics Question

Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

1. Have you been diagnosed as having a chromosomal or genetic abnormality?

- ◯ Yes
- ◯ No

If you answered yes, please specify.

12. Urogenital Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Kidney disease	○	○
Kidney stones	○	○
Bladder disease	○	○
Urogenital defects requiring surgery (urinary tract or genital defects)	○	○

2. Have you been diagnosed with any other renal disease/disorders?

○ Yes

○ No

If you answered yes, please specify.

13. Oncological (Cancer) Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Blood cancers (such as lymphoma, leukemia etc)	○	○
Melanoma or other skin cancers	○	○
Bowel cancer	○	○
Breast cancer	○	○
Prostate cancer	○	○
Bone cancer	○	○
Brain cancer	○	○
Lung or tracheal cancer	○	○
Pancreatic cancer	○	○

2. Have you been diagnosed with any other cancer/malignancy?

○ Yes

○ No

If you answered yes, please specify.

14. Ears/Eyes/Nose/Throat Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Eye disorders (such as glaucoma and cataracts but excluding glasses or contact lenses)	○	○
Eye problems requiring corrective glasses or contact lenses	○	○
Eye defects requiring surgery	○	○
Hearing loss (but not total deafness)	○	○
Deafness (total hearing loss)	○	○
Nasal allergies/hayfever	○	○
Tonsilectomy (tonsils removed)	○	○
Ear tubes/grommets	○	○
Adenoidectomy (adenoids removed)	○	○
Tinnitus (constant ringing in the ears)	○	○
Meniere's disease	○	○

2. Have you been diagnosed with any other ears, eyes, nose, throat, disease/disorders?

○ Yes

○ No

If you answered yes, please specify.

15. Dermatology (Skin) Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Eczema	○	○
Psoriasis	○	○
Urticaria (hives)	○	○

2. Have you been diagnosed with any other skin disease/disorders?

- ○ Yes
- ○ No

If you answered yes, please specify.

16. Musculoskeletal Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Joint problems	○	○
Osteoporosis (weak and brittle bones)	○	○
Scoliosis (abnormal curvature of the spine)	○	○
Growth disorder (such as excessively short or tall, ie dwarfism, gigantism)	○	○
Muscular dystrophy	○	○

2. Have you been diagnosed with any other musculoskeletal disease/disorder?

○ Yes

○ No

If you answered yes, please specify.

17. Allergies and Immunological Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Arthritis	○	○
Rheumatoid arthritis	○	○
Spleen problems or removal of spleen	○	○
Gout	○	○
Lupus	○	○
Ankylosing spondylitis	○	○
Hashimoto's disease	○	○
Connective tissue disorders (such as Sjorgen's syndrome)	○	○

2. Are you allergic to anything?

○ Yes

○ No

If yes, please specify allergy.

3. Do you have recurrent or chronic infectious disease? *(A chronic disease is one which lasts a long time)*

○ Yes

○ No

If yes, please specify infection if known.

4. Have you been diagnosed with any other immune or autoimmune disease/disorder?

○ Yes

○ No

If you answered yes, please specify.

18. Female Reproductive System Questions (Women Only)

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".
If you are male please skip this section by clicking "next".

	Yes	No
Ovarian cysts	○	○
Endometriosis	○	○
Menstrual problems (such as irregular menstruation)	○	○
Polycystic ovary syndrome (PCOS)	○	○
Infertility	○	○

2. Have you been diagnosed with any other female reproductive system disease/disorders?

○ Yes

○ No

If you answered yes, please specify.

3. Have you ever been pregnant?

○ Yes

○ No

If yes what is the number of pregnancies carried to term and delivered?

19. Male Reproductive System Questions (Men Only)

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".
If you are female please skip this section by clicking "next".

	Yes	No
Testicular problems (such as torsion, epididymal cysts, undescended testes)	○	○
Prostate problems (but excluding cancer)	○	○
Low sperm count or poor sperm quality	○	○
Infertility	○	○

2. Have you been diagnosed with any other male reproductive system disease/disorders?

- ○ Yes
- ○ No

If you answered yes, please specify.

20. Cardiovascular Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Congenital heart disease	○	○
Cardiovascular disease (including heart attack, stroke, angina, cardiomyopathy, cerebrovascular disease, arteriosclerosis, atherosclerosis, rheumatic heart disease, peripheral arterial disease, aneurysm, deep vein thrombosis)	○	○
Bleeding disorders (such as hemophilia)	○	○
Heart murmur	○	○
Palpitations (rapid or strong heartbeat)	○	○
High blood pressure (over 140/90, either or both reading(s) can be higher)	○	○
Low blood pressure (below 90/60, either or both reading(s) can be lower)	○	○
Anemia (low levels of iron in your blood)	○	○
Poor peripheral circulation leading to white/blue fingers and or toes (such as Raynaud's syndrome)	○	○
High cholesterol	○	○
Aneurysm (swelling of artery wall - except brain aneurysm)	○	○
Phlebitis (inflammation of the walls of the vein)	○	○

	Yes	No
Varicose veins	○	○
Heart defects requiring surgery	○	○

2. Have you been diagnosed with any other cardiovascular disease/disorders?

○ Yes

○ No

If you answered yes, please specify.

21. Mental Health Questions

1. Do you have or have you ever had any of the following?
Note: please only respond yes if you have been diagnosed by a medical health professional.
If you are unsure please answer "no".

	Yes	No
Diagnosed depressive disorder	○	○
Diagnose anxiety disorder	○	○
Diagnosed bipolar	○	○
Diagnosed with ADD/ADHD (attention deficit hyperactivity disorder)	○	○
Diagnosed with autism or autistic spectrum disorder	○	○

2. Have you been diagnosed with any other mental health condition?

○ Yes

○ No

If you answered yes, please specify.

22. Mental Health Questions (page 2) (Note: change of instructions below)

1. The following responses do not require diagnosis by a health professional but are rather a reflection of your own experience. There are no right or wrong answers.
Do you currently experience or have you ever experienced any of the following?

	Yes	No
Panic attacks	○	○
Difficulty forming your identity	○	○
Suffer from recurrent nightmares	○	○
Alcohol or chemical/drug dependency (addiction)	○	○
Eating disorder (such as anorexia or bulimia)	○	○
Insomnia	○	○
Learning difficulties at school	○	○

2. Have you ever seen a mental health professional?

○ Yes

○ No

If yes, was it a psychiatrist, psychologist, other (please specify).

23. Mental Health Questions (page 3) (Note: another change of instructions below)

The following questions are to determine what level of stress, depression and anxiety you may have experienced over the past week.
Please read each statement and determine how the statement applied to you in the last week.
There are no right or wrong answers.
The rating scale is as follows:
0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of the time
3 Applied to me very much, or most of the time

1. How I have felt in the last week...

	Did not apply to me at all 0	Applied to me to some degree, or some of the time 1	Applied to me to considerable degree, or a good part of the time 2	Applied to me very much, or most of the time 3
I found it hard to wind down	○	○	○	○
I was aware of dryness of my mouth	○	○	○	○
I couldn't seem to experience any positive feeling at all	○	○	○	○
I experienced breathing difficulty (eg excessively rapid breathing, breathlessness in the absence of physical exertion)	○	○	○	○
I found it difficult to work up the initiative to do things	○	○	○	○
I tended to over-react to situations	○	○	○	○
I experienced trembling (eg in the hands)	○	○	○	○
I felt that I was using a lot of nervous energy	○	○	○	○
I was worried about situations in which I might panic and make a fool of myself	○	○	○	○
I felt that I had nothing to look forward to	○	○	○	○
I felt myself getting agitated	○	○	○	○
I found it difficult to relax	○	○	○	○
I felt down-hearted and blue	○	○	○	○
I was intolerant of anything that kept me from getting on with what I was doing	○	○	○	○
I felt I was close to panic	○	○	○	○

	Did not apply to me at all 0	Applied to me to some degree, or some of the time 1	Applied to me to considerable degree, or a good part of the time 2	Applied to me very much, or most of the time 3
I was unable to become enthusiastic about anything	○	○	○	○
I felt I wasn't worth much as a person	○	○	○	○
I felt that I was rather touchy	○	○	○	○
I was aware of the action of my heart in the absence of physical exertion (eg sense of heart rate increase, heart missing a beat)	○	○	○	○
I felt scared without any good reason	○	○	○	○
I felt that life was meaningless	○	○	○	○

24. Thankyou

Thankyou for completing our survey.
Your responses will greatly assist in understanding the long term health outcomes for donor conceived people.
It would be greatly appreciated if you could pass on information about this survey to anyone else who may wish to participate, whether they be donor conceived or naturally conceived. To assist in demographic matching of people between groups, those of a similar age to yourself would be extremely beneficial, however, anyone of a differing age is more than welcome to participate too. The more responses we receive the better our data will be. Please share the original message, post or link you received, or you can use this link:
https://www.surveymonkey.com/r/VWCFLR2
If they need to use the same computer that you used to complete the survey you will need to clear the cache in your web browser.
Thankyou sincerely for your time and assistance.

Appendix 3.8 Complete Table of Countries of Birth and Residency

	Spontaneous				All Donor-Conceived				Donor Sperm-Conceived			
	Birth n	Birth %	Resid. n	Resid. %	Birth n	Birth %	Resid. n	Resid. %	Birth n	Birth %	Resid. n	Resid. %
Argentina	0	0	1	0.1	0	0	0	0	0	0	0	0
Australia	372	46.3	490	55.9	82	31.1	89	31.6	78	30.7	85	31.3
Austria	0	0	1	0.1	0	0	0	0	0	0	0	0
Azerbaijan	1	0.1	0	0	0	0	0	0	0	0	0	0
Belgium	23	2.9	21	2.4	16	6.1	19	6.7	16	6.3	19	7
Bosnia and Herzegovina	1	0.1	0	0	0	0	0	0	0	0	0	0
Brazil	1	0.1	1	0.1	0	0	0	0	0	0	0	0
Bulgaria	1	0.1	0	0	0	0	0	0	0	0	0	0
Canada	5	0.6	3	0.3	4	1.5	2	0.7	4	1.6	2	0.7
Fiji	1	0.1	0	0	0	0	0	0	0	0	0	0
France	0	0	2	0.2	0	0	0	0	0	0	0	0
Germany	2	0.2	0	0	0	0	0	0	0	0	0	0
Hong Kong	0	0	1	0.1	0	0	0	0	0	0	0	0
India	2	0.2	1	0.1	0	0	0	0	0	0	0	0
Iran (Islamic Republic of)	1	0.1	0	0	0	0	0	0	0	0	0	0
Ireland	2	0.2	0	0	0	0	0	0	0	0	0	0
Italy	2	0.2	0	0	0	0	0	0	0	0	0	0
Lebanon	1	0.1	0	0	0	0	0	0	0	0	0	0
Malaysia	2	0.2	0	0	0	0	0	0	0	0	0	0
Nepal	1	0.1	0	0	0	0	0	0	0	0	0	0
Netherlands	89	11.1	70	8	58	22	60	21.3	57	22.4	59	21.7
New Zealand	8	1	1	0.1	4	1.5	3	1.1	4	1.6	3	1.1
Nicaragua	1	0.1	0	0	0	0	0	0	0	0	0	0
Norway	1	0.1	1	0.1	0	0	0	0	0	0	0	0
Papua New Guinea	1	0.1	0	0	0	0	0	0	0	0	0	0
Poland	2	0.2	0	0	0	0	0	0	0	0	0	0
Portugal	0	0	1	0.1	0	0	0	0	0	0	0	0
Russian Federation	1	0.1	0	0	0	0	0	0	0	0	0	0
Singapore	1	0.1	1	0.1	0	0	0	0	0	0	0	0
South Africa	3	0.4	0	0	0	0	1	0.4	0	0	1	0.4
Spain	0	0	3	0.3	0	0	0	0	0	0	0	0
Sweden	0	0	2	0.2	2	0.8	2	0.7	2	0.8	2	0.7
Thailand	1	0.1	0	0	0	0	0	0	0	0	0	0
Ukraine	1	0.1	0	0	0	0	0	0	0	0	0	0
United Kingdom	190	23.7	186	21.2	17	6.4	18	6.4	16	6.3	17	6.3
United States	86	10.7	90	10.3	81	30.7	88	31.2	77	30.3	84	30.9

Descriptive table of the respondent's country of birth and current residence.

Appendix 3.9 Effect of Sex on Physical Health Outcomes

Table of cardiovascular outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Congenital Heart Disease	6 (669)	0.9	1 (159)	0.6	1.000^	1.000	1 (211)	0.5	0 (34)	0	1.000^	1.000
Cardiovascular Disease	13 (658)	2.0	5 (159)	3.1	0.368^	0.631	1 (211)	0.5	0 (34)	0	1.000^	1.000
Bleeding Disorders	5 (662)	0.8	0 (160)	0	0.589^	0.873	2 (211)	0.9	0 (33)	0	1.000^	1.000
Heart Murmur	42 (660)	6.4	4 (158)	2.5	0.060	0.203	14 (210)	6.7	2 (33)	6.1	1.000^	1.000
Palpitations	80 (659)	12.1	8 (157)	5.1	0.011	0.054	31 (209)	14.8	3 (33)	9.1	0.589^	1.000
High Blood Pressure	66 (660)	10.0	20 (159)	12.6	0.341	0.604	17 (210)	8.1	1 (34)	2.9	0.481^	1.000
Low Blood Pressure	114 (660)	17.3	9 (159)	5.7	< 0.001	**0.002***	38 (209)	18.2	2 (34)	5.9	0.073	0.710
Anaemia	219 (660)	33.2	8 (160)	5.0	< 0.001	**< 0.001***	57 (211)	27.0	3 (34)	8.8	0.022	0.475
Poor Peripheral Circulation	34 (661)	5.1	4 (160)	2.5	0.153	0.376	13 (211)	6.2	2 (34)	5.9	1.000^	1.000
High Cholesterol	57 (659)	8.6	15 (159)	9.4	0.754	1.000	20 (210)	9.5	3 (34)	8.8	1.000^	1.000
Aneurysm	2 (658)	0.3	0 (159)	0	1.000^	1.000	0 (209)	0	0 (34)	0	n/a	n/a
Phlebitis	2 (660)	0.3	0 (158)	0	1.000^	1.000	1 (211)	0.5	0 (33)	0	1.000^	1.000
Varicose Veins	61 (660)	9.2	1 (160)	0.6	< 0.001	**0.001***	14 (211)	6.6	1 (34)	2.9	0.701^	1.000
Heart Defect Surgery	6 (659)	0.9	0 (160)	0	0.603^	0.880	2 (209)	1.0	0 (34)	0	1.000^	1.000
Other	23 (658)	3.5	2 (158)	1.3	0.199^	0.445	9 (210)	4.3	0 (34)	0	0.671^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of chromosomal and genetic abnormality outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Chromosomal or Genetic Abnormality	15 (667)	2.2	5 (160)	3.1	0.565^	0.859	9 (216)	4.2	0 (34)	0	0.614^	1.000

^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people.

Table of dermatological outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Eczema	168 (671)	25.0	31 (160)	19.4	0.132	0.347	58 (215)	27.0	6 (34)	17.6	0.247	1.000
Psoriasis	49 (668)	7.3	4 (159)	2.5	0.026	0.108	18 (214)	8.4	2 (34)	5.9	1.000^	1.000
Urticaria	73 (669)	10.9	2 (160)	1.3	< 0.001	**0.001***	30 (212)	14.2	2 (34)	5.9	0.272^	1.000
Other[#]	56 (661)	8.5	8 (157)	5.1	0.157	0.377	25 (212)	11.8	2 (34)	5.9	0.391^	1.000
Acne	15 (661)	2.3	3 (157)	1.9	1.000^	-	11 (212)	5.2	0 (34)	0	0.370^	-
Colouring	34 (661)	5.1	3 (157)	1.9	0.080	-	12 (212)	5.7	1 (34)	2.9	1.000^	-
Infections	4 (661)	0.6	2 (157)	1.3	0.325^	-	1 (212)	0.5	0 (34)	0	1.000^	-
Ungrouped	4 (661)	0.6	0 (157)	0	1.000^	-	0 (212)	0	1 (34)	2.9	0.138^	-

[#] = Other conditions not classified which were then subjected to quantitative content analysis which is reported below the dashed line. Acne = also includes other conditions such as hormonal cysts, hidradenitis suppurativa, and eccrine hidrocystoma. Colouring = includes conditions that change the colour of the skin such as rosacea, dermatitis, pityriasis rosea, Henoch-Schonlein purpura, and vitiligo. Infections = includes conditions involving bacterial, viral or fungal infections of the skin such as impetigo, cellulitis, shingles, and tinea versicolour. Ungrouped = all other conditions not grouped into the above categories. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

* = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of EENT outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Eye Disorders	27 (670)	4.0	7 (160)	4.4	0.843	1.000	9 (216)	4.2	0 (34)	0	0.614^	1.000
Corrective Glasses/Lenses	400 (671)	59.6	79 (158)	50.0	0.028	0.112	137 (216)	63.4	9 (33)	27.3	< 0.001	**0.005**
Eye Surgery	16 (667)	2.4	4 (158)	2.5	1.000^	1.000	4 (212)	1.9	0 (34)	0	1.000^	1.000
Hearing Loss	35 (670)	5.2	14 (159)	8.8	0.085	0.255	18 (216)	8.3	1 (34)	2.9	0.485^	1.000
Deafness (total)	1 (666)	0.2	0 (158)	0	1.000^	1.000	0 (214)	0	0 (34)	0	n/a	n/a
Nasal Allergies/Hayfever	285 (671)	42.5	41 (159)	25.8	< 0.001	**0.001***	103 (216)	47.7	12 (32)	37.5	0.281	1.000
Tonsilectomy	119 (670)	17.8	13 (158)	8.2	0.003	**0.019***	39 (214)	18.2	3 (34)	8.8	0.175	1.000
Ear Tubes/Grommets	44 (669)	6.6	7 (159)	4.4	0.305	0.596	24 (213)	11.3	4 (34)	11.8	1.000^	1.000
Adenoidectomy	47 (670)	7.0	3 (158)	1.9	0.015	0.070	24 (214)	11.2	2 (34)	5.9	0.547^	1.000
Tinnitus	52 (671)	7.7	18 (158)	11.4	0.138	0.347	24 (214)	11.2	5 (35)	14.3	0.574^	1.000
Meniere's Disease	3 (669)	0.4	0 (158)	0	1.000^	1.000	3 (215)	1.4	0 (34)	0	1.000^	1.000
Other	26 (669)	3.9	9 (158)	5.7	0.309	0.596	9 (214)	4.2	3 (34)	8.8	0.217^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of endocrinological outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Type 1 Diabetes	2 (679)	0.3	1 (161)	0.6	0.472^	0.774	7 (217)	3.2	0 (36)	0	0.598^	1.000
Type 2 Diabetes	18 (679)	2.7	3 (161)	1.9	0.780^	1.000	1 (216)	0.5	0 (35)	0	1.000^	1.000
Pancreatitis	5 (679)	0.7	0 (160)	0	0.590^	0.873	1 (216)	0.5	0 (35)	0	1.000^	1.000
Adrenal Disorders	9 (678)	1.3	0 (161)	0	0.220^	0.454	2 (217)	0.9	0 (36)	0	1.000^	1.000
Thyroid Disease	31 (679)	4.6	2 (159)	1.3	0.054	0.194	21 (217)	9.7	1 (36)	2.8	0.333^	1.000
Pituitary Disorders	6 (679)	0.9	1 (160)	0.6	1.000^	1.000	3 (215)	1.4	1 (36)	2.8	0.464^	1.000
Other	18 (678)	2.7	0 (160)	0	0.033^	0.123	8 (215)	3.7	1 (35)	2.9	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table of gastrointestinal outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Liver Disease	12 (679)	1.8	1 (161)	0.6	0.481^	0.775	9 (215)	4.2	0 (36)	0	0.366^	1.000
IBS	100 (679)	14.7	8 (161)	5.0	0.001	**0.007***	33 (216)	15.3	3 (36)	8.3	0.270	1.000
IBD	13 (677)	1.9	2 (161)	1.2	0.748^	1.000	7 (214)	3.3	1 (36)	2.8	1.000^	1.000
Ulcers	24 (679)	3.5	2 (160)	1.3	0.202^	0.445	4 (216)	1.9	1 (36)	2.8	0.540^	1.000
Coeliac	20 (675)	3.0	0 (160)	0	0.020^	0.090	2 (216)	0.9	1 (36)	2.8	0.372^	1.000
Appendicitis	55 (680)	8.1	8 (161)	5.0	0.176	0.404	17 (216)	7.9	3 (36)	8.3	1.000^	1.000
Gall Bladder	45 (678)	6.6	2 (161)	1.2	0.007	**0.038***	11 (216)	5.1	1 (36)	2.8	1.000^	1.000
GERD	90 (677)	13.3	15 (161)	9.3	0.171	0.401	25 (217)	11.5	4 (36)	11.1	1.000^	1.000
Other	23 (679)	3.4	1 (160)	0.6	0.065^	0.213	8 (217)	3.7	1 (36)	2.8	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of immunological outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Arthritis	56 (667)	8.4	9 (160)	5.6	0.242	0.484	18 (216)	8.3	2 (32)	6.3	1.000^	1.000
Rheumatoid Arthritis	15 (667)	2.2	3 (160)	1.9	1.000^	1.000	7 (213)	3.3	0 (34)	0	0.598^	1.000
Spleen Problems	1 (666)	0.2	0 (160)	0	1.000^	1.000	1 (214)	0.5	0 (34)	0	1.000^	1.000
Gout	6 (668)	0.9	4 (160)	2.5	0.105^	0.296	2 (214)	0.9	0 (34)	0	1.000^	1.000
Lupus	3 (668)	0.4	0 (160)	0	1.000^	1.000	2 (213)	0.9	0 (34)	0	1.000^	1.000
Ankylosing Spondylitis	3 (668)	0.4	0 (160)	0	1.000^	1.000	1 (213)	0.5	0 (34)	0	1.000^	1.000
Hashimoto's Disease	7 (667)	1.0	0 (159)	0	0.357^	0.622	9 (213)	4.2	1 (34)	2.9	1.000^	1.000
Connective Tissue Disorders	10 (665)	1.5	0 (155)	0	0.223^	0.454	4 (213)	1.9	0 (34)	0	1.000^	1.000
Allergic to Anything#	258 (665)	38.8	38 (159)	23.9	< 0.001	**0.004***	99 (214)	46.3	0 (34)	0	< 0.001	**< 0.001***
Chronic Infectious Disease	15 (665)	2.2	1 (159)	0.6	0.333^	0.599	7 (212)	3.3	1 (34)	2.9	1.000^	1.000
Other	12 (665)	1.8	6 (160)	3.8	0.136^	0.347	7 (214)	3.3	1 (34)	2.9	1.000^	1.000
Environmental	115 (665)	17.3	22 (159)	13.8	0.293	-	63 (214)	29.4	10 (34)	29.4	0.997	-
Ingested	70 (665)	10.5	11 (159)	6.9	0.170	-	29 (214)	13.6	3 (34)	8.8	1.000^	-
Medication	105 (665)	15.8	5 (159)	3.1	**< 0.001**	-	28 (214)	13.1	1 (34)	2.9	0.145	-
Ungrouped	21 (665)	3.2	3 (159)	1.9	0.599^	-	4 (214)	1.9	0 (34)	0	1.000^	-

= Allergies which had free text input and were then subjected to quantitative content analysis which is reported below the dashed line. Environmental = contact allergies such as animals, plants, pollen, cosmetics, mould, latex. Ingested = food type allergies (medication excluded). Medication = such as antibiotics (can be ingested, topical or intravenous). Ungrouped = other allergies not covered by the above categories such as insect bites and stings. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

* = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of musculoskeletal outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Joint Problems	114 (670)	17.0	21 (158)	13.3	0.623	0.885	52 (215)	24.2	3 (34)	8.8	0.045	0.540
Osteoporosis	7 (668)	1.0	2 (160)	1.3	0.687^	0.964	3 (213)	1.4	0 (34)	0	1.000^	1.000
Scoliosis	59 (665)	8.9	8 (160)	5.0	0.107	0.296	25 (213)	11.7	2 (35)	5.7	0.389^	1.000
Growth Disorder	0 (668)	0	0 (160)	0	n/a	n/a	0 (215)	0	0 (34)	0	n/a	n/a
Muscular Dystrophy	1 (666)	0.2	2 (159)	1.3	0.097^	0.283	0 (214)	0	0 (34)	0	n/a	n/a
Other	40 (660)	6.1	7 (156)	4.5	0.448	0.756	14 (212)	6.6	1 (34)	2.9	0.701^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table of neurological outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Epilepsy/Seizures	22 (675)	3.3	4 (161)	2.5	0.611	0.880	4 (215)	1.9	2 (36)	5.6	0.207^	1.000
Tremors	17 (676)	2.5	2 (161)	1.2	0.554^	0.855	5 (217)	2.3	1 (36)	2.8	1.000^	1.000
Migraines	207 (675)	30.7	24 (159)	15.1	< 0.001	**0.001***	68 (215)	31.6	3 (36)	8.3	0.004	0.108
Multiple Sclerosis	3 (675)	0.4	0 (157)	0	1.000^	1.000	0 (217)	0	0 (36)	0	n/a	n/a
Vertigo	74 (676)	10.9	8 (161)	5.0	0.022	0.095	23 (216)	10.6	2 (36)	5.6	0.547^	1.000
Cerebral Palsy	1 (673)	0.1	0 (161)	0	1.000^	1.000	0 (216)	0	0 (36)	0	n/a	n/a
Fibromyalgia	18 (675)	2.7	0 (161)	0	0.032^	0.123	8 (217)	3.7	0 (36)	0	0.606^	1.000
Parkinson's Disease	2 (674)	3.0	1 (160)	0.6	0.473^	0.774	0 (216)	0	0 (36)	0	n/a	n/a
Other	10 (672)	1.5	4 (160)	2.5	0.324^	0.597	8 (213)	3.8	1 (35)	2.9	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of oncological outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Blood Cancers	3 (674)	0.4	0 (161)	0	1.000^	1.000	0 (216)	0	0 (35)	0	n/a	n/a
Skin Cancers	14 (674)	2.1	1 (162)	0.6	0.326^	0.597	9 (217)	4.1	0 (34)	0	0.614^	1.000
Bowel Cancer	0 (674)	0	0 (161)	0	n/a	n/a	0 (216)	0	0 (35)	0	n/a	n/a
Breast Cancer	4 (675)	0.6	1 (161)	0.6	1.000^	1.000	3 (215)	1.4	0 (35)	0	1.000^	1.000
Prostate Cancer (males only)	-	-	0 (161)	0	n/a	n/a	-	-	1 (36)	2.8	n/a	n/a
Bone Cancer	0 (674)	0	0 (160)	0	n/a	n/a	0 (216)	0	0 (35)	0	n/a	n/a
Brain Cancer	0 (669)	0	0 (160)	0	n/a	n/a	0 (216)	0	0 (35)	0	n/a	n/a
Lung/Tracheal Cancer	0 (672)	0	0 (161)	0	n/a	n/a	0 (216)	0	0 (35)	0	n/a	n/a
Pancreatic Cancer	0 (673)	0	0 (160)	0	n/a	n/a	0 (216)	0	0 (34)	0	n/a	n/a
Other	16 (667)	2.4	2 (158)	1.3	0.549^	0.855	4 (215)	1.9	0 (35)	0	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table of reproductive outcomes by sex

These were already stratified by sex (see Tables 4.13 and 4.14).

Table of respiratory outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Asthma	190 (680)	27.9	23 (160)	14.4	< 0.001	**0.003***	65 (219)	29.7	9 (34)	26.5	0.702	1.000
COPD	4 (674)	0.6	0 (161)	0	1.000^	1.000	3 (216)	1.4	0 (34)	0	1.000^	1.000
Acute Bronchitis	103 (680)	15.1	8 (162)	4.9	0.001	**0.007***	45 (218)	20.6	12 (36)	33.3	0.091	0.710
Sleep Apnoea	18 (679)	2.7	5 (162)	3.1	0.788^	1.000	15 (217)	6.9	2 (35)	5.7	1.000^	1.000
Pneumonia	88 (675)	13.0	9 (161)	5.6	0.008	**0.041***	35 (218)	16.1	4 (35)	11.4	0.599	1.000
Other	15 (681)	2.2	4 (162)	2.5	0.772^	1.000	6 (219)	2.7	0 (36)	0	0.599^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of urogenital outcomes by sex

	Spontaneous						Donor Sperm-Conceived					
	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*	Female n (Total)	%	Male n (Total)	%	*p*	BH *p*
Kidney Disease	4 (676)	0.6	2 (161)	1.2	0.326^	0.597	2 (216)	0.9	0 (35)	0	1.000^	1.000
Kidney Stones	20 (676)	3.0	8 (161)	5.0	0.216^	0.454	11 (216)	5.1	1 (35)	2.9	1.000^	1.000
Bladder Disease	7 (673)	1.0	1 (161)	0.6	1.000^	1.000	6 (215)	2.8	0 (35)	0	1.000^	1.000
Urogenital Defects	5 (675)	0.7	4 (160)	2.5	0.074^	0.235	1 (216)	0.5	0 (34)	0	1.000^	1.000
Other	17 (674)	2.5	1 (159)	0.6	0.222^	0.454	4 (215)	1.9	0 (35)	0	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Appendix 3.10 Effect of Maternal Complications on Physical Health Outcomes

Table of cardiovascular outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Congenital Heart Disease	0 (100)	0	6 (616)	1.0	1.000^	1.000	0 (44)	0	1 (152)	0.7	1.000^	1.000
Cardiovascular Disease	2 (101)	2.0	14 (615)	2.3	1.000^	1.000	0 (44)	0	1 (152)	0.7	1.000^	1.000
Bleeding Disorders	0 (101)	0	4 (619)	0.6	1.000^	1.000	0 (44)	0	2 (151)	1.3	1.000^	1.000
Heart Murmur	9 (100)	9.0	29 (617)	4.7	0.075	0.241	1 (44)	2.3	9 (150)	6.0	0.460^	1.000
Palpitations	17 (101)	16.8	64 (614)	10.4	0.060	0.209	7 (44)	15.9	21 (149)	14.1	0.764	1.000
High Blood Pressure	15 (101)	14.9	59 (616)	9.6	0.106	0.308	5 (43)	11.6	9 (152)	5.9	0.197^	1.000
Low Blood Pressure	17 (101)	16.8	96 (616)	15.6	0.750	1.000	7 (43)	16.3	22 (151)	14.6	0.781	1.000
Anaemia	37 (100)	37.0	160 (618)	25.9	0.021	0.099	14 (44)	31.8	32 (152)	21.1	0.138	1.000
Poor Peripheral Circulation	6 (101)	5.9	27 (618)	4.4	0.446^	0.830	3 (44)	6.8	8 (152)	5.3	0.713^	1.000
High Cholesterol	9 (101)	8.9	48 (617)	7.8	0.697	1.000	6 (44)	13.6	9 (151)	6.0	0.110^	1.000
Aneurysm	0 (100)	0	1 (615)	0.2	1.000^	1.000	0 (44)	0	0 (150)	0	n/a	n/a
Phlebitis	1 (101)	1.0	0 (617)	0	0.141^	0.374	0 (44)	0	1 (152)	0.7	1.000^	1.000
Varicose Veins	10 (101)	9.9	43 (617)	7.0	0.296	0.645	1 (44)	2.3	10 (152)	6.6	0.461^	1.000
Heart Defect Surgery	0 (100)	0	5 (617)	0.8	1.000^	1.000	0 (42)	0	1 (152)	0.7	1.000^	1.000
Other	2 (100)	2.0	18 (615)	2.9	1.000^	1.000	1 (44)	2.3	6 (151)	4.0	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table of chromosomal and genetic abnormality outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Chromosomal or Genetic Abnormality	2 (103)	1.9	16 (631)	2.5	1.000^	1.000	1 (44)	2.3	7 (158)	4.4	1.000^	1.000

^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people.

Table of dermatological outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Eczema	42 (103)	40.8	131 (626)	20.9	< 0.001	**< 0.001***	10 (44)	22.7	40 (155)	25.8	0.678	1.000
Psoriasis	14 (103)	13.6	34 (623)	5.5	0.002	**0.019***	4 (44)	9.1	10 (154)	6.5	0.517^	1.000
Urticaria	13 (103)	12.6	51 (625)	8.2	0.138	0.374	8 (44)	18.2	19 (153)	12.4	0.218	1.000
Other[#]	10 (101)	9.9	46 (617)	7.5	0.396	0.779	6 (44)	13.6	13 (153)	8.5	0.383^	1.000
Acne	4 (101)	4.0	11 (617)	1.8	0.248^	-	1 (44)	2.3	7 (153)	4.6	0.687^	-
Colouring	7 (101)	6.9	26 (617)	4.2	0.208^	-	3 (44)	6.8	5 (153)	3.3	0.381^	-
Infections	0 (101)	0	6 (617)	1.0	1.000^	-	1 (44)	2.3	0 (153)	0	0.223^	-
Ungrouped	0 (101)	0	3 (617)	0.5	1.000^	-	0 (44)	0	1 (153)	0.7	1.000^	-

[#] = Other conditions not classified which were then subjected to quantitative content analysis which is reported below the dashed line. Acne = also includes other conditions such as hormonal cysts, hidradenitis suppurativa, and eccrine hidrocystoma. Colouring = includes conditions that change the colour of the skin such as rosacea, dermatitis, pityriasis rosea, Henoch-Schonlein purpura, and vitiligo. Infections = includes conditions involving bacterial, viral or fungal infections of the skin such as impetigo, cellulitis, shingles, and tinea versicolour. Ungrouped = all other conditions not grouped into the above categories. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

* = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of EENT outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Eye Disorders	6 (103)	5.8	23 (625)	3.7	0.281^	0.641	2 (44)	4.5	6 (156)	3.8	1.000^	1.000
Corrective Glasses/Lenses	62 (103)	60.2	357 (624)	57.2	0.570	0.979	24 (43)	55.8	95 (156)	60.9	0.547	1.000
Eye Surgery	2 (103)	1.9	14 (620)	2.3	1.000^	1.000	1 (44)	2.3	2 (153)	1.3	0.534^	1.000
Hearing Loss	10 (103)	9.7	29 (624)	4.6	0.035	0.142	6 (44)	13.6	9 (156)	5.8	0.103^	1.000
Deafness (total)	0 (101)	0	0 (623)	0	n/a	n/a	0 (43)	0	0 (155)	0	n/a	n/a
Nasal Allergies/Hayfever	55 (103)	53.4	233 (625)	37.3	0.002	**0.019***	21 (44)	47.7	71 (155)	45.8	0.822	1.000
Tonsilectomy	16 (102)	15.7	102 (624)	16.3	0.867	1.000	7 (43)	16.3	24 (156)	15.4	0.886	1.000
Ear Tubes/Grommets	11 (103)	10.7	31 (623)	5.0	0.022	0.099	8 (43)	18.6	17 (154)	11.0	0.205	1.000
Adenoidectomy	8 (102)	7.8	35 (624)	5.6	0.376	0.752	5 (43)	11.6	15 (155)	9.7	0.775^	1.000
Tinnitus	11 (103)	10.7	47 (624)	7.5	0.275	0.641	5 (43)	11.6	18 (156)	11.5	1.000^	1.000
Meniere's Disease	0 (102)	0	3 (624)	0.5	1.000^	1.000	0 (43)	0	1 (156)	0.6	1.000^	1.000
Other	2 (103)	1.9	25 (622)	4.0	0.408^	0.790	3 (44)	6.8	8 (154)	5.2	0.711^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of endocrinological outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Type 1 Diabetes	1 (106)	0.9	1 (632)	0.2	0.267^	0.639	0 (44)	0	5 (159)	3.1	0.587^	1.000
Type 2 Diabetes	3 (106)	2.8	12 (632)	1.9	0.463^	0.831	0 (44)	0	1 (159)	0.6	1.000^	1.000
Pancreatitis	0 (106)	0	5 (631)	0.8	1.000^	1.000	0 (44)	0	1 (159)	0.6	1.000^	1.000
Adrenal Disorders	1 (105)	1.0	6 (632)	0.9	1.000^	1.000	0 (44)	0	1 (159)	0.6	1.000^	1.000
Thyroid Disease	3 (106)	2.8	26 (630)	4.1	0.787^	1.000	3 (44)	6.8	13 (159)	8.2	1.000^	1.000
Pituitary Disorders	0 (106)	0	5 (631)	0.8	1.000^	1.000	0 (44)	0	3 (157)	1.9	1.000^	1.000
Other	4 (106)	3.8	13 (630)	2.1	0.289^	0.641	1 (44)	2.3	4 (156)	2.6	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table of gastrointestinal outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Liver Disease	2 (106)	1.9	9 (632)	1.4	0.664^	1.000	1 (44)	2.3	5 (158)	3.2	1.000^	1.000
IBS	20 (106)	18.9	79 (632)	12.5	0.075	0.241	8 (44)	18.2	19 (159)	11.9	0.281	1.000
IBD	2 (106)	1.9	13 (630)	2.1	1.000^	1.000	2 (44)	4.5	2 (158)	1.3	0.207^	1.000
Ulcers	5 (106)	4.7	16 (632)	2.5	0.208^	0.529	2 (44)	4.5	2 (159)	1.3	0.206^	1.000
Coeliac	4 (105)	3.8	13 (630)	2.1	0.286^	0.641	0 (44)	0	2 (159)	1.3	1.000^	1.000
Appendicitis	12 (106)	11.3	42 (633)	6.6	0.086	0.269	5 (44)	11.4	9 (159)	5.7	0.190^	1.000
Gall Bladder	4 (106)	3.8	35 (632)	5.5	0.452	0.830	5 (44)	11.4	6 (159)	3.8	0.063^	0.961
GERD	20 (106)	18.9	73 (630)	11.6	0.037	0.146	5 (44)	11.4	14 (159)	8.8	0.568^	1.000
Other	4 (106)	3.8	19 (631)	3.0	0.761^	1.000	2 (44)	4.5	6 (159)	3.8	0.685^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table of immunological outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Arthritis	14 (102)	13.7	43 (623)	6.9	0.018	0.092	4 (44)	9.1	11 (154)	7.1	0.747^	1.000
Rheumatoid Arthritis	5 (102)	4.9	10 (623)	1.6	0.047^	0.174	2 (44)	4.5	5 (153)	3.3	0.654^	1.000
Spleen Problems	1 (102)	1.0	0 (622)	0	0.141^	0.374	0 (44)	0	1 (154)	0.6	1.000^	1.000
Gout	2 (102)	2.0	7 (624)	1.1	0.368^	0.748	0 (44)	0	2 (154)	1.3	1.000^	1.000
Lupus	1 (102)	1.0	2 (624)	0.3	0.365^	0.478	1 (44)	2.3	1 (154)	0.6	0.396^	1.000
Ankylosing Spondylitis	0 (102)	0	3 (624)	0.5	1.000^	1.000	0 (43)	0	1 (154)	0.6	1.000^	1.000
Hashimoto's Disease	2 (101)	2.0	5 (623)	0.8	0.254^	0.627	1 (44)	2.3	4 (153)	2.6	1.000^	1.000
Connective Tissue Disorders	3 (101)	3.0	7 (618)	1.1	0.154^	0.400	2 (43)	4.7	2 (154)	1.3	0.208^	1.000
Allergic to Anything[#]	48 (102)	47.1	214 (622)	34.4	0.014	0.085	19 (44)	43.2	70 (154)	45.5	0.789	1.000
Chronic Infectious Disease	3 (102)	2.9	12 (621)	1.9	0.456^	0.830	1 (44)	2.3	5 (152)	3.3	1.000^	1.000
Other	3 (102)	2.9	12 (621)	1.9	0.456^	0.830	2 (44)	4.5	6 (154)	3.9	1.000^	1.000
Environmental	22 (102)	21.6	98 (621)	15.8	0.145	-	12 (44)	27.3	45 (154)	29.2	0.801	-
Ingested	19 (102)	18.6	55 (621)	8.9	0.003	-	6 (44)	13.6	20 (154)	13.0	1.000^	-
Medication	6 (102)	5.9	80 (621)	12.9	0.043	-	7 (44)	15.9	16 (154)	10.4	0.314	-
Ungrouped	0 (102)	0	19 (621)	3.1	0.093^	-	2 (44)	4.5	2 (154)	1.3	0.214^	-

[#] = Allergies which had free text input and were then subjected to quantitative content analysis which is reported below the dashed line. Environmental = contact allergies such as animals, plants, pollen, cosmetics, mould, latex. Ingested = food type allergies (medication excluded). Medication = such as antibiotics (can be ingested, topical or intravenous). Ungrouped = other allergies not covered by the above categories such as insect bites and stings. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table of musculoskeletal outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Joint Problems	28 (102)	27.5	90 (624)	14.4	0.001	**0.011***	14 (44)	31.8	27 (155)	17.4	0.037	0.961
Osteoporosis	2 (102)	2.0	5 (624)	0.8	0.257^	0.627	0 (43)	0	3 (154)	1.9	1.000^	1.000
Scoliosis	9 (102)	8.8	46 (622)	7.4	0.614	0.999	6 (44)	13.6	16 (154)	10.4	0.592^	1.000
Growth Disorder	0 (102)	0	0 (624)	0	n/a	n/a	0 (44)	0	0 (155)	0	n/a	n/a
Muscular Dystrophy	0 (102)	0	1 (621)	0.2	1.000^	1.000	0 (44)	0	0 (154)	0	n/a	n/a
Other	10 (101)	9.9	34 (614)	5.5	0.091	0.278	3 (44)	6.8	8 (152)	5.3	0.713^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of neurological outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Epilepsy/Seizures	6 (104)	5.8	15 (630)	2.4	0.102^	0.304	3 (44)	6.8	1 (157)	0.6	0.034^	0.961
Tremors	6 (104)	5.8	11 (631)	1.7	0.023^	0.100	2 (44)	4.5	2 (159)	1.3	0.206^	1.000
Migraines	49 (104)	47.1	161 (628)	25.6	< 0.001	**< 0.001***	14 (44)	31.8	44 (157)	28.0	0.624	1.000
Multiple Sclerosis	0 (104)	0	3 (629)	0.5	1.000^	1.000	0 (44)	0	0 (159)	0	n/a	n/a
Vertigo	17 (104)	16.8	53 (631)	8.4	0.011	0.071	5 (44)	11.4	12 (158)	7.6	0.538^	1.000
Cerebral Palsy	1 (103)	1.0	0 (630)	0	0.141^	0.374	0 (43)	0	0 (159)	0	n/a	n/a
Fibromyalgia	6 (103)	5.8	10 (631)	1.6	0.016^	0.085	2 (44)	4.5	4 (159)	2.5	0.612^	1.000
Parkinson's Disease	1 (103)	1.0	2 (630)	0.3	0.366^	0.748	0 (44)	0	0 (158)	0	n/a	n/a
Other	2 (104)	1.9	12 (626)	1.9	1.000^	1.000	4 (43)	9.3	3 (157)	1.9	0.040^	0.961

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table of oncological outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Blood Cancers	3 (104)	2.9	0 (629)	0	0.003^	**0.026***	0 (44)	0	0 (157)	0	n/a	n/a
Skin Cancers	2 (104)	1.9	10 (630)	1.6	0.683^	1.000	0 (44)	0	6 (157)	3.8	0.343^	1.000
Bowel Cancer	0 (104)	0	0 (629)	0	n/a	n/a	0 (44)	0	0 (157)	0	n/a	n/a
Breast Cancer (all sexes)	0 (104)	0	5 (630)	0.8	1.000^	1.000	1 (44)	2.3	2 (156)	1.3	0.527^	1.000
Breast Cancer (females only)	0 (96)	0	4 (497)	0.8	1.000^	1.000	1 (39)	2.6	2 (134)	1.5	0.538^	1.000
Prostate Cancer (males only)	0 (8)	0	0 (133)	0	n/a	n/a	0 (5)	0	0 (22)	0	n/a	n/a
Bone Cancer	0 (104)	0	0 (629)	0	n/a	n/a	0 (44)	0	0 (157)	0	n/a	n/a
Brain Cancer	0 (102)	0	0 (626)	0	n/a	n/a	0 (44)	0	0 (157)	0	n/a	n/a
Lung/Tracheal Cancer	0 (102)	0	0 (629)	0	n/a	n/a	0 (44)	0	0 (157)	0	n/a	n/a
Pancreatic Cancer	0 (103)	0	0 (628)	0	n/a	n/a	0 (44)	0	0 (157)	0	n/a	n/a
Other	3 (100)	3.0	15 (623)	2.4	0.727^	1.000	0 (44)	0	3 (156)	1.9	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of reproductive outcomes (female) by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Ovarian Cysts	20 (93)	21.5	84 (492)	17.1	0.305	0.653	9 (39)	23.1	25 (133)	18.8	0.555	1.000
Endometriosis	12 (93)	12.9	30 (491)	6.1	0.020	0.098	3 (38)	7.9	6 (133)	4.5	0.418^	1.000
Menstrual Problems	43 (93)	46.2	132 (491)	26.9	< 0.001	**0.004***	16 (39)	41.0	33 (133)	24.8	0.049	0.961
PCOS	9 (92)	9.8	38 (491)	7.7	0.509	0.900	4 (39)	10.3	9 (133)	6.8	0.495^	1.000
Infertility	7 (92)	7.6	47 (488)	9.6	0.540	0.941	6 (39)	15.4	7 (133)	5.3	0.077^	1.000
Other	9 (92)	9.8	22 (492)	4.5	0.045^	0.172	4 (39)	10.3	5 (133)	3.8	0.119^	1.000
Pregnancy	38 (93)	40.9	277 (487)	56.9	0.004	**0.033**	17 (39)	43.6	81 (131)	61.8	0.043	0.961
Parity (Mean (SD))	1.72 (1.21)	-	1.91 (1.04)	-	0.377	-	1.71 (0.85)	-	1.61 (1.11)	-	0.706	-

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. Parity data is continuous data analysed by two-tailed student's t-test. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of reproductive outcomes (male) by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Testicular Problems	0 (8)	0	8 (129)	6.2	1.000^	1.000	1 (5)	20	0 (21)	0	0.192^	1.000
Prostate Problems	0 (8)	0	2 (129)	1.6	1.000^	1.000	0 (5)	0	0 (21)	0	n/a	n/a
Low Sperm Count/Quality	0 (8)	0	2 (129)	1.6	1.000^	1.000	0 (5)	0	0 (21)	0	n/a	n/a
Infertility	0 (8)	0	1 (129)	0.8	1.000^	1.000	0 (5)	0	0 (21)	0	n/a	n/a
Other	0 (8)	0	4 (128)	3.1	1.000^	1.000	0 (5)	0	0 (21)	0	n/a	n/a

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table of respiratory outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Asthma	36 (105)	34.3	152 (634)	24.0	0.025	0.105	14 (43)	32.6	43 (159)	27.0	0.476	1.000
COPD	0 (105)	0	3 (628)	0.5	1.000^	1.000	0 (43)	0	3 (157)	1.9	1.000^	1.000
Acute Bronchitis	25 (106)	23.6	75 (634)	11.8	0.001	**0.011***	13 (44)	29.5	33 (160)	20.6	0.210	1.000
Sleep Apnoea	3 (106)	2.8	17 (633)	2.7	1.000^	1.000	2 (43)	4.7	7 (159)	4.4	1.000^	1.000
Pneumonia	20 (106)	18.9	67 (628)	10.7	0.016	0.085	8 (43)	18.6	23 (160)	14.4	0.494	1.000
Other	2 (105)	1.9	14 (636)	2.2	1.000^	1.000	2 (44)	4.5	3 (160)	1.9	0.294^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. * = *p* value significant after Benjamini-Hochberg adjustment ($p < 0.05$).

Table of urogenital outcomes by maternal complications

	Spontaneous						Donor Sperm-Conceived					
	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*	Yes n (Total)	%	No n (Total)	%	*p*	BH *p*
Kidney Disease	1 (104)	1.0	5 (631)	0.8	0.601	0.991	0 (44)	0	0 (157)	0	n/a	n/a
Kidney Stones	5 (104)	4.8	23 (631)	3.6	0.578^	0.979	3 (44)	6.8	6 (157)	3.8	0.414	1.000
Bladder Disease	1 (103)	1.0	5 (629)	0.8	0.599^	0.991	1 (44)	2.3	3 (156)	1.9	1.000^	1.000
Urogenital Defects	1 (104)	1.0	6 (629)	1.0	1.000^	1.000	0 (44)	0	0 (157)	0	n/a	n/a
Other	2 (104)	1.9	14 (628)	2.2	1.000^	1.000	0 (44)	0	4 (156)	2.6	0.578^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Appendix 3.11 Effect of the Country of Birth (Australia) on Physical Health Outcomes

Table of cardiovascular outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Congenital Heart Disease	0 (339)	0	0 (70)	0	n/a	n/a
Cardiovascular Disease	6 (338)	1.8	0 (70)	0	0.595^	1.000
Bleeding Disorders	1 (339)	0.3	1 (70)	1.4	0.313^	1.000
Heart Murmur	21 (336)	6.3	3 (70)	4.3	0.780^	1.000
Palpitations	44 (333)	13.2	8 (70)	11.4	0.686	1.000
High Blood Pressure	43 (338)	12.7	0 (70)	0	0.002	0.081
Low Blood Pressure	72 (337)	21.4	13 (70)	18.6	0.601	1.000
Anaemia	113 (339)	33.3	31 (70)	44.3	0.081	0.760
Poor Peripheral Circulation	15 (338)	4.4	6 (70)	8.6	0.144^	0.912
High Cholesterol	39 (338)	11.5	5 (70)	7.1	0.281	1.000
Aneurysm	1 (338)	0.3	0 (70)	0	1.000^	1.000
Phlebitis	0 (337)	0	0 (70)	0	n/a	n/a
Varicose Veins	31 (338)	9.2	7 (70)	10.0	0.828	1.000
Heart Defect Surgery	2 (338)	0.6	0 (69)	0	1.000^	1.000
Other	10 (336)	3.0	4 (70)	5.7	0.268^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table of chromosomal and genetic abnormality outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Chromosomal or Genetic Abnormality	11 (348)	3.2	2 (71)	2.8	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table of dermatological outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Eczema	100 (344)	29.1	20 (71)	28.2	0.879	1.000
Psoriasis	30 (341)	8.8	8 (70)	11.4	0.489	1.000
Urticaria	45 (343)	13.1	11 (68)	16.2	0.502	1.000
Other[#]	35 (340)	10.3	9 (71)	12.7	0.555	1.000
Acne	8 (340)	2.3	4 (71)	5.6	0.135^	-
Colouring	25 (340)	7.4	5 (71)	7.0	0.927	-
Infections	1 (340)	0.3	0 (71)	0	1.000^	-
Ungrouped	1 (340)	0.3	0 (71)	0	1.000^	-

[#] = Other conditions not classified which were then subjected to quantitative content analysis which is reported below the dashed line. Acne = also includes other conditions such as hormonal cysts, hidradenitis suppurativa, and eccrine hidrocystoma. Colouring = includes conditions that change the colour of the skin such as rosacea, dermatitis, pityriasis rosea, Henoch-Schonlein purpura, and vitiligo. Infections = includes conditions involving bacterial, viral or fungal infections of the skin such as impetigo, cellulitis, shingles, and tinea versicolour. Ungrouped = all other conditions not grouped into the above categories. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. BH correction not performed on content analysis. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table of EENT outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Eye Disorders	11 (344)	3.2	2 (71)	2.8	1.000^	1.000
Corrective Glasses/Lenses	191 (343)	55.7	34 (71)	47.9	0.230	1.000
Eye Surgery	8 (343)	2.3	0 (71)	0	0.361^	1.000
Hearing Loss	22 (344)	6.4	4 (71)	5.6	1.000^	1.000
Deafness (total)	0 (341)	0	0 (71)	0	n/a	n/a
Nasal Allergies/Hayfever	157 (344)	45.6	35 (70)	50.0	0.505	1.000
Tonsilectomy	62 (344)	18.0	8 (71)	11.3	0.166	0.912
Ear Tubes/Grommets	21 (343)	6.1	8 (71)	11.3	0.128^	0.912
Adenoidectomy	24 (344)	7.0	7 (71)	9.9	0.400	1.000
Tinnitus	28 (344)	8.1	9 (71)	12.7	0.222	1.000
Meniere's Disease	3 (343)	0.9	1 (71)	1.4	0.530^	1.000
Other	12 (342)	3.5	9 (70)	12.7	0.004^	0.098

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table of endocrinological outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Type 1 Diabetes	1 (349)	0.3	3 (71)	4.2	0.016^	0.279
Type 2 Diabetes	6 (349)	1.7	0 (71)	0	0.595	1.000
Pancreatitis	2 (348)	0.6	1 (71)	1.4	0.428^	1.000
Adrenal Disorders	7 (349)	2.0	0 (71)	0	0.608	1.000
Thyroid Disease	17 (348)	4.9	5 (71)	7.0	0.396^	1.000
Pituitary Disorders	4 (348)	1.1	2 (71)	2.8	0.269^	1.000
Other	12 (348)	3.4	4 (69)	5.8	0.316^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table of gastrointestinal outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Liver Disease	5 (348)	1.4	4 (71)	5.6	0.049^	0.598
IBS	40 (349)	11.5	6 (71)	8.5	0.459	1.000
IBD	8 (346)	2.3	1 (71)	1.4	1.000^	1.000
Ulcers	10 (348)	2.9	0 (71)	0	0.224^	1.000
Coeliac	10 (347)	2.9	3 (71)	4.2	0.470	1.000
Appendicitis	31 (349)	8.9	6 (71)	8.5	0.933	1.000
Gall Bladder	19 (348)	5.5	3 (71)	4.2	1.000^	1.000
GERD	54 (348)	15.5	6 (71)	8.5	0.121	0.912
Other	14 (348)	4.0	3 (71)	4.2	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table of immunological outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Arthritis	39 (340)	8.5	4 (71)	0.6	0.144	0.912
Rheumatoid Arthritis	6 (340)	1.8	1 (70)	1.4	1.000^	1.000
Spleen Problems	1 (341)	0.3	0 (70)	0	1.000^	1.000
Gout	5 (341)	1.5	0 (71)	0	0.593^	1.000
Lupus	1 (341)	0.3	0 (70)	0	1.000^	1.000
Ankylosing Spondylitis	2 (341)	0.6	0 (71)	0	1.000^	1.000
Hashimoto's Disease	1 (340)	0.3	0 (71)	0	1.000^	1.000
Connective Tissue Disorders	3 (340)	0.9	1 (71)	1.4	0.523^	1.000
Allergic to Anything#	122 (341)	35.8	29 (71)	40.8	0.420	1.000
Chronic Infectious Disease	7 (340)	2.0	2 (70)	2.9	0.654^	1.000
Other	3 (340)	0.9	3 (71)	4.2	0.067^	0.743
Environmental	47 (340)	13.8	20 (71)	28.2	**< 0.001**	-
Ingested	28 (340)	8.2	12 (71)	16.9	**0.025**	-
Medication	57 (340)	16.8	9 (71)	12.7	0.393	-
Ungrouped	14 (340)	4.1	1 (71)	1.4	0.485^	-

= Allergies which had free text input and were then subjected to quantitative content analysis which is reported below the dashed line. Environmental = contact allergies such as animals, plants, pollen, cosmetics, mould, latex. Ingested = food type allergies (medication excluded). Medication = such as antibiotics (can be ingested, topical or intravenous). Ungrouped = other allergies not covered by the above categories such as insect bites and stings. Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. BH correction not performed on content analysis. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Table of musculoskeletal outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Joint Problems	56 (341)	16.4	15 (71)	21.1	0.340	1.000
Osteoporosis	5 (341)	1.5	1 (69)	1.4	1.000^	1.000
Scoliosis	33 (339)	9.7	7 (71)	9.9	0.974	1.000
Growth Disorder	0 (341)	0	0 (71)	0	n/a	n/a
Muscular Dystrophy	1 (340)	0.3	0 (71)	0	1.000^	1.000
Other	24 (334)	7.2	4 (70)	5.7	1.000^	1.000

Pearson chi-squared (two-tailed) *P* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *P* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *P* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *P* values cannot be calculated.

Table of neurological outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Epilepsy/Seizures	11 (348)	3.2	3 (71)	4.2	0.715^	1.000
Tremors	10 (348)	2.9	2 (71)	2.8	1.000^	1.000
Migraines	103 (346)	29.8	23 (69)	33.3	0.557	1.000
Multiple Sclerosis	2 (348)	0.6	0 (71)	0	1.000^	1.000
Vertigo	46 (348)	13.2	9 (71)	12.7	0.902	1.000
Cerebral Palsy	0 (348)	0	0 (71)	0	n/a	n/a
Fibromyalgia	9 (347)	2.6	1 (71)	1.4	1.000^	1.000
Parkinson's Disease	3 (347)	0.9	0 (70)	0	1.000^	1.000
Other	6 (345)	1.7	3 (68)	4.4	0.172^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table of oncological outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Blood Cancers	2 (347)	0.6	0 (71)	0	1.000^	1.000
Skin Cancers	7 (347)	2.0	3 (71)	4.2	0.384^	1.000
Bowel Cancer	0 (347)	0	0 (71)	0	n/a	n/a
Breast Cancer (all sexes)	4 (347)	1.2	1 (71)	1.4	1.000^	1.000
Breast Cancer (females only)	3 (310)	1.0	1 (60)	1.7	0.509^	1.000
Prostate Cancer (males only)	0 (34)	0	0 (11)	0	n/a	n/a
Bone Cancer	0 (347)	0	0 (71)	0	n/a	n/a
Brain Cancer	0 (345)	0	0 (71)	0	n/a	n/a
Lung/Tracheal Cancer	0 (346)	0	0 (71)	0	n/a	n/a
Pancreatic Cancer	0 (346)	0	0 (71)	0	n/a	n/a
Other	8 (343)	2.3	0 (71)	0	0.361^	1.000

Pearson chi-squared (two-tailed) *P* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *P* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *P* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *P* values cannot be calculated.

Table of reproductive outcomes in female Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Ovarian Cysts	60 (307)	19.5	7 (59)	11.9	0.162	0.912
Endometriosis	24 (307)	7.8	1 (58)	1.7	0.151^	0.912
Menstrual Problems	99 (306)	32.4	18 (59)	30.5	0.781	1.000
PCOS	25 (306)	8.2	4 (59)	6.8	1.000^	1.000
Infertility	25 (305)	8.2	1 (59)	1.7	0.096^	0.837
Other	19 (307)	6.2	5 (59)	8.5	0.564^	1.000
Pregnancy	145 (309)	46.9	30 (58)	51.7	0.502	1.000
Parity (Mean (SD))	1.84 (1.09)	-	1.72 (1.03)	-	0.598	-

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. Parity data is continuous data analysed by two-tailed student's t-test.

Table of reproductive outcomes in male Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Testicular Problems	3 (34)	8.8	1 (11)	9.1	1.000^	1.000
Prostate Problems	0 (34)	0	0 (11)	0	n/a	n/a
Low Sperm Count/Quality	0 (34)	0	1 (11)	9.1	0.244^	1.000
Infertility	0 (34)	0	1 (11)	9.1	0.244^	1.000
Other	1 (33)	3.0	0 (11)	0	1.000^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table of respiratory outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Asthma	99 (346)	28.6	23 (72)	31.9	0.572	1.000
COPD	0 (345)	0	0 (71)	0	n/a	n/a
Acute Bronchitis	63 (349)	18.1	12 (72)	16.7	0.780	1.000
Sleep Apnoea	12 (349)	3.4	3 (72)	4.2	0.729^	1.000
Pneumonia	51 (347)	14.7	13 (72)	18.1	0.471	1.000
Other	12 (350)	3.4	1 (72)	1.4	0.706^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5. n/a = not applicable as chi-squared *p* values cannot be calculated.

Table of urogenital outcomes in Australian respondents

	Spontaneous		Donor Sperm-Conceived			
	n (Total)	%	n (Total)	%	*p*	BH *p*
Kidney Disease	2 (348)	0.6	0 (71)	0	1.000^	1.000
Kidney Stones	12 (348)	3.4	3 (71)	4.2	0.727^	1.000
Bladder Disease	1 (346)	0.3	0 (71)	0	1.000^	1.000
Urogenital Defects	5 (348)	1.4	1 (71)	1.4	1.000^	1.000
Other	10 (346)	2.9	1 (71)	1.4	0.699^	1.000

Pearson chi-squared (two-tailed) *p* value versus spontaneously conceived people. BH = Benjamini-Hochberg procedure adjusted *p* value versus spontaneously conceived people. ^ = Fisher's Exact Test (two-tailed) *p* value versus spontaneously conceived people used instead of Pearson chi-squared for when > 20% of cells in chi-squared table have expected values less than 5.

Appendix 4 Publication: Conceptualising a child-centric paradigm: do we have freedom of choice in donor conception reproduction? (Chapter 5)

See next page

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ORIGINAL RESEARCH

Conceptualising a Child-Centric Paradigm

Do We Have Freedom of Choice in Donor Conception Reproduction?

Damian H. Adams

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Abstract Since its inception, donor conception practices have been a reproductive choice for the infertile. Past and current practices have the potential to cause significant and lifelong harm to the offspring through loss of kinship, heritage, identity, and family health history, and possibly through introducing physical problems. Legislation and regulation in Australia that specifies that the welfare of the child born as a consequence of donor conception is paramount may therefore be in conflict with the outcomes. Altering the paradigm to a child-centric model, however, impinges on reproductive choice and rights of adults involved in the process. With some lobby groups pushing for increased reproductive choice while others emphasise offspring rights there is a dichotomy of interests that society and legislators need to address. Concepts pertaining to a shift toward a child-centric paradigm are discussed.

Keywords Reproductive techniques, assisted · Ethics · Policy · Child welfare

Introduction

Choosing when, with whom, and how we procreate is often viewed as an inalienable human freedom. This freedom to reproduce has been a cornerstone of society and family life for those biologically capable of reproducing.[1] For those suffering from infertility, the introduction and implementation of donor conception (DC) finally enabled many to create the family they long desired.[2] Prior to this, while the infertile may have been legally free to procreate they were thwarted biologically. Donor conception has provided individuals and couples struggling with infertility with increased freedom to procreate, to choose to start a

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[1] While it is assumed in general society that the average citizen is and has typically been able to enjoy this freedom of procreation, this has not always been uniformly acknowledged or applied. For example, forced sterilisations have occurred around the world, mainly in the 20th century. Some forced sterilisations were a direct result of a flawed and discriminatory eugenics-based approach to try to "improve" a society's gene pool; others have been carried out in a related vein under different circumstances, including the sterilisation of HIV-positive women in South Africa; forced sterilisations in China, according to Amnesty International, following the adoption of the one-child policy; and involuntary or coerced sterilisation of people with disabilities, a subject that is currently before a Senate Inquiry in Australia. Thus, in past and current human societies, procreative freedom may be available only in certain jurisdictions to those deemed "fit" to enjoy it.

[2] Donor conception refers to a method of reproduction whereby a third-party's gametes are used to create a pregnancy. This circumvents infertility rather than treating the cause of it. The use of donor sperm is widely acknowledged to have been first performed by a physician in 1884 (Gregoire and Mayer 1965); however, the use of donor sperm as a fertility treatment became mainstream practice with the introduction of fertility clinics starting predominantly in the 1960s and 1970s. The first pregnancy established from a donor embryo was recorded in 1983 (Trounson et al. 1983), and the first successful birth from a donor oocyte was reported in 1984 (Lutjen et al. 1984).

family via a treatment process if they so wish. This has resulted in improved choice and control over family creation.

Ethical, moral, and legal perspectives of DC practices became institutionalised in Australia during the 1980s, when the first laws concerning this form of fertility treatment were enacted. Legislation varies considerably between Australian states, providing a mosaic of disproportionate rights to donor-conceived offspring—a situation aptly described by Schneller as "chaotic" (2005, 244). The psychological and medical welfare of any donor-conceived person hinges on these rights and subsequently the very state in which that person was conceived and/or the era of the conception, due to the ever-changing landscape of legislation and regulations. It is this modern period of donor conception practice governed by legislation and regulation and how these relate to child welfare that is the focus of this article. During the early bureaucratic period of DC, there were suggestions that the physical, medical, and psychological well-being of a child may be dependent on the ability to discover and access information about the donating progenitor(s) (Rowland 1985; Vetri 1988). Additionally, it was suggested that policy should be predicated on the best interests of the child (Annas 1981) and disclosure should follow the precedent set by adoption (Brandon and Warner 1977). If we are to uphold the claim that offspring have certain rights such as the right to know their genetic origins (Freeman 1996), then the current practice of DC does not consistently accommodate such a right (Frith 2001). This is because the rights of donors to anonymity can still override a donor-conceived person's right to information, depending on what era and jurisdiction he or she was conceived in. Additionally, the right of parents to deceive a child of his or her origins is universal in all jurisdictions and eras. In effect, the offspring's postulated right is subject to various regulations and laws as well as the choices of the participating adults. Subsequently, the freedom of procreation in this context has the potential to adversely affect the rights of donor-conceived offspring.

Should the potential for a donor-conceived child/person to suffer negative outcomes thereby influence or hinder an adult's freedom to procreate as he or she sees fit? This paper seeks to address this question within the Australian context by focusing on the child's outcomes.

Current Procreative Freedoms

A broad definition of procreative autonomy as prescribed by Robertson (1983, 406) is the freedom of choice to either bring or not bring a child into the world. Refining this freedom within a DC legal framework may be more accurately described as the ability to produce a child with the assistance of third parties that is not prohibited by law. In effect, any person who fulfils the eligibility requirements (and has the means) to receive fertility treatment from a clinic in Australia could be viewed as having the procreative freedom to conceive a child through DC. There are some who are now also conducting DC within their own homes through private arrangements; however, these will not form part of the discussion in this paper, as these arrangements are not addressed by donor conception legislation and regulation directly but rather by family and other laws, where applicable. While there may be some people who are also technically unable to conceive a child through this technique, they are not excluded based on law or regulation. The aforementioned refined definition of procreative freedom of adults in the context of DC will be used for this analysis.

The ability to start a family may unfortunately have little to do with choice and more to do with situational circumstances and one's biological ability to produce viable gametes and a subsequent embryo that is carried to term. Nature does not provide this as an automatic right—rather, it is a biological function of which not everyone is not always capable. Donor conception is a means to an end, a choice that circumvents infertility. It also can allow for genetic continuity for one partner, which is seen as an overriding and important concern for some parents when opting for DC over adoption (Milsom and Bergman 1982; Daniels 2004). The biological and social desire to raise children, then, forces those struggling with infertility to make decisions about their child that other parents do not normally face.

Once parent(s) have decided to utilise DC, they also must confront additional choices and other freedoms: the selection of clinics; which state or country to conceive in (reproductive tourism), as each may have differing legislation or regulations; which donor(s) to use (some clinics offer donor catalogues); whether or not they intend to tell the child about his or her origins and, if so, when; and whether or not to tell anyone

else. These decisions typically are protected in terms of a parent's freedom of choice; however, due to the complexities and profound effects that this can have on the child, do would-be parents ethically or morally have such freedoms?

Before the complexities or potential harms of being donor-conceived can be analysed and used as arguments for or against unconstrained procreative freedoms in relation to DC, we must first establish whether or not a child's interests can outweigh those of an adult and what framework should be used.

Child Welfare Paramountcy

It is proposed that there is a moral and ethical duty of care to ensure that the well-being of any child created through assisted reproductive technologies (ART)—including donor conception—is of paramount importance. One of the first states to legislate in this field, South Australia, also documented this countenance by stating: "The welfare of any child to be born in consequence of an artificial fertilisation procedure must be treated as of paramount importance, and accepted as a fundamental principle" (1988, 7). This principle has since been echoed in Victoria (1995) and the guidelines of the National Health and Medical Research Council (NHMRC 2004), and Western Australia (1991) requires that the interests and welfare of the child be taken into consideration. The only other state to enact legislation in this field, New South Wales (2007), merely refers to the welfare of the child in relation to information disclosure and consent to contact between various parties, as well as any person whom the Director-General considers to be a representative of the child's interests and welfare (for example, the parents), but not the welfare of the child as a general principle of the Act. Regardless of a law's locale, it is the intentionality of procreation through an institutionalised and publicly funded medical procedure that instils a higher level of responsibility on all parties involved, whether they are the commissioning parents, donors, clinicians, clinics, or government. An analogous elevated duty of care is evident in the field of adoption in Australia, whereby adoptive parents undergo screening and assessment of their suitability to parent an adoptee because the state has played an active role in the placement of that child. For the aforementioned states and regulating body, this principle of duty of care in DC appears to have found resonance.

While constraint on procreation occurring within natural conception is deemed unethical, to apply the same rationale to a completely artificial construct incorporating the input of another person (sperm or egg donation) or two other people (sperm and egg donation or embryo donation) could be viewed as unsound. The addition of third parties has the potential to cloud the relationship between the commissioning parents and between these parents and the child, as well as having profound and lifelong effects on the offspring. Therefore, DC requires a greater duty of care by the states. As the states already have a duty of care to children in general, then a supposition could be that donor-conceived children would be appropriately cared for by existing legal frameworks and thus do not require additional consideration. However, the possibility to induce harm (to be discussed later) as a direct result of these procreative freedoms suggests that further consideration is required. So how should we analyse the potential harms in light of the child welfare paramountcy principle?

Applying Neo-Aristotelian Virtue Ethics

In an analysis of procreative actions, McDougall (2007) uses neo-Aristotelian virtue ethics to create 3 Parental Virtues (3PVs), which can then be used to determine if reproductive choices are right or wrong based on whether a virtuous person/parent would choose them. The neo-Aristotelian virtue ethics concerns itself with virtuous character and the flourishing of the human being. It has already been established through either legislation or regulation in Australia that the welfare or *flourishing* of the child is paramount and, as such, McDougall's 3PV framework is a suitable model for analysis. It should be noted that the child welfare paramountcy principle and the 3PVs certainly do not preclude the flourishing or interests of parents, just that when there is conflict that the child's interests should take precedence. The implementation of McDougall's framework may be more difficult in other jurisdictions around the world where this welfare paramountcy principle is not enshrined.

McDougall's 3PVs are (paraphrased for brevity):

1) Acceptingness—that the parent will accept the child for whoever or whatever that child is or represents.

2) Committedness—that the parent undertakes the responsibility to actively parent the child and to be there for the child.
3) Future-agent-focus—the principle that the foetus and child will become an adult one day and an agent of his or her own free will, such that the parenting and the decisions made in regard to the child should not adversely interfere with the child's current and future opportunities, but should also be value-structured to reinforce virtue and morals.

McDougall's premise is that this framework should be used to determine whether a virtuous parent would do something, not whether the action will harm anyone. It is my postulation that virtuous parents in the aim of being virtuous would want to know of any potential harm(s) to their child so as to ensure that they make the appropriate decisions in the best interests of their children. Assessing levels of risk is the duty of care any committed parent undertakes in the day-to-day care of a child and is not confined to reproductive choices. As such, the 3PVs can be used for analysis in conjunction with a harms-based approach.

Potential Harms of Being Donor-Conceived

Procreative freedoms related to the use of DC have the ability to produce outcomes for a child that would not normally be encountered by naturally conceived children. Therefore, it is important to assess these outcomes to determine if they are serious enough to warrant a review of and/or reduction in these freedoms based on the 3PVs. However, given that parents of donor-conceived children go to great lengths to have them (Lorbach 2003; Daniels 2004), it could be argued that they have already passed the committedness test and the potential harms will be weighed up against the remaining 2 Parental Virtues.

Deception of Their Origins

Current practice in Australia centres around identity-release donors and encouragement of the recipient couple to tell the offspring about their conception and to tell them early (Johnson and Kane 2007). Yet studies (Golombok et al. 2002; Broderick and Walker 2001; Brewaeys et al. 1997; Rumball and Adair 1999; Lycett et al. 2005) reveal that the majority of parents are unwilling to disclose and prefer to keep the secret. Nondisclosure is typically coupled by a belief that the child does not need to know and that keeping the secret protects the child (Murray and Golombok 2003). During the infancy of DC practice, the trend was to use anonymous donation and for recipients not to tell. Irrespective of the period in which they were conceived, the majority of donor-conceived people will therefore not be aware of their DC status. The freedom for parents to parent as they see fit, which also includes the choice to disclose, is something that governments are extremely disinclined to legislate. Certainly the Victorian Law Reform Committee (VLRC 2012), in its inquiry into donor conception, was reluctant to recommend the forcing of parents to inform their children of their DC status, even though the committee felt that such knowledge was in the child's best interest. Under current practice, most offspring will never seek information about their progenitor(s) because they will be deprived of and shielded from the truth.

Parents who have initially decided not to tell may change their minds in the future, disclosing their child's method of conception (Daniels, Gillett, and Grace 2009). Parental attitudes toward disclosure over the years has changed considerably, with the majority during the 1980s and 1990s intending not to tell (Leeton and Backwell 1982; Milsom and Bergman 1982; Klock, Jacob, and Maier 1994; Durna et al. 1997) while more recent evidence has seen a reversal in this view (Godman et al. 2006; MacDougall et al. 2007; Shehab et al. 2008). Intent, however, does not always lead to actual disclosure, even within families that support truth-telling (Blyth and Ryll 2005), and the majority are still not disclosing (Freeman and Golombok 2012). The freedom of parents who choose not to inform and, thus, deceive their offspring about their conception potentially creates a psychologically and socially harmful environment that is ethically unacceptable (Landau 1998), as well as a level of dysfunction in the family (Paul and Berger 2007). While improvements are being made in the realm of disclosure, at the ethical and moral heart of the matter is that if children are deceived then "they are being wrongly treated" (Warnock 1987, 151).

There is an argument that if the children are deceived about their origins then there will be no harm caused to them. Cowden, however, argues that the

concept of "no harm, no foul" (a term she uses to describe this) should not apply and that openness facilitates the respect that offspring deserve (Cowden 2012, 122). When donor-conceived people have been asked whether they believe they should be told the truth of their conception, the majority do feel this way (Jadva et al. 2009), suggesting that not only should openness be practiced as a matter of principle but also that it is how donor-conceived people wish to be treated.

The origin of a person is central to who they are. It is the story of their coming into being. If parents choose to deceive the child of his or her origins, I postulate that they are not entirely comfortable with the notion that the child is not biologically related to one or both of them and therefore they have not completely accepted the entirety of the child and everything the child represents. The child may be seen as a reminder of their infertility. This less-than-full acceptance fails the acceptingness test; moreover, perhaps a more simplistic analysis is that we commonly associate truthfulness and openness, rather than deception and lies, as virtuous.

Kinship Separation

All DC offspring, irrespective of their knowledge of their conception, are separated from their next of kin on their donor's side. For some who are aware of their conception, this loss has the potential to be traumatic. The National Health and Medical Research Council (NHMRC), which provides the framework for clinic accreditation, states that a donor-conceived person is entitled to know his or her genetic parent(s) and stipulates that all clinics must not use donors unless they have consented to the release of identifying information (NHMRC 2004). This stance was reaffirmed by the Australian Senate Legal and Constitutional Affairs Committee (SLCAC) inquiry into DC practices. The SLCAC recommended that there be nationally consistent legislation ensuring the right of a donor-conceived person to access not only identifying information on donors but also donor half-siblings (SLCAC 2011). Clearly, the importance of and reverence to biological kinship is being valued at the level of governance.

Additionally, the majority of offspring believe that they should know the identity of their donors (86 percent, Scheib, Riordan, and Rubin 2005; 87 percent, Mahlstedt, Labounty, and Kennedy 2010; 77 percent, Jadva et al. 2010) and also the identity of any half-siblings (89 percent, Scheib, Riordan, and Rubin 2005; 78 percent, Jadva et al. 2010). The parity between the desire to know their progenitors and half-siblings exhibits the value that offspring put into all biological connections. Discussion regarding offspring's right to genealogy has typically focussed on the donor and only rarely has included consideration of the entire genetic family, which has been shown to be equally important to DC offspring. The search and desire for biological family is not borne out through poor sociological parent relationships (Mahlstedt, Labounty, and Kennedy 2010), thereby also highlighting the importance of genetic kinship to offspring.

If the importance of biological kinship is indeed profound and an intrinsic component of who we are as humans—as suggested by the NHMRC and SLCAC—then surely the deprivation of this kinship is a failure to accept the child and the biological kin that make up the child's "complete" family, the entirety of who that child is. However, I argue that this is not necessarily a failure on the parents' part but rather one that has been forced upon them to a certain degree. As a general rule in Australia, a child will not be able to access identifying information on a donor until the age of 18, provided that the child has been informed of the conception and chooses to seek out this information.

For offspring that may eventually know and meet their donor, the knowledge and interactions obtained may not completely erase their trauma. They may still suffer a lingering loss of not having shared a life together, of not having the intimate knowledge of each other that family members do, and of still feeling disconnected (Walker 2006). This deprivation of interaction with the donor(s) and associated kin (donor family) during a child's formative years has reduced the ability for that child to form relationships with them that would be analogous to those normally associated with the immediate family. It has in effect reduced the child's future options and fails the future-agent-focus test.

Complete acceptingness and future-agent-focus has failed to be upheld, but perhaps through no fault of the parent. Parents who wish to provide their children with knowledge of the donor family are being prevented from doing so through bureaucracy and, they, therefore may still retain this virtue. Unless the model of DC information exchange is altered to allow earlier identification, this harm cannot be appropriately assessed under the 3PVs criteria.

Loss of Identity

Loss of kinship can equate to a loss of heritage and is also associated with identity loss (Weigert and Hastings 1977). Adolescence is a critical time for a person in terms of identity formation: It is the transition to adulthood and is often highlighted with confusion (Erikson 1968). The absence of one or both biological links clouds this process by removing the mirror in which we see ourselves, our looks, our personality and behaviour that are evident in our progenitors and our kin. When approximately 41 percent of our behaviour is inherited (Malouff, Rooke, and Schutte 2008), this is a substantial mirror missing from these offspring's lives. The right to an identity is as much about not being deceived as it is about knowing the truth of one's origins (Freeman 1996).

Discovering and even meeting one's progenitor(s) after the age of 18 is potentially too late to avoid the damage associated with forcibly removing vital components of a person's identity. These factors contribute to genealogical or genetic bewilderment (Sants 1964), resulting in a person whose own identity and place in the world remains unclear to him or her, putting that person in a perpetual state of identity limbo. The genetic void created by lack of information about biological parentage is not in a person's best psychological interests (Cooper and Glazer 1994).

Not only do most offspring feel a strong need to know the identity of their donor(s) but, according to Mahlstedt, Labounty, and Kennedy (2010), 62 percent would also like to meet him and/or her at least once. Curiosity concerning donors appears to slightly outweigh the need for identification, with 96.6 percent of offspring studied by Scheib, Riordan, and Rubin (2005) desiring a picture of their donor and 89.7 percent wishing to know other non-identifying information such as vocation, marital status, and children. Since this study focused on teenage offspring, findings suggest that curiosity about donors is intrinsically a component of the identity-construction process during adolescence. It could be postulated that the discrepancy between figures of curiosity about donors and actual knowledge of their identities is the result of the imprinting onto and conditioning of many offspring under current and previous ideological climates as to having to feel grateful for their existence, to carry an existential debt (described by Rushbrooke 2004 and Rose 2009), not wanting to interfere with a donor's life, and for fear of hurting the feelings of their raising parents (Lorbach 2003).

One assessment of the harm of identity loss is that it runs in parallel with the harm of kinship loss. The two harms are linked through the lack of knowledge and interaction with the child's donor family, providing the same outcome in the analysis against the 3PVs. An alternative approach is that if the parents let the child's identity develop freely rather than wilfully force an identity construct on the child (i.e., tell the child early about the DC), then they are being accepting of who the child chooses to become and therefore not restricting the future-agent, even though the identity and the paths the child may choose to take may be different if they had access to the donor family.

Late Discovery

A compounding aspect is late discovery, whereby offspring who find out in adulthood—through open disclosure or extreme circumstances such as arguments or after the death of a parent—have altered perceptions of identity and family, creating great distrust, confusion, feelings of deceit, and possibly anger between themselves and those who withheld the truth from them (McWhinnie 2000; Turner and Coyle 2000). It has been reported that less damage may occur if the child is told of his or her conception at an early age (Hewitt 2002; Jadva et al. 2009), before the identity-construct window of adolescence occurs (Kirkman 2003). The emotional trauma associated with late discovery is similar to that occurring in the adoption community and may remain unresolved for several decades post-disclosure (Riley 2009).

It is clear that some offspring have difficulty assimilating this newfound information and dealing with the changed family and identity constructs that they had previously formed. A substantial argument is that if the donor-conceived person wasn't told of his or her conception then the harm would be avoided; however, this fails to satisfy Cowden (2012) and the offspring themselves. Yet dichotomously, disclosure has not only caused harm but reduced the neo-Aristotelian flourishing of the now adult. We can address this dilemma by returning to the remaining two of the 3PVs. As outlined in the deception of origins harm, by not disclosing for a significant portion of the child's life the parent has failed the acceptingness test even if this failure has been temporary. A similar temporary

failure is the future-agent-focus as described in the kinship separation harm.

Incomplete Medical Histories

All offspring have incomplete medical histories in some form. Believing that a nonbiological parent is in fact one's progenitor is disadvantageous in any clinical setting and can result in poor diagnosis. Even when offspring are aware of their conception, an incomplete medical history through either having no access to a progenitor's medical history or access to one that is outdated also creates problems for any consulting physician. This lack of knowledge has serious implications for early diagnosis (Hastrup 1985; Centers for Disease Control and Prevention 2004) as well as lifestyle choices for the offspring. Reports of how this can adversely affect a person's health prospects were highlighted in the VLRC inquiry, which showed that in 2011 there were three incidences of a donor or DC person unable to pass on medical information to those directly affected and, in one instance, a person was diagnosed with a terminal illness that possibly could have been screened and treated at an earlier stage if a health history had been available (VLRC 2012).

Theoretically and evidentially there is a strong case for the provision of medical information to DC individuals. This is also mirrored in data that show that the majority of those conceived through DC desire updated medical history of their donor(s) for their own physical health (Hewitt 2002). For those who are unable to obtain medical information, some are resorting to expensive and, in many instances, inconclusive genetic health analyses to provide some familial health history and enable lifestyle and other choices to be made (Adams and Lorbach 2012).

Some dispute that the previously mentioned harms are sufficient grounds for altering the current paradigm. For example, one argument is that nondisclosure will not lead to negative outcomes provided that the child never knows about his or her conception and is raised in a loving home. The nondisclosure effect postulation is difficult to determine empirically from studies of offspring unaware of their conception, due to the problem of unethical treatment of study participants who are unaware of why they are being studied. Additionally, in psychological and emotional well-being studies there can be a wide range of outcomes, thus raising doubt. It is difficult to envisage, however, that the deprivation of a medical health history can ever be viewed as justified in light of current understanding of how genetics can influence our physical well-being.[3] Such deprivation fails the future-agent-focus test, as the child's ability to flourish and remain in a physically healthy state can be severely hampered without knowledge of a complete familial health history. Interestingly, while the majority of donors have for some time agreed to the release of medical records (Robinson et al. 1991; Mahlstedt and Probasco 1991), there is yet to be a system put into place to ensure that these records are updated and that vital information is disseminated to offspring and recipient parents.[4] Thereby any possibility of maintaining virtuous future-agent-focus becomes compromised over time.

Physical Harms

Robertson (1983) describes conception as usually not being harmful in itself and therefore it could be argued

[3] The notion of access to a medical health history does not necessitate that family members have immediate access to a relative's medical records; rather, by virtue of their relationship and interactions with each other, they will in many instances be privy to information about a relative's health, especially when illnesses are particularly severe. For example, most immediate family members will be aware if their close relative has had a history of heart attacks, stroke, or even diabetes, among other major health problems. That said, in Australia, the *Privacy Act* 1988 (Cth) does allow for the disclosure of a person's private medical information to relatives if the life or health of those relatives is threatened by the lack of this information (Adams 2012). Without a mechanism whereby life-threatening information can be disclosed to donor offspring, the provisions of the *Privacy Act* cannot be implemented. Such concerns were highlighted in the Victorian Law Reform Committee's inquiry into donor conception (VLRC 2012), whereby case studies were presented before the committee as examples of how the deprivation of such information and the means to disseminate it has adversely affected individuals.

[4] In general, a person's medical information is treated as private; however, as stated in the previous footnote, the *Privacy Act* 1988 (Cth) does allow for the disclosure of a person's medical information in certain situations, although the information disclosed is restricted to that which is vitally important. The release of medical information does not necessarily breach any agreements of anonymity if the information is de-identified, which is also specified as a recommendation of the NHMRC guidelines on the "Use and Disclosure of Genetic Information to a Patient's Genetic Relatives Under Section 95AA of the *Privacy Act 1988* (Cth)" (2009). As such, without identifying information the donor's private and family life are not intruded upon. The release of medical information in this instance could be restricted to that which is pertinent to the welfare of the offspring such as those illnesses known to have a familial link.

that DC should be a procreative freedom if it is not harmful. However, Robertson's argument was written during a period where our medical knowledge of conception was rather limited compared to now.

For example, preeclampsia (hypertension during pregnancy) is a leading cause of foetal and maternal morbidity and mortality (Backes et al. 2011). There is an increased risk of preeclampsia among in women who have become pregnant with the assistance of donated gametes or embryos (Smith et al. 1997; Salha et al. 1999). These studies show that there is an underlying immune response to becoming pregnant with an oocyte that is not one's own and to being impregnated with sperm that is not from one's partner. This is supported by additional evidence whereby further exposure to the same donor sperm reduces the risk of preeclampsia, as the immune system has become tolerant of the novel antigen (Kyrou et al. 2010).

Current DC practice involves the use of frozen gametes so that appropriate screening of donors for transmissible diseases and certain genetic conditions can be undertaken. The mere manipulation of sperm in the laboratory introduces DNA fragmentation (Toro et al. 2009), as do cryopreservation (Zribi et al. 2010) and the thawing process (Gosálvez et al. 2009). This sperm DNA fragmentation results in poorer embryo quality as well as poorer fertilisation and pregnancy rates (Simon et al. 2011). In some instances, sperm DNA damage can be repaired after fertilisation but it can also persist (Yamauchi, Riel, and Ward 2012), suggesting that these changes can be carried on into the resulting embryo or child. As cryopreservation-induced DNA damage is primarily mediated by oxidative stress (Thomson et al. 2009), and oxidative stress-induced damage is linked with childhood cancer and may make male offspring infertile themselves (Aitken and Krausz 2001), there is considerable cause for concern.

Large-scale DNA damage may result in either non-fertilisation or failure of the embryo to develop properly —therefore not being carried to term (Robinson et al. 2012). However, given that single base changes in DNA (single nucleotide polymorphisms) can result in increases in the incidence of outcomes such as autism spectrum disorders and schizophrenia (Kong et al. 2012), the effect that small-scale DNA changes can have on the resulting child should not be underestimated. The physical long-term health effects on people conceived using donated gametes is somewhat unclear and further research needs to be conducted.

What is apparent is that Robertson's broad procreative freedom is too broad, because his assumption that conception usually causes no harm and that the risk is speculative is flawed, as the aforementioned potential physical harms occur during the conception processes associated with DC. While outcomes such as preeclampsia can be treated, the incidence of preeclampsia occurring in the next generation is also increased (Esplin et al. 2001), and the resultant child has an elevated risk of developing cardiovascular disease and diabetes in adulthood (Simmons 2009). The effects of conception can have far-reaching and long-term effects with what is now a widely accepted concept known as the foetal origins of adult disease (Barker 1990).

The potential physical harm outcome is analogous to the incomplete medical history harm and subsequently fails the future-agent-focus test.

Consanguineous Relationships

Australia precludes consanguineous relationships on moral and biological grounds and prohibits them by the *Australian Marriage Act* (Commonwealth of Australia 1961, s 23). The current ability of donor offspring to know who their siblings and half-siblings are is severely hampered. Not only must they have been informed of their conception status, they must also have access to the identity of their donor's biological children —born both "naturally" and via other donations. While current practice restricts the number of recipient families for one donor, for those conceived before restrictions were imposed there is concern about the possibility of a consanguine event, as records show that the number of donations for some donors exceeded several hundred (Donor Conception Support Group of Australia 2011). Thus, there is the very real potential for a donor offspring to have numerous siblings. A compounding factor for these children is that they are often born within a relatively short timeframe when compared to normal sibship construction, and birth generally occurs within geographical boundaries. Coupled with a sizable proportion of a person's behaviour and other attributes being inherited, there is a possibility that these offspring could meet through vocational interests. There has since been very little achieved, apart from a reduction in the number of families assisted, to prevent consanguinity

from occurring, even though this was recognised as a concern more than 30 years ago (Curie-Cohen, Luttrell, and Shapiro 1979).

Exacerbating the problem is the possibility of genetic sexual attraction (Gonyo 1987; Greenberg 1993), whereby kin who have been separated since birth or conception become attracted to each other due to shared similarities, which normally is quashed due to the Westermarck effect (Westermarck 1921) of cohabitation in early childhood. Removing cohabitation, as can occur in donor offspring, potentially also removes the kin recognition model of the persons involved and their aversion to consanguinity; this aversion is nonconscious and predicated by individuals' cohabitation and not their beliefs (Lieberman, Tooby, and Cosmides 2003). The onus is then forced on the offspring themselves to ask all potential partners of their conception status and to possibly test them genetically to ensure that they are not related, provided that they know of their mode of conception themselves. The emotional and financial burdens of ensuring non-consanguinity is already being carried by donor offspring but is not being addressed by states or clinics that hold records that could prevent such an event from occurring. Recently, the concern has been highlighted by federal and Victorian inquiries (SLCAC 2011; VLRC 2012).

Knowledge of kinship reduces the total number of possible relationships a person is able to have when consanguinity is entered into the equation, even though the reduction in number is insignificant. At first glance, this would appear to be counter to one component of the future-agent-focus test, which is concerned with not closing certain doors and keeping as many options as possible open. However, the other component of this parental virtue is to ensure that the child develops into a future moral agent with appropriate virtues, which would include being law-abiding citizens. Balancing these two outcomes would see the virtuous law-abiding agent component as having greater weight than would the removal of the small number of relationship options. Hence, the possibility to form a consanguineous relationship by not having knowledge of all next-of-kin fails the future-agent-focus test.

Reconceptualising the Paradigm

The outcomes outlined earlier are an analysis of possible (as not all children are equally affected) downstream effects of procreative freedoms, which should then be used as a framework for discussing how these potential effects might influence policy and paradigm reconceptualisation. As such, means of accommodating the welfare of the child for each of the potential harms in a pragmatic context will not be discussed, as these are outside the scope of this paper.

In addressing the question of whether adults have freedom of choice in DC reproduction, the current situation follows a Robertson procreative freedom, although it is somewhat constrained to fit within the refined legalised and practical freedom described earlier. However, if we apply the 3PVs, then it is apparent that the current paradigm fails to be ethically virtuous in a neo-Aristotelian way and that the freedom is in fact too free.

Concurrently, a parent's freedom of reproductive choice is also being restricted. Through the current DC practice bureaucracy, parents are being denied the procreative freedom, in the neo-Aristotelian virtue ethics sense described by McDougall, to be the virtuous parents that they may choose to be. This is based on the assumption that a virtuous parent would assess the potential harms that could adversely impact on their donor-conceived child and make the appropriate decisions and subsequent actions to ameliorate or reduce those possibilities. Therefore, the paradigm should be altered so that parents have the ability to make choices such as providing information about the donor and access to donor families, if so desired, and in an manner that allows them the ability to fulfil the 3PVs without constraint (as described earlier) and thereby reclaim the autonomy of which they are being deprived.

Support for such a frame-shift also comes from the offspring themselves. Evidence from studies of adult offspring's perceptions shows that some are distressed by some DC procreative choices that their parents were able to make, as well as how the paradigm is regulated, and that they can be adversely affected physically, mentally, and emotionally (Turner and Coyle 2000; Lorbach 2003; McWhinnie 2006; Victorian Law Reform Commission 2007). Additionally, what was originally deemed appropriate to fit an adult's own agenda may not fit with the welfare of the child (McWhinnie 2001). While progress is slow and the welfare of the child is still not being placed as the primary concern, Australia has moved to an identifiable-only donor paradigm; elsewhere there is also an increase in the usage of identifiable donors

(Greenfeld 2008). This shows a donor conception culture that is in transition (Daniels 2007), reflecting the research findings of donor offspring experiences. Additionally, some offspring are resorting to lobbying for legislative change, paying for DNA tests, and forming social support groups to help each other deal with the effects of current and past procreative freedoms (Adams and Lorbach 2012).

There are no regulatory or legislative impositions on adults as to when or how they procreate using normal biological means, and provided that they meet eligibility criteria and are able to pay certain costs, there are no restrictions to their access to fertility treatment, either. I posit that reproductive choice constrained by child welfare interests does not significantly diminish this freedom. With appropriate reconceptualisation of the paradigm, virtuous parents could still have a family through DC and use appropriate parental decisions to help ameliorate some of the potential harms their children could face, although the possibility of avoiding the unknown physical harms is somewhat more problematic.

Social change, however, is creating a push for increased reproductive choice and freedoms. Increasing reproductive freedom in these instances is diametrically opposed to an improvement in the conceptualised welfare of the offspring. Somerville (2007) argues that children from reproductive technologies such as DC have been failed by the processes that create them, in that many of the possible consequences to the child have been neglected because children are desirable objects and a component of big business. This argument shows how freedom of procreation coupled with deep-rooted desires to procreate can be utilised for commercial gain while ignoring the actual "product" that they create.

When balancing the opposing rights of individuals or parties, ethically we should provide protection to the party that is most vulnerable. In donor conception this is the child, as recognised through legislation and regulation. In the issue of welfare, the child's rights must take precedence and override those of the adults (Gollancz 2001). While it may be argued that some children are naturally born into scenarios where they may be equally disadvantaged, this does not automatically provide ethical approval of harms or the justification of children being a means to an end in a state-sanctioned manner (Laing and Oderberg 2005). Chisholm (2012) describes this means-to-an-end argument as being in conflict with the Kantian principle—the principle of humanity—in which people should always be treated as ends in themselves. Privacy concerns and other agendas of the adults involved should be outweighed by the possible negative consequences of withholding such information, which also violates the offspring's autonomy (McGee, Brakman, and Gurmankin 2001). Such a moral countenance supports reconceptualisation of the donor conception paradigm.

While some legislative efforts have been enacted to cater for the welfare of offspring and their right to a genetic heritage and knowledge of their progenitors, these efforts have been suppressed to cater for the desires of the infertile (van den Akker 2006). Public funding of fertility treatments imposes a greater level of responsibility than would otherwise occur due to the community investment and the intentionality of the process; thereby, the principle of duty of care and the welfare of the child should indeed restrict freedom of choice in DC reproduction.

It could be argued that, no matter how much the paradigm was reconceptualised toward a child-centric model, there will always be some children who will be unhappy or harmed by their method of conception and that therefore the whole practice of DC should be banned and this procreative freedom/choice be prohibited. Such arguments are counterproductive, as DC has been in practice for a long time, has been accepted by a large portion of Australian society, is entrenched as a common fertility treatment, and is enshrined in legislation and regulation as an acceptable procreative freedom. However, due to the child welfare paramountcy principle, these freedoms do not have to follow the broad Robertson definition with an "anything goes" approach, but rather there is an intrinsic legal obligation of the states to ensure that an appropriate paradigm is implemented that acknowledges this freedom but constrains it, not only in the interests of child welfare but also in the interests of the parents to allow them to be as virtuous as possible. As such, a child-centric model has the potential to improve the outcomes for not only the child but also the parent.

Conclusion

Acknowledging the harm and consequences that may have occurred and may continue to occur as a direct result of the implementation of previous and current models of DC is the first step toward addressing the

question of whether adults should have unmitigated freedom of procreation using DC. Shifting the focus of these models to a child-centric paradigm will enable society to ameliorate some of the potential harms outlined. The child welfare paramountcy principle should be adopted by all jurisdictions rather than just a few, and reproductive freedoms utilising DC must not be absolute but restrained to cater for this welfare as an intrinsic applied principle. The purpose of this discussion is not to propose a specific model that will meet the needs of the Donated Generation in an ethical and moralistic manner but, rather, to provide a framework of fields that require investigation and critical debate in the formation of a child-enabling model incorporating the freedoms deprived of these people. It is shown that the 3 Parental Virtues can possibly be used as a means for conducting this analysis and aid reconceptualisation based on child welfare paramountcy in a neo-Aristotelian manner.

Competing Interests The author is an advocate of and lobbies for the equitable treatment of donor-conceived individuals.

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