Maternal cardiovascular function in women at high-risk for pre-eclampsia

by

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BAppSc PostGradDip

Thesis

submitted to Flinders University

for the degree of

Doctor of Philosophy

School of Medicine

May 2020

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.

Kate Russo

October 2019

Abstract

Background

Pre-eclampsia complicates 3-5% of pregnancies and is a leading cause of maternal, fetal and neonatal morbidity and mortality. The disease was first thought to be related primarily to poor placentation; however, it is now considered a multifactorial entity also involving alterations to the immune system, genetics, pre-existing disease and adaptation of the cardiovascular system. Maladaptation of the cardiovascular system has been described in women with pre-eclampsia and other adverse pregnancy outcomes including gestational hypertension and delivery of a small for gestational age infant. Screening for pre-eclampsia using the Fetal Medicine Foundation model (FMF) has demonstrated the algorithm predicted early-onset pre-eclampsia in 95% of women at a 10% false positive rate, with therapeutic low dose aspirin commenced prior to 16 weeks' gestation reducing the prevalence of early-onset disease. The FMF model works less well for the prediction of late-onset disease, with aspirin ineffective in this group.

Aims

The aim of this thesis was to identify potential maternal cardiovascular indices that may make the current screening algorithm more specific for prediction of pre-eclampsia and determine whether there is potential to assess cardiovascular function as a second tier of pre-eclampsia screening. This may improve the positive predictive value of pre-eclampsia screening and better direct therapeutic intervention.

Methods

This was a prospective longitudinal study between 14 and 30 weeks' gestation investigating cardiovascular structure and function assessed by echocardiography. The study included women who were screened high-risk and low-risk for early-onset pre-eclampsia using the FMF first trimester algorithm. Cardiovascular variables were compared between women grouped by pregnancy outcome.

Results

Women screened low-risk for early-onset pre-eclampsia with a subsequent normal pregnancy outcome demonstrated an appropriate cardiovascular adaptation to pregnancy as evidenced by an increase in cardiac output and a decrease in total peripheral resistance, primarily due to an increase in heart rate. In women screened high-risk with a subsequent normal pregnancy outcome, the increase in cardiac output and concomitant decline in total peripheral resistance was observed; however, these changes were not to the same degree as seen in low-risk women with a normal pregnancy outcome. Coupled with significantly higher mean arterial pressure these findings suggest high-risk women with a normal pregnancy outcome have mildly inhibited vascular tone adaptation leading to reduced cardiac output expansion during pregnancy.

The current strategy was so effective as reducing the prevalence of early- onset pre-eclampsia that evaluation of high-risk women that developed the disease proved difficult. The cardiovascular profile of women stratified as high-risk who developed pre-eclampsia was of low cardiac output and high total peripheral resistance prior to the symptoms and signs of late-onset disease compared to high-risk women with a normal pregnancy outcome. This finding was replicated when these variables were indexed. Cardiac output and stroke volume were lower with total peripheral resistance increased secondary to the combination of lower cardiac output and higher mean arterial pressure. Consequently, women who developed pre-eclampsia clearly showed maladaptation of their cardiovascular system.

One of the most important findings of high-risk women who developed pre-eclampsia was that their haemodynamic profile was different to those that developed gestational hypertension. In these women, cardiac output was in keeping with high-risk women with a normal pregnancy outcome, thereby suggesting their elevated mean arterial pressure did not have the same impact on vascular tone as women who developed pre-eclampsia. Women who develop gestational hypertension showed better vascular adaptation which facilitated a greater increase in cardiac output with gestation.

With respect to the different haemodynamic profiles of women who developed pre-eclampsia and gestational hypertension compared to high-risk women with a normal pregnancy outcome, a number of cardiovascular markers with potential value that could improve current pre-eclampsia screening algorithms were identified.

Conclusions

Women who develop pre-eclampsia have cardiac maladaptation that is evident from 14 weeks' gestation. Cardiac output and total peripheral resistance are the most significant cardiovascular indices that could potentially be incorporated into the current algorithm or alternatively be used as a second tier of screening at 20 weeks' gestation to improve the positive predictive value of the test.

Acknowledgements

This PhD journey has been a unique experience, certainly longer than I had hoped for and lonely at times, but not without reward. The challenges that I faced have truly tested my resolve and character at times. I have gained more knowledge and experience than I ever imagined, well beyond academia, that will serve me well in life. For this, I am very grateful to Professor Jon Hyett for the opportunity to do this project and learn from one of the most committed researchers in the field of obstetrics. I have so much admiration for your exceptional work ethic and dedication to improving the lives of women and their babies. The obstacle of me travelling from Adelaide every fortnight was easily overcome by your kind and generous hospitality. Sue and Alex welcomed my visits for three years and I am forever appreciative of their care and friendship. Jon, you have been steadfast in your patience and support and have taught me well.

I was fortunate enough to have the brilliant cardiologist Clare Arnott take an interest in my study. I will never forget the enormous amount of time and effort she contributed to my research. Clare provided insightful feedback in a timely manner and consulted over the phone while pregnant and completing her own PhD. Nothing was ever too much trouble and I am quite in awe of her abilities.

I have also met many wonderful people that have provided support, guidance and encouragement during my thesis. The staff at Royal Prince Alfred were supportive and made me feel most welcome to the department. I would not have had such great recruitment if it was not for the amazing midwife Rachel who was simply delightful with women. Wendy, I am forever indebted to you for your kindness and friendship to accommodate me while Jon was away on one of his many teaching expeditions. Lars, I am truly thankful for your time and our Norway-Australia Skype conversations. Your insight and effort to assist me was always greatly appreciated. Thank you to my supervisors Rosalie and Clare B for always being there when I needed support and reassurance. Louise came to my rescue late in the game with awesome statistical help. I would still be drowning in my data if it was not for you.

I would also like to acknowledge all the wonderful women that volunteered to be in my study; your interest and commitment to the project was fantastic.

Finally, to my wonderful parents Cynthia and Tony, none of this would have been possible without your ongoing support of our family. Your practical help was as always caring, reliable and a great comfort in my absence. Chris, Isobel and Hannah, thank you for giving me the space and time to complete my thesis. Your unconditional love, support and understanding has been unwavering. And to Scout, having you by my side was priceless.

Dedication

To my wonderful family: Chris, Isobel, Hannah and Scout.

You are my favourites.

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Grants and Presentations

Grant

2012 Australasian Society for Ultrasound in Medicine, Research Grant

- Maternal cardiac function in women high-risk for pre-eclampsia.

Presentations

2013 International Society of Ultrasound in Obstetrics and Gynaecology, oral presentation

- A comparison of maternal cardiac function in women deemed high-risk for pre-eclampsia with normal and adverse outcomes.
  Russo K, Simmons L, Grivell R, Hyett J.

2013 Australasian Society for Ultrasound in Medicine, oral presentation

- Maternal cardiac function as a predictive tool for pre-eclampsia.
  Russo K, Simmons L, Grivell R, Hyett J.

Posters

2013 Perinatal Society of Australia and New Zealand

- Maternal cardiac function in women deemed at high risk of pre-eclampsia with subsequent normal pregnancy outcome.
  Russo K, Simmons L, Grivell R, Hyett J.

2014 International Society for Prenatal Diagnosis

- Maternal tissue Doppler imaging in women screened high risk for pre-eclampsia with subsequent normal outcomes.
  Russo K, Grivell R, Simmons L and Hyett J.

List of Abbreviations

Abbreviation	Definition
2CH	2-chamber
4CH	4-chamber
5CH	5-chamber
a	Mitral annular *a* wave velocity
ACOG	American College of Obstetricians and Gynecologists
ADAM-12	A-disintegrin and metalloprotease 12
ADMA	Asymmetric dimethyl-L-arginine
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
APLS	Antiphospholipid syndrome
APPT	Activated partial thromboplastin time
ART	Assisted reproductive technologies
ASE	American Society of Echocardiography
AST	Aspartate aminotransferase
AUC	Area under receiver-operating characteristics curve
bHCG	Beta human gonadotropin hormone
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
BSA	Body surface area
CHIPS	Control of Hypertension in Pregnancy Study
CI	Cardiac index
CO	Cardiac output
Cr	Creatinine
CSA	Cross-sectional area
CV	Cardiovascular
CVD	Cardiovascular disease
CVS	Chorionic villus sampling
CW	Continuous wave
D	Diameter

DBP	Diastolic blood pressure
DT	Deceleration time
DNA	Deoxyribonucleic acid
e	Mitral annular *e* wave velocity
EACVI	European Association of Cardiovascular Imaging
ECG	Electrocardiograph
EF	Ejection fraction
Eng	Endoglin
ePE	Early-onset pre-eclampsia
ESC	European Society of Echocardiography
ESS	End systolic wall stress
FGR	Fetal growth restriction
FHR	Fetal heart rate
FMD	Flow-mediated dilation
FMF	Fetal Medicine Foundation
FPR	False positive rate
FS	Fractional shortening
GDM	Gestational diabetes mellitus
GH	Gestational hypertension
HELLP	Haemolysis elevated liver enzymes low platelets
HF-B	Heart failure stage B
HIF-1α	Hypoxia-inducible factor 1-α
HO-1	Heme oxygenase 1
HO-2	Heme oxygenase 2
H-R	High-risk
HR	Heart rate
HT	Hypertension
IL-1	Interleukin-1
IL-6	Interleukin-2
IL-10	Interleukin-10
INR	International normalised ratio
IUGR	Intrauterine growth restriction
ISSHP	International Society for the Study of Hypertension in Pregnancy

IVF	In-vitro fertilisation
IVRT	Isovolumetric relaxation time
IVS	Interventricular septum
IVST	Interventricular septum thickness
LA	Left atrium
LDH	Lactate dehydrogenase
lPE	Late-onset pre-eclampsia
L-R	Low-risk
LV	Left ventricle
LVEDD	Left ventricle end diastolic diameter
LVEDV	Left ventricle end diastolic volume
LVESD	Left ventricle end systolic diameter
LVESV	Left ventricle end systolic volume
LVFW	Left ventricular free wall
LVID	Left ventricular internal dimension
LVM	Left ventricular mass
LVMI	Left ventricular mass index
LVOT	Left ventricular outflow tract
LVPWT	Left ventricular wall thickness
MA	Maternal age
MAP	Mean arterial pressure
M-mode	Motion mode
MV	Mitral valve
MV A	Mitral valve A wave velocity
MV A dur	Mitral valve A wave duration
MV DT	Mitral valve deceleration time
MV E	Mitral valve E wave velocity
NICE	National Institute of Clinical Excellence
NICOM	Non-invasive Cardiac Output Monitor
NO	Nitric oxide
PAPP-A	Pregnancy associated plasma protein A
PCOS	Polycystic ovary syndrome
PE	Pre-eclampsia
PI	Pulsatility index

PlGF	Placental growth factor
PPROM	Preterm premature rupture of membranes
PP-13	Plasma protein 13
Pr	Protein
PSLAX	Parasternal long axis
PW	Pulsed wave
PWT	Posterior wall thickness
RCOG	Royal College of Obstetricians and Gynaecologists
ROC	Receiver operating characteristics
ROS	Reactive oxygen species
RV	Right ventricle
RVFW	Right ventricular free wall
RWT	Relative wall thickness
s	Mitral annular systolic wave velocity
SD	Standard deviation
SBP	Systolic blood pressure
sEng	Soluble endoglin
sFlt1	Soluble fms-like tyrosine kinase-1
SGA	Small for gestational age
SLE	Systemic lupus erythematous
SOGC	The Society of Obstetricians and Gynaecologists of Canada
SOMANZ	Society of obstetric medicine of Australia and New Zealand
STB	Syncytiotrophoblastic
SV	Stroke volume
SVI	Stroke volume index
TDI	Tissue Doppler imaging
TGF-β1	Transforming growth factor Beta 1
TNFα	Tumour necrosis factor alpha
TPR	Total peripheral resistance
TPRI	Total peripheral resistance index
UA-PI	Uterine artery Doppler pulsatility index
UK	United Kingdom
US	United States of America
USCOM	Ultrasonic Cardiac Output Monitor

USPSTF	The United States Preventive Services Task Force
Vcf	The velocity of circumferential fibre shortening
VEGF	Vascular endothelial growth factor
VTI	Velocity time integral
WBC	White blood count
WHO	World Health Organisation
2D	Two dimensional

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Chapter 1 Introduction

Pre-eclampsia is a significant complication of pregnancy, affecting 3-5% of women worldwide (1, 2). The major conflict in managing pre-eclampsia is balancing the well-being of the fetus with that of the mother, as the only known cure is delivery of the placenta and fetus. The fetus clearly benefits from a longer gestation to minimise the damaging effects of prematurity, while prompt delivery will improve maternal well-being and prevent a potentially life-threatening cascade of events. Without this intervention maternal deaths resulting from severe complications, including eclampsia, stroke, haemorrhage, kidney failure, liver failure, and pulmonary edema can prevail (3-6). Pre-eclampsia is also associated with intrauterine growth restriction, further complicating the optimal time for delivery and contributing to high perinatal mortality (6-8). Infants who do survive can have major morbidities such as neurodevelopmental and respiratory disorders attributable to preterm birth and growth restriction (9-11). These health issues are not limited to the neonate, with the association of significant life-long implications reported (12-14). The consequences for pre-eclamptic women also extend beyond the perinatal period, with there being an increased risk of hypertension, diabetes, renal and cardiovascular disease later in life (15-18).

Pre-eclampsia is a multisystem disorder typically characterised by new-onset hypertension and at least one other sign or symptom of organ dysfunction (3, 19, 20). While the cause of pre-eclampsia is not well understood, the disease is considered to be multifactorial, associated with abnormal placentation, altered maternal immune response and upregulation of anti-angiogenic factors. Consequently, these changes disrupt normal endothelial function leading to systemic vasoconstriction and hypertension (21-29). Early detection of pre-eclampsia can improve pregnancy outcomes through increased antenatal surveillance and by appropriately timed intervention. Furthermore, early identification of women at risk of developing pre-eclampsia can enable therapeutic administration of aspirin to reduce the prevalence of the disease or delay the gestational age of onset (30-34).

An extensive body of research related to pre-eclampsia has focused on placentation, recognising that this is a condition only seen in pregnancy that resolves after delivery of both the fetus and the placenta. The placenta is intrinsically linked to the maternal cardiovascular system; however, the involvement of the heart has received less attention with there being limited

research assessing the burden of pre-eclampsia. There is evidence to suggest that maladaptation of the cardiovascular system has a significant role in the development of the disease (35-45), although it is unknown whether this is a primary mechanism or a secondary response (46). Studies have shown that maternal cardiac structure and function are altered in women who develop pre-eclampsia (36-41, 44, 45, 47-57) and that these differences are evident as early as 14 weeks' gestation (42, 43). Additionally, there is evidence that preceding the clinical syndrome of pre-eclampsia, women have abnormal endothelial dysfunction, as evidenced by reduced retinal microvascular calibre and brachial artery dilatation (58, 59). Thus, the inclusion of cardiovascular measures, such as cardiac output and total peripheral resistance, may make the current screening algorithm more specific for prediction of pre-eclampsia. Importantly, however the complex issue of addressing appropriate indexation of echocardiographic measures in pregnancy may overshadow the validity and reliability of these measures and therefore complicate the potential for inclusion within a screening algorithm. In the long term, with resolution of indexation methodology, these maternal cardiovascular measures may help to identify those truly at risk, and better direct therapeutic intervention to reduce the prevalence of clinically significant disease.

This literature review will first explore the current understanding of the pathogenesis of pre-eclampsia and how this has evolved over time. A discussion of current practices used to identify women at risk of pre-eclampsia and the effectiveness of these strategies will be included. Furthermore, the review will provide background knowledge relating to what is already known of cardiovascular changes in normal pregnancy and assess the maladaptation in pregnancies affected by the development of pre-eclampsia or the birth of small for gestational age infants. The different methods through which cardiovascular function can be assessed will also be discussed with particular reference to the complexities surrounding the application of cardiac indexation and the interpretation of cardiac variables.

1.1 Hypertensive disorders in pregnancy

The development of hypertension is a common complication of pregnancy, with population-based rates of up to 10% (21, 60-62). Hypertensive disorders in pregnancy include chronic hypertension, gestational hypertension, pre-eclampsia and eclampsia. Pre-eclampsia is associated with higher rates of maternal and perinatal mortality and morbidity, preterm birth, and intrauterine growth restriction especially when severe or onset is less than 34 weeks' gestation (4-6, 63). HELLP syndrome is considered a variant or complication of severe pre-eclampsia, occurring in 10-20% of cases (64). These women present with haemolysis, elevated liver enzymes and thrombocytopenia. The majority of women with HELLP also have hypertension, but this may be absent in 10-20% of cases (65).

Gestational hypertension is generally regarded as a benign condition however, one study has suggested that at least a quarter of such cases will progress to pre-eclampsia (66). Additionally, the earlier the presentation and the more severe the hypertension, the more likely the progression to pre-eclampsia or an adverse pregnancy outcome (3). Pregnancies complicated by chronic hypertension account for 11% of stillbirths, while a further 5% are associated with pre-eclampsia-eclampsia (67). In terms of women who present with white-coat hypertension, this group should not be overlooked as they have an increased risk of developing gestational hypertension or pre-eclampsia (68).

An increase in the prevalence of hypertensive disorders has been reported in the United States with the association linked to changing maternal characteristics: older mothers, increased obesity and diabetes, and higher rates of multiple pregnancies (69, 70). This is in contrast to other developed countries within Northern Europe, Canada and Australia, where the rate of pregnancy hypertension and eclampsia has reduced (62). The widespread use of prophylactic treatments such as magnesium sulphate has contributed to the decrease in eclampsia, with improved maternal and fetal outcomes (4, 61). Less developed nations do not have access to antenatal care and treatment resulting in an overwhelming majority of maternal deaths occurring in these countries. Hypertensive disorders in pregnancy annually account for 30,000 deaths worldwide (1), with a recent review of neonatal mortality estimated at 1.5-2 million

deaths annually, secondary to complications relating to prematurity, associated growth restriction and lack of neonatal care resources (6).

1.2 Sub-classification of hypertensive disorders

1.2.1 Chronic hypertension

Chronic hypertension refers to high blood pressure confirmed prior to pregnancy. High blood pressure is defined as systolic pressure greater than or equal to 140mmHg systolic and diastolic pressure greater than or equal to 90mmHg, confirmed by repeated readings over several hours (3). Most cases are due to essential hypertension; that is, high blood pressure without an identified cause and can be diagnosed during pregnancy when onset is prior to 20 weeks' gestation. Often these women will have a family history of hypertension and be overweight or obese (71). Secondary causes of chronic hypertension include glomerulonephritis; reflux nephropathy; adult polycystic disease; fibromuscular hyperplasia of the renal arteries; endocrine disorders, such as primary hyperaldosteronism; Cushing's syndrome; and systemic disease with renal involvement, such as diabetes mellitus and systemic lupus erythematosus (72, 73).

1.2.2 Gestational hypertension

Gestational hypertension is defined as the new onset of high blood pressure after 20 weeks' gestation, without any of the abnormalities that define pre-eclampsia, followed by the return of normal blood pressure within three months post-partum. An alternative description for gestational hypertension is pregnancy induced hypertension.

1.2.3 White coat hypertension

White coat hypertension refers to transiently high blood pressure measurements when taken in a medical setting. The diagnosis can be confirmed by repeated blood pressure readings in the normal range, normal self-measurement at home, or 24-hour ambulatory blood pressure monitoring to differentiate white coat hypertension from gestational hypertension.

1.2.4 Pre-eclampsia

Pre-eclampsia is the development of hypertension accompanied by one or more signs of maternal organ dysfunction after 20 weeks' gestation. It may present *de novo* or be superimposed on chronic hypertension. Signs of maternal organ dysfunction may involve the renal, liver, haematological, cardiovascular, or central nervous systems. The presence of proteinuria is the most common feature accompanying hypertension, but is no longer considered mandatory for the diagnosis of pre-eclampsia (19, 20).

1.3 Defining pre-eclampsia

The International Society for the Study of Hypertension in Pregnancy (ISSHP) clarified the classification and diagnostic criteria for hypertensive disorders in pregnancy in 2014, due to a lack of consensus regarding the definition of pre-eclampsia (20, 21). The importance of well-defined diagnostic criteria for hypertensive disorders in pregnancy is essential for effective management and the prevention of adverse maternal and fetal outcomes. The following organisations: Society of Obstetric Medicine of Australia and New Zealand (SOMANZ); Society of Obstetricians and Gynaecologists of Canada (SOGC); American College of Obstetricians and Gynecologists (ACOG); and Royal College of Obstetricians and Gynaecologists (RCOG), all endorse the ISSHP definition of hypertension in pregnancy defined as systolic blood pressure greater than or equal to 140mmHg and/or diastolic blood pressure greater than or equal to 90mHg (Korotkoff 5). These measurements need to be confirmed by repeated readings over several hours (3, 19, 74, 75). Further investigations, including blood tests and urine analysis to determine the presence of signs of pre-eclampsia, are subsequently needed to enable differentiation from gestational hypertension. Unfortunately, the criteria to define pre-eclampsia differ between these organisations and are outlined in Table 1.

Table 1. Definitions of pre-eclampsia

SOMANZ 2014 (3)	Gestational hypertension plus one or more of the following: Proteinuria (Pr:Cr ratio ≥30mg/mmol) Creatinine >90*u*mol/L Oliguria <80mL/4hr Platelet count <100,000*u*/L Haemolysis; disseminated intravascular coagulation; raised serum transaminases; severe epigastric/RUQ pain; convulsions; hyperflexia with sustained clonus; persistent new headache or visual disturbances; stroke, pulmonary edema; fetal growth restriction.
SOGC 2014 (19)	Gestational hypertension plus one or more of the following: New proteinuria; ≥1+ dipstick, random Pr:Cr ratio > 30mg/mmol or 0.3g/24h One or more adverse conditions or severe complications; headache; visual symptoms; chest pain; dyspnea, oxygen saturation <97%, elevated WBC count, elevated INR or APTT; low platelet count: elevated serum creatinine or uric acid; nausea; vomiting; epigastric/RUQ pain; elevated AST, ALT, LDH or bilirubin; low plasma albumin; abnormal FHR, fetal growth restriction, oligohydramnios; absent or reversed end-diastolic flow by Doppler velocimetry.
ACOG 2013 (75)	Gestational Hypertension AND Proteinuria (dipstick >1+, Pr:Cr ratio ≥ 0.3 or 0.3g/24h) OR in the absence of proteinuria one or more of the following: Platelet count <100,000/*u*L Serum creatinine >1.1mg/dL or doubling of creatinine in the absence of other renal disease Elevated liver transaminases twice normal concentration; pulmonary oedema; cerebral or visual symptoms
ACOG 2019 (76)	Hypertension and proteinuria Proteinuria criteria: 24 hour urine collection ≥300 mg protein **or** Single voided urine protein/creatinine ratio ≥0.3 mg/dl Dipstick reading of 2+ (use only if other quantitative methods not available. In absence of proteinuria, new-onset hypertension with the new onset of any of the following: Thrombocytopenia: Platelets <100,000/microliter Renal insufficiency: serum creatinine >1.1 mg/dl or doubling of serum creatinine in the absence of other renal disease Elevated liver transaminases: Twice normal concentration Pulmonary edema Neuro: Unexplained new-onset headache unresponsive to medication **or** visual symptoms
RCOG 2010 (74)	Gestational hypertension with significant proteinuria (Pr:Cr ratio > 30mg/mmol or 0.3g/24h)
RCOG 2019 (77)	New onset hypertension (>140 mm Hg systolic or >90 mm Hg diastolic) after 20 weeks of pregnancy and the coexistence of one or both of the following new-onset conditions: Proteinuria (urine protein:creatinine ratio ≥30 mg/mmol, or albumin:creatinine ratio ≥8 mg/mmol, or ≥1 g/L [2+] on dipstick testing) Other maternal organ dysfunction, including features such as renal or liver involvement, neurological or haematological complications, or uteroplacental dysfunction (such as fetal growth restriction, abnormal umbilical artery Doppler waveform analysis, or stillbirth)

ACOG: American College of Obstetricians and Gynecologists, ALT: alanine aminotransferase, APPT: activated partial thromboplastin time, AST: aspartate aminotransferase, Cr: creatinine, FHR: fetal heart rate, INR: international normalised ratio, LDH: lactate dehydrogenase, Pr: protein, RCOG: Royal College of Obstetricians and Gynaecologists, RUQ: right upper quadrant pain, SOGC: Society of Obstetricians and Gynaecologists of Canada, SOMANZ: Society of Obstetric Medicine of Australia and New Zealand, WBC: white blood count. Note: These guidelines were current at the time of data collection, however, both ACOG and RCOG subsequently updated their definitions so they have also been included.

1.4 Significance of pre-eclampsia

Pre-eclampsia complicates 3-5% of pregnancies (60, 61, 78) and is associated with increased risk of maternal, fetal and neonatal mortality and morbidity (4-6, 23, 63, 79). Prevalence rates have been reported up to three times higher in some populations due to geographic, social, economic and racial differences (23). Maternal and neonatal morbidity both have acute and long-term sequelae, with the majority of these outcomes linked with the severity of disease and the gestational age at delivery.

Complications of pre-eclampsia include progression to eclampsia or HELLP syndrome, maternal organ damage, placental abruption, fetal growth restriction, and preterm birth (21). Early-onset pre-eclampsia is associated with small for gestational age fetuses and fetal growth restriction and this is unsurprising given these entities share similar aeitology regarding poor placentation (80). In terms of the association of pre-eclampsia with preterm birth, there is evidence particularly with preterm pre-eclampsia of shared pathophysiological mechanisms involving placental dysfunction (81) and chronic maternal inflammation (82).

1.4.1 Maternal mortality and morbidity

Hypertensive disorders account for 9% of maternal mortality in Africa and Asia, and 26% in Latin America and the Caribbean (63). Despite low maternal mortality in developed countries, pre-eclampsia-eclampsia contributes significantly to the number of overall maternal deaths. In the United Kingdom, pre-eclampsia-eclampsia accounts for 15% of direct maternal deaths (83), which is similar to Australia and the United States of America at 18% (84) and 20% (85) respectively.

High maternal mortality and morbidity occurs more often in less developed countries due to inadequate resources including a lack of antenatal care or hospital access. In developed countries these rates are lower; however, the causes are related to critical symptoms being unrecognised, delayed diagnosis, delayed or inadequate treatment, and discharge without timely follow up (5, 86).

When left untreated pre-eclamptic women can become eclamptic or develop other severe complications, such as stroke, liver rupture, liver failure, renal failure, cardiac failure or infarction, disseminated intravascular coagulation, haemorrhage, and pulmonary edema, all of which can be fatal (21). These deaths are largely considered preventable through the provision of timely and effective care (87). Major morbidity remains significant in women who survive these complications, with hypertensive disorders the main cause of maternal intensive care admission (88, 89).

1.4.2 Long-term maternal outcomes

Women with a history of hypertensive complications in pregnancy are predisposed to chronic hypertension, diabetes, stroke, premature cardiac arrest, thromboembolism and kidney disease (18, 90). Pre-eclampsia and cardiovascular disease (CVD) share common risk factors such as obesity, diabetes mellitus, hypertension, hyperglycaemia, and metabolic disease; however, it is unknown whether pre-eclampsia contributes directly to future cardiovascular risk, (which may be due to residual vascular injury secondary to endothelial dysfunction) or alternatively, pre-eclampsia uncovers risk (91). CVD and pre-eclampsia may also share genetic risk factors (92, 93).

Pre-eclamptic women have a relative risk of 3.7 of developing chronic hypertension (16), with an estimated risk of myocardial infarction and ischaemic heart disease two to five times higher (17, 90, 94) and a risk of stroke twice that of unaffected women (17, 94). The relative risks of these conditions also increase with the severity of the disorder. Several population studies have found a clear correlation with pre-eclampsia and type 2 diabetes mellitus, with odds ratios between 1.4 and 1.9 (95, 96). Other studies have also found an association of metabolic syndrome (97) and hyperlipidaemia (98) with pre-eclampsia, all of which are predisposing risk factors for CVD.

Women with a history of pre-eclampsia have a four-fold relative risk of developing microalbuminuria, increasing to eight-fold with severe pre-eclampsia (99). Microalbuminuria is an early sign of renal vascular damage and is considered a marker of general CVD (100). Studies have also shown that hypertensive disorders are also associated with an increased risk of developing end stage renal disease (101, 102).

1.4.3 Neonatal and fetal mortality and morbidity

Pre-eclampsia is a major cause of perinatal death, preterm birth and intrauterine growth restriction, (4, 6, 7, 23). In terms of prematurity alone, mortality and morbidity rates are significantly higher in preterm infants compared to term infants (7). Furthermore, preterm infants (32-37 weeks') born to pre-eclamptic mothers had significantly higher rates of SGA and neonatal intensive care admission compared to infants delivered prematurity to other aetiologies, while the rate of respiratory distress syndrome was similar between the groups (103).

The HYPITAT 1 trial (104) found that induction of labour after 36 weeks' gestation compared to expectant management resulted in better maternal outcomes for women presenting with either gestational hypertension or mild pre-eclampsia, without a significant difference in adverse neonatal outcomes between the outcome groups. This study was repeated by the same researchers (HYPITAT 2), involving women at an earlier gestation of 34-37 weeks' (105). In contrast to the results of trial one, the study showed an increased risk of neonatal respiratory distress syndrome in infants born to women who delivered immediately compared to those who had expectant management, with only the possibility that the small risk of adverse maternal outcomes might be reduced. There has been some controversy expressed over these findings as hypertension was used both as the entry and major endpoint criterion in determining whether interruption of pregnancy advantages the mother in ways that matter (106). Furthermore, pre-eclampsia and gestational hypertension were treated as a single entity when they don't have the same endpoints. Another study that evaluated planned early delivery or expectant management for late preterm (34-37 weeks' gestation) pre-eclampsia, found that planned delivery reduced maternal morbidity and severe hypertension compared to the expectant management group however, there were more neonatal admissions relating to prematurity but no indicators of greater neonatal morbidity (107).

Complications relating to prematurity and small for gestational age infants primarily result in neurodevelopmental, respiratory and retinopathy problems, requiring specialised care in neonatology units and prolonged hospitalisation. Infants born to mothers with pre-eclampsia have an increased risk of cerebral palsy, blindness, deafness, and cognitive dysfunction (9, 10), bronchopulmonary

dysplasia (108), respiratory distress syndrome, pulmonary hypertension or haemorrhage, respiratory failure, intraventricular haemorrhage, necrotising enterocolitis, seizures, jaundice, abnormalities of glucose regulation, and temperature instability (7, 8, 11).

Studies have shown increased rates of stillbirth associated with pre-eclampsia, with relative risks reported as two-fold (109) and seven-fold (110) compared to stillbirth without pre-eclampsia. The risk of intrauterine fetal death is markedly higher in women who develop pre-eclampsia earlier in pregnancy and is also significantly higher in women with severe disease compared to those with mild disease (111).

1.4.4 Long-term neonatal outcomes

Long-term morbidity of neonate survivors born to pre-eclamptic women often results in ongoing health problems and disability relating to neurological and respiratory complications that can continue through childhood and their adult lives. Infants born to pre-eclamptic women have a greater risk of developing hypertension and diabetes in adulthood, with increased cardiovascular morbidity (12, 13). A recent systematic review and meta-analysis of children and adolescents born to pre-eclamptic mothers found they had increased body mass index (BMI) and blood pressure, compared to controls, which are known risk factors for cardiovascular disease (14).

Evidence suggests that fetuses are highly susceptible to alterations in the intrauterine environment (112) and that the impact of pre-eclampsia exposure during sensitive phases of development may predispose these infants to increased risk of chronic diseases (113). The causal pathways of these mechanisms are not well understood, with limited knowledge on the impact pre-eclampsia has on fetal programming (114).

1.5 Clinical presentation

Pre-eclampsia is often diagnosed during routine antenatal care, as most women with mild to moderate disease are asymptomatic (115). Hypertension is generally the first clinical sign, with surveillance and further investigations needed to determine the coexistence of maternal organ involvement (3). Specific signs and

symptoms have been established to determine multisystem dysfunction, which are outlined in Table 2.

Women who are symptomatic for pre-eclampsia commonly experience a new persistent headache. They may have visual disturbances such as blurring or flashing before the eyes or light sensitivity, which are all signs of neurological involvement. Other frequent symptoms include vomiting, nausea, epigastric pain or right upper quadrant pain suggestive of liver involvement, with abnormal renal function tests the most common laboratory finding (21, 116). Significant proteinuria, elevated creatinine levels and oliguria are signs of renal insufficiency, with mixed results on the accuracy of the protein to creatinine ratio as a diagnostic tool (115, 117, 118). Elevated levels of uric acid are often observed with pre-eclampsia but are not diagnostic of the disease (3). Raised serum liver enzymes are an indication of pre-eclampsia, however this is not an uncommon finding and needs to be differentiated from other causes such as acute fatty liver of pregnancy (115, 119).

Pre-eclampsia may manifest as HELLP syndrome characterised by haemolytic anaemia, liver dysfunction and low platelet count occurring in 0.5-0.9% of all pregnancies (64). 10-20% of women with severe pre-eclampsia develop HELLP syndrome, which can occur without hypertension or proteinuria (23, 64, 120). In women who develop pre-eclampsia, the rate of eclampsia has been reported between <1% and 2.6% (23, 121)

Fetal and / or placental manifestations may occur before, with, or after maternal signs and symptoms (122). This includes placental insufficiency, evidenced by high resistance umbilical artery Doppler, intrauterine growth restriction or oligohydramnios, placental abruption, or stillbirth (123).

Table 2. Clinical presentation of pre-eclampsia

Renal
Significant proteinuria: a spot urine protein/creatinine ratio ≥30mg/mmol
Serum or plasma creatinine >90*u*mol/L
Oliguria: <80mL/4 hour
(Urate is not included as a diagnostic feature, despite the common presentation with PE. Gestational corrected normal ranges should be used.)
Haematological system
Thrombocytopenia <100 000/*u*L
Haemolysis: schistocytes or red cell fragments on blood film, raised bilirubin, raised lactate dehydrogenase >600mIU/L, decreased haptoglobin
Disseminated intravascular coagulation
Gastrointestinal system
Raised serum transaminases (liver enzymes).
Severe epigastric and/or right upper quadrant pain.
A subset of women with severe pre-eclampsia develop HELLP syndrome characterised by haemolysis, raised liver enzymes and low platelets with or without other pre-eclamptic features. Often only two of three components are recognizable.
Central nervous system
Convulsions (eclampsia)
Hyperflexia with sustain clonus
Persistent, new headache
Persistent visual disturbances (photopsia, scotomata, cortical blindness, posterior reversible encephalopathy syndrome, retinal vasospasm)
Stroke
Cardiovascular system
Pulmonary oedema
Chest pain
Dyspnoea
Fetal involvement
Fetal growth restriction is generally associated with a small for gestation age fetus, and often accompanied with features suggestive of placental disease such as abnormal umbilical artery Doppler or oligohydramnios. These findings should be present as criteria to diagnose superimposed pre-eclampsia.

HELLP: Haemolysis, elevated liver enzymes, low platelets, PE: pre-eclampsia. Adapted from Lowe *et al* 2015 (3).

1.6 Classification of pre-eclampsia

The traditional diagnosis of pre-eclampsia was based on the development of concurrent hypertension and proteinuria, and further sub-classified as mild, moderate or severe depending on the extent of clinical manifestation. More recently, pre-eclampsia has been defined based on the gestational age requiring delivery, due to the clinical problems facing obstetricians. 34 weeks is considered an important gestational milestone in terms of better outcomes for the infant after this time point. Early-onset pre-eclampsia is most often defined when the onset of symptoms and signs require delivery before 34 weeks' gestation, with late-onset pre-eclampsia diagnosed from 34 weeks' gestation (24, 25, 41, 124). Some experts define early-onset pre-eclampsia when disease occurs before 32 weeks, while others consider 28 weeks' gestation appropriate (125).

Although the terms early and late-onset pre-eclampsia are widely used, there is a lack of consistency in the literature. This sub-classification is not defined in the guidelines of leading international societies (3, 19, 74, 75). Preterm and term pre-eclampsia are also cited, with preterm pre-eclampsia developing before 37 weeks and term pre-eclampsia developing after 37 weeks (24, 25, 126). Early, intermediate and late pre-eclampsia have also been used in the literature, defining pre-eclampsia in terms of gestational age at delivery: <34 weeks, 34-37 weeks and >37 weeks respectively (127).

The terms mild, moderate and severe pre-eclampsia have been used to describe the severity of signs and symptoms of the disease, which can apply to both early and late-onset pre-eclampsia. More recent ISSHP guidelines recommend avoiding terms such as mild as this can give false security for such cases (128). Variation in the definition of severe pre-eclampsia exists within the international community, however there is general agreement that it applies to women who have signs of multi-organ involvement (3, 19, 74, 87, 129). In terms of hypertension, a systolic pressure of 160mmHg is generally the threshold to define severe pre-eclampsia, while others use 170mmHg or 180mmHg. In regard to diastolic pressure, 110mmHg is considered the threshold to define severe pre-eclampsia, although a minority use 100mmHg (125). Other indicators of severe disease include poor blood pressure control, deteriorating clinical condition, development of HELLP syndrome, worsening thrombocytopenia, or deterioration

of growth-restricted fetuses (3, 19). Unfortunately, pre-eclampsia can progress at an unpredictable rate, with there being no specific prognostic features that readily identify those women and infants who are more at risk and require greater monitoring.

1.7 Pathogenesis

Pre-eclampsia is no longer considered a single disease entity, but rather a multifactorial disorder associated with abnormal placentation. Factors that have been proposed to contribute to the development of pre-eclampsia include underlying maternal susceptibility, altered anti-angiogenic response, altered maternal immune response, and inadequate adaptation of the spiral arteries (21, 23, 24, 130, 131). Pre-eclampsia is characterised by a systemic anti-angiogenic response resulting in endothelial dysfunction, vasoconstriction and hypertension. Alternative pathophysiological pathways leading to these vascular changes have been identified, supporting the concept of early and late-onset forms of the disease (24, 25, 124). Furthermore, studies have shown early-onset and late-onset pre-eclampsia have different clinical features, maternal and fetal outcomes, biochemical markers and genetic and environmental risk factors (126, 132, 133).

Early-onset pre-eclampsia primarily involves early abnormal placentation, which is generally not evident in late-onset pre-eclampsia. Histological assessment of early-onset pre-eclampsia placentas demonstrate abnormal placental morphology (134) with increased placental lesions compared to late-onset pre-eclampsia placentas (135). Placentas of women with early-onset pre-eclampsia have similarities to placentas of growth-restricted fetuses (136). This evidence suggests that late-onset pre-eclampsia is not specifically a placental disease, but rather a disorder of maternal origin (134, 137), giving rise to the concept of two distinct pre-eclampsia phenotypes: a placental phenotype and a maternal phenotype. Underlying maternal susceptibility seems to play a role in both disease forms, however the mechanisms are unclear. It is possible that pre-existing maternal disease or an altered immune state may lower the threshold at which these mechanisms are initiated (19). These factors may also have a bidirectional influence, thereby adding complexity to understanding the processes involved (22). Some authors suggest the key mechanism in late-onset

pre-eclampsia relates to the maternal immune response to the pregnancy (24), while others hypothesize maladaptation of the cardiovascular system plays a central role (46, 138). Figure 1 outlines the factors associated with the development of placental and maternal phenotypes of pre-eclampsia. Despite this distinction of placenta and maternal phenotypes, it is important to note that there is significant overlap between these groups, making an assessment of maternal phenotype useful in a high-risk cohort define through 'placental testing', which essentially describes the FMF pre-eclampsia screening algorithm.

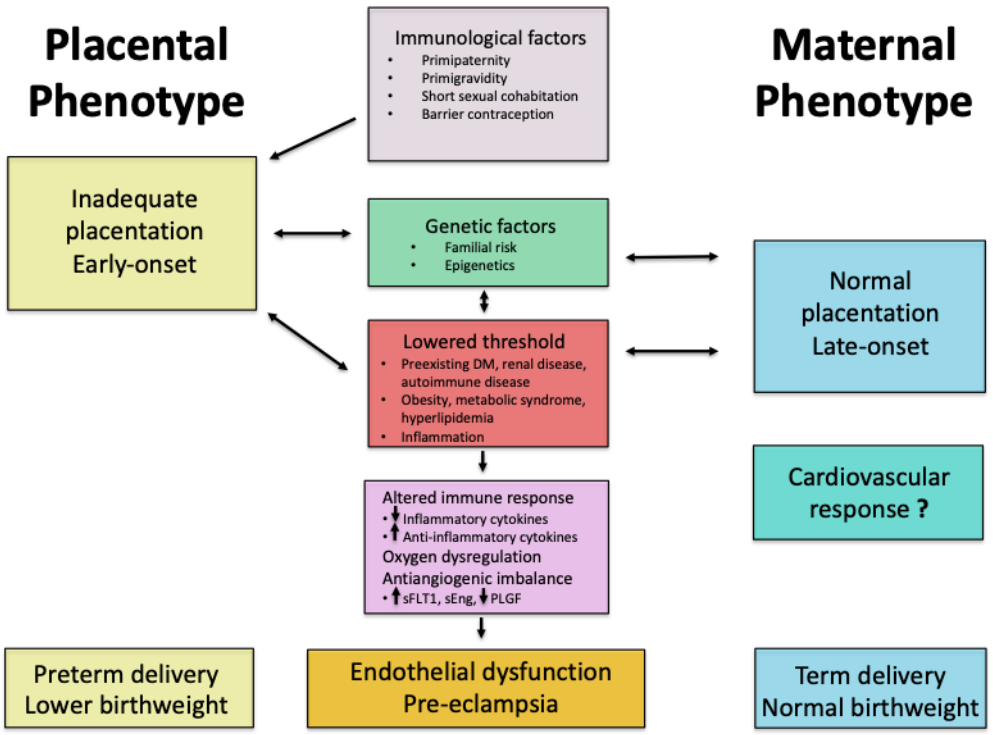

Figure 1. Factors associated with the development of placental and maternal phenotypes of pre-eclampsia.

Adapted from Magee *et al*, 2014 (139).

1.7.1 Abnormal placentation

In a normal pregnancy, structural and functional changes result in the spiral arteries becoming low resistance vessels, resulting in a ten-fold increase in blood volume to the uterus and placenta. The spiral arteries supply the inner

myometrium and endometrium and undergo modification during pregnancy in two phases: firstly, the decidual segments at 8-10 weeks' gestation, followed by the myometrial segments at 16-18 weeks' gestation. Studies have shown early-onset pre-eclampsia is associated with incomplete remodelling of the spiral arteries, evidenced by high resistance uterine artery flow compared to women with a normal pregnancy outcome (24, 140, 141).

Prior to the remodelling of the decidual spiral arteries in normal pregnancy, the vessels are obstructed by invasive trophoblast plugs, thereby minimising placental perfusion during organogenesis when the fetus is particularly vulnerable to teratogenic damage from free radicals (142). After 9 weeks' gestation the cytotrophoblast cells from the trophoblastic outer layer of the blastocyst invade the decidual segments of the spiral arteries. These arteries lose their endothelium and musculoelastic tissue and are replaced by a fibrinoid material that enables the trophoblastic cells to embed themselves within the wall (143). The loss of smooth muscle allows the arteries to progressively dilate and increase the volume of blood flow. The immune system facilitates deep myometrial invasion of the cytotrophoblast cells through the action of natural killer cells and macrophages (142).

In early-onset pre-eclampsia there is inadequate remodelling of the spiral arteries and poor trophoblastic invasion within the superficial decidua (144) (Figure 2). The arterial walls maintain smooth muscle, thereby preventing dilatation and reduced permeability of the arteries. This results in hypoperfusion, leading to chronic placental hypoxia and ischaemia. These features are also observed in fetal growth restriction without hypertension, indicating poor vascular remodelling of the spiral arteries is not the sole mechanism in the development of pre-eclampsia (19, 25). A study of placental vasculature and morphology showed that, isolated early-onset pre-eclampsia was associated with abnormal placental morphology – (specifically reduced terminal villi volume) – whereas placentas from late-onset pre-eclampsia were morphologically similar to placentas from gestational-age-matched controls (134).

The permeability of the vessel wall is also altered by the presence of the embedded trophoblasts, permitting maternal blood to pass out through the arterial wall and into the intervillous spaces of the developing placenta. Normally,

the cytotrophoblast cells convert from an epithelial to endothelial phenotype to enable the cells to adhere to the fibrinoid material in the vessel wall, in a process referred to as pseudovasculogenesis. In pre-eclampsia this process is thought to be defective, preventing cell adhesion (145).

1.7.2 Angiogenic factors

Placental angiogenesis is essential for a normal pregnancy, requiring a balance between the pro-angiogenic stimulation of new vessel growth and anti-angiogenic inhibition of vessel overgrowth (146). There is strong evidence to suggest that alterations in circulating levels of angiogenesis regulators contribute to the development of pre-eclampsia. During normal pregnancy, placental angiogenesis is regulated by vascular endothelial growth factor (VEGF), placental growth factor (PlGF) and transforming growth factor Beta 1 (TGF-β1). PlGF is a member of the VEGF sub-family and has a key role in placental angiogenesis. These cytokines (cell signalling proteins) maintain endothelial health by interacting with their endogenous endothelial receptors - soluble VEGF receptor-1, also known as soluble fms-like tyrosine kinase-1 (sFlt1) and soluble endoglin (sEng).

Pre-eclampsia is associated with excess secretion of these anti-angiogenic proteins (sFlt1 and sEng) inhibiting normal VEGF, PlGF and TGF- β1 signalling, triggering an inflammatory response and endothelial dysfunction (Figure 3). Increased levels of sFlt1 and sEng, and decreased levels of PlGF, are evident in women who develop both early-onset and late-onset pre-eclampsia, weeks prior to the onset of clinical symptoms (147, 148). Overexpression of sFlt1 appears to be a key mechanism linking placental dysfunction with maternal endothelial dysfunction, as sFlt1 levels return to normal within several days of delivery, whilst coinciding with resolving proteinuria and hypertension (149).

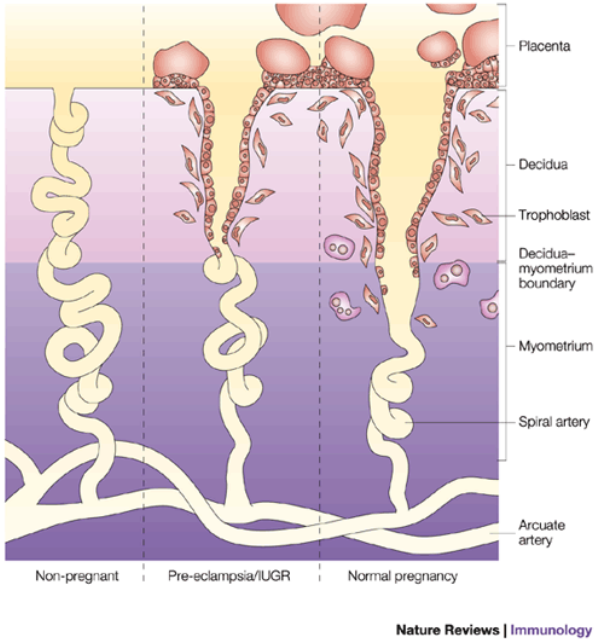

Figure 2. Abnormal placentation.

Maladaptation of the spiral arteries in early-onset pre-eclampsia and IUGR (intrauterine growth restriction). There is inadequate remodelling and poor trophoblastic invasion (150).

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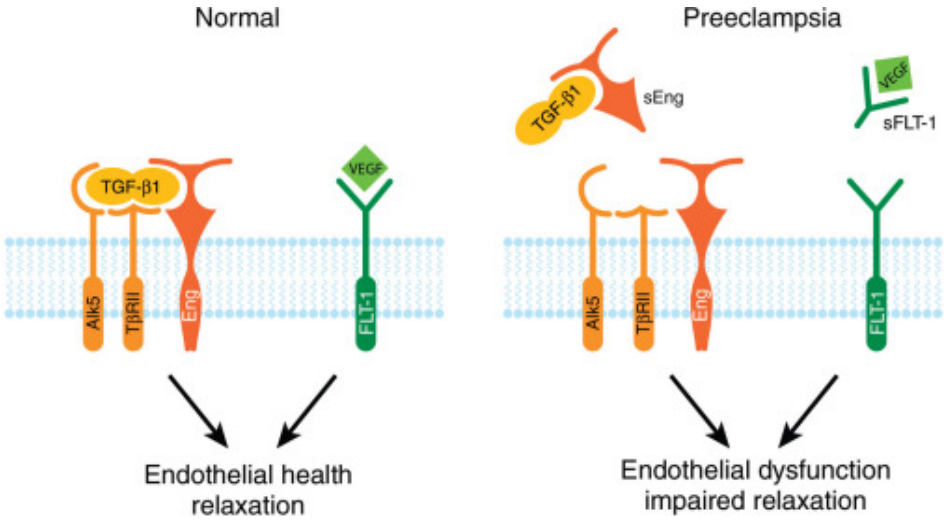

Figure 3. Endothelial dysfunction in pre-eclampsia.

In pre-eclampsia, excess placental secretion of soluble fms-like tyrosine kinase-1 (sFLT-1) and soluble endoglin (sEng) (two endogenous circulating antiangiogenic proteins) inhibits VEGF and TGF-β1 signalling, respectively. This results in endothelial-cell dysfunction, including decreased prostacyclin, nitric oxide production, and release of procoagulant proteins.

Eng: endoglin, sEng: soluble endoglin, FLT-1: fms-like tyrosine kinase 1 (151).

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1.7.3 Oxygen dysregulation and reactive oxygen species

Hypoxia, secondary to defective spiral artery adaptation, is thought to play a role in the pathogenesis of pre-eclampsia (152). A possible explanation is the hypoxia-reoxygenation theory, rather than just the presence of hypoxia. This theory is based on the idea that remodelled arteries do not lose their smooth muscle, and are therefore sensitive to vasoconstriction, resulting in alternate periods of hypoxia and normoxia as the arteries contract and dilate (153). Hypoxia-inducible factor 1-α (HIF-1α) is a transcriptional regulator of cellular development, released in response to hypoxia. It has also been proposed that inappropriate activation of hypoxic factors, such as HIF-1α, may contribute to the development of pre-eclampsia, rather than hypoxia alone. Experiments with animal models have not definitely supported either hypothesis (154, 155).

Hypoxia is also known to trigger oxidative stress, characterised by an increase in reactive oxygen species (ROS) such as superoxide, nitric oxide (NO) and peroxynitrite. This results in an imbalance between the levels of ROS and anti-oxidants (156), with excessive ROS causing structural and functional damage to cellular DNA, proteins and cell membranes (157, 158). ROS are involved in cell signalling pathways critical for the development of normal placental tissue, however the underlying mechanism of their involvement is unclear (159). Microvascular injury of the capillaries and arterioles also occurs with hypoxia and reperfusion injury. The permeability of the vessel wall consequently increases, activating endothelial cells to produce more ROS (160). Oxidative stress can induce the adhesion of leucocytes and platelets to the endothelium, promoting the inflammatory response seen in pre-eclampsia (131, 161). This leads to generalised vasoconstriction and increased resistance in the placental circulation, thereby contributing to vascular placental dysfunction and hypertension.

NO has an important role in maintaining vascular tone during pregnancy and is a strong anticoagulant factor (156). Increased levels of estrogen up-regulate the endothelial cell production of NO, thereby facilitating vasodilatation through smooth muscle relaxation resulting in greater uterine blood flow. NO also prevents the adhesion of leucocytes and platelets to the endothelium, impeding the pro-inflammatory state. The ROS superoxide is known to inactivate NO, with

accumulation of the tissue damaging bi-product peroxynitrite found in placental tissue of pre-eclamptic women (156). ROS also seem to suppress the function of the NO precursor, endothelial NO synthase (162), reducing the bioavailability of NO, leading to endothelial dysfunction and pre-eclampsia. This finding is supported by a first trimester study showing that women who subsequently develop pre-eclampsia have low serum NO concentration levels (163). Studies have also shown levels of Asymmetric dimethyl-L-arginine (ADMA) are higher in women with pre-eclampsia prior to the onset of signs and symptoms of the disease (164-166). ADMA is a by-product created during protein methylation, which interferes with L-arginine in the synthesis of NO, essential for healthy endothelial function.

Heme oxygenase (HO-1) is an enzyme that catalyses the breakdown of heme metabolites into iron, carbon monoxide and biliverdin, with recent studies suggesting this enzyme plays an important regulatory role in the vascular development of a healthy placenta (167, 168). Increased levels of HO-1 have been reported in response to oxidative stress, with the actions of the heme breakdown metabolites providing a protective mechanism to hypoxic and inflammatory cellular injury (169). Studies have also shown a decrease in the levels of HO-1 have been associated with pre-eclampsia (170, 171).

1.7.4 Altered immune response

Recent studies have demonstrated an altered immune response may play an important role in the pathogenesis of pre-eclampsia (161, 172-175). The findings of large epidemiological studies support the relationship between pre-eclampsia and the immune system, with pre-eclampsia associated with several immune related risk factors (176-178). These risk factors include autoimmune diseases, nulliparity, and paternal factors such as primipaternity, short period of sperm exposure preceding conception and assisted reproductive technologies. This suggests that the immune response to paternal antigens may play a causal role in the development of the disease (179-181).

Normal pregnancy is characterised by a mild systemic inflammatory response of the innate immune system, with activation of neutrophils, monocytes and natural killer cells. In pre-eclampsia the inflammatory response of the innate system is excessive (174). Studies suggest that placental hypoxia, secondary to poor

placentation, triggers oxidative stress and the release of placenta factors into the maternal circulation, causing systemic inflammation and endothelial dysfunction (174, 175). The excessive inflammatory response also occurs in the setting of normal placentation, with trophoblastic cell debris and secondary necrosis of apoptotic particles overloading the maternal immune system (24). Studies have also found that pre-eclampsia is associated with an increased production of inflammatory cytokines (IL-1, IL-6, TNFα) and decreased levels of anti-inflammatory cytokines (IL-10), suggesting an imbalance in immune regulation (182-184), although, these studies did not differentiate between early-onset and late-onset forms of the disease.

1.7.5 Maternal susceptibility

Genetics and underlying maternal diseases, such as obesity, diabetes, metabolic syndrome, autoimmune and renal diseases, are associated with an increased risk of the developing pre-eclampsia (62, 92, 176, 177). Several genes appear to increase susceptibility for pre-eclampsia, with the genetic theory suggesting these genes probably interact in the haemostatic and cardiovascular systems, as well as in the inflammatory response (185). The risks associated with these conditions are discussed in *Chapter 1, section 1.9.1. maternal risk factors.*

1.8 Clinical manifestation

Hypertension is most often the first sign of pre-eclampsia. Evidence suggests that endothelial dysfunction, increased vascular reactivity, vascular remodelling and decreased compliance may contribute to blood pressure elevation, rather than be the consequence (186). Endothelial dysfunction is the primary mechanism attributed to the clinical manifestations of pre-eclampsia, present in both early and late forms of the disease (26, 27). Changes to normal endothelial function are evident prior to signs and symptoms of pre-eclampsia, with retinal imaging studies showing constriction of the microvasculature that then fail to dilate appropriately in women who subsequently develop disease (58), while flow-mediated dilation studies reported impairment in women before, during and after pre-eclampsia, suggesting poorer vascular function in this group of women (59).

In early-onset pre-eclampsia, poor placentation, secondary to insufficient trophoblastic invasion, leads to hypoxia and ischaemia resulting in oxidative stress. The stressed placenta releases syncytiotrophoblastic (STB) debris, reactive oxygen species, and anti-angiogenic factors such as sFlt1 and sEng, into the maternal circulation (24, 28, 174). The imbalance of these factors inhibits the normal function of endothelial cells and also triggers an exaggerated maternal systemic inflammation response. In cases of late-onset pre-eclampsia with normal placentation, the mechanisms leading to endothelial dysfunction are unclear. One theory suggests that when placental growth reaches its limits near term, terminal villi within the placenta become overcrowded, reducing perfusion, leading to hypoxia and STB stress. In these cases, the fetuses are well grown, however the maximum function of the placenta has been reached (187). Other possible theories include the maternal immune system's response to apoptosis of the placenta later in pregnancy, being initiated at a lower threshold due to an underlying maternal condition, or that the immune system's response is overloaded (24). Alternatively, maladaptation of the cardiovascular system may trigger abnormal endothelial function and potentially lead to placental dysfunction (46, 138, 188).

Endothelial cells are involved in mediating coagulation, immune function, vasodilatation and vasoconstriction, as well as the redistribution of fluid between the intravascular and extravascular spaces. Dysfunctional endothelial cells reduce the synthesis of vasorelaxing agents such as prostacyclin and nitric oxide and increase the production of vasoconstrictors, such as endothelin-1 and Thromboxane A2, leading to increased arterial resistance and hypertension (189). The dysfunction also enhances blood vessel permeability, thereby increasing fluid into the extravascular space and thus causing organ edema and subcutaneous tissue edema. Cerebral edema produces symptoms of headaches and convulsions, while abdominal pain results from liver edema, and breathlessness secondary to lung edema. The subsequent decrease in fluid within the intravascular space also results in hypoperfusion of the organs (29).

Endothelial dysfunction within the kidneys is characterised by glomerular capillary lesions known as glomerular endotheliosis. The glomeruli enlarge due to endothelial cell swelling occluding the capillary lumens, thereby creating these distinctive lesions (190). These lesions can be focally present in other conditions,

however in pre-eclampsia they are prominent and widespread (191). The damaged capillaries no longer function properly, resulting in renal insufficiency and proteinuria. Creatinine and uric acid levels also rise in pre-eclampsia, primarily due to decrease renal excretion, secondary to a lower intravascular blood volume (83). Within the liver, edema obstructs sinusoid blood flow, increasing the risk of haemorrhage. Leakage across liver cell membranes also occurs in pre-eclampsia resulting in hepatic dysfunction, evidenced by elevated levels of the enzymes alanine aminotransferase and aspartate aminotransferase (83).

1.9 Risk factors

The incomplete understanding of the pathogenesis of pre-eclampsia makes it challenging to clearly identify women at risk. What is known is that the disorder is multifactorial, primarily involving the placenta and the maternal response to the pregnancy. The aetiological process is also influenced by maternal and fetal genetics, paternity and environmental factors (92, 179, 192), however the extent to which these factors contribute to the disease is not well known. Initial evaluations of risk factors for the development of pre-eclampsia considered the disease as a single entity (176, 193). Recent studies have shown that not all risk factors are attributable to both early and late-onset pre-eclampsia (126, 133, 137, 194-196). Table 3 outlines the factors that have been linked with pre-eclampsia and their relative risks based primarily on two large meta-analyses by Duckitt *et al,* 2005 (176) and Bartsch *et al,* 2016 (177), while Table 4 summarises the differences associated with early-onset and late-onset pre-eclampsia. The majority of studies in this Table define early-onset disease as delivery before 34 weeks' gestation (133, 197-199), with the exception of two that use less than 32 weeks' gestation to define early-onset ((132, 140) and one that uses greater than 35 weeks' gestation to define late-onset disease (132).

1.9.1 Maternal risk factors

A number of studies have found an increased risk of pre-eclampsia in association with the following maternal factors: previous pre-eclamptic pregnancy; nulliparity; raised body mass index; advanced maternal age (>40 years); non-white race; autoimmune diseases, such as systemic lupus erythematosus (SLE) and

antiphospholipid syndrome (APLS); chronic renal disease; chronic hypertension; diabetes; pregnancy interval greater than 10 years; in-vitro fertilisation (IVF); a family history of pre-eclampsia; and multiple pregnancy (176, 177, 193, 200). Marked differences in relative risks have been reported for some of these demographic factors and are discussed below. Different pre-eclampsia definitions, study populations and study design contribute to some of the heterogeneity in the results.

Women who have pre-eclampsia in their first pregnancy are reported to be seven to eight times more likely to develop pre-eclampsia in their second pregnancy (176, 177), while another study found that the relative risks were four-fold and two-fold for early-onset and late-onset pre-eclampsia respectively (197, 201). A family history of pre-eclampsia nearly triples the risk of pre-eclampsia, with the association linked to the woman's mother (176, 197). One study found the risk of pre-eclampsia rises mildly with increasing maternal age over 32-34 years, but only in association with late-onset disease (197). This is in contrast to another study that found the increased association in women over 40 years linked to both forms of pre-eclampsia (133).

Chronic hypertension is one of the stronger risk factors for pre-eclampsia, with a recent meta-analysis reporting a relative risk of five (177). Other individual studies have reported lower relative risks in the range of one to three (176), while one study found a nine-fold increase in women with early-onset pre-eclampsia and no increase with late-onset pre-eclampsia (197). The prevalence of renal disease is higher in women who develop pre-eclampsia, however the strength of the association is less, with a relative risk of 1.5 - 2.1(177).

The risk of pre-eclampsia increases as prepregnancy BMI increases (177, 202-204) and is four times greater when BMI is over 35 (176) compared to women with a BMI in the range 19-27. There is also a higher association of obesity with late-onset pre-eclampsia compared to early-onset pre-eclampsia (197, 205). Obesity is known to impair the immune function and induces an inflammatory response. This results in an increased production of pro-inflammatory proteins including C-reactive protein, with higher levels reported in pre-eclamptic women in the first trimester of pregnancy (206). Increased BMI is also linked to polycystic ovary syndrome (PCOS), however several studies have identified PCOS as an

independent risk factor for pre-eclampsia (207-209). The relative risk of pre-eclampsia with PCOS has been reported to be four-fold (208).

Insulin resistance (210, 211) and hyperlipidaemia (212, 213) are risk factors for the development of pre-eclampsia. Both of these conditions are associated with obesity and PCOS, however the data is conflicting on whether they are independent risk factors, as all of these conditions are associated with metabolic dysregulation (214). Obesity, hyperlipidaemia and insulin resistance are thought to stimulate inflammatory cytokine release and oxidative stress, leading to endothelial dysfunction (215), the primary mechanism in the development of pre-eclampsia. The relative risk of pre-eclampsia in women with pre-gestational diabetes has been reported to be between two and four (176, 177, 216). Gestational diabetes mellitus (GDM) is also associated with pre-eclampsia, however this may be because these conditions share a similar aetiological pathway (216).

Specific autoimmune diseases are associated with pre-eclampsia, with relative risks varying for the different disorders. APLS and SLE are independently reported in association with pre-eclampsia, whereas other autoimmune disorders, such as Sjogren's disease and rheumatoid arthritis, did not show significance unless grouped with other disorders (217). One report based on two studies found that APLS was associated with a relative risk of 9.7 (95% CI, 4.3 to 21.8) (176), while a more recent assessment included three cohorts and found the relative risk was 2.8 (95% CI 2.6-3.1) (177). The relative risk of developing pre-eclampsia with SLE is 2.5 (95% CI 2.0-6.3) (177).

Black women have a higher risk of developing early-onset and late-onset pre-eclampsia compared to Caucasian and Hispanic women (178, 197), while Black and South-Asian women have an increased risk of late-onset pre-eclampsia (197, 218). Ethnicity may mediate some of its effect on the development of pre-eclampsia through its association with other risk factors, such as raised BMI and diabetes (219). The prevalence of pre-eclampsia in Chinese women is low compared to Caucasians, with a recent study suggesting this difference may be attributable to dependent factors including lower BMI and lifestyle such as longer sexual cohabitation (220).

1.9.2 Smoking

One of the most interesting findings is the consistent reporting of the protective effect maternal smoking has on the development of pre-eclampsia (221, 222). Smoking has been associated with a decreased risk of pre-eclampsia in both primiparous and multiparous women, as well as both singleton and multifetal pregnancies. Compared to non-smokers, the relative risk of pre-eclampsia is 0.5-0.8 (178). The mechanism for the protective effect of smoking is not clear, however a recent study suggests that the combustion products of tobacco such as carbon monoxide are involved, and not nicotine (223).

Smoking has been associated with lower levels of the anti-angiogenic proteins, sFlt1 and sEng, and higher levels of the pro-angiogenic protein, PlGF with the suggestion that smoking exposure may moderate the impact these angiogenic factors have on the development of pre-eclampsia (224). Despite the decreased risk of pre-eclampsia, women who do develop the disease have poorer outcomes compared to non-smokers with pre-eclampsia (225).

1.9.3 Paternal risk factors

Studies have also determined paternal factors play an important role in the aetiology of pre-eclampsia, but to a lesser extent than maternal factors (181). Paternity patterns and sperm exposure such as the duration of the unprotected sexual cohabitation prior to conception and barrier contraception appear to influence the risk of pre-eclampsia (179, 181, 226). Women with a short period of sperm exposure due to a short sexual relationship (< 6 months), or prolonged use of barrier contraception, have a higher incidence of pre-eclampsia compared to women with a longer period of exposure (227, 228). Donor insemination and embryo donation are also associated with a higher risk of pre-eclampsia in keeping with the short partner-specific sperm exposure theory (180). It is thought that longer sperm exposure has a ‘protective’ effect due to maternal immunological tolerance to paternal antigens (179). Another protective factor was also found in a study assessing the risk of pre-eclampsia in women with a previous abortion. The findings suggest that a history of abortion in nulliparous women reduced the risk of pre-eclampsia in the subsequent pregnancy (229). A subsequent study supported this finding only when the previous abortion was with the same partner (230).

Women in their first pregnancy are generally considered to have an increased risk of pre-eclampsia compared to multiparous women, however this protective effect is lost with a change in partner (226, 230-232). These studies inferred primipaternity rather than primigravidity has a greater significance in terms of the risk of pre-eclampsia. Another study suggested that the effect of a change in partner was eliminated when the inter-birth interval was taken into account, concluding multiparous women who become pregnant ten years or more after their previous pregnancy are as likely to develop pre-eclampsia as nulliparous women (233).

Table 3. Relative risks for the development of pre-eclampsia

Risk Factors	Unadjusted Relative Risks or Adjusted Odds ratio* (95% CI)		
	Duckitt (176)	Bartsch (177)	Individual studies
Previous pre-eclampsia	7.19 (5.85-8.83)	8.4 (7.1-9.9)	
Previous HT in pregnancy			^
Chronic HT		5.1 (4.0-6.5)	8.7 (2.77-27.33)* [a]
Chronic renal disease		1.8 (1.5-2.1)	
Pregestational diabetes	3.56 (2.54-4.99)	3.7 (3.1-4.7)	
Autoimmune disease	6.9 (1.1-42.3)		
APLS	9.72 (4.34-21.75)	2.8 (1.8-4.3)	
SLE		2.5 (2.0-6.3)	
Nulliparous	2.91 (1.28-6.61)	2.1 (1.9-2.4)	
BMI >35kg/m^2 at 1st visit			1.55 (1.28-1.88)[b]
Family history PE	2.90 (1.7-4.93)	2.9 (2.6-3.1)	
MA ≥40 years primiparous	1.68 (1.23-2.29)		
MA ≥40 years multiparous	1.96 (1.34-2.87)		
MA >35 years		1.2 (1.1-1.3)	
MA >40 years		1.5 (1.2-2.0)	
Raised BMI	2.47 (1.66-3.67)		
Prepregnancy BMI >25		2.1 (2.0-2.2)	
Prepregnancy BMI >30		2.8 (2.6-3.1)	
Multiple pregnancy		2.9 (2.6-3.1)	
Twin vs singleton	2.93 (2.04-4.21)		
Triplet vs twin	2.83 (1.25-6.40)		
SBP ≥130mmHg at booking	2.37 (1.78-3.15)		
DBP ≥80mmHg, at booking	1.38 (1.01-1.87)		
ART		1.8 (1.6-2.1)	
Prior IUGR		1.4 (0.6-3.0)	
Prior stillbirth		2.4 (1.7-3.4)	
Prior placental abruption		2.0 (1.4-2.7)	
Ethnicity			
Black			3.64 (1.84-7.21)* ePE[a]
			2.97 (1.98-4.46)* lPE[a]
Indian or Pakistani			2.66 (1.29-5.48)* lPE[a]
Mixed			3.31 (1.55-7.06)* lPE[a]
New partner			8.6 (3.1-23.5)*[c]
Pregnancy interval			1.12 (1.11-1.13)* per year[d]
Short sperm exposure			
<6months			1.88 (1.05-3.36)* [e]
<3months			2.32 (1.03-5.25)* [e]
1st intercourse			5.75 (1.13-29.3)* [e]

Adapted from Duckitt *et al* 2005 (176), Bartsch *et al* 2016 (177) [a]Poon *et al* 2010 (197), [b]Milne *et al* 2005 (234), [c]Tubbergen *et al* 1999 (232), [d]Skjaerven *et al* 2002 (233), [e]Kho *et al* 2009 (227), ^NICE guidelines (74).

APSL: antiphospholipid syndrome, ART: assisted reproductive technologies, BMI: body mass index, DBP: diastolic blood pressure, ePE: early-onset pre-eclampsia, HT: hypertension, IUGR: intrauterine growth restriction, lPE: late-onset pre-eclampsia, MA: maternal age, PE: pre-eclampsia SBP: systolic blood pressure, SLE: systemic lupus erythematous.

Table 4. An overview of the differences between early-onset and late-onset pre-eclampsia

	Early-onset pre-eclampsia	Late-onset pre-eclampsia
Prevalence	0.38[a] - 0.4[b]%	2.72[a], 2.8[b], 4[d]%
Placentation		
Abnormal spiral artery remodelling	Yes	No
Placental lesions^	Yes	No
Angiogenic factors*		
s-Flt	Increased (higher than lPE)	Increased
PlGF	Decreased (lower than lPE)	Decreased
PP-13	Decreased	Decreased
Low PAPP-A	Yes	No
Uterine Artery Doppler	Increased PI	
Maternal risk factors		
Increased BMI	No	Yes
Advanced Age	No[c]	Yes[c]
Maternal age <20 years	Lower[a]	Higher[a]
Nulliparous	Lower[a]	Higher[a]
Ethnicity: Black	Yes[c]	Yes[c]
African/American	Higher[a]	Slightly higher (<ePE) [a]
Indian, Pakistani	No[c]	Yes[c]
Chronic HT	Yes [a,c]	No [c],Yes (<ePE) [a]
Ovulation induction	Yes[c]	No[c]
Diabetes	Lower[a]	Higher[a]
MAP	Increased (ePE > lPE)	Increased
Fetal factors		
Small for gestation age infants	Yes	No
IUGR	Yes	No
Congenital abnormalities	Higher[a]	Lower[a]
First Trimester Screening	High sensitivity	Low sensitivity
Aspirin therapy	Effective	Ineffective

This table has been compiled from: [a]Lisonkova *et al* (2013) (133), Crispi *et al* (2008) (140), [b]Park *et al* (2013) (198), [c]Poon *et al* (2010) (194), [d]Seeho *et al* (2016) (199), *Wikstrom *et al* (2007) (132), ^Ogge *et al* (2011) (135) and Odegard *et al* (2000) (196).

BMI: body mass index, ePE: early-onset pre-eclampsia, HT: hypertension, IUGR: intrauterine growth restriction, lPE: late-onset pre-eclampsia, MAP: mean arterial pressure, PAPP-A: pregnancy associated plasma protein A, PI: pulsatility index, PlGF: plasma growth factor, PP-13: plasma protein 13.

1.10 Early-onset and late-onset pre-eclampsia associations

There is an extensive list of risk factors associated with pre-eclampsia, with limited large population studies assessing the independent predictive value of some of these markers. Confounding the assessment of maternal demographic characteristics, medical history, obstetric history and paternity is that, pre-eclampsia was initially considered a single disease entity, with a lack of differentiation between the placental and maternal phenotypes associated with early-onset and late-onset pre-eclampsia respectively. Although these phenotypes share some aetiological features including an altered maternal immune response, there are several risk factors that differ. Identifying specific risk factors associated with the two phenotypes is important in terms of the different implications for the patient and her infant. Both early and late-onset pre-eclampsia have a higher risk of fetal, neonatal and maternal complications, however poorer outcomes are more prevalent with early-onset disease and the long-term cardiovascular risks for women are significantly higher.

There are only a few studies that have assessed risk factors in terms of early-onset and late-onset pre-eclampsia. Irrespective of gestational age at disease onset, pre-eclampsia is associated with increased mean arterial pressure and Black ethnicity (197). Characteristics of women at increased risk for developing late-onset pre-eclampsia include raised BMI, diabetes, South-Asian ethnicity, advanced maternal age or pregnancy prior to 20 years of age, and first pregnancy (133, 197). These women generally deliver appropriately sized infants with no evidence to suggest inadequate placentation. Women with an increased risk of early-onset pre-eclampsia are associated with abnormal placentation, with high resistance uterine artery flow seen in the first and second trimesters of pregnancy, and low PAPP-A. Consequently, there is an increased risk of SGA and IUGR infants born to these women. Other features associated with early-onset pre-eclampsia include a history of ovulation induction and chronic hypertension and prior pre-eclampsia (197).

1.11 Prevention of pre-eclampsia

Therapeutic interventions such as anti-platelet agents, heparin, vitamin supplementation, calcium, dietary salt and fruit intake have been investigated for their ability to reduce the risk of pre-eclampsia. Most of these agents have shown no or only limited improvement in reducing the prevalence of pre-eclampsia, with the exception of aspirin.

Prophylactic low dose aspirin has been evaluated by a number of groups with mixed results, lending this therapeutic intervention to controversy. Some of the early studies evaluating the value of low dose aspirin did not distinguish between early-onset and late-onset disease and showed little or no benefit (235-240). The dose of aspirin has also been controversial, with the groups using 50-60mg showing no benefit (236, 239, 240) compared to 150mg in other trials, which have shown benefit (33, 241). Table 5 outlines the results of the Cochrane database systematic review of the effect various supplementation agents have in reducing the risk of pre-eclampsia.

It has become evident through recent studies and meta-analyses that the differentiation of early-onset and late-onset disease and the timing of treatment has a significant effect on the value of aspirin in reducing the prevalence of pre-eclampsia (31, 34, 241, 242). When low dose aspirin is prescribed prior to 16 weeks' gestation there is a significant decrease in early-onset pre-eclampsia (32-34, 242), with Bujold *et al* reporting a 90% reduction (RR 0.11: 95% CI, 0.04 - 0.33). Furthermore, low dose aspirin started before 16 weeks' gestation is associated with a reduction in the prevalence of perinatal mortality and morbidity (32, 33, 243). A recent 2017 meta-analysis found that that low dose aspirin and other anti-platelet agents reduced the risk of pre-eclampsia and adverse outcomes even when therapy is started after 16 weeks (244).

The use of low dose aspirin in high-risk women has been recommended by leading international and national organisations, including the World Health Organisation (87), the National Institute for Health and Clinical Excellence (NICE) (245, 246), the Society of Obstetricians and Gynaecologists of Canada (SOGC) (71), the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) (3), and the United States Preventive Services Task Force (USPSTF) (247) in

conjunction with the American College of Obstetricians and Gynecologists (ACOG) (75). These groups recommend low dose aspirin from the first trimester, however there is a lack of consistency regarding how women are defined as high-risk and the recommended dosage of the drug. ACOG advises 81mg per day, NICE states 75mg per day, whilst others advocated at least 100mg (30). The effectiveness of aspirin for the prevention of preterm pre-eclampsia has been shown to be dose dependent, with 100mg of aspirin seeming more effective than lower doses (30) (248). In regard to how women are defined as high-risk, this is covered in *Chapter 1, section 1.12 Screening for pre-eclampsia* and summarised in Table 6.

Table 5. Cochrane reviews for preventing pre-eclampsia

Author	Year	Substance	Summary	Recommendations
Hofmeyr (249)	2014	Calcium	High dose (≥1g/day) calcium supplementation is associated with a reduction in PE risk, particularly in women with low dietary intake. Preterm birth and composite maternal morbidity and mortality rates were also reduced. Limited evidence on low dose calcium supplementation (<1g/day) suggests a reduction in PE. Larger quality trials needed.	WHO recommends calcium supplementation of 1.5-2g/day for pregnant women with low dietary calcium.
Rumbold (250)	2008	Anti-oxidants	Combined vitamin C and E therapy did not reduce the risk of pre-eclampsia.	The review does not support the routine use of antioxidant supplementation during pregnancy to reduce the risk of pre-eclampsia.
Meher (251)	2010	Nitric oxide	There is insufficient evidence that nitric oxide donors (glyceryl trinitrate) or precursors (L-arginine) reduce the risk of pre-eclampsia.	No recommendation. Caution in regard to further studies as some women suffered severe headaches.
Duley (252)	2012	Salt	There was insufficient evidence for reliable conclusions about the effects of reducing dietary salt for the prevention of pre-eclampsia. No evidence that a low salt diet would benefit patient or infant.	Salt consumption during pregnancy should remain a personal preference.
Duley (253)	2010	Anti-platelet agents	Low-dose aspirin showed moderate benefit, reducing the risk of pre-eclampsia, preterm birth, fetal or neonatal deaths and small for gestational age infants.	NICE guidelines recommend 75mg aspirin per day after 12 weeks to reduce the incidence of pre-eclampsia in women at risk. USPSTF High risk women. 81mg aspirin per day after 12 weeks.

NICE: National Institute for Health and Care Excellence, USPSTF: The United States Preventive Task Force, WHO: World Health Organization.

1.12 Screening for pre-eclampsia

Women presenting in their first trimester for antenatal care have an extensive general and obstetric history taken to determine if she or her unborn infant are at risk of developing pregnancy complications, including pre-eclampsia. Currently, women at risk of pre-eclampsia are identified on the basis of epidemiological and clinical risk factors as outlined in guidelines recommended by professional bodies, such as NICE, ACOG, SOGC and SOMANZ, with limited data on how well these guidelines are adhered too. A recent Australian study showed that only 25% of women were recognised as high-risk at the booking visit using just demographic risk factors as outlined in SOMANZ guidelines (254). With the emergence of maternal biomarkers and biophysical measurements identified in association with pre-eclampsia, the effectiveness of these guidelines for identifying women at high-risk have come under scrutiny (200, 255-259), with only one study assessing the performance of different screening strategies (260). The effectiveness of screening by maternal demographic risk factors is relatively low compared to screening that combines these factors with maternal biochemical and biophysical markers (194, 198, 258, 261-263).

1.12.1 Screening by maternal characteristics and history

NICE recommends that women who are high-risk for pre-eclampsia are identified before week 13 of gestation and advised to take low-dose aspirin until 36 weeks' gestation. Women are regarded as high-risk for developing pre-eclampsia if they have one high-risk factor or at least two moderate risk factors based on maternal characteristics and history. SOGC guidelines outline an extensive list of risk factors for recognising high-risk women, while ACOG lists only a handful (75). This approach to identifying women high-risk for pre-eclampsia is supported by the international community (19, 87), with guidelines for defining women high-risk for pre-eclampsia by these leading professional bodies outlined in Table 6. The recommendations by the aforementioned associations are effectively screening women for pre-eclampsia solely on the basis of maternal history and advising therapeutic intervention without any data on the performance of such screening strategies (258, 261). A subsequent independent assessment on the performance of NICE guidelines by Verghese *et al* 2012 (264), showed a

sensitivity of 77% for the detection of pre-eclampsia at any gestation, however this was for a false positive rate (FPR) of 46%. In terms of screening performance, this is far from reasonable.

Table 6. International professional associations' definitions of women high-risk for pre-eclampsia

	High risk factors	Moderate risk Factors
NICE (74)	Hypertensive disease during previous pregnancy Chronic hypertension Chronic renal disease Autoimmune diseases (SLE, APLS) Type 1 or type 2 diabetes	Nulliparous Age >40 years Pregnancy interval greater >10 years BMI >35kg/m^2 at first visit Family history of pre-eclampsia Multiple pregnancy
	Risk Factors	
SOGC (19)	Previous pre-eclampsia APLS, overweight or obesity Pre-existing hypertension, diabetes mellitus, renal disease or booking proteinuria Elevated blood pressure at booking (SBP >130mmHg, or DBP >80mmHg) Multiple pregnancy Maternal age ≥40 years Family history of pre-eclampsia (mother or sister) Family history of early-onset cardiovascular disease Lower maternal birthweight and/or preterm delivery Heritable thrombophilia's Increased prepregnancy triglycerides Cocaine and methamphetamine use Reproductive technologies First ongoing pregnancy New partner Interpregnancy interval of >10 years Short duration of sexual relationship Gestational trophoblastic disease Vaginal bleeding in early pregnancy Abnormal PAPP-A or free bHCG	
ACOG (75)	History of pre-eclampsia (especially if adverse outcome) Multifetal gestation Diabetes (Type 1 and 2) Renal disease Autoimmune disease (SLE, APLS) Chronic Hypertension	

ACOG: American College of Obstetricians and Gynecologists, APLS: antiphospholipid syndrome, bHCG: beta human gonadotropin hormone, BMI: body mass index, DBP: diastolic blood pressure, NICE: National Institute of Clinical Excellence, SBP: systolic blood pressure, SLE: systemic lupus erythematous, SOGC: The Society of Obstetricians and Gynaecologists of Canada.

1.12.2 Screening by maternal blood pressure

Numerous studies have clearly demonstrated increased blood pressure in women destined to develop pre-eclampsia, in both the first and second trimesters of pregnancy (265-268). A meta-analysis by Cnossen *et al* (2008) (269), found that the mean arterial pressure (MAP) is a better predictor for pre-eclampsia than systolic blood pressure, diastolic blood pressure, or an increase in blood pressure (269). MAP measured at 11-13 weeks' gestation has been shown to improve the effectiveness of screening for pre-eclampsia compared to maternal characteristics and history alone (194, 198, 261, 270).

1.12.3 Screening by uterine artery Doppler

Early uterine artery Doppler studies showed high resistance flow associated with pre-eclampsia when measured at 11-14 weeks' or 18-22 weeks' gestation, thereby demonstrating the value of this marker as a predictor of pre-eclampsia (271-273). Figure 4 shows a forest plot of studies assessing uterine artery Doppler sensitivity in the prediction of pre-eclampsia with a marked diversity in the results evident (274). The association of an abnormal uterine artery pulsatility index (UA-PI) was strongest with severe pre-eclampsia and early-onset pre-eclampsia, and also correlated well with fetal growth restriction (275-278). This is not surprising given a histological study of placentas from women with pre-eclampsia showed abnormal morphology in association with high impedance uterine artery flow (279). Subsequent studies have incorporated UA-PI measured at 11-14 weeks into integrated regression models for the prediction of pre-eclampsia and found a significant improvement in the prediction of pre-eclampsia compared to maternal factors alone (141, 194, 195, 263, 270, 280-284).

1.12.4 Screening by maternal biochemical markers

An extensive number of biochemical markers have been investigated as potential predictors of pre-eclampsia in both the first and second trimesters. The most widely investigated markers include pregnancy-associated plasma protein A (PAPP-A), placental growth factor (PlGF), plasma protein 13 (PP13), soluble fms-like tyrosine kinase-1(sFlt1), A-disintegrin and metalloprotease 12 (ADAM12) and soluble endoglin (sEng). Decreased levels of PAPP-A have been shown in association with pre-eclampsia (194, 195, 285-288) but are also evident with

aneuploidy, intrauterine growth restriction and placental abruption (289-291). Figure 5 outlines a forest plot of studies assessing the sensitivity of PAPP-A in the detection of pre-eclampsia, with mixed results (274, 292). Overall, multiple studies have clearly demonstrated that PAPP-A in a combined model improves the detection of pre-eclampsia (194, 198, 256, 261, 263, 284).

Lower levels of PlGF have been consistently reported in women with pre-eclampsia (293-297). Figure 6 outlines a forest plot of the studies that have assessed PlGF in the prediction of pre-eclampsia, with considerable variability in the results evident (292). This marker when combined in a screening algorithm with maternal history, characteristics and uterine artery Doppler, clearly demonstrated an improvement in the prediction of pre-eclampsia (201, 259, 297). The biochemical marker PP-13 level has been evaluated at 11-13 weeks' gestation and although PP-13 was reduced in early-onset pre-eclampsia, the marker did not improve the prediction of the disease (255, 284, 298). Studies of the biochemical marker ADAM-12 have demonstrated conflicting results, with some reporting increased levels associated with pre-eclampsia (288, 299), while others have reported decreased levels (300, 301). One study that performed a multivariable analysis of maternal characteristics and biochemical markers including PAPP-A, PlGF, ADAM-12 and PP-13 in the first trimester did not identify a model that had clinical utility for predicting pre-eclampsia in a low-risk nulliparous population (288).

Elevated circulating sFlt-1 and sEng levels have been linked to women destined to develop pre-eclampsia (302, 303). One study showed increased levels of sFlt1, sEng and PlGF in the pre-clinical phase of pre-eclampsia during the second trimester, with no difference between early and late-onset disease (304). The study also looked at the sFlt1/PlGF ratio and found greater accuracy in the prediction of pre-eclampsia than individual markers alone. This finding has been confirmed by a number of recent studies (305-308), indicating the potential for clinical utility in the prediction of pre-eclampsia (primarily early-onset disease), and in the third trimester to help in the diagnosis, risk stratification and management of women with suspected pre-eclampsia.

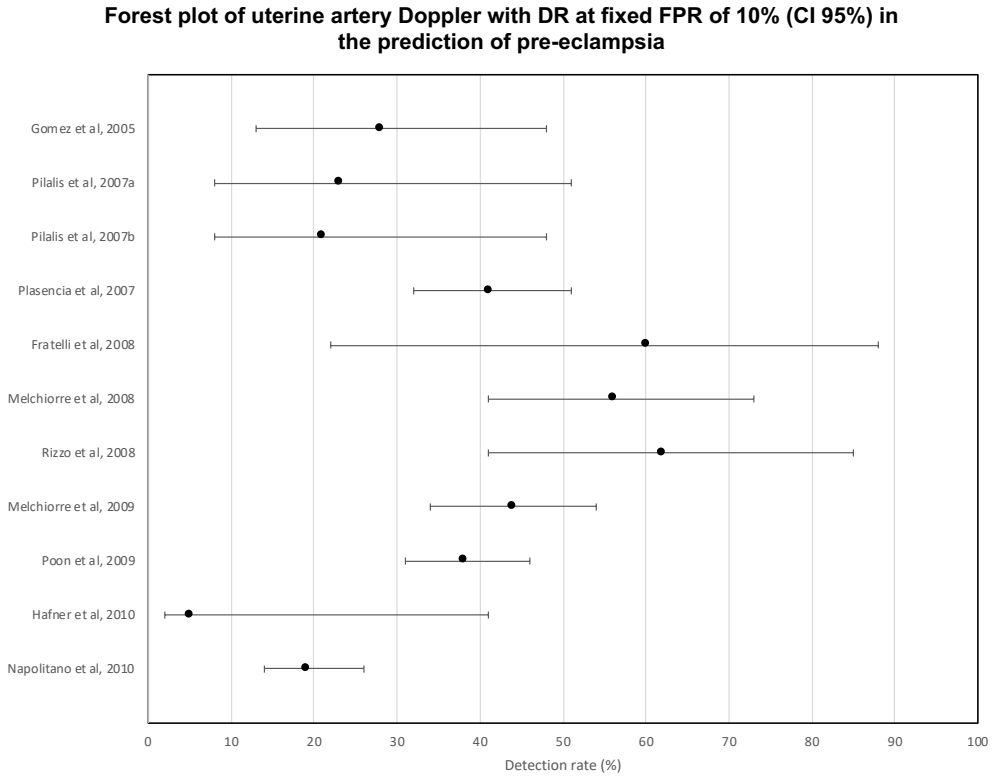

Figure 4. Forest plot of uterine artery Doppler studies in the first trimester prediction of pre-eclampsia.

CI: confidence interval, DR: detection rate, FPR: false positive rate. Adapted from Kuc *et al*, 2011 **(274)**.

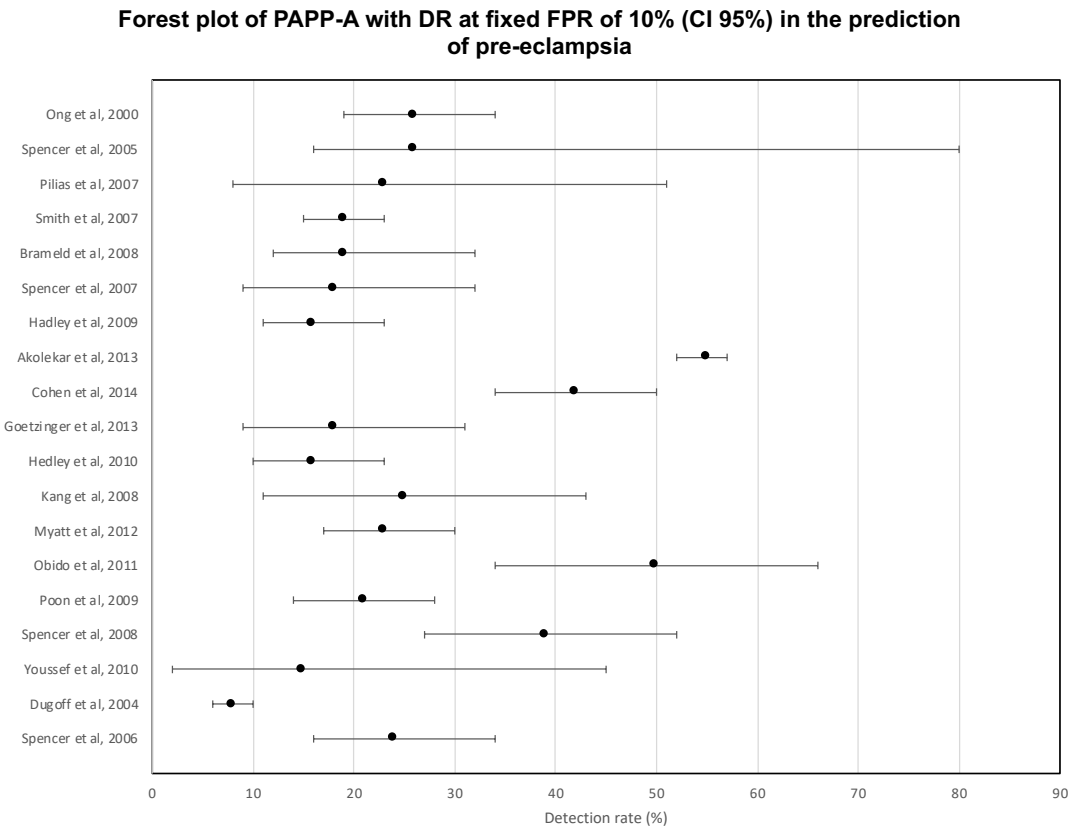

Figure 5. Forest plot of PAPP-A studies with detection rates in the first trimester prediction of pre-eclampsia.

CI: confidence interval, DR: detection rate, FPR: false positive rate. Adapted from Kuc *et al*, 2011 **(274)** and Wu *et al*, 2015 **(292)**.

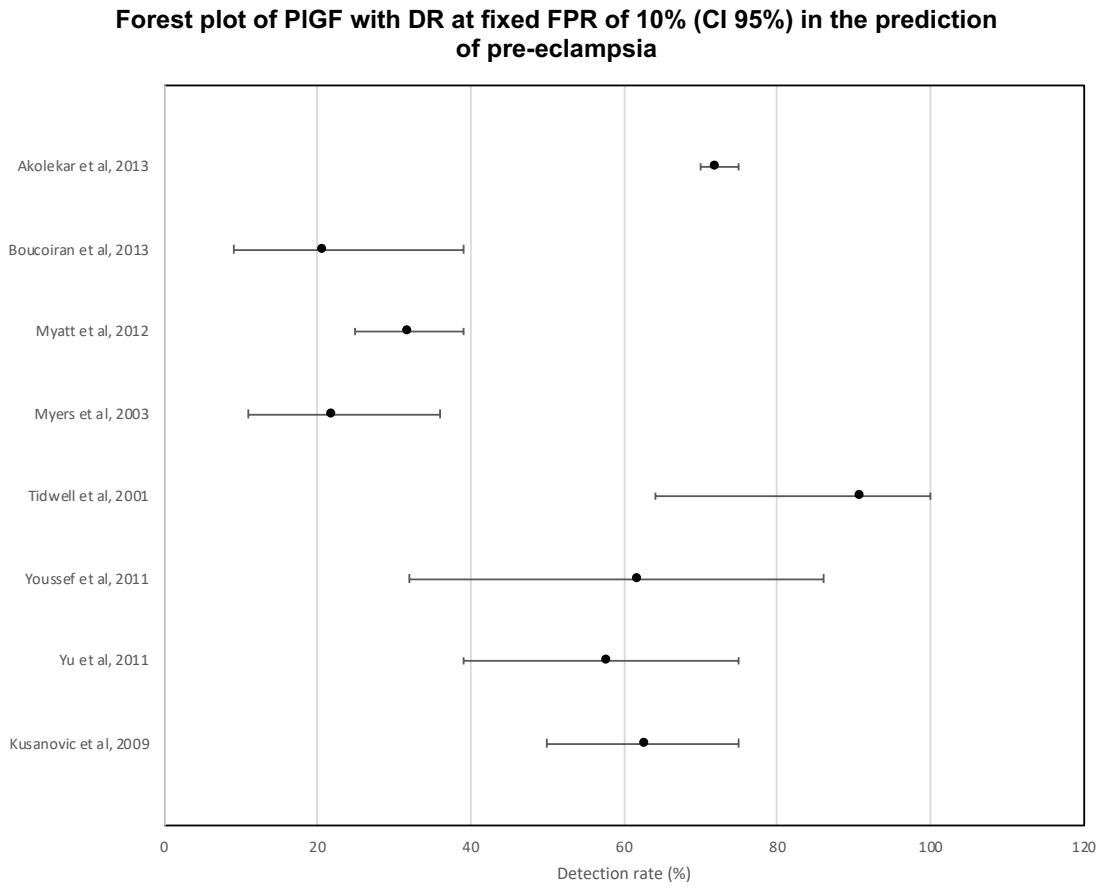

Figure 6. Forest plot of PlGF studies with detection rates in the first trimester prediction of pre-eclampsia.

CI: confidence interval, DR: detection rate, FPR: false positive rate. Adapted from Wu *et al*, 2015 (292).

1.12.5 Combined first trimester screening

There has been mixed reporting on the performance of combined screening algorithms. Some studies show modest prediction (255, 257, 283, 309), while others show very good prediction (195, 198, 256, 262). The efficacy of screening depends on the study population, what biochemical and biophysical markers have been used in the prediction model and whether the screening differentiates between early-onset and late-onset pre-eclampsia. Other factors relating to the model design, such as adjustments for cofounders, treatment of missing data, overfitting and the treatment of continuous variables, may result in deficiencies within the model that impact its reliability and validity (310). Combined models for the prediction of early-onset pre-eclampsia perform substantially better than for the prediction of late-onset disease (194, 195, 256, 263, 311, 312). The Fetal Medicine Foundation (FMF) integrated multiple regression model combining maternal history and characteristics, MAP, PAPP-A and UA-PI, have reported detection rates for early-onset and late-onset pre-eclampsia at 93.1% and 35.7% respectively, for a FPR of 5% (195). This algorithm has been validated in an Australian population yielding a detection rate of 91.7% and 35.2% for early-onset and late-onset pre-eclampsia respectively, at a 10% fixed false positive rate. A logistic based regression model developed by Scazzochio *et al* (2013) based on the same markers used within the FMF model, reported slightly lower detection rates of 80.8% and 39.6% for early-onset and late-onset pre-eclampsia respectively, for a 10% fixed false positive rate (263). In 2013 the FMF group added PlGF to the algorithm, improving the detection rate of early and late-onset pre-eclampsia to 96% and 54% for early and late-onset pre-eclampsia respectively, at a 10% FPR (256).

Only one study has evaluated the accuracy of screening women high-risk for pre-eclampsia at 11-13 weeks' gestation using the NICE or ACOG guidelines, compared to the multivariate screening approach developed by the FMF group. The study of 8775 women showed that the FMF algorithm was far superior to the recommended NICE and ACOG methods, with significantly higher detection rates and lower false positive rates (258).

1.13 Treatment

The only known way of curing pre-eclampsia is to deliver the fetus. Despite this intervention, women remain at risk of developing pre-eclampsia and eclampsia in the peri-partum period, irrespective of an antecedent diagnosis of a hypertensive disorder (313). The 72 hours post-partum is a period of clinical vulnerability, with almost all maternal deaths as a consequence of pre-eclampsia in developed countries occurring during this time (21, 115). Delayed post-partum pre-eclampsia can also occur up to 6 weeks' post-delivery (313).

Antihypertensive therapy is the primary therapeutic intervention aimed at reducing the complications relating to hypertension and disease progression. Untreated severe hypertension can result in placental abruption, stroke or organ infarction (3, 21, 115, 139). Therapeutic intervention is dependent on the degree of hypertension, with a range of antihypertensive medications demonstrating safety and efficacy (3, 314). There is controversy regarding treating women with mild to moderate hypertension – (defined as systolic blood pressure 140-159mmHg or diastolic blood pressure 90-109mmHg) – in order to prevent progression to more severe disease. The latest Cochrane review suggests there is not enough evidence to suggest treating these women will inhibit progression to pre-eclampsia (315), while evidence from the Control of Hypertension in Pregnancy Study (CHIPS) randomised control trial concluded that anti-hypertensive treatment of non-severe pregnancy hypertension is of benefit to mother without associated perinatal risk (316).

Eclampsia is a rare but serious complication of pre-eclampsia, defined as the occurrence of one or more seizures in a woman with pre-eclampsia. Magnesium sulphate has been effectively used in the treatment and prevention of eclampsia (317), with the most recent Cochrane review showing magnesium sulphate more than halves the risk of seizure (318). It is also recommended that magnesium sulphate should be administered to women requiring preterm delivery for fetal neuroprotection, with 63 women needed to treat in order to prevent one case of cerebral palsy (319).

Reduced plasma volume has been described in pre-eclamptic women (320), which previously led to the use of intravenous fluid therapy to expand plasma

volume. The aim of this intervention was to improve the maternal and uteroplacental circulation and potentially improve outcomes for both patient and her infant. A review of plasma volume expansion trials found limited evidence to support the clinical rationale or economic value of this practice (321).

1.14 Screening summary

Early identification of women at risk of developing pre-eclampsia allows timely intervention of therapeutic low dose aspirin and increased antenatal surveillance to improve pregnancy outcomes for both mother and baby. The current guidelines for identifying women high-risk for pre-eclampsia are inconsistent across the leading international organisations. There is no consensus on risk factors for pre-eclampsia and no endorsement of multivariate screening algorithms that have shown to dramatically improve detection rates compared to traditional screening methods. This method effectively treats each of the risk factors as separate screening tests. Furthermore, there has only been one assessment on the performance of this recommended strategy. When the appropriate dose of aspirin is prescribed before 16 weeks' gestation to women at risk of inadequate placentation, the prevalence of early-onset pre-eclampsia is reduced. Women high-risk for late-onset pre-eclampsia do not benefit from aspirin, as the pathophysiology for the development of pre-eclampsia appears to be different despite the same clinical endpoint. In order to target the administration of aspirin to the appropriate women, they need to be readily identified through an effective screening approach. The inclusion of cardiovascular parameters within a screening algorithm may be a useful addition to help differentiate between these pre-eclamptic phenotypes.

1.15 Cardiac function and structure

The heart undergoes a continuous cycle of filling and contracting to maintain blood circulation. Ventricular diastole refers to the part of the cardiac cycle whereby the ventricle expands and fills with blood, following the contraction and ejection that defines systole. The ability of the left ventricle (LV) to work effectively as a pump relies primarily on the contractility of the myofibres, however the geometry of the LV, loading conditions and heart rate also contribute to overall ventricular function. Contractility is an intrinsic function of the myocardium, while function relates to the overall effectiveness of the left ventricle as a pump.

The myocardium is primarily composed of myocardial fibres, surrounded by a network of fibrocollagenous connective tissue. Within the LV the myofibres are arranged in three interweaving layers according to their alignment: superficial (subepicardial), middle and deep (subendocardial). The deep fibres extend longitudinally from the apex, inserting into the aortic and mitral valves and the membranous septum at the base of the heart. The fibres in the middle layer occupy over half of the wall thickness and are circumferentially arranged almost parallel to the mitral valve orifice. The fibres within the superficial layer run obliquely, giving rising to a spiral pattern (322). The varied orientation and interweaving nature of these fibres results in a simultaneous thickening and twisting during systole, as they shorten or contract with the resulting ventricular wall motion in longitudinal, circumferential and radial directions. In a normal heart, the fibres shorten approximately 15%, resulting in 25-40% thickening of the wall, and the ejection of 60-70% of blood volume (323).

During systole, the LV contracts secondary to fibre shortening, followed by lengthening during diastole. This process is energy dependent, with energy stored by the myocardial cells as they contract, and energy released with elastic recoil as the fibres lengthen. To enable a contraction and the ejection of blood, the myocardial cells need to generate enough energy to counteract the tension of force within the ventricular walls. Wall tension is determined by the size of the chamber, the pressure within the chamber, and the thickness of the chamber wall (323).

There are four phases to diastole, commencing with the closure of the aortic valve that marks the end of systole and the start of the isovolumetric relaxation phase, whereby the myocardial fibres relax to their pre-systolic length. During relaxation, the chamber volume remains constant, with a decline in LV pressure. This phase ends with the opening of the mitral valve (MV) and is referred to as the isovolumetric relaxation time (IVRT) (323).

As the LV expands following a contraction, the LV pressure falls below that of the left atrium (LA), causing the MV to open. During this early phase of diastole, ventricular suction causes a rapid filling of the ventricle. LV filling is primarily determined by the rate of relaxation, the elastic recoil of the ventricle, chamber compliance and the pressure within the LA. These factors combined contribute to the pressure gradient across the LA and LV, thereby driving blood across the MV. The LV volume subsequently increases, with a concomitant pressure increase within the ventricle. There is a concurrent decline in LA volume, resulting in a decrease in atrial pressure. The pressure gradient subsequently decreases, reflecting the rate of ventricular filling or atrial emptying. With normal early diastolic function, these rates are rapid, with approximately 80% of ventricular filling occurring in this phase (323).

The third phase of diastole is referred to as diastasis, occurring when the LA and LV pressures reach equilibrium. Consequently, only a small amount of blood flows across the MV due to inertia during this time period. Diastasis has a linear relationship with heart rate, resulting in shorter periods of diastasis as heart rate increases. Atrial contraction marks the onset of the final phase of diastole, referred to as the atrial filling phase. The atrial contraction results in a small increase in the LA-LV pressure gradient, propelling a bolus of blood into the ventricle, contributing approximately 20% of the total LV filling (323). The phases of diastole are outlined in Figure 7.

Diastolic function depends primarily upon two processes; the ability of the myocardium to relax and fill, and the compliance or stiffness of the LV. LV relaxation is a complex energy dependent process that occurs early in diastole. The rate of relaxation depends on the cessation of the excitation-contraction coupling mechanism, loading conditions and age. LV compliance is primarily determined by the structural properties of the myocardium, that is, the myocardial

cells and interstitial matrix. Normal diastolic function involves ventricular filling without an abnormal increase in diastolic pressure (324). When diastolic dysfunction develops there is delayed relaxation, the ventricle stiffens and is less compliant which then requires greater LV intracavity pressure to maintain an adequate stroke volume. LA pressure consequently increases, secondary to the increase in LV pressure to restore the pressure gradient across the MV. There is also the unwanted effect of increased pressure reflected back to the pulmonary circulation which can lead to pulmonary venous congestion and heart failure.

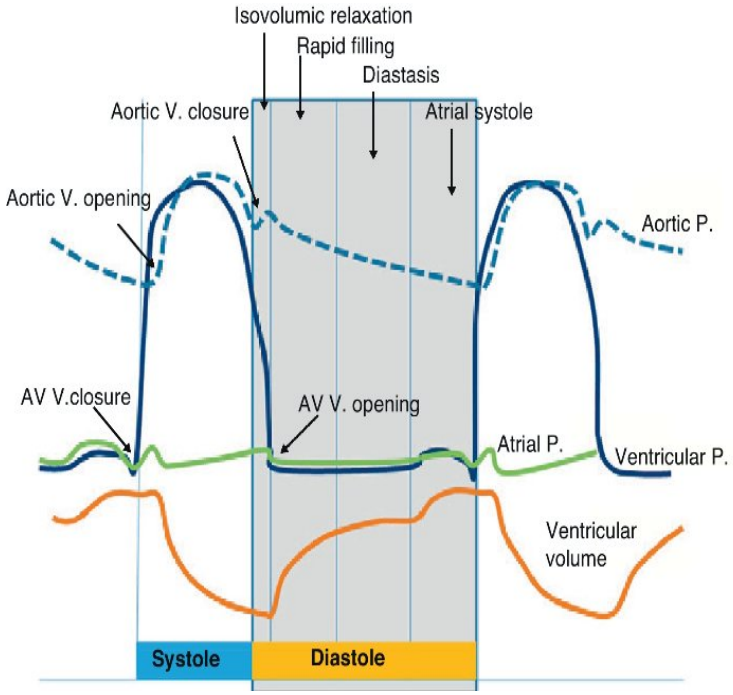

Figure 7. Phases of the cardiac cycle.

Changes in the left; ventricular pressure, ventricular volume, atrial pressure and aortic pressure from Fernandez-Perez *et al* (2012) (325). AV V: atrioventricular valve, P: pressure.

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1.16 Cardiovascular adaption in normal pregnancy

Physiological adaptation of the cardiovascular system in pregnancy is essential to meet the increasing metabolic demands of the patient and developing fetus. The structural and functional changes that take place within the cardiovascular (CV) system and other organ systems to meet this demand are highly complex and entwined. This section will discuss the changes to the CV system with gestation, the different techniques that have been used to evaluate the CV system and the associated limitations, as well as compare and contrast the results of published studies.

In pregnancy, blood volume increases and systemic vascular resistance decreases resulting in a concomitant increase in cardiac output (CO) (39, 45, 326-335). This requires significant alterations to the kidneys, heart, vessels, hormones and neurohumoral system (336-338). Consequently, changes to cardiac preload and afterload facilitate the increase in CO and blood volume, with redistribution of flow to the uteroplacental circulation without compromising maternal well-being.

1.16.1 Haemodynamic changes

A normal pregnancy requires adequate blood volume expansion and this is dependent on a number of factors, including normal adaptive endothelial and vascular function (339). A decrease in systemic vascular resistance is evident from as early as 5 weeks' gestation (326, 340, 341), secondary to vasodilatation (338, 342, 343). Vasodilatation is enabled by elevated levels of progesterone (344) and prostaglandins such as prostacyclin (345). Simultaneously, the smooth muscle within vessel walls relaxes due to increased levels of nitric oxide produced by the endothelium and the activation of the neurohumoral system, which includes stimulation of the renin-angiotensin-aldosterone, sympathetic, and non-osmotic vasopressin systems (26, 336). Relaxation of smooth muscle results in a loss of vascular tone; this increases the arterial compliance or elasticity of the vessel, thereby further enhancing vasodilatation (342). The development of the low resistance uteroplacental circulation, through remodelling of the uterine arteries, also contributes to reducing the overall systemic vascular resistance (142, 143). Afterload is effectively decreased due to enhanced

vasodilatation and decreased arterial compliance, which reduces the contractile force the left ventricle myocardium must overcome to propel blood out into the systemic circulation.

The combination of these changes ultimately increases the arterial compartment, creating a state of relative under-filling (340, 343). In response to this state, the blood volume begins to expand from 6 weeks' gestation, increasing 40-50% more than prepregnancy levels, equivalent to 1.2-1.6L (338, 346, 347). The expanded blood volume increases venous return and consequently preload.

Systolic, diastolic and mean arterial blood pressures decrease in pregnancy from 6-8 weeks' gestation, secondary to a decrease in systemic vascular resistance and an increase in arterial compliance (348-350). The decline in blood pressure reaches a nadir mid-second trimester, with a greater decrease noted with diastolic pressure compared to systolic pressure (326, 331, 339, 350-352). This is followed by a progressive increase to prepregnancy levels until term (326, 333, 350-357). The explanation for this mid-gestation drop in mean arterial pressure (MAP) has in part been explained by completion of the second phase of uterine artery adaptation, further developing the low-resistance uteroplacental system (357-359) and modification of the renin-angiotensin-aldosterone system (360, 361).

The combined changes in MAP and cardiac output have resulted in the majority of studies reporting that total peripheral resistance is higher in the first trimester compared to non-pregnant women, followed by a gradual decline with gestation to levels lower than non-pregnant women (35, 45, 328, 331, 332, 362-364). Fewer studies observed that the total peripheral resistance declines, reaching a nadir in the second trimester, which is then maintained at a constant level (334, 351, 358), while some studies have found an increase towards term (326, 330, 365).

1.16.2 Cardiac output

Cardiac output (CO) is the quantity of blood pumped out of the left ventricle each minute and is the product of stroke volume (SV) and heart rate (HR). In pregnancy, CO increases by 30-50% (326, 331, 366), although recent data indicate that 30% is more accurate (367, 368). CO increases secondary to an

increase in HR and SV, however there are conflicting views on the timing of these changes, in addition to a wide range of reported values. In the first trimester, CO has been reported between 4.3-6.8 L/min, increasing to 5.5-8.7L/min in the third trimester (35, 39, 45, 326-329, 331, 333, 365, 367, 369).

There is a general consensus that CO increases during the first and second trimesters, however there are mixed reports regarding the change from the second to third trimesters. Robson *et al* (1989) reported that CO peaked at 24 weeks' gestation and was maintained until term (326). Other studies have supported this finding (327, 363), while some report that CO continues to increase until term (35, 328, 329, 362). This is in contrast to the majority of studies that found a small decline in CO towards term (331, 333, 368-374). A recent meta-analysis found a mean CO of 5.7L/min in the first trimester, increasing to 6.48L/min early in the third trimester, before declining to 6.07 L/min towards term (368). Importantly, this meta-analysis included a range of CO assessment methods that are not all comparative to each other, with considerable diversity in absolute values of CO. Different assessment methods is just one factor confounding the lack of consistency in regard to the size and time course of CO change. Other factors include different SV calculations, study design, patient position, choice of control group and maternal characteristics.

CO can be calculated from a range of methods attributing to some of the discrepancy in results, including thermodilution, echocardiography, impedance and bio-reactance cardiography, automated Doppler monitors, non-invasive partial gas breathing, and pulsed contour analysis. The gold standard method for monitoring CO is thermodilution, however this technique is highly invasive, requiring pulmonary artery catheterisation (375).

Doppler echocardiography has emerged as the leading method for non-invasive, accurate and reproducible measurement of CO, in addition to anatomical and functional assessment of the heart. The Doppler technique is widely used in clinical practice and demonstrates excellent correlation with thermodilution, including studies of pregnant women (39, 376-379). A disadvantage of this technique is the high level of specialised skill required to perform the examination.

Automated Doppler monitors such as the Ultrasonic Cardiac Output Monitor (USCOM) and impedance cardiography devices are also non-invasive and do not

require a highly trained operator. One study of the USCOM in healthy pregnant women found good interobserver reliability in a small subset of women, however a comparison to echocardiography or thermodilution was not undertaken (380). A major limitation of these machines is that they have device specific reference ranges and issues with validity, including contrasting reports on their correlation with thermodilution and pulsed wave Doppler methods (381-387). One validation study of electrical cardiography in pregnant women found an unacceptably high bias and mean percentage error in the computation of both SV and CO (388), in contrast to a review that concluded cardiography measurements seemed reliable in pregnancy (389). Total blood volume, blood viscosity, pulmonary vascular resistance, body weight and HR are altered in pregnancy, these factors all impact the calculation of SV when measured by electrical bioimpedance (390). Studies have also shown that CO is affected by maternal position (391-393), with the majority of bioimpedance studies conducted with the women supine and most echocardiography Doppler exams performed in the lateral decubitus position (368).

The design of cardiovascular studies in pregnancy also influence outcomes. Longitudinal studies have greater accuracy compared to cross-sectional studies; however, the drawback is that generally smaller populations are studied. Post-partum baseline values are often used as a control; however, the cardiovascular system may not have fully recovered depending on the time lapsed (351, 394). Baseline values using non-pregnant controls may not be well matched to the characteristics of the pregnant population, and first-trimester baseline measures may also be inappropriate as haemodynamic changes occur from as early as 5 weeks' gestation (340, 341).

CO is affected by age, gender and ethnicity, with the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) publishing normative echocardiographic reference ranges for LV size, mass and systolic function (395). Body size also has a major impact on these measures, with a number of studies in nonpregnant women showing SV is significantly higher in overweight women (396-398). All of these factors contribute to the heterogeneity of CO results.

1.16.3 Stroke volume

Stroke volume (SV) is the quantity of blood pumped out of the left ventricle during each cardiac cycle. SV increases in pregnancy, however there is considerable variation in the magnitude and timing of this increase underpinning the discrepancy in CO results. Absolute values of SV are significantly different between studies, with different measurement techniques and methods of calculation contributing to this disparity. In the first trimester, SV has been reported between 59 - 95ml, while third trimester values are in the range of 64 - 99ml (367, 399). There has also been considerable variation in the time course of SV change. Some studies have reported that SV reaches a maximum in the second trimester to early third trimester, followed by a decline towards term (44, 326, 330, 333, 335, 369), while others reported a continual increase (35, 328, 329, 331, 332, 362) and some observed a peak in the second trimester that is then maintained through the third trimester (334, 351, 358, 365, 399).

SV can be calculated using a number of echocardiographic methods, including assessment of continuous wave (CW) or pulsed wave (PW) Doppler velocity time integral (VTI) through the left ventricular outflow tract (LVOT); use of the unmodified Simpson's or Simpson's biplane summation of discs model; or by using estimates of left ventricular end diastolic and systolic volumes obtained by two-dimensional (2D) linear or motion mode (M-mode) measurements, which can then be incorporated into the Teicholz or cube formulae (400). The different SV calculations have limitations and are not comparative in accuracy. For example, SV derived from PW Doppler VTI is based on the hydraulic principle which states that the flow rate through a tube of a constant diameter is directly proportional to the cross-sectional areas (CSA) of the tube and the mean velocity of the fluid moving through the tube when the orifice of the tube is fixed and constant (400). To overcome the variability in velocity through the LVOT diastole and systole, an integrated velocity over time approach is used for the calculation. Two assumptions are made in the calculation of the VTI: that the geometry of the vessel CSA is circular and that flow in systole is laminar.

The accuracy of the LVOT PW Doppler technique for the calculation of SV has been validated in a number of studies (377, 379). This method is recommended by the ASE (401), as calculations derived from linear 2D and M-mode

measurements are considered inaccurate (402). For greatest accuracy, the Doppler velocity sampling site also needs to correspond to the anatomical measurement of the LVOT, which is unachievable with CW Doppler (403). Another potential source of error in calculating SV using the Doppler technique is the LVOT diameter measurement. A small measurement error can result in large deviations in SV, as the radius of the outflow tract is squared in the calculation of the cross-sectional LVOT area (400).

The Teicholz method for calculating SV makes geometric assumptions in regard to LV cavity shape which may not be valid in pregnancy (326, 340). Despite this problem, the approach has been used in a number of pregnancy studies (351, 358, 363, 393). The Simpson's methods for calculating SV can also be problematic, with foreshortening of the LV apex and difficulty defining the endocardial surface common issues. Nevertheless, this technique has been used in a few pregnancy studies (365, 404).

1.16.4 Heart rate

Maternal heart rate (HR) begins to increase from approximately 5 weeks' gestation (326, 405) peaking in the third trimester (35, 39, 45, 326, 328, 329, 331-333, 363, 369, 372, 406, 407). HR increases around 10-20 bpm (326, 366, 408), or between 15-29% (328, 332, 369, 409) secondary to increased sympathetic tone and a decrease in parasympathetic tone (410, 411).

1.16.5 Contractility

Left ventricular contractility is another aspect of systolic function, which also includes SV and CO. Contractility of the left ventricle and can be assessed in numerous ways, including calculation of ejection fraction and fractional shortening, and TDI measurements of *s* wave velocity (412, 413). There are also different evaluation methods reflecting contractile motion specific to the radial, transverse and longitudinal orientation of the myocardial fibres. Additionally, there are newer indices such as myocardial performance index, tissue tracking and strain rate imaging, however these echocardiographic techniques in pregnancy are scant and beyond the scope of this study (35, 414).

Radial function of the left ventricle can be assessed by ejection phase and wall stress indices. Ejection phase indices include ejection fraction (EF), fractional shortening (FS), and velocity of circumferential shortening (Vcf), however they are dependent on HR, preload and afterload, which are all altered in pregnancy. Robson *et al* (1989) and Laird-Meeter *et al* (1979) both reported an increase in EF and FS with increasing gestation (326, 415). The Robson study found a slight decline towards term consistent with two other studies (330, 362). Kametas *et al* (2001) showed a significant decrease in both EF and FS from 30 and 32 weeks respectively (369) in keeping with Zentner *et al* (2009) (416), with the majority of reports showing no change (327, 331, 332, 363-365). A number of studies that assessed Vcf observed an increase in normal pregnancy (45, 326, 417), while others found no change (327, 363, 372). The discrepancy in results may be partly due to differences in the gestational age at the time of the scan, circulating blood volume, and the method for calculating the EF.

End systolic wall stress (ESS) is the tension within the wall of the ventricle, determined by the intraventricular pressure, internal radius of the ventricle and the thickness of the myocardium. Intraventricular pressure is dependent of preload and afterload, so for a given pressure, the wall stress will increase proportionally with the ventricular radius and decrease with wall thickening. Hypertrophy in pregnancy is a protective mechanism against wall stress as a result of the change in loading conditions. Studies that have assessed the relationship between left ventricular Vcf and ESS have found this is unaffected by the alterations to loading during pregnancy. Reports in normal pregnancy are conflicting, with studies observing decreased contractility (330, 404) and no change in contractility (45, 331, 364), while one group found enhanced contractility (365).

The Zentner study assessed systolic longitudinal function using tissue Doppler and found the *s* wave velocity was slightly higher in pregnancy at 16 weeks' gestation compared to non-pregnant controls although statistical significance was not reached (416). The group also showed that the *s* velocity declined late in pregnancy, while two studies found no change (404, 409). The study by Fok *et al* (2006) assessed s wave velocity at four sites of the LV and found a significant increase between the first and second trimesters at only the anterior and lateral sites, returning in the third trimester to the same velocities as recorded in the first

trimester. There was also no significant difference in velocity between the pregnancy and post-partum measures. Another study that assessed longitudinal systolic function using m mode through the mitral annulus, found increased LV displacement at four sites, peaking at 23 weeks' gestation, followed by a decline to term (369). The group suggested longitudinal changes in systolic function occur prior to measures of radial function. A subsequent study found long axis shortening decreased significantly with gestation at the septum but not at the lateral margin of the mitral valve annulus, however tissue Doppler imaging revealed no change in systolic velocity with gestation at either site (409).

In normal pregnancy, contractility in all three planes is largely preserved with only a few studies finding a decrease in the radial indices (EF and FS). In regard to the few studies of longitudinal function (*s* wave) there are conflicting reports as to whether this is compromised.

1.16.6 Cardiac structure

During pregnancy, blood volume expansion results in remodelling of the heart to compensate for an increase in preload, with a progressive rise in the dimensions of the cardiac chambers (373, 399). Changes to the left side of the heart have been more widely studied, with significant alterations to the geometry and function of the left ventricle observed (35, 37, 45, 48, 49, 327, 331, 332, 334, 365, 418, 419).

1.16.6.1 Left ventricular outflow tract

The majority of studies report that the cross-sectional area (CSA) of the left ventricular outflow tract (LVOT) does not change with gestation (44, 327, 328, 332, 335, 358, 372, 373, 399), however a few studies have shown that there was a significant increase in area from the first to third trimesters (326, 327, 364). The LVOT measurement has been reported in the range of 18-20mm (358, 373, 399), while others have used the aortic root measurement in the SV calculation which is wider at 27mm (372). It has been suggested that the CSA of the aortic valve should be indexed for body size (402).

1.16.6.2 Left ventricular geometry

There is consistent reporting in the literature that the left ventricular mass (LVM) increases with gestation in pregnancy (35, 45, 326-328, 331, 334, 358, 362, 364, 367, 418). This increase ranges from 21-52% (45, 326, 328, 331, 334, 418), primarily due to an 11-30% increase in left ventricle wall thickness (45, 326, 328, 331, 332, 334, 362, 418), evident from 12 weeks' gestation (326). The posterior wall and interventricular septum thicken in response to the expanded blood volume imposing greater wall stress. The physiological hypertrophy of the left ventricle is a compensatory mechanism to minimise the impact of wall stress and maintain adequate myocardial oxygenation and cardiac output. A number of studies report a proportional enlargement of the LV chamber size and the wall thickness, in keeping with eccentric hypertrophy (37, 45, 48, 326, 327, 334, 358, 367, 373).

1.16.7 Diastolic function

Diastolic function can be evaluated by echocardiography using a number of approaches including PW Doppler through the MV and tissue Doppler imaging (TDI). In terms of assessing for diastolic dysfunction, a combination of different measures from these methods are used within specific algorithms dependent on ejection fraction (324, 420). The MV inflow waveform consists of an E wave; representing the peak velocity of blood flow during early diastole and an A wave; representing the peak velocity of blood flow in late diastole due to the left atrium contracting. In a healthy individual, the normal MV profile can be seen overlying the diastolic phase of the cardiac cycle in Figure 8.

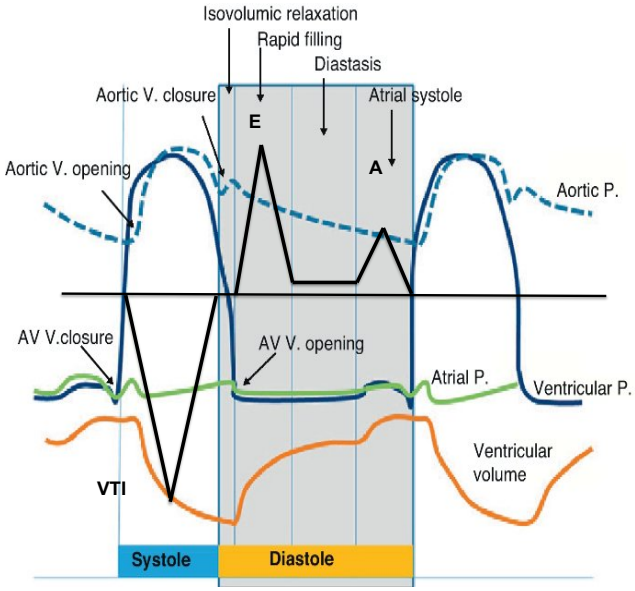


Figure 8. Mitral valve inflow profile overlapping the diastolic phase of the cardiac cycle.

Modified from Fernandez-Perez *et al* (2012) (325). A: peak A wave velocity, AV V: atrioventricular valve, E: peak E wave velocity, P: pressure, VTI: velocity time integral.

The mitral E wave velocity primarily reflects the pressure gradient across the left atrium (LA) and left ventricle (LV) during early diastole, which is affected by preload and changes in LV relaxation. The mitral A wave reflects the LA-LV pressure gradient in late diastole and is therefore affected by compliance of the LV and contractility of the LA (421). The deceleration time (DT) is the time required for the E wave slope to fall from the peak velocity to the zero baseline, while the A wave duration represents the time of the atrial contraction. The DT is affected by LV relaxation and compliance, as well as LV diastolic pressures after MV opening. The mitral E/A ratio was also calculated using the averaged peak E and A wave velocities. This ratio and the DT are used to identify LV filling patterns: normal, impaired relaxation, pseudonormal and restrictive filling.

There is a general consensus in the literature in regard to the MV inflow Doppler changes that occur during diastole in normal pregnancy from the first to second trimesters, with disparity in the change from the second to third trimesters (332, 362, 406, 418, 422). These traditional measures of diastole are dependent on

preload, which is increased in pregnancy and change with gestation. There are some differences between authors in regard to certain measures, however some of this variation may be attributed to study design, technical factors and the circulating blood volume of subjects. Modern measures of diastolic function include TDI which is considered relatively independent of loading conditions (423, 424), while others report some dependency (425, 426). There are only a few studies that have assessed tissue Doppler imaging in pregnancy, with mixed results (35, 404, 416, 422, 427). Overall, the majority of studies found normal pregnancy was associated with a deterioration of diastolic function towards term.

1.16.7.1 Mitral inflow

Early studies used MV inflow to assess diastolic function with changes to loading conditions in pregnancy impacting relaxation patterns. Left atrial pressure, LV relaxation and preload all affect the E wave velocity of the MV inflow. Furthermore, the A wave velocity is affected by LV compliance and the contractile function of the left atrium (324). During pregnancy, the blood volume expansion results in an increase in the rate of LV filling, evident by an initial increase in peak E velocity (332, 358, 362, 406, 418, 422) and peak A velocity (332, 358, 406, 418, 422). There is evidence to suggest that as preload increases further, the rate of LV relaxation is prolonged, resulting in a reduction in LV filling time during early diastole, as seen by a decline in E wave velocity. A number of studies reported a decline in the E wave peak velocity during the third trimester (332, 362, 406, 422), while others found a decrease with gestation from the first trimester (358, 404, 409, 427). Studies by Mabie *et al* (1994) (328) and Simmons *et al* (2001) (45) both reported the E wave velocity did not change during pregnancy.

In order to maintain CO as a result of prolonged LV relaxation and reduced LV filling during early diastole, increased SV filling needs to occur during late diastole. An increase in peak A velocity reflects this change, which may be due to an alteration in LV compliance or greater atrial contraction. The mechanisms involved in the shift of LV filling from early to later diastole in pregnancy are not clearly understood. Most authors (45, 328, 332, 358, 362, 406, 409, 418, 422, 427) report an increase in the A wave peak velocity with gestation, except one study by Estensen *et al* (2013) (404). Despite this, Estensen concurred with other

authors that the E/A ratio decreases from the first trimester to term (35, 45, 332, 358, 362, 404, 406, 418, 422).

Effectively, in the majority of studies there is a shift in transmitral filling from early diastole to late diastole. This is evident by the decline in peak E velocity from a maximum in the first trimester, the progressive increase in peak A velocity with gestation, and an overall decrease in the E/A ratio. Moran *et al* (2002) suggests these findings indicate an increase in LV compliance, contrary to the interpretation by Kametas *et al* (2001). Kametas suggested the decline in E velocity after the first trimester was due to a decrease in LV compliance, secondary to the progressive hypertrophy that is well reported in pregnancy. The group also suggested that the decrease in E wave velocity seen in the third trimester correlated to the increase in peripheral resistance (afterload) at the equivalent gestation (418).

There are conflicting results in regard to deceleration time (DT) in pregnancy, with a number of studies showing that DT remains unchanged (332, 404, 406, 422). Two studies (358, 416) observed the DT increase from the second to the third trimesters, while Schannwell *et al* (2003) (362) and Simmons *et al* (2002) (45) observed an increase with gestation from the first trimester. The DT values returned to normal 3 months post-partum in the Schannwell study, however they remained increased in the Simmons study. It is suggested that the DT increase reflects the longer LV filling time during early diastole, secondary to changes in the LA-LV pressure gradient. Reporting of the isovolumetric relaxation time (IVRT) also varied between studies, with some finding the IVRT increased (35, 362, 406) while the study by Mesa *et al* (1999) reported no change. In contrast, Simmons reported a progressive decrease in pregnancy, with second and third trimester values significantly shorter compared to non-pregnant controls (45). Valensise *et al* (2000) (358) also observed a decline, however this was just between the second and third trimesters. Only a few studies have reported the A wave duration in pregnancy. Valensise *et al* (2000) (358) observed a decrease in A wave duration between the second and third trimesters, while Mesa *et al* (1999) (332) and Schannwell *et al* (2003) (362, 428) found no change.

1.16.7.2 Tissue Doppler imaging

Tissue Doppler Imaging (TDI) reflects the velocity of myocardial fibres and can be measured by PW or colour Doppler techniques. The TDI waveform shows peak *e* and *a* wave velocities representing ventricular lengthening during early and late diastole respectively. There are only a few studies that have used TDI in the assessment of diastolic function in pregnancy, with inconsistent results (35, 404, 409, 416, 422, 427). This may be in part due to the location of the LV sampling site, the size of the sample volume, study design, TDI method, and population characteristics. Tissue velocities are not uniformly distributed across the myocardium, with velocity decreasing from base to apex (428). The velocities are also affected by translational movement and tethering, making it difficult to discriminate akinetic segments that are pulled from actively contracting segments (429). Akinetic segments, secondary to ischaemic heart disease or infarction, are unlikely to be relevant in a population of healthy pregnant women. Multiple studies have clearly demonstrated that mitral and tricuspid annular velocities decline with age (429-432) and are gender specific, with specific reference ranges needed to determine dysfunction (324, 420).

During pregnancy, Fok *et al* (2006) (422) observed the *e* velocity at both the lateral and septal LV sites increase from the first to second trimester. This was followed by a significant decrease in the third trimester, despite all *e* velocities being within the normal range for a non-pregnant population. Zentner *et al* (2009) (416) demonstrated *e* decrease from 16-37 weeks, however these velocities were all significantly higher than non-pregnant controls. Estensen *et al* (2013) (404) also demonstrated a decrease in peak *e* velocity over the same time frame. This is in contrast to the study by Bamfo *et al* (2007) (427) which observed *e* values were less than non-pregnant controls and that there was a nonsignificant decline in e velocity with gestation. The studies by Fok, Bamfo and Zentner all observed the peak *a* velocity increased with advancing gestation at both lateral and septal sites, resulting in a decrease in the *e/a* ratio (409, 422, 427). Estensen reported no change in peak velocities, however there was a significant, progressive decrease in the *e/a* ratio. Melchiorre *et al* (2016) (35) also observed this progressive decline in *e/a* ratio with gestation, at both the septal and lateral sites.

The ratio of transmitral E velocity over early diastolic mitral annulus velocity (E/*e*) is considered a valid index of LV filling pressure (429, 433), however this has not been validated in pregnancy. Studies also recommend age-dependent cut-off values (432, 434, 435) and that diastolic indices should not be used in isolation, rather in conjunction with other measures using a diagnostic algorithm (324, 420). The studies that did investigate E/*e* were contradictory, with Fok *et al* (2006) (422) reporting the E/*e* ratio declined at all four sites sampled, reaching statistical significance just at the septal and inferior sites, while Melchiorre *et al* (2016) (35) found the E/*e* ratio averaged from two sites increase significantly from the second trimester to term. The majority of studies showed that the E/*e* ratio remained essentially unaltered (404, 416, 427). Recommendations published by the ASE and EACVI state that the E/*e* ratio is not a reliable index of LV filling pressures in normal subjects (324, 420), with no guidelines on what indices should be used in pregnancy outlined in the joint ASE/EACVI statements.

In summary, the observed change in TDI peak velocities mirror those seen in the MV inflow peak velocities. Diastolic function is altered, with the majority of studies indicating this is decreased or dysfunctional in the third trimester (418) (35, 362, 404, 416).

Table 7. Summary of systolic cardiovascular changes in normal pregnancy

CV parameter	First trimester	Second trimester	Third trimester
Stroke volume (ml)	Increases	Increases Peaks and maintained	Increases Maintained from second trimester Decreases towards term
		MAn: Increases mildly early in the trimester followed by marked decreased to nadir	MAn: Increases from nadir, with small decline late in trimester
Heart rate (bpm)	Increases	Increases	Increases Maintained
Cardiac output (L/min)	Increases	Increases	Increases Decreases Late decline Maintained
		MAn: Increases early in the trimester with a decrease late in the trimester	MAn: Increases early in the trimester with a late decline towards term
Mean arterial pressure (mmHg)	Decreases	Decreases, reaches nadir	Decreases further Maintained
			MAn: Slight increase early in the trimester, then plateaus
Total peripheral resistance ($Dynes.s^{-1}cm^{-5}$)	Decreases	Decreases	Decreases early in the trimester, increasing mildly towards term
Left ventricular mass (g)	Increases	Increases	Increases

MAn: meta-analysis by Meah *et al* (2016) (368).

1.16.8 Summary

In normal pregnancy cardiac output (CO) increases secondary to a multitude of changes, including increased blood volume, stroke volume (SV) and heart rate, decreased systemic vascular resistance and a concomitant reduction in mean arterial pressure. The structure of the heart adapts to facilitate these changes, resulting in an increase in left ventricular mass and change in geometry, whilst maintaining normal function. There is controversy in regard to the size and time course of change in parameters such as SV and CO, with different evaluation methods and technological differences adding to the disparity of published findings. These issues will be discussed further in relation to the results of this study. There is also inconsistent reporting of systolic function in normal pregnancy during the third trimester, with some authors reporting no change and others showing a reduction (362, 404, 416).

In regard to diastolic function, the progressive change in loading conditions that occur in normal pregnancy results primarily in altered left ventricle (LV) compliance and filling. There is agreement amongst studies that changes to diastolic function do occur secondary to increased blood volume, resulting in LV filling shifting from early to late diastole and that this is generally reflected in both traditional transmitral and Tissue Doppler imaging measurements. However, there is inconsistent reporting of some of these indices giving rise to different interpretations of the changes that place in pregnancy. Schannwell *et al* (2002) (345), Zentner *et al* (2009) (395) and Melchiorre *et al* (2016) (35) all report normal pregnancy is associated with abnormal relaxation patterns in the third trimester consistent with diastolic dysfunction (35, 345, 395) while Fok *et al* (2006) (386) and Estensen *et al* (2013) (404, 422) did not find impaired diastolic function. Evaluating diastolic dysfunction during pregnancy is complex and challenging as there is limited published data outlining normal reference ranges, with no guidelines from national bodies on how algorithms from non-pregnant populations should be applied.

1.17 Cardiovascular adaptation in pre-eclampsia

Cardiovascular studies of women with pre-eclampsia are limited and mostly contain a small number of cases (38-40, 45, 49, 52, 54, 56), with more recent work focused on cardiac function and structure in the pre-clinical phase of the disease (36, 44, 48, 53). Studies have suggested that altered maternal cardiac geometry, systolic and diastolic function are associated with pre-eclampsia and / or fetal growth restriction (36-45, 47, 48, 50-52, 56, 57, 358, 419, 436-442) and that these changes are evident as early as 14 weeks' gestation (42, 43). The reported cardiovascular changes are inconsistent; although, there is a general consensus that the haemodynamic profile of pre-eclamptic women is different to normotensive women, with the pattern dependent on the severity of the disease, presence of comorbidities, phase of labour, medication use and fluid management (48). Furthermore, research suggests that this profile is different prior to the development of signs and symptoms of disease and that there are haemodynamic differences between early and late-onset pre-eclampsia (36, 37, 41, 42, 51, 443).

1.17.1 Haemodynamic changes

Initial assessments of central haemodynamics using thermodilution on pre-eclamptic women demonstrated considerable variation in the expression of the disease (444-447). This was considered in part to be the result of anti-hypertensive medication, magnesium sulphate and intravenous fluids given during the procedure. Later studies (54, 448, 449) demonstrated that untreated pre-eclamptic women had a uniform pattern of low cardiac output (CO) and high peripheral resistance, and that previous studies were most likely artefactual due to treatment intervention. A study by Visser *et al* (1991) (54) also found that untreated pre-eclamptic women had normal blood plasma volume, in contrast to other studies which showed a reduction (450, 451). Inadequate blood volume expansion has also been associated with fetal growth restriction (450, 452, 453).

Subsequent research showed that women in the preclinical phase of pre-eclampsia had a higher CO and normal or low total peripheral resistance (TPR) compared to normotensive women (39, 40). Bosio *et al* (1990) (40) also demonstrated a significant change in the haemodynamics of women once they

developed pre-eclampsia, with a decrease in CO and an increase in TPR. The group postulated that there was a crossing over from a hyperdynamic circulation to a low CO / high TPR state with the clinical onset of pre-eclampsia. These papers were published in 1990, prior to the conceptualisation of alternate pathophysiological pathways in the development of early and late-onset disease. It is most likely these studies reflect women with late-onset pre-eclampsia given the 'cross over' from a high CO to a low CO was noted between 34 and 36 weeks' gestation in the Bosio study (40) and both studies had a mean gestational age at delivery of 39.4 weeks' (40) and 36.4 weeks' (39) gestation.

More recent papers assessing the preclinical phase of the disease in women who develop late-onset pre-eclampsia replicated the hyperdynamic circulation findings (41-44, 50), with two studies demonstrating this was evident in the first trimester (42, 43). Conversely, the study by Melchiorre *et al* (2013) (36) found that TPR was increased in women destined to develop late-onset pre-eclampsia, but with no change in CO. Additionally, a study by Guy *et al* (2017) (53) also showed a higher TPR and lower CO compared to normotensive women in the third trimester prior to the onset of signs and symptoms of the disease, contradicting earlier work. One study found seven haemodynamic models of pre-eclampsia, although there was no differentiation between early-onset or late-onset pre-eclampsia and some of these women were having treatment (55). A number of studies assessing early-onset pre-eclampsia consistently found a low CO / high TPR state prior to the onset of signs and symptoms (36, 41, 442). When pre-eclampsia associated with small for gestational age (SGA) was investigated, these studies also showed a similar haemodynamic profile to early-onset pre-eclampsia (42, 44, 52).

The echocardiography study by Dennis *et al* (2012) (38) of untreated women with late-onset pre-eclampsia found TPR and CO were both significantly higher suggesting a hyperdynamic circulation when symptomatic. This finding is not in keeping with the Visser thermodilution study (54), or the crossing over theory proposed by Bosio which found pre-eclamptic women had a high TPR / low CO state in the clinical phase (40). Simmons *et al* (2002) (45) also studied untreated pre-eclampsia late in the third trimester and replicated the finding that TPR was significantly higher in these women, however; in contrast to Dennis, the CO was comparative to normotensive women (45).

Unsurprisingly, the mean arterial pressure (MAP) results largely support the TPR findings. MAP is consistently higher in women destined to develop early-onset pre-eclampsia with or without a SGA fetus (36, 41, 42, 49) and late-onset pre-eclampsia (36, 42, 454) compared to normotensive women in the preclinical phase of the disease. Interestingly, the study by Valensise *et al* (2008) (41) did not demonstrate a significant difference in MAP between women who developed late-onset pre-eclampsia and those with a normal outcome.

Thermodilution is considered the gold standard in assessing haemodynamics, however studies of pre-eclampsia utilising this technique are scarce, small and were conducted when pre-eclampsia was considered a single disease entity. Some of the more recent echocardiography studies have differentiated between early and late-onset forms of pre-eclampsia but there are limited studies and not all make this distinction. The concept of a hyperdynamic circulation in the preclinical phase of pre-eclampsia that significantly changed with the onset of signs and symptoms of disease seemed to fit with the historical data. This concept fits less well with newer evidence challenging the hyperdynamic circulation and crossing over theory. In regard to pre-eclampsia associated with SGA, or SGA in isolation, there is more consistent data that the haemodynamic profile is a low CO / high TPR state.

1.17.2 Cardiac output

The majority of older studies have shown women in the pre-clinical phase of late-onset pre-eclampsia have an increased CO (39-43, 50). The absolute values of CO differed between studies and were confounded by different evaluation techniques and variable gestational age at time of assessment, with some studies reporting indexed CO values. One mid-gestational study showed that CO was reduced in women who developed late-onset pre-eclampsia compared to low-risk women with a normal outcome of 5.2 L/min versus 5.6 L/min, although this was not statistically significant. The equivalent indexed CO measure showed no difference (36). In contrast to the majority of studies, the study by Guy *et al* (2017) (53) reported a lower CO in the late third trimester prior to signs and symptoms of pre-eclampsia.

Two studies have found CO to be lower in women who develop early-onset pre-eclampsia in the preclinical phase of the disease compared to those with a normal

outcome (36, 41). A lower CO has also been observed in women with early-onset pre-eclampsia associated with fetal growth restriction (FGR) (49) and in normotensive women with a growth restricted or SGA fetus (42, 419, 438, 441).

In women with untreated late-onset pre-eclampsia, there is inconsistent reporting of CO. One study showed CO is increased compared to normal pregnancy (4.1 L/min versus 4.8 L/min) (38), while others reported that the cardiac index (CI) was unchanged (4.1 versus 4.2 L/min/m^2 and 3.2 L/min/m^2 versus 3.2 L/min/m^2) when diastolic function was normal (45). The later study also reported the CI was lower in the presence of diastolic dysfunction (2.9 L/min/m^2), but this was not statistically significant. The study by Hibbard *et al* (2004) (56) reported a lower cardiac index in untreated pre-eclamptic women of 3.3 L/min/m^2 versus 4.2 L/min/m^2 ($p < 0.001$), however this study was conducted when pre-eclampsia was considered a single disease entity.

The increase in CO with gestation observed in women destined to develop pre-eclampsia compared to normotensive women is largely unclear. Initial studies did not differentiate between placental and maternal phenotypes of pre-eclampsia and generally reported a higher CO prior to the onset of disease. Recent studies that have assessed CO in the context of these phenotypes have clearly shown early-onset pre-eclampsia (placental phenotype) is strongly associated with a lower CO in the latent phase of disease. The small number of studies that have assessed CO specifically in terms of late-onset pre-eclampsia (maternal phenotype) have conflicting results both in the preclinical and clinical phases of pre-eclampsia.

1.17.3 Stroke volume

In untreated pre-eclamptic women, two studies have shown that SV and stroke volume index (SVI) were significantly higher compared to normotensive women (38, 45), one study found SV decreased (52) while another reported SVI was unchanged (37). Studies investigating late-onset pre-eclampsia in the preclinical phase have demonstrated conflicting SV results with some of these differences attributed to the same factors that impact CO assessment: study design, methodology, and gestational age. In this group of women, studies have shown variable SV results: an increase (41, 42, 44, 50), a non-statistical decrease (53) and no change when indexed (36). In terms of women destined to develop early-

onset pre-eclampsia, studies consistently reported lower SV and SVI compared to women with a normal outcome (36, 41, 49).

1.17.4 Heart rate

Heart rate (HR) has been reported to be unchanged in women with pre-eclampsia (37, 38), although the study by Simmons *et al* (2002) (45) showed HR was lower compared to normotensive women. In the preclinical phase of late-onset pre-eclampsia there are mixed reports: no difference in HR was observed in two studies (36, 42), one study reported a lower HR (53), while another two studies reported a significantly higher HR (41, 50). In women who subsequently develop early-onset pre-eclampsia, the majority of studies reported HR unchanged compared to women with a normal pregnancy outcome (36, 42, 49). Only one study reported a lower HR (41).

1.17.5 Contractility

In untreated pre-eclamptic women, Dennis *et al* (2012) (38) found fractional shortening (FS) and fractional area change both increased, indicating enhanced contractility. The FS increase was also reported by Simmons *et al* (2002) (45), however this group also assessed contractile function using the Vcf-ESS. No difference in the Vcf-ESS relation was evident between the pre-eclamptic and normotensive women, with the group concluding that contractility was preserved despite the increase in afterload in the pre-eclamptic women. This work supported two earlier studies that observed contractility was unchanged in pre-eclamptic women using the same indices (56, 455).

In the pre-clinical phase, the mid-gestational study by Melchiorre *et al* (2013) (36) reported radial systolic function and contractility were preserved in women who developed both early-onset and late-onset pre-eclampsia. The longitudinal function results were different: only women who developed early-onset pre-eclampsia showed a reduction in the lateral *s* wave velocity, inferring systolic dysfunction. This was not evident when longitudinal function was assessed at the septum. In terms of women in the preclinical phase of late-onset pre-eclampsia, one study found global systolic function preserved when assessed by conventional indices and tissue Doppler *s* wave velocities (37).

1.17.6 Left ventricular geometry

A number of studies have shown alterations to left ventricular geometry in women with pre-eclampsia compared to normotensive women (37, 38, 41, 45, 456). The most significant finding is that the increase in left ventricular mass (LVM) observed in pregnancy was greater in pre-eclamptic women compared to women with a subsequent normal outcome (37, 38, 45, 456) and that the remodelling of the left ventricle (LV) was consistent with concentric hypertrophy (37, 45). Valensise *et al* (2008) (41) also reported concentric hypertrophy, with this observation seen at 24 weeks' gestation in women destined to develop early-onset pre-eclampsia. The authors suggested that these changes represented a state of underfilling with pressure overload and were not seen in normotensive women or those who developed late-onset pre-eclampsia. The women who developed late-onset pre-eclampsia had larger LV diameters with intermediate relative wall thickening, suggesting a state of overfilling with pressure overload (41).

A mid-gestational study of early-onset and late-onset pre-eclampsia did not show any significant difference in left ventricular mass index (LVMI) compared to normotensive women, however the relative wall thickness (RWT), which is a ratio of LV posterior wall thickness and the diameter of the LV at end diastole, was significantly increased (36). The RWT was also significantly higher in early-onset disease compared to late-onset disease, with a higher prevalence of remodelling in these women compared to normotensive controls (36).

1.17.7 Diastolic function and pre-eclampsia

Diastolic dysfunction results when LV filling occurs with increased LV pressure (324, 420), leading to venous congestion and heart failure. Alterations in diastolic function are generally observed before systolic changes, with studies of nonpregnant populations showing the importance of identifying symptom-free LV dysfunction for early therapeutic intervention and improved long-term outcomes (431, 457, 458). The evaluation of diastolic dysfunction in pregnancy is hindered by issues relating to changes in loading conditions, thereby adding complexity to the interpretation of results. Furthermore, only a small number of studies have assessed diastolic function in pre-eclamptic women during or prior to the onset of disease. A recent study assessed the prevalence of asymptomatic structural

heart disease, termed heart failure stage B (HF-B) (457), one to four years after pre-eclampsia. The group found that 23% or these women had HF-B at one year, with resolution in approximately 60% at two years, however HF-B was newly developed in 19% of initially unaffected women (459). This finding supports an earlier study that found the majority of women with preterm pre-eclampsia had HF-B one to two years postpartum, with 40% developing essential hypertension (460).

1.17.7.1 Mitral inflow

There is limited information on MV inflow patterns in women prior to the onset of pre-eclampsia and those with the disease. The reports are often conflicting, confounded by different study designs and methodologies. The study by Simmons *et al* (2002) (45) found E wave velocities were higher in women with untreated late-onset pre-eclampsia compared to normotensive women, while the A wave velocity remained unchanged. This is in contrast to a number of studies that showed increased A wave velocities, resulting in a lower E/A ratio (37, 38, 456). Statistical significance was only reached in one of these studies (456) and was only evident in cases of pre-eclampsia when diastolic dysfunction was present (37). In this study, pre-eclamptic women with normal diastolic function actually had a higher E/A ratio.

In women assessed mid-gestation prior to clinical onset of pre-eclampsia, the E/A ratio was lower in those destined to develop preterm pre-eclampsia but similar to women with term pre-eclampsia (36). This is in contrast to the study by Valensise *et al* (2008) (41) which found the E/A ratio was significantly higher in early-onset pre-eclampsia due to higher E wave velocity and lower A wave velocity, while slightly lower in late-onset pre-eclampsia secondary to a lower A wave velocity, when compared to normotensive women.

Some studies have reported the E wave deceleration time (DT) was unchanged (45, 456), while other studies have shown a prolonged DT (37, 38). The isovolumetric relaxation time (IVRT) was also longer in untreated pre-eclamptic women in a few studies (37, 38, 456), while Simmons *et al* (2002) (45) observed the IVRT was the same as normotensive women. The mid-gestation study by Melchiorre *et al* (2013) (36) found the IVRT was prolonged in the preclinical phase

of term disease but not preterm disease, in contrast, the study by Valensise *et al* (2008) (41) showed the IVRT was increased in early-onset pre-eclampsia and prolonged with late-onset pre-eclampsia.

A study by Sep *et al* (2011) (442) assessed early pregnancy changes in diastolic function between formerly pre-eclamptic women with recurrent early-onset pre-eclampsia and those who did not develop recurrent pre-eclampsia. In the ten women who developed recurrent early-onset disease (29%), by 12 weeks the E/A ratio had increased in the recurrent group but not in the women who did not develop pre-eclampsia. This increase was primarily due to a difference in A wave velocity adaptation; the A wave increased in women who did not develop early-onset pre-eclampsia and decreased slightly in those that did.

1.17.7.2 Tissue Doppler imaging

Only one study has used TDI in the assessment of pre-eclampsia prior to the onset of signs and symptoms of disease (36). This study showed at 20-24 weeks' gestation, women with early-onset pre-eclampsia showed lower septal and lateral *e* wave velocities with a reduced *e/a* septal ratio compared to normotensive women. These changes were not seen in women with late-onset pre-eclampsia. The E/*e* ratio was lower in both early-onset and late-onset disease compared to those with an uneventful pregnancy, however this was not statistically significant. The group concluded that diastolic dysfunction and impaired myocardial relaxation at mid-gestation is only seen in women who develop preterm pre-eclampsia and not term pre-eclampsia (36).

Studies of women with untreated pre-eclampsia have shown *e* wave and *a* wave tissue Doppler velocities and the associated *e/a* and E/*e* ratios are significantly different to women with a healthy pregnancy (37, 38, 456). The study by Dennis *et al* (2012) (38) reported a reduced *e* wave velocity, an increased *a* wave velocity and an increased E/*e* ratio associated with pre-eclampsia. The increased E/*e* ratio was also seen in the Rafik *et al* (2009) (456) study of pre-eclamptic women and in the Melchiorre *et al* study (37), however this finding was only evident in pre-eclamptic women with diastolic dysfunction and not in those with normal diastolic function (37). Bamfo *et al* (2008) (49) also reported a lower *e* wave velocity in women with pre-eclampsia associated with intrauterine growth

restriction (IUGR) in addition to a higher E/*e* ratio, concluding higher filling pressures are evident in pre-eclamptic women.

When evaluating the heart for diastolic dysfunction, all authors reiterated the need to assess indices collectively and not in isolation, with two groups advocating the use of diagnostic assessment algorithms (37, 38). The ASE and EAE have jointly published an algorithm for the assessment of diastolic function, however this is based on a non-pregnant population (420). The Melchiorre study modified the algorithm to take into consideration maternal age and volume loading that occurs during pregnancy, but this method has not been validated (37). The group reported grade 1 and 1a diastolic dysfunction occurred more often in late-onset pre-eclampsia compared to normotensive pregnancies (40% versus 14%) using the modified algorithm they developed. Dennis *et al* (2012) (38) used the standard algorithm for evaluating diastolic dysfunction and showed 44% of untreated pre-eclamptic women had grade 1 or 2 diastolic dysfunction.

Assessment of diastolic function in pregnancy is complex due to the change in loading conditions with gestation. There are only a few studies that have evaluated diastolic function in pre-eclampsia, with inconsistent findings reported. These issues confound the interpretation of changes that occur with either form of pre-eclampsia, both in the preclinical and clinical phases of the disease. A direct comparison between studies is further challenged by different measurement indices and methodologies as well as variability in gestation at the time of the investigations. Despite the scarcity of diastolic function studies, there is some evidence suggesting diastolic dysfunction is associated with pre-eclampsia and that this is more evident with early-onset disease.

Table 8. Cardiovascular parameters with early-onset pre-eclampsia (placental phenotype) and late-onset pre-eclampsia (maternal phenotype) in the preclinical phase of disease, untreated pre-eclampsia and SGA compared to normotensive women.

Cardiovascular parameter	Early-onset pre-eclampsia	Late-onset pre-eclampsia	Pre-eclampsia	SGA/IUGR
Stroke volume (ml) / Stroke volume index (ml/m^2)	Decreased[1,2,3]	Increased[3,4,5,6] N-S Decrease[7] Unchanged[2]	Increased[8,9] Decreased[10] Unchanged[11]	Decreased[17,19,6] Unchanged[18]
Heart rate (bpm)	Unchanged[1,2,6] Lower[3]	Unchanged[2,6] Lower[7] Higher[3,4]	Unchanged[8,11] Lower[9]	Unchanged[17] Lower[18,19]
Cardiac output (L/min) / Cardiac Index (L/min/m^2)	Decreased[6,12]	Increased[3,4,6,12,13,14] Decreased[7] Unchanged[2]	Increased[8] Decreased[14,15] Unchanged[9,11]	Decreased[17,18,19]
Total peripheral resistance (Dynes.$s^{-1}cm^{-5}$) / Total peripheral resistance index (Dynes.$s^{-1}cm^{-5}$)m^2	Increased[6]	Lower[4,13,14] Unchanged[6] Increased[2,7]	Increased[8,9,10,15] Lower[14]	Increased[17,18,19] Unchanged[6]
Left ventricular mass (g) / Left ventricular mass index (g/m^2)	Unchanged[2] Increased[3]	Unchanged[2] Increased[3]	Increased[8,9,11,16]	Unchanged[18] Decreased[19]
Mena arterial pressure (mmHg)	Increased[1,2,3,6]	Increased[2,4,6,7] Unchanged[3]	Increased[8,9,11,13,14,15,16]	Increased[18,19] Unchanged[6,17]

1. Bamfo *et al* (2008) (49), 2. Melchiorre *et al* (2013) (36), 3. Valensise *et al* (2008) (41), 4. Kazerooni *et al* (2006) (50), 5. Rang *et al* (2008) (44), 6. Khaw *et al* (2008) (42), 7. Guy *et al* (2017) (53), 8. Dennis *et al* (2012) (38), 9. Simmons *et al* (2002) (45), 10. Jia *et al* (2010) (52), 11. Melchiorre *et al* (2011) (37), 12. De Paco *et al* (2008) (43), 13. Easterling *et al* (1990) (39), 14. Bosio *et al* (1999) (40), 15. Hibbard *et al* (2004) (56), 16.Rafik *et al* (2009) (456), 17. Bamfo *et al* (2007) (438), 18. Melchiorre *et al* (2012) (419), 19. Vasapollo *et al* (2002) (441). IUGR: intra-uterine growth restriction, N-S: non-significant, PE: pre-eclampsia, SGA: small for gestational age fetus.

1.17.8 Summary

The maternal cardiovascular system is integral to delivering oxygen and nutrients to the growing fetus via the placenta, with significant alterations to multiple organ systems required to facilitate the increased metabolic demand. Effectively, with increasing gestation blood volume, cardiac output and heart rate increase with a decline in peripheral resistance. Changes in normal pregnancy were initially studied using thermodilution, however this invasive technique was eclipsed with the advent of echocardiography and other non-invasive techniques such as impedance cardiography, which utilises electrical conductivity to measure the level of change in impedance in the thoracic fluid over time. These studies yielded mixed results, primarily pertaining to the magnitude and time course of change in SV and CO, with differences in evaluation techniques and methodologies confounding the disparity. With echocardiographic technological advances, the cardiovascular system was subsequently evaluated in terms of systolic and diastolic function. Again, studies showed conflicting results in normal pregnancy, mainly relating to cardiovascular changes in the third trimester and whether diastolic function and contractility were preserved with advancing gestation.

In women with pre-eclampsia, initial studies of the maternal cardiovascular system found CO reduced and peripheral resistance increased, fitting with the concept that pre-eclampsia was caused by defective placentation, leading to hypoperfusion. Concurrent histological studies also showed inadequate placentation was associated with pre-eclampsia and growth restriction, further supporting the placental cause for pre-eclampsia. Subsequent research of women in the pre-clinical phase of the disease demonstrated a hyperdynamic profile (High CO / low TPR), leading to the postulation of the crossing over theory. That is, the profile changed to a low CO / high TPR state with symptoms and signs of pre-eclampsia. The concept of early and late pre-eclampsia was concurrently evolving, with the gestational milestone of 34 weeks considered important in terms of pregnancy outcome. Further research into the causation of pre-eclampsia elucidated that the disease was likely multifactorial, with defective placentation more closely related to women who developed pre-eclampsia early in pregnancy and not women with pre-eclampsia late in their pregnancy.

With the focus shifting towards two distinct forms of pre-eclampsia, cardiovascular studies showed an array of haemodynamic profiles. Generally, early-onset pre-eclampsia was associated with a low CO / high TPR state, similar to women with SGA infants in the pre-clinical phase, while late-onset pre-eclampsia was associated with a high CO / low TPR state that changed or 'crossed over' with signs and symptoms of disease. This fitted with the historical data as there was a significantly higher prevalence of women with pre-eclampsia late in their pregnancy included in those studies.

Recent studies showed that late-onset pre-eclampsia is not associated with failure of the placenta to develop adequately during the first half of pregnancy. Alternative explanations suggest maternal cardiovascular maladaptation may be the primary mechanism leading to placental dysfunction. Studies that have evaluated the cardiovascular profile of women in terms of early and late-onset pre-eclampsia show conflicting results in the late-onset group, both in the clinical and pre-clinical phases of disease, thereby challenging the concept of a haemodynamic circulation and the crossing over theory. The cardiovascular system and placenta are intrinsically linked but the role these entities have in the development of endothelial dysfunction and, consequently, pre-eclampsia is clearer when the concept of disease is considered to have placental and maternal phenotypes that closely align, respectively, to early and late-onset pre-eclampsia. Our understanding of the placental origin of pre-eclampsia is significantly better compared to our knowledge of maternal disease origins, namely the adaptation of the cardiovascular system in pregnancies destined to develop late-onset pre-eclampsia.

This raises the need for further longitudinal assessment of the cardiovascular system in pregnancy, especially in the preclinical phase of pre-eclampsia. Specifically, by assessing women in terms of their risk of abnormal placentation, further information regarding SV, HR, CO and TPR could help to better characterise the haemodynamic profile of women destined to develop late-onset disease and identify parameters which may help to distinguish the disease from gestational hypertension, as these women and their infants are still as significant risk of morbidity and mortality.

Chapter 2 Hypothesis and Aims

2.1 Hypothesis

Women destined to develop early-onset or late-onset pre-eclampsia have altered cardiovascular function prior to the development of symptomatic disease.

Evaluation of maternal cardiovascular function in women deemed to be at high-risk for pre-eclampsia (through other forms of screening) will enable identification of a subgroup that are truly at risk.

This will allow more focused prophylactic intervention in true high-risk women and appropriate reassurance for other women who were 'false positive' cases identified with the initial screening.

2.2 Aims

The aims of this thesis are:

- To serially evaluate haemodynamic function at four time points in pregnancy (14 to 30 weeks) in cohorts of women who were deemed to be either low or high-risk through a first trimester screening program for pre-eclampsia and who subsequently had either a normal or adverse pregnancy outcome (pre-eclampsia, gestational hypertension, small for gestational age fetus or preterm birth).

- To determine whether changes in cardiovascular function are significant enough to adopt as secondary screening tools to distinguish between high-risk pregnancies that go on to develop pre-eclampsia or other adverse outcomes or that have a normal pregnancy outcome.

  And if there are significant cardiovascular changes, also;

- Identify the most appropriate gestational point for second tier screening.

Chapter 3 Methodology

3.1 Patients

This was a prospective, longitudinal study of maternal cardiac function in singleton pregnancies involving two groups of women: those deemed either low or high-risk for developing early-onset pre-eclampsia. The Fetal Medicine Foundation (FMF) screening algorithm was used to define women as either 'high-risk' or 'low-risk' for developing early-onset pre-eclampsia. Risks of pre-eclampsia were generated through a screening test conducted at 12 weeks. This test combined factors derived from maternal history with results of biophysical (blood pressure) and biochemical (PAPP-A) investigation. The findings were recorded in a risk engine, produced by FMF (London, UK) in order to define individual levels of risk. A risk of $\geq$ 1 in 50 was defined as high-risk, while a risk of < 1 in 50 was considered to demonstrate a low-risk for pre-eclampsia.

Women who agreed to participate in the study as per local ethical requirements (HREC/11/RPAH/383, protocol Number X11-0251) were offered assessment of maternal cardiac function by echocardiography and blood pressure monitoring. These women were recruited from the Royal Prince Alfred Hospital antenatal clinic after completing first trimester screening, with echocardiograms performed between March 2012 and July 2015.

Echocardiograms were carried out at four time points with maternal weight and fetal characteristics, such as fetal biometry, measured at each scan. The initial baseline scan was performed at 14 weeks' gestation, shortly after the first trimester risk assessment was performed. Subsequent scans were arranged at 20, 24 and 30 weeks' gestation, as outlined in Figure 9. This schedule was selected to support the aims of the study, which included assessment of maternal cardiovascular structure and function as a second-tier screening tool for the prediction of pre-eclampsia, with the anticipation that such a screening program would be completed by 30 weeks' gestation.

Demographic information was collected from the self-reported questionnaire that women completed at the time of attendance for their first trimester (11-13+6 weeks) screening scan. Data relating to first trimester screening, including measures of gestational age (crown rump length), biochemical measurement of maternal serum PAPP-A, measurement of mean arterial pressure, sonographic

Doppler assessment of maternal uterine arteries, and the calculated risk for pre-eclampsia occurring before 34 weeks. Women who had a risk of ≥1 in 50 were considered to be high-risk of pre-eclampsia. Women who had a risk of <1 in 50 were considered to be low-risk of pre-eclampsia. Additional data related to pregnancy course and pregnancy outcome were added to the database as the pregnancy progressed and women were delivered. Data on pregnancy outcome included gestational age at delivery, birthweight, birthweight centile according to locally constructed charts, gender and the development of a hypertensive disorder. Pregnancy outcome data were collated from the electronic and hard copy hospital medical records. These data were collated by the primary investigator and each patient was allocated a study number so that the data could be de-identified prior to analysis.

3.2 Definitions

A high-risk for pre-eclampsia was defined through first trimester screening as a risk of ≥1 in 50.

A low-risk for pre-eclampsia was defined through first trimester screening as a risk of <1 in 50.

A normal pregnancy outcome was defined as a normotensive pregnancy that progressed to term (≥ 37 weeks' gestation) delivery of an infant with normal birthweight (≥ 10th centile for gestation) according to gender specific growth charts constructed from the local population (461).

An adverse pregnancy outcome was defined as a pregnancy impacted by the following:

> Pre-eclampsia, defined as the development of hypertension accompanied by one or more signs of maternal organ dysfunction after 20 weeks' gestation. It may present de novo or be superimposed on chronic hypertension.
>
> Gestational hypertension, defined as the new onset of high blood pressure after 20 weeks' gestation, without any of the abnormalities that define pre-eclampsia.

Preterm birth, defined as infants born alive before 37 weeks' gestation.

Miscarriage, defined as the spontaneous loss of a pregnancy before 20 weeks' gestation.

Stillbirth, defined as an infant born with no signs of life at or after 20 weeks' gestation.

Primary cardiovascular outcomes: The main cardiac parameters to be investigated relate to cardiovascular haemodynamics including: heart rate, mean arterial pressure, stroke volume, cardiac output, total peripheral resistance and the indexed equivalents for the last three parameters.

Secondary cardiovascular outcomes: This refers to all other systolic and diastolic cardiac parameters measured during the echocardiogram.

3.3 Maternal Echocardiography

3.3.1 Patient selection

Women stratified as high-risk were contacted by the fetal medicine registrar, advised of their risk, and counselled to take 150mg of aspirin each evening until the 36th week of pregnancy as per the current standard of care. These women were then invited to participate in the study, provided they were screened low-risk for fetal chromosomal abnormalities. Women that were high-risk for a fetal chromosomal abnormality and underwent invasive testing (CVS), were also invited to participate when the result was normal. Women stratified as low-risk were informed by a research midwife and invited to participate in the study.

Exclusion criteria

Women with pre-existing cardiac disease or hypertension were excluded, as well as women with a multiple pregnancy, or major fetal anomaly.

3.3.2 Ethical considerations

Ideally, it would have been preferential to assess women deemed high-risk for early-onset pre-eclampsia (ePE) without the therapeutic intervention of low dose aspirin. Given the strong evidence that aspirin significantly reduced the prevalence of ePE, it was not considered appropriate to deny women this treatment.

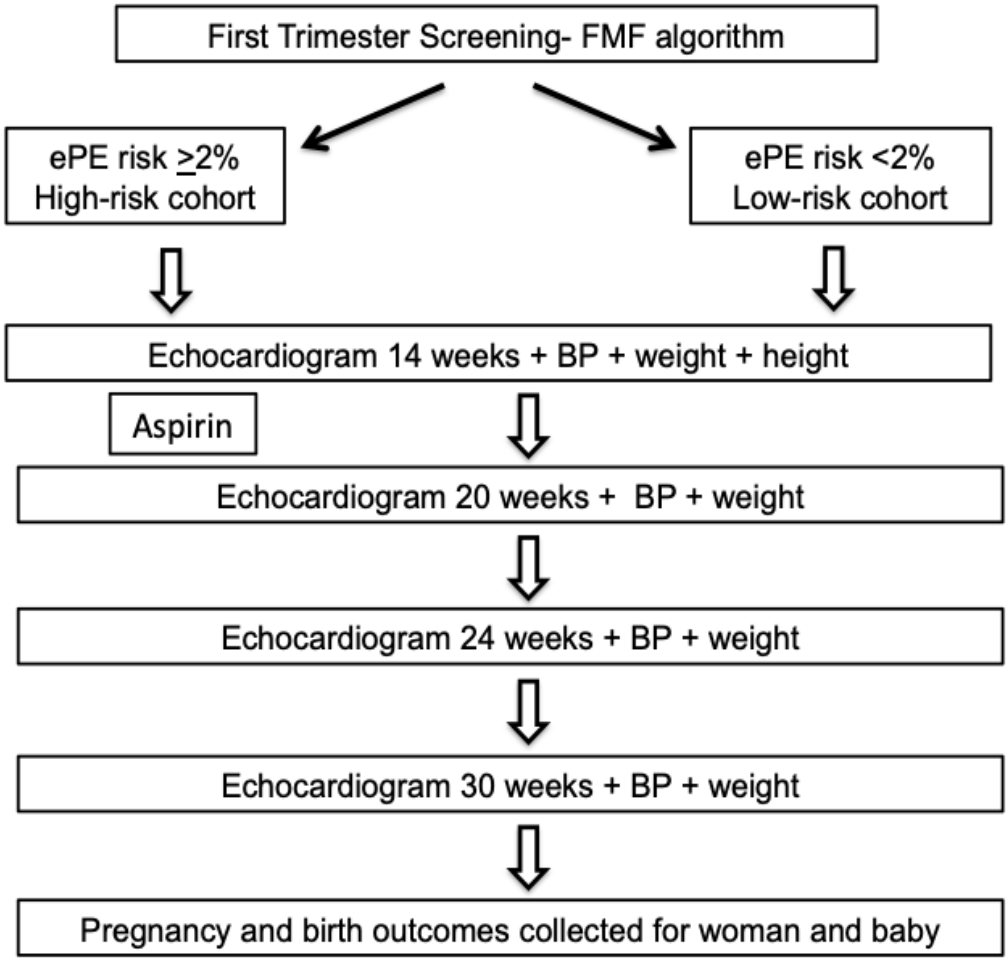


Figure 9. Screening for pre-eclampsia and echocardiography

BP: blood pressure, ePE: early-onset pre-eclampsia, FMF: Fetal Medicine Foundation.

3.3.3 Blood pressure methods

Automated blood pressure measurements were obtained using the Microlife 3BTO-A2 machine (Taipei, Taiwan) (Figure 10). The machine was regularly calibrated in accordance with manufacturer instructions and has been validated for use in pregnancy and pre-eclampsia (462).

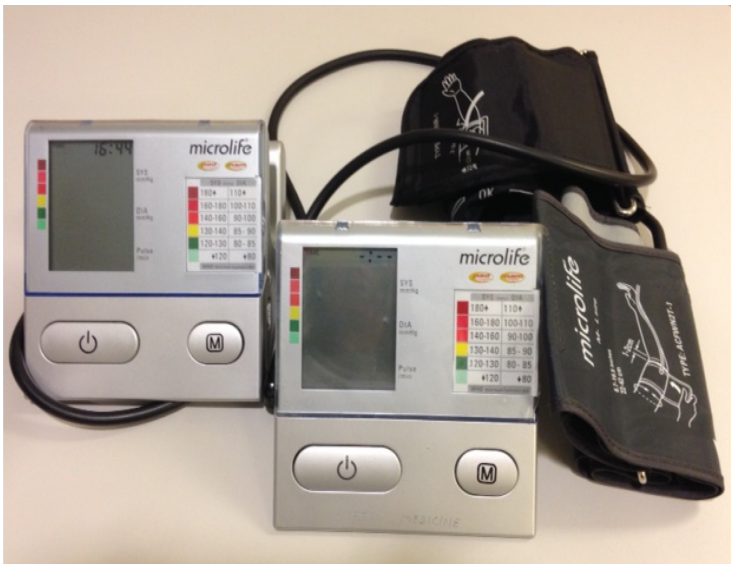


Figure 10. Microlife 3BTO-A2 machine

Measurements were taken by a registered nurse in a dedicated room within the fetal medicine department. Blood pressure was measured with the patient in the seated position with their arms supported at the level of the heart. A small (<22 cm), normal (22-32 cm) or large (33-42 cm) adult cuff was used depending on the mid-arm circumference. After rest of 5 minutes the blood pressure was measured in both arms simultaneously and a series of recordings made at one minute intervals until variations between consecutive readings fell within 10mmHg in systolic and 6mmHg in diastolic pressure in both arms. The mean arterial pressure (MAP) was calculated for each arm as the average of the last two stable measurements (463).

Equation 1. Mean arterial pressure

$$MAP = DBP + \left[\frac{SBP - DBP}{3}\right]$$

MAP: mean arterial pressure, DBP: diastolic blood pressure, SBP: systolic blood pressure

3.3.4 Height and weight methods

Height and weight were measured using the Wedderburn professional weight scale with an integrated height rod: model WM204. Women removed their shoes but remained clothed.

3.4 Echocardiogram experimental conditions

3.4.1 Environment

The echocardiograms were performed in a quiet room after at least 10 minutes rest in the waiting room. All scans were performed in the same climate-controlled room with low level lighting.

3.4.2 Investigator

All echocardiograms were performed by the lead investigator, Kate Russo, seated on the left-hand side of the patient.

3.4.3 Electrocardiogram

In privacy, all women removed their upper clothing and changed into a gown with the opening at the front. They then lay supine on the bed and were connected to a three-lead electrocardiogram (ECG). Standard placement of the three electrodes were the right arm, left arm, and left leg as seen in Figure 11. The right arm electrode is positioned directly below the clavicle near the right shoulder. The left arm electrode is positioned directly below the clavicle near the left shoulder. The left leg electrode is positioned in the lateral left iliac fossa.

Once the electrodes were correctly positioned, the patient was rolled onto her left side. Her body was supported by a pillow to maintain the left lateral decubitus

position, with her left arm extended above her head. A towel was then placed over her chest (Figure 12).

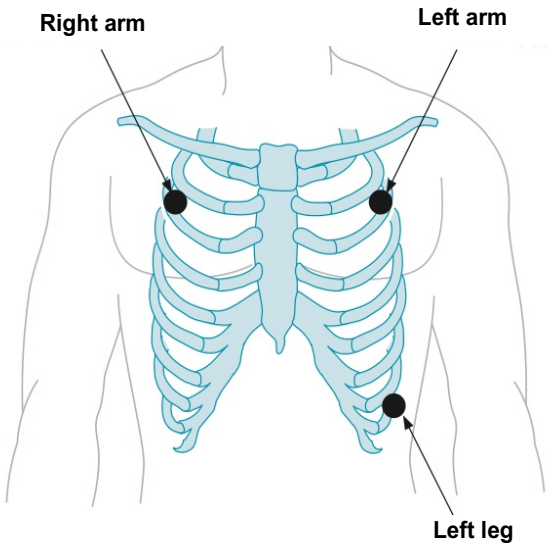


Figure 11. Three lead electrode placement (464)

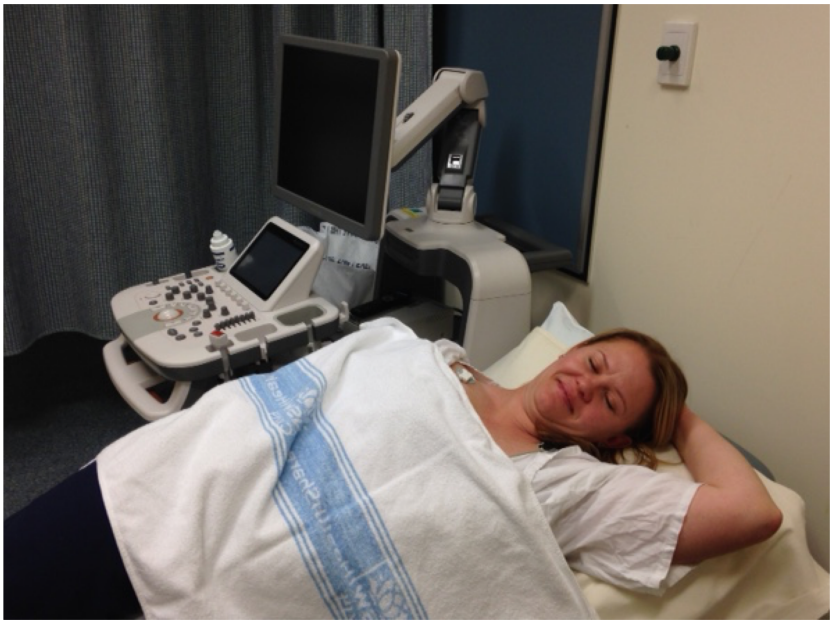


Figure 12. Woman in the left lateral position with her left arm raised

3.4.4 Equipment

The Samsung Accuvix XG ultrasound machine (Figure 13) with the P2-4BA probe (2 - 4 megahertz transducer) was used for all the transthoracic echocardiograms in the study. The echocardiogram was performed using the left parasternal and apical windows (Figures 14 and 15). Two-dimensional (2D) imaging, motion mode (M-mode), pulsed wave (PW) Doppler, and colour Doppler were all employed in the assessment of the heart. Three lead continuous ECG monitoring was utilised to obtain the end diastolic and end systolic time points for accurate measurement placement. Images were recorded and uploaded to the department's database storage.

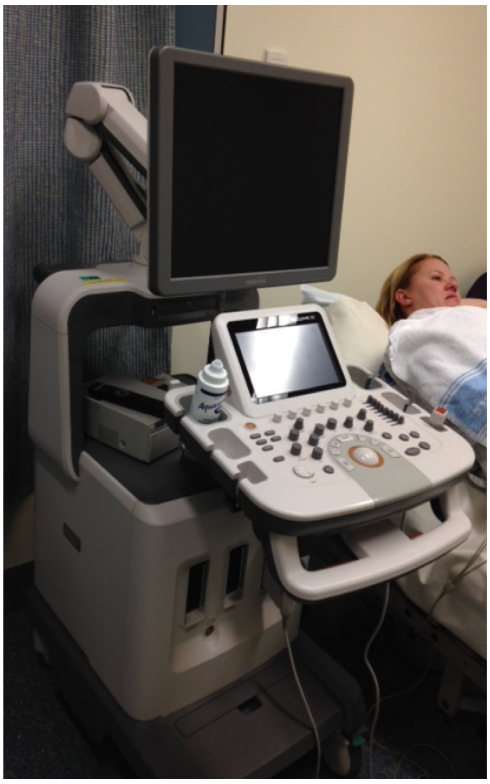


Figure 13. Samsung Accuvix XG ultrasound machine

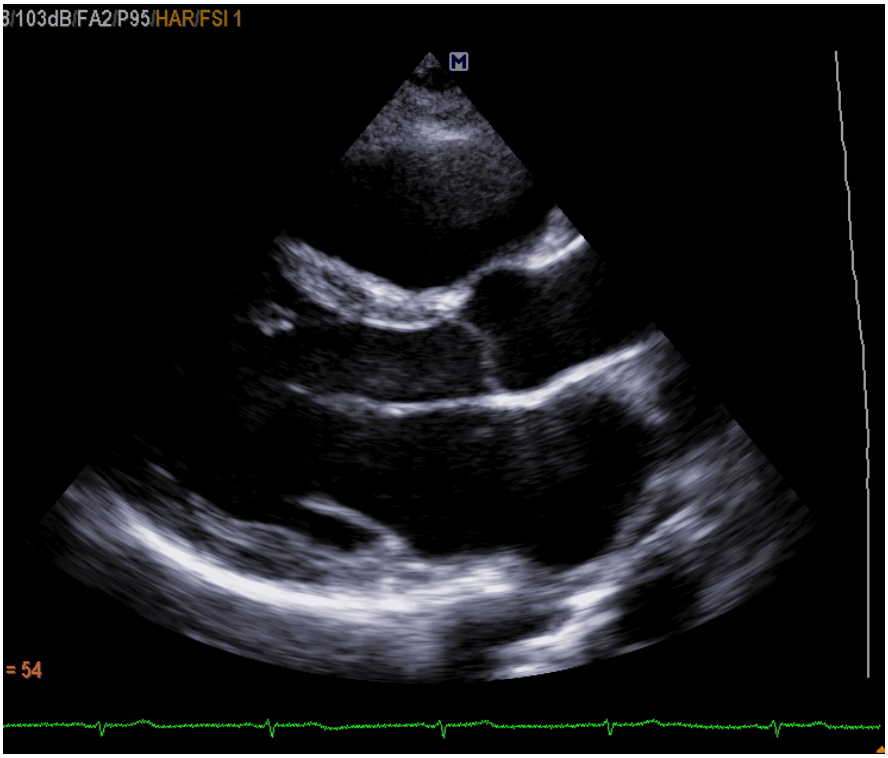


Figure 14. Parasternal long-axis view

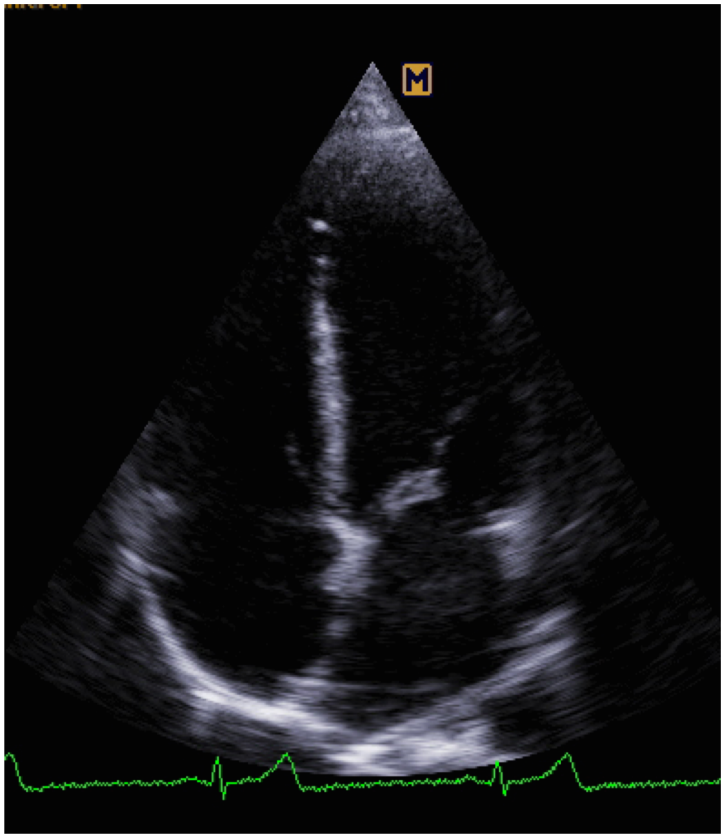


Figure 15. Apical 4-chamber view

3.5 General measurement technique and calculations

Echocardiography is a reliable, accurate, non-invasive method for assessing cardiac structure and function. Ejection fraction, fractional shortening (FS), stroke (SV) volume, cardiac output (CO) and tissue Doppler systolic velocity were calculated to assess left ventricular systolic function, while the mitral valve (MV) inflow profile and tissue Doppler were used to assess diastolic function. Systemic vascular resistance was calculated using blood pressure and CO measurements. All echocardiographic measurements and calculations were in accordance with American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) guidelines (324, 401, 402, 420).

3.5.1 Left ventricular mass

The left ventricular mass (LVM) was calculated to identify and quantify hypertrophy of the left ventricle (LV), using the product of the left ventricular muscle volume and the specific gravity of muscle (465). LV muscle volume is equal to the total left ventricular volume contained within the epicardial boundaries of the ventricle minus the chamber volume contained by the endocardial surfaces. A 2D image in the parasternal long axis view was used to acquire a M-mode trace perpendicular to the LV, with the cursor positioned level to the MV leaflets. LVM measurements were taken at end diastole, identified as the onset of the QRS complex from the ECG trace using a leading edge to leading edge technique (Figure 16). The interventricular septum thickness was measured between the anterior and posterior endocardial surfaces of the septum. The left ventricular internal diameter was measured from the posterior endocardial surface of the interventricular septum to the endocardial surface of the posterior wall. The posterior left ventricular wall thickness was measured from the endocardial surface to the epicardial surface of the posterior wall of the left ventricle (400, 402). The LVM was calculated twice and averaged.

Equation 2. Left ventricular mass

$$LV\ mass\ =\ 1.04\ ([LVID\ +\ PWT\ +\ IVST]^3 - LVID^3)\ X\ 0.8\ + 0.6$$

1.04 = specific gravity of the myocardium (g/ml), LVID: left ventricular internal dimension (cm), PWT: posterior wall thickness (cm), IVST: interventricular septal thickness (cm) (465)

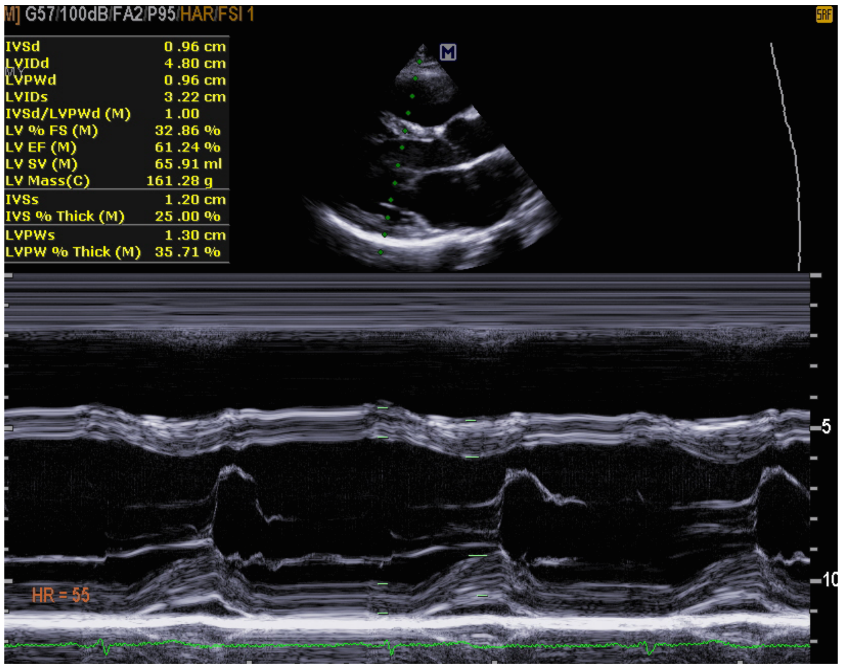


Figure 16. Parasternal long axis M-mode trace

Caliper placement of left ventricular dimensions used in the calculation of left ventricular mass, ejection fraction and fractional shortening.

3.5.2 Systolic function measurements

3.5.2.1 Left ventricular ejection fraction and fractional shortening

The left ventricular ejection fraction (EF) is the percentage of the left diastolic volume that is ejected with systole, representing the amount of blood pumped out of the ventricle with each contraction. The left ventricular FS is the percentage of change in the left ventricular cavity dimension with systole. To calculate the EF and FS, a parasternal long axis 2D image was used to record a M-mode trace through the LV, level with the MV leaflets. The LV diameter was measured from the posterior endocardial surface of the interventricular septum to the epicardial

surface of the posterior wall at end diastole and end systole (Figure 16). End diastole was defined as the onset of the QRS complex of the ECG, while the end systolic measurements of the LV were based on the motion of the interventricular septum. The end-systolic measurement was taken from the lower point of the septum (400, 402). The measurements were repeated twice and averaged.

Equation 3. Ejection fraction

$$EF\ (\%) = \frac{LVEDD^2 - LVESD^2}{LVEDD^2}\ x\ 100$$

LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter

Equation 4. Fractional shortening

$$FS\ (\%) = \frac{LVEDD\ -\ LVESD}{LVEDD} x\ 100$$

LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter

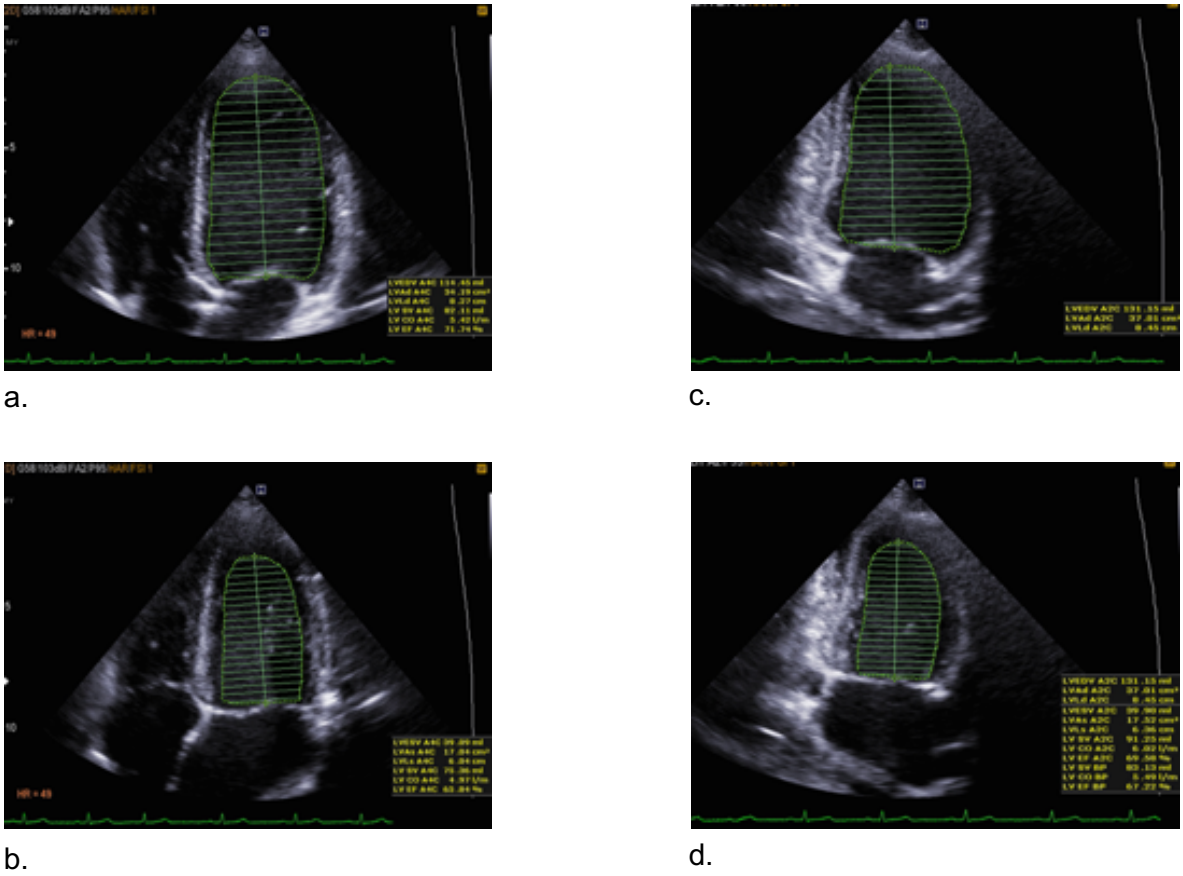
3.5.2.2 Modified Simpson's biplane method ejection fraction

The left ventricular EF was also calculated using the modified Simpson's biplane method, using measurements of LV end diastolic and LV end systolic volumes in the apical 4-chamber (4CH) and 2-chamber (2CH) views. Volume calculations were based on the summation of 20 discs of equal height acquired from two orthogonal planes. The volumes were traced following the interface between the compacted myocardium and the LV cavity at end diastole and end systole (Figure 17). The ECG was used to determine the 2D image representing end diastole and end systole. The approach is considered independent of LV geometry and is regarded as more accurate than the M-mode approach which calculates the EF based on a single point through the LV (402, 466).

Equation 5. Simpson's method ejection fraction

$$EF\ (\%) = \left[\frac{LVEDV - LVESV}{LVEDV}\right] x\ 100$$

EF: ejection fraction, LVEDV: left ventricular end diastolic volume, LVESV: left ventricular end systolic volume.



a. c.

b. d.

Figure 17. Simpson's biplane method of calculating ejection fraction

Apical 4-chamber end diastolic (a) and end systolic (b) volumes. Apical 2-chamber end diastolic (c) and end systolic (d) volumes.

3.5.2.3 PW Doppler stroke volume

Stroke volume is the volume of blood ejected by the LV during a single cardiac cycle and was calculated using PW Doppler through the left ventricular outflow tract (LVOT). The cross-sectional area (CSA) of the LVOT at the level of the aortic annulus and the PW Doppler velocity through this site were used in the calculation of SV.

Equation 6. Stroke volume

$$SV = CSA \; x \; VTI$$

SV: Stroke volume (ml), CSA: Cross sectional area (cm^2), VTI: Velocity time integral (cm)

3.5.2.4 Left ventricular outflow tract

The LVOT image was acquired from the parasternal long axis view and magnified to increase caliper placement accuracy. The LVOT was measured at the onset of systole, defined by the Q wave of the QRS complex. The measurement calipers were placed from the inner edge of the junction between the anterior aortic wall and the interventricular septum to the inner edge of the junction between the posterior aortic wall and the anterior leaflet of the MV (Figure 18). The LVOT was measured three times, each time on a newly acquired image. An average of the three measures was recorded. This measurement was then used to determine the CSA.

3.5.2.5 Velocity time integral

The velocity time integral (VTI) was used in the calculation of SV. The VTI was acquired from modification of the 4CH apical view. The probe was angled superiorly to elongate the LVOT, creating the apical 5CH view. A cursor with a sample volume of 3mm was placed at the level of the aortic valve annulus, with PW Doppler sampled at this site until 3 consecutive, identical waveforms were displayed. The area under the curve was measured by tracing the leading edge of the Doppler waveform (Figure 19). This measurement was repeated three times and averaged.

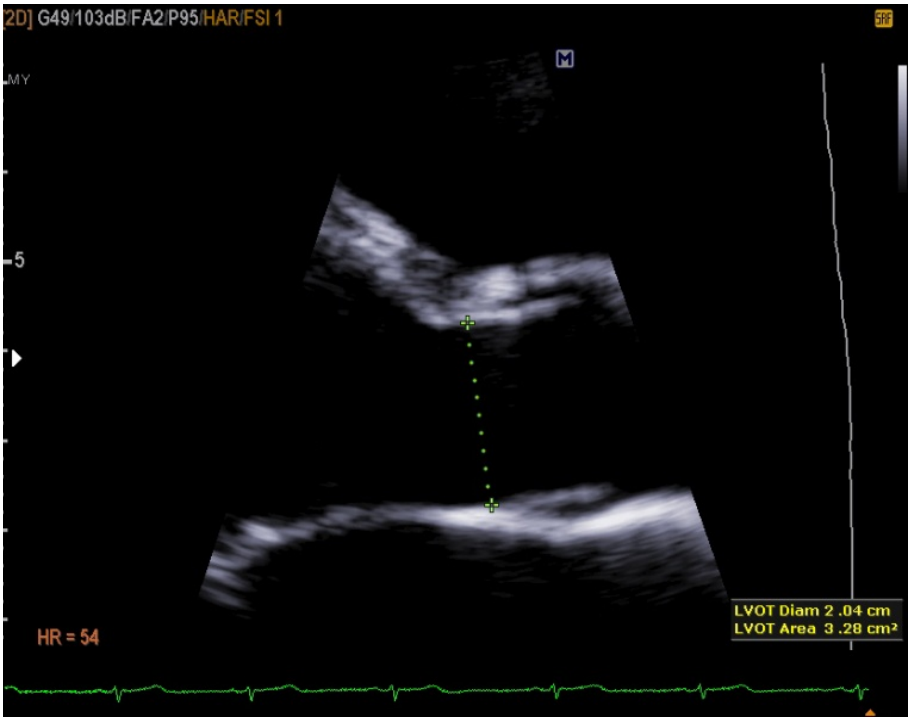


Figure 18. LVOT measurement from the parasternal long-axis view

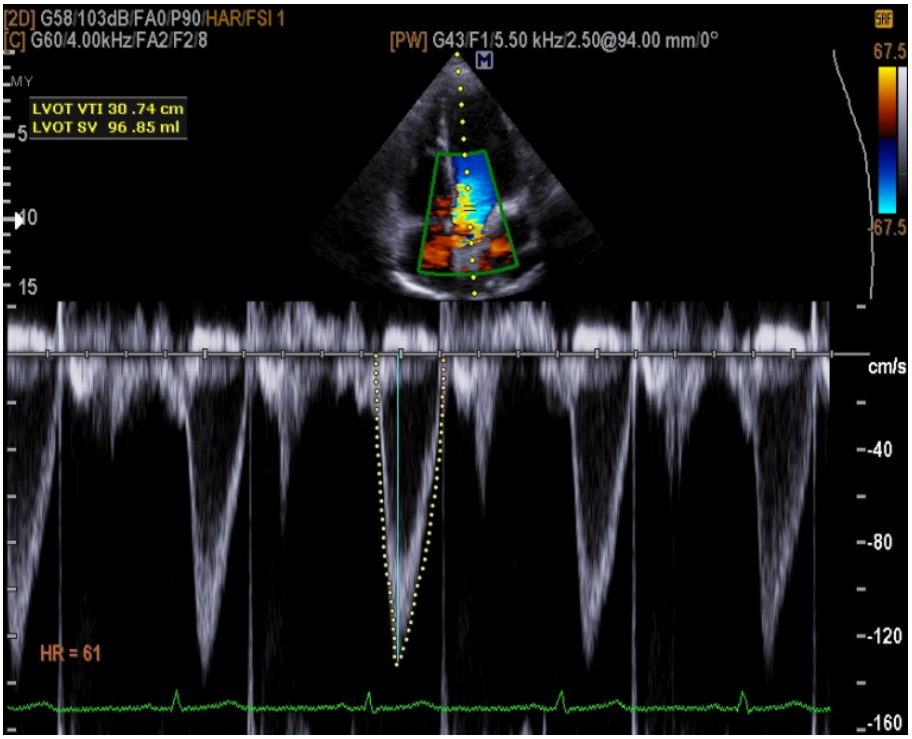


Figure 19. Velocity time integral measurement

3.5.2.6 Cardiac output

Cardiac Output (CO) is the volume of blood pumped by the heart per minute, calculated from the product of SV and heart rate (HR). The SV was derived from the PW Doppler method. The HR was determined from the R-R interval on the VTI Doppler trace. The R-R interval correlated to the time between two consecutive beats as indicated by the opening of the aortic valve. The R-R interval was averaged over four cycles (Figure 20).

Equation 7. Cardiac output

$$CO = SV \; x \; \frac{HR}{1000}$$

CO: cardiac output (L/min), SV: stroke volume (ml), HR: heart rate

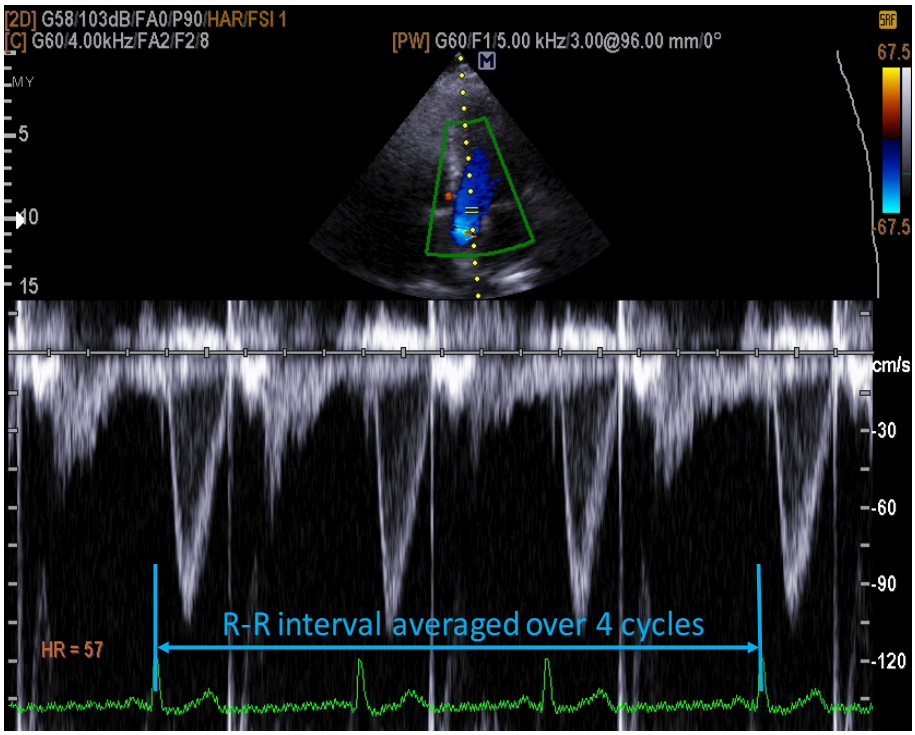


Figure 20. PW Doppler R-R interval averaged over 4 cycles

3.5.2.7 Tissue Doppler systolic velocity

The mitral annular systolic velocity (*s*) was measured at three sites in the apical 4CH view, the interventricular septum, the left lateral ventricular wall, and the right lateral ventricular wall reflecting the velocity of the ventricular myocardium in systole. Studies have shown that the *s* wave velocity correlates with measurements of ejection fraction (467, 468). The PW Doppler sample volume of 5-10mm was positioned within 1cm of the septal and lateral insertion sites of the MV, and within 1cm of the lateral insertion site of the tricuspid valve, thereby ensuring the longitudinal excursion of the respective annuli were covered in systole and diastole (324, 469). The *s* wave velocity at each site was obtained with no angle correction after three consecutive cycles were recorded (Figures 23-25). The measure was repeated and averaged.

3.5.3 Total peripheral resistance

Total peripheral resistance (TPR) is a measure of resistance from the systemic circulation, excluding the pulmonary vasculature. The measurement is calculated from the MAP and CO. The MAP was calculated from the systolic and diastolic blood pressure measurements, while the CO was derived from echocardiographic SV and HR measures.

Equation 8. Total peripheral resistance

$$TPR = MAP\ x\ \frac{80}{CO}$$

TPR: total peripheral resistance (Dyn.s.cm^{-5}), MAP: mean arterial pressure (mmHg), CO: cardiac output (L/min)

3.5.4 Body surface area indexation

The current recommendations by the ASE and EACVI to allow comparison amongst individuals with different body sizes is to index chamber measurements to body surface area (402). This includes measurements of LVM, SV, CO and TPR. No recommendations are made specifically in regard to pregnancy. Body

surface area is calculated from the DuBois and DuBois formula using weight and height (470).

Equation 9. Body surface area

$$BSA = (W\ 0.425\ x\ H\ 0.725)\ X\ 0.007184$$

BSA: body surface area

Equation 10. Left ventricular mass index

$$LVMI = \frac{LVM}{BSA}$$

LVMI: left ventricular mass index (g/m²), LVM: left ventricular mass (gm), BSA: body surface area (m²)

Equation 11. Stroke volume index

$$SVI = \frac{SV}{BSA}$$

SVI: stroke volume index (ml/m2), SV: stroke volume (ml), BSA; body surface area (m2)

Equation 12. Cardiac index

$$CI = \frac{CO}{BSA}$$

CI: cardiac index (L/min/m²), CO: cardiac output (L/min), BSA: body surface area (m²)

Equation 13. Total peripheral resistance index

$$TPRI : TPRI\ X\ BSA$$

TPRI: total peripheral resistance index (Dyn.s.cm^{-5}.m²), TPR: total peripheral resistance Dyn.s.cm^{-5}), BSA: body surface area (m²)

3.5.5 Diastolic function measurements

3.5.5.1 Mitral valve inflow

PW Doppler of the mitral inflow was assessed from the apical 4CH window using a 3mm sample volume placed centrally at the tips of the open MV leaflets (324, 471). The following measurements were taken from the transmitral velocity profile: peak E wave velocity (E), peak A wave velocity (A), E wave deceleration time (DT) and A wave duration (MV A dur) (Figure 21). The spectral Doppler trace was acquired until 3 consecutive waveforms were displayed, with measurements taken on one cardiac cycle. The process was repeated on a newly acquired Doppler trace, and the measurements were averaged. The mitral E/A ratio was also calculated using the averaged peak E and A wave velocities. This ratio and the deceleration time (DT) are used to identify LV filling patterns: normal, impaired relaxation, pseudonormal and restrictive filling.

The Isovolumetric relaxation time (IVRT) was measured with the 3mm sample gate positioned so that the PW Doppler beam overlapped the transmitral inflow and aortic outflow (Figure 22). The IVRT reflects the time between the aortic valve closure and MV opening and is affected by alterations in LV end-systolic and / or end diastolic volumes, elastic recoil of the left ventricle and LV diastolic pressures (324, 420). This measurement was repeated on a reacquired image and then averaged.

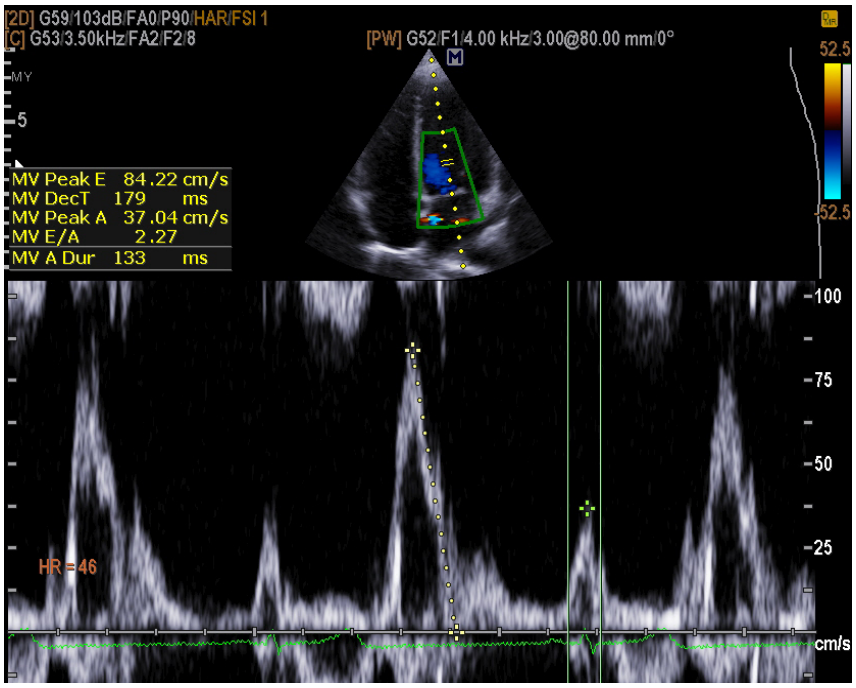


Figure 21. Mitral valve inflow waveform with peak E, peak A wave velocities, DT and A wave duration measured

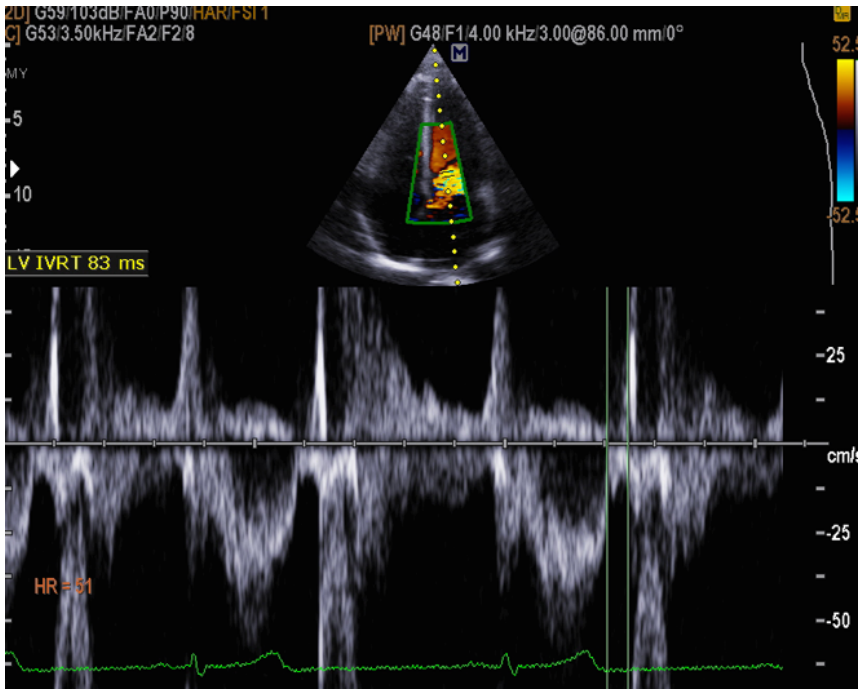


Figure 22. Isovolumetric relaxation time measurement from the aortic valve closure to the onset of mitral valve opening

3.5.5.2 Tissue Doppler imaging

PW tissue Doppler imaging was performed in the apical 4CH view to acquire mitral and tricuspid annular velocities. A 5-10mm sample volume was positioned within 1cm of the septal insertion site of the MV annulus, aligned to cover the longitudinal excursion during both systole and diastole (324, 420, 429, 469). When three consecutive waveforms were displayed, measurements of peak *s* velocity, peak *e* velocity and peak *a* velocity were taken (Figures 23). The spectral display was reacquired and the velocity measurements repeated, with the average recorded. These steps were repeated with the sample volume positioned within 1 cm of the lateral insertion of the MV annulus (Figure 24), and again when sampling the tricuspid valve annulus at the lateral right ventricle (Figure 25).

The *e/a* ratio was calculated using the averaged peak *e* and *a* velocities for the interventricular septum, left lateral and right lateral sites. The septal E/*e* ratio was calculated using the peak E velocity from the mitral inflow Doppler spectral trace, and the peak e velocity from the septal tissue Doppler spectral trace. The left lateral E/*e* ratio was also calculated, using the peak *e* velocity from the lateral MV annulus instead. Studies have shown that mitral annular velocities can be used to make inferences about LV relaxation and mitral E/*e* ratio can be used to determine LV filling pressures, a surrogate for pulmonary capillary wedge pressure (324, 420, 423, 429, 433); however, these parameters should be used in conjunction with other data in order to make conclusions about diastolic function. Studies have shown that in normal individuals when LV ejection fraction is greater than 50%, the E/*e* ratio is not accurate for estimating LV filling pressures (324, 420, 472).

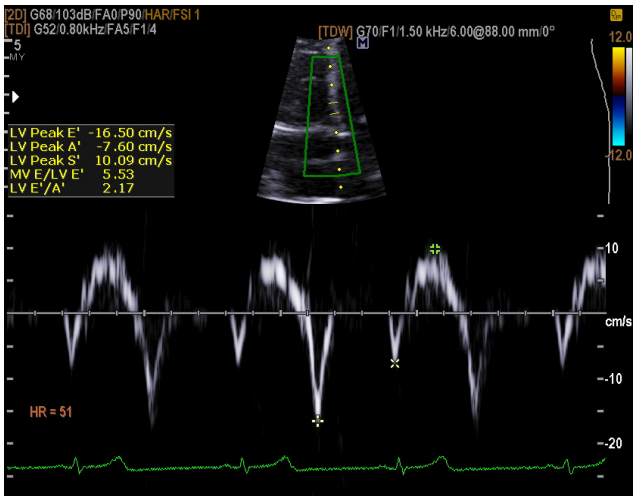


Figure 23. LV septum TDI showing peak *e*, *a* and *s* wave velocities

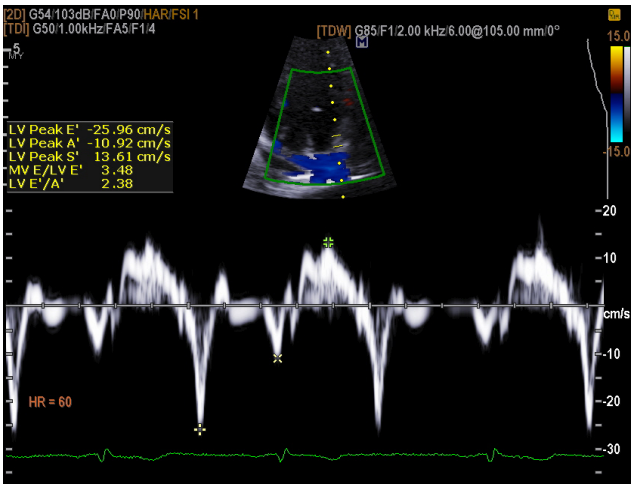


Figure 24. LV lateral TDI showing peak *e*, *a* and *s* velocities

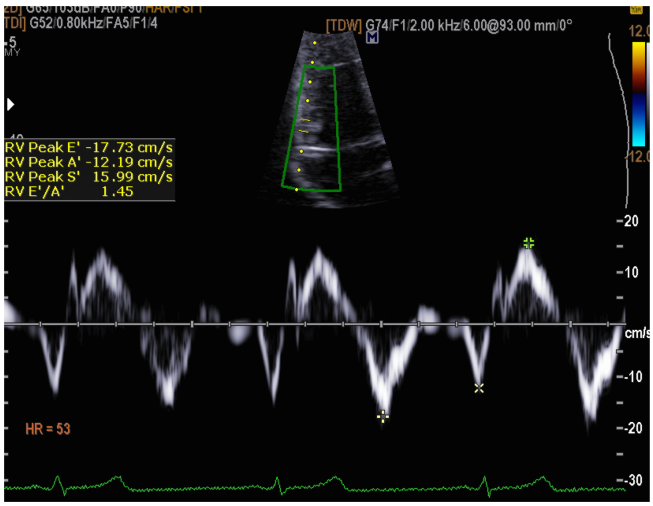


Figure 25. RV lateral TDI showing peak *e*, *a* and *s* velocities

Table 9. Echocardiogram images and measurements recorded in pregnant women

Window	Scan plane	Recorded image	Measurement
Parasternal	Long axis	Magnified LVOT	LVOT diameter (cm) CSA
	Long axis	LV M-Mode LVEDD (mm) LVESD (mm) IVS thickness systole and diastole (mm) LV posterior wall thickness systole and diastole (mm)	Ejection fraction Fractional shortening LV mass
Apical	4-chamber	PW Doppler mitral inflow	Peak E wave (cm/s) Peak A wave (cm/s) Deceleration time (ms) A wave duration (ms)
	4-chamber 2-chamber	LVEDV and LVESV LVEDV and LVESV	Simpson's modified biplane ejection fraction
	4-chamber	PW Tissue Doppler 3 sites: LV septum, LV lateral wall and RV lateral wall	Peak e wave (cm/s) Peak a wave (cm/s) Peak s wave (cm/s)
	5-chamber	PW Doppler LVOT	VTI (cm) HR (R-R interval)
	5-chamber	PW Doppler mitral inflow/aortic outflow overlap	IVRT (ms)

CSA: cross-sectional area, IVRT: isovolumetric relaxation time, IVS: interventricular septum, HR: heart rate, LV: Left ventricle, LVEDD: left ventricular end diastolic diameter, LVEDV: left ventricular end diastolic volume, LVESD: left ventricular end systolic diameter, LVESV: left ventricular end systolic volume, LVOT: left ventricular outflow tract, PW: pulsed-wave, VTI: velocity time integral.

Table 10. Haemodynamic and systolic calculations

Variable	Calculation
MAP (mmHg)	MAP = DBP + [(SBP-DBP) / 3]
LVOT CSA (cm^2)	CSA = 0.785 x (LVOT) D^2
SV (ml)	SV = VTI x CSA
SVI (ml/m^2)	SVI = SV / BSA
CO (L/min)	CO = (SV X HR) / 1000
CI ($L/min/m^2$)	CI = CO /BSA
TPR ($Dyn.s.cm^{-5}$)	TPR = (MAP x 80) / CO
TPRI ($Dyn.s.cm^{-5}.m^2$)	TPRI = TPR X BSA
Ejection fraction (%)	EF = ($LVEDD^2$ – $LVESD^2$/ $LVEDD^2$) X 100
Fractional shortening (%)	FS = (LVEDD-LVESD/LVEDD) x 100
LV Mass (g)	LVM = 1.04 ([LVID + PWT + IVST]^3 – $LVID^3$) x 0.8 +0.6

BSA: body surface area, CI: cardiac index, CO: cardiac output, CSA: cross-sectional area, D: diameter, DBP: diastolic blood pressure, EF: ejection fraction, FS: fractional shortening, HR: heart rate, IVST: intraventricular septal thickness, LVEDD: left ventricular end diastolic diameter, LVESD: left ventricular end systolic diameter, LVID: left ventricular internal dimension, LVM: left ventricular mass, LVOT: left ventricular outflow tract, MAP: mean arterial pressure, PWT: posterior wall thickness, SBP: systolic blood pressure, SV: stroke volume, SVI: stroke volume index, TPR: total peripheral resistance, TPRI: total peripheral resistance index, VTI: velocity time integral.

3.6 Study Outline

The data are presented through the four separate studies below.

The first study compares and contrasts cardiovascular parameters measured at 14 weeks' gestation, in women stratified as low or high-risk through first trimester screening for pre-eclampsia. This comparison is made prior to the commencement of aspirin (used as prophylaxis against pre-eclampsia in the high-risk group).

The second study compares birth outcomes, maternal characteristics and cardiovascular parameters of women deemed high-risk who subsequently had a normal or an adverse pregnancy outcome. The cardiovascular comparison is based on the data collected at 14 weeks' gestation, prior to prescription of aspirin.

The third study is an observational longitudinal study between 14 and 30 weeks' gestation of cardiovascular parameters in low-risk and high-risk women with a subsequent normal pregnancy outcome. These results will be compared to the literature.

The fourth study reviews longitudinal changes in maternal cardiovascular status in women stratified as high-risk between 14 and 30 weeks' gestation. The analysis compares women with a subsequent normal pregnancy outcome to those with an adverse pregnancy outcome, specifically: pre-eclampsia, gestational hypertension, SGA or preterm birth. An outline of these studies can be seen in Figure 26.

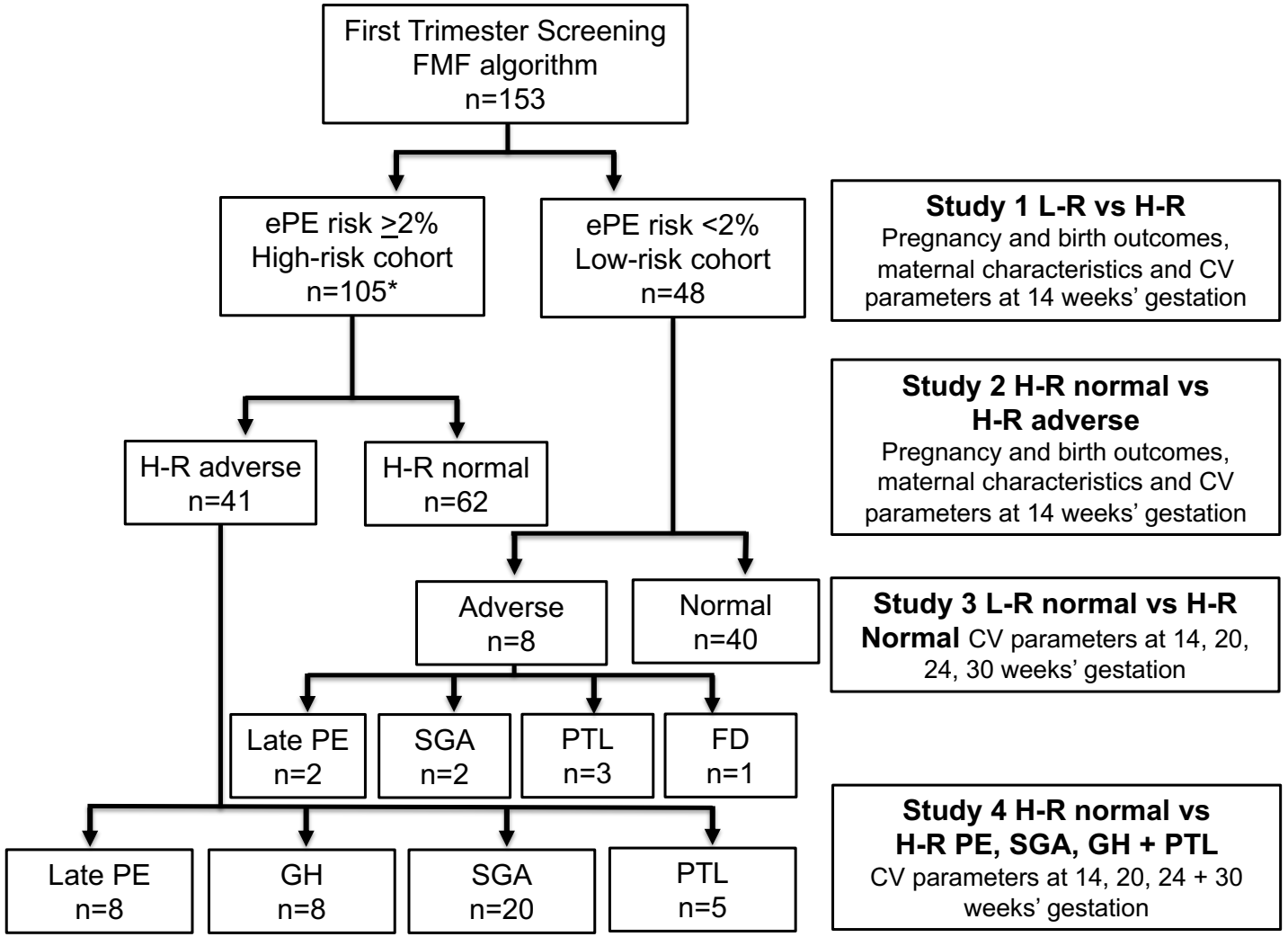


Figure 26. Outline of study groups for data analyses

CV: cardiovascular; ePE: early-onset pre-eclampsia; H-R: high-risk; FD: fetal demise; FMF: Fetal Medicine Foundation; GH: gestation hypertension; L-R: low-risk; PE: pre-eclampsia; PTL: preterm birth; SGA: small for gestational age. * 2 essential hypertension cases excluded.

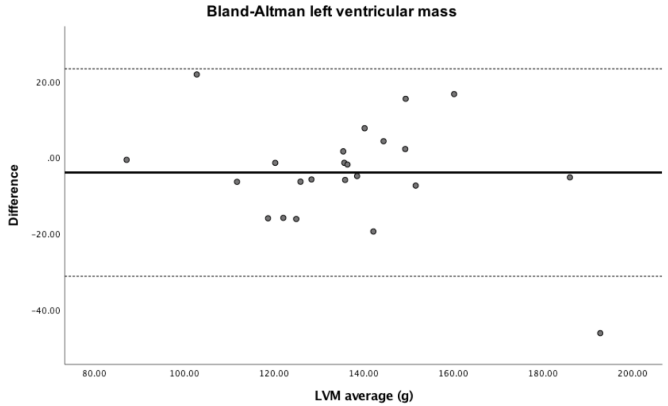
3.7 Statistical Analysis

All statistical analyses were performed using SPSS version 25.0. (IBM Corp: Armonk, NY) or Stata version 15 (College Station. TX: Statacorp, LLC). Issues relating to the reliability of some echocardiography measurements are known within cardiology. Intra-observer reproducibility was evaluated to provide a robust methodological assessment of the data collected. Intra-observer reproducibility was analysed using the Bland-Altman method with 95% limits of agreement (473), as well as the Pearson's correlation coefficient and Spearman rank test (474).

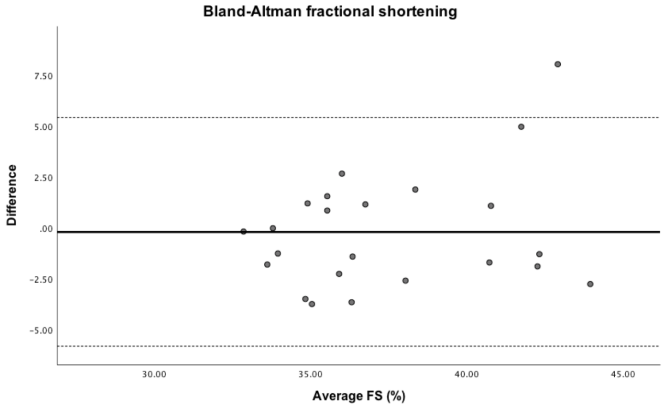
Descriptive data were expressed as medians with interquartile range for non-normally distributed data. Group comparisons at baseline were made using independent student t-tests, with longitudinal comparison between groups undertaken using linear regression models, with Generalised Estimating Equations used to account for correlation between repeated measures on the same participant. A two tailed value of $p < 0.05$ was considered statistically significant.

3.7.1 Intra-observer echocardiography reproducibility

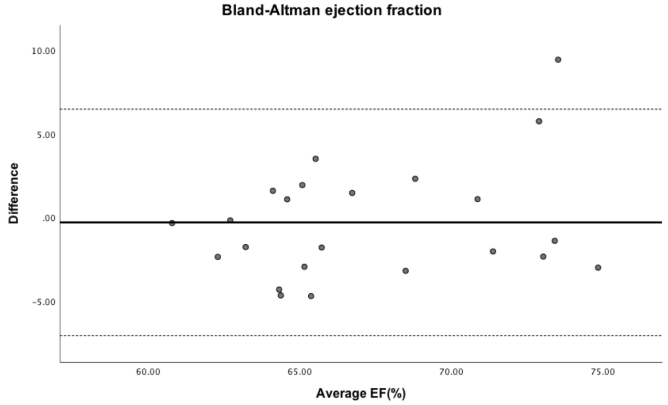
The intra-observer variability study was performed by K Russo who was blinded to the echocardiography measurements. This was achieved by placing a cover over the region of the screen displaying the results. The measurements of 23 participants were included in the Bland-Altman, Pearson's correlation coefficient and Spearman's rank test analyses. Correlation was described using the definitions: very strong (0.80-0.99), moderate (0.60-0.79) and fair (0.40-0.59) (474, 475). Very strong correlation was seen between measurements for the variables LVOT, VTI and HR that contribute to the primary outcomes: SV, CO and TPR. The tissue Doppler velocities at the septum, left lateral and right lateral walls also showed moderate correlation. The majority of the traditional measures of diastolic function showed moderate to very strong correlation. Details are summarised in Table 11 and Figures 27 to 31.



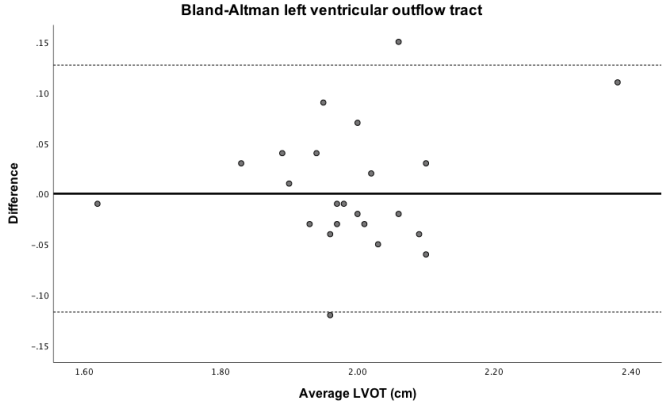
LVM repeatability coefficient = 38.5g, p=0.18



FS repeatability coefficient = 7.9%, p=0.74



EF repeatability coefficient = 9.6%, p=0.68

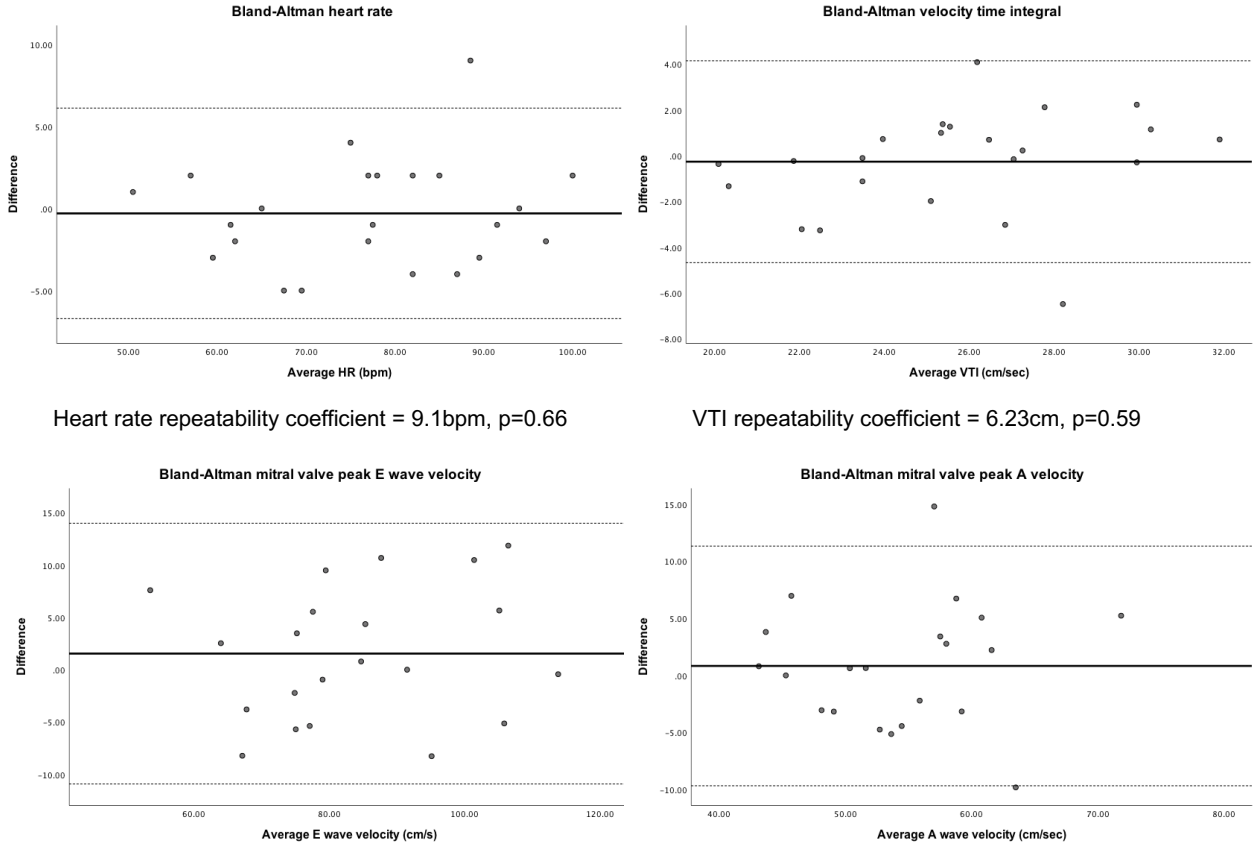


LVOT repeatability coefficient = 0.17cm, p=0.68

Figure 27. Bland-Altman intra-observer reproducibility of LVM, FS, EF and LVOT measurements

Solid lines represent no difference between observations; dotted lines on the plot represent mean difference and 95% agreement lines.

EF: ejection fraction, FS: fractional shortening, LVM: left ventricular mass, LVOT: left ventricular outflow tract diameter.



Heart rate repeatability coefficient = 9.1bpm, p=0.66

VTI repeatability coefficient = 6.23cm, p=0.59

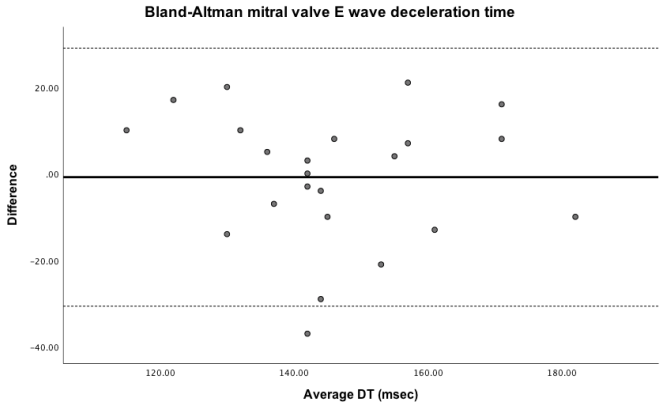
MV E wave repeatability coefficient = 17.62cm/sec, p=0.28

MV A wave repeatability coefficient = 15.07cm/sec, p=0.50

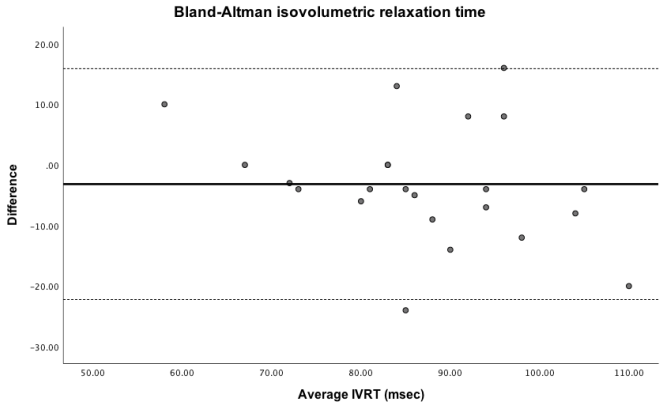
Figure 28. Bland-Altman intra-observer reproducibility of HR, VTI, MV E wave and MV A wave measurements

Solid lines represent no difference between observations; dotted lines on the plot represent mean difference and 95% agreement lines.

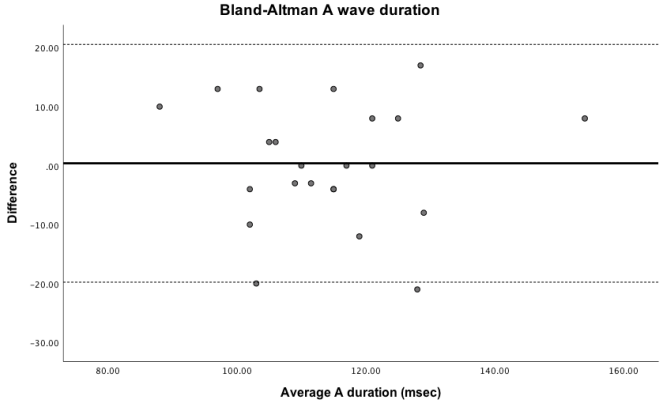
HR: heart rate, MV: mitral valve, VTI: velocity time integral.



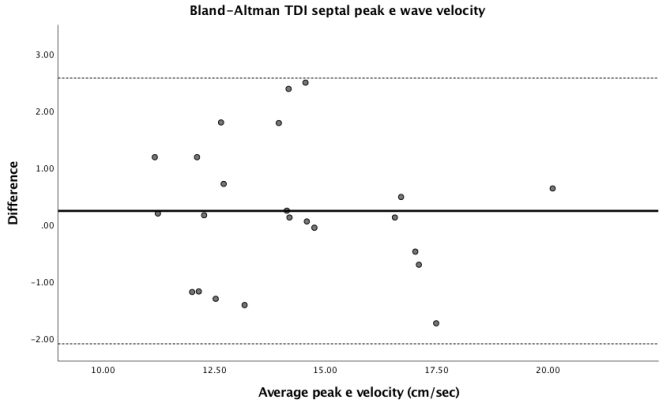
MV E wave deceleration time repeatability coefficient = 42.13msec, p=0.80



Isovolumetric relaxation time repeatability coefficient =26.9msec, p=0.13



MV A wave duration repeatability coefficient = 28.5msec, p=0.86

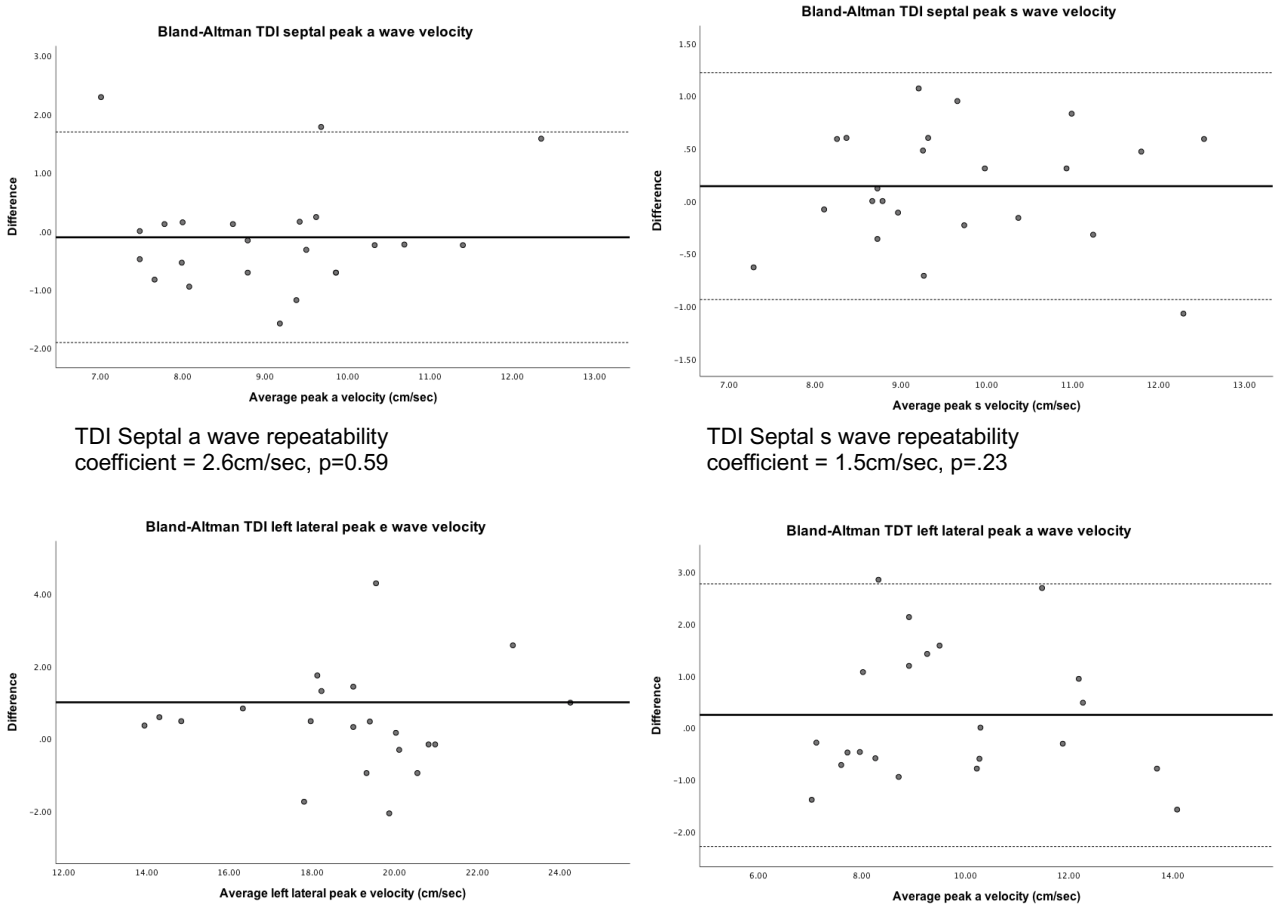


TDI Septal e wave repeatability coefficient = 3.3cm/sec, p=0.36

Figure 29. Bland-Altman intra-observer reproducibility of DT, IVRT, MV A wave duration and septal *e* wave measurements

Solid lines represent no difference between observations; dotted lines on the plot represent mean difference and 95% agreement lines.

DT: deceleration time, IVRT: isovolumetric relaxation time, MV: mitral valve, TDI: tissue Doppler imaging.



TDI Septal a wave repeatability coefficient = 2.6cm/sec, p=0.59

TDI Septal s wave repeatability coefficient = 1.5cm/sec, p=.23

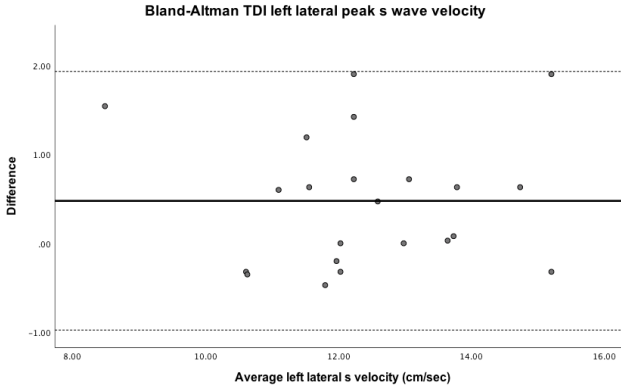
TDI Left lateral e wave repeatability coefficient =3.9cm/sec, p=0.15

TDI Left lateral a wave repeatability coefficient = 3.6cm/sec, p=0.39

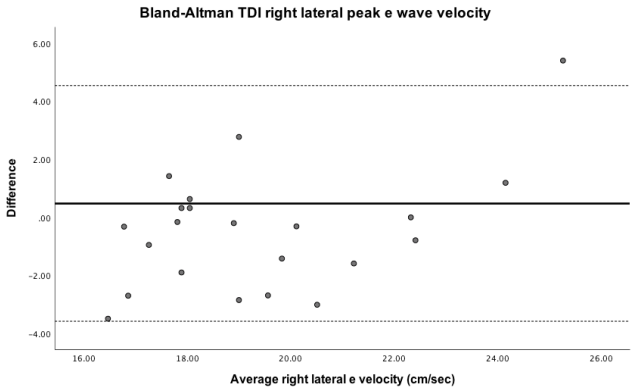
Figure 30. Bland-Altman intra-observer reproducibility of septal *a* wave, septal *s* wave, left lateral *e* wave and left lateral *a* wave measurements

Solid lines represent no difference between observations; dotted lines on the plot represent mean difference and 95% agreement lines.

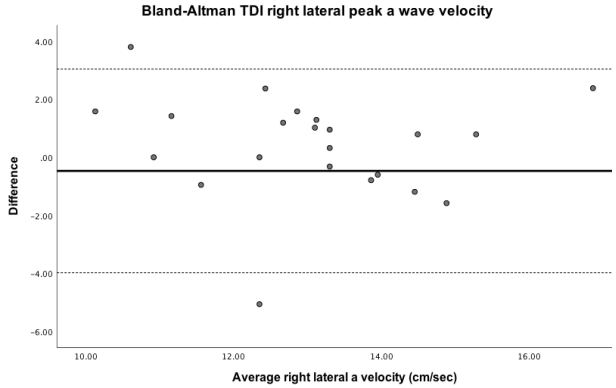
TDI: tissue Doppler imaging.



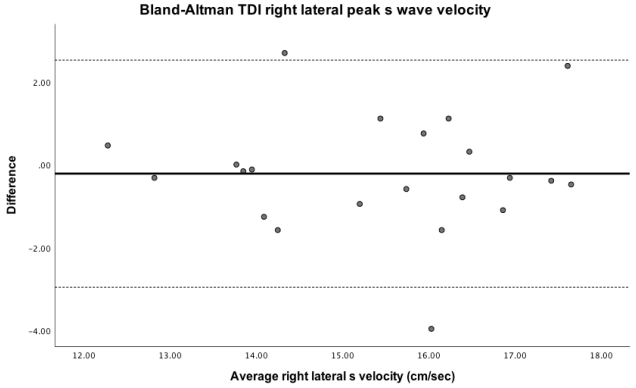
TDI Left lateral s wave repeatability coefficient =2.1cm/sec, p=0.007



TDI Right lateral e wave repeatability coefficient =5.7cm/sec, p=0.30



TDI Right lateral a wave repeatability coefficient = 5.0cm/sec, p=0.30



TDI Right lateral s wave repeatability coefficient = 3.9cm/sec, p=0.47

Figure 31. Bland-Altman intra-observer reproducibility of left lateral *s* wave, right lateral *e* wave, right lateral *a* wave and right lateral *s* wave measurements

Solid lines represent no difference between observations; dotted lines on the plot represent mean difference and 95% agreement lines.

TDI: tissue Doppler imaging.

Table 11. Reproducibility of echocardiography measurements

Parameter	Pearson's R	P value	Spearman's R	P value
LVM	0.85	<0.001	0.89	<0.001
FS	0.72	<0.001	0.73	<0.001
EF	0.73	<0.001	0.72	<0.001
LVOT	0.91	<0.001	0.75	<0.001
VTI	0.79	<0.001	0.80	<0.001
HR	0.97	<0.001	0.97	<0.001
MV E	0.93	<0.001	0.91	<0.001
MV A	0.75	<0.001	0.72	<0.001
DT	0.63	0.001	0.61	0.002
IVRT	0.75	<0.001	0.71	<0.001
Adur	0.76	<0.001	0.78	<0.001
Septal e	0.82	<0.001	0.79	<0.001
Septal a	0.79	<0.001	0.83	<0.001
Septal s	0.92	<0.001	0.92	<0.001
Left lateral e	0.86	<0.001	0.76	<0.001
Left lateral a	0.83	<0.001	0.79	<0.001
Left lateral s	0.90	<0.001	0.87	<0.001
Right lateral e	0.73	<0.001	0.63	0.002
Right lateral a	0.54	0.01	0.63	0.002
Right lateral s	0.66	0.001	0.67	0.001

LVM: left ventricular mass, FS: fractional shortening, EF: ejection fraction, LVOT: left ventricular outflow tract, VTI: velocity time integral, HR: heart rate, MV E: mitral valve inflow peak E wave velocity, MV A: mitral valve inflow peak A wave velocity, DT: deceleration time of E wave, IVRT: isovolumetric relaxation time, Adur: A wave duration, Septal e: septal peak e wave velocity, Septal a: septal peak a wave velocity, Septal s: septal peak s wave velocity, Left lateral e: left lateral peak e wave velocity, Left lateral a: left lateral peak a' wave velocity, Left lateral s: left lateral peak s wave velocity, Right lateral e: right lateral peak e wave velocity, Right lateral a: right lateral peak a wave velocity, Right lateral s: right lateral peak s wave velocity.

Chapter 4

Study 1 - Cardiovascular function in women characterised as being either low or high-risk for pre-eclampsia

4.1 Introduction

Early-onset pre-eclampsia is thought to occur secondary to poor placental implantation where maladaptation of the spiral arteries results in placental hypoxia that in turn leads to the production of various angiogenic tissue mediators that affect the maternal endothelium (22, 156). The endothelium becomes dysfunctional, leading to peripheral vasoconstriction and organ failure – features that are the basis of the clinical symptoms and signs of this disease (476).

Although the placenta is still a significant contributor to disease for women who develop late-onset pre-eclampsia, it is likely that there are some differences in the aetiologies underlying these two phenotypes. It has been suggested that late-onset pre-eclampsia is driven by maternal cardiovascular dysfunction causing vasoconstriction that in turn impacts on the placenta. The placenta then releases angiogenic factors that have further effect on the maternal endothelium. It has also been proposed that a failure of the maternal cardiovascular system to adapt to pregnancy may well be the primary mechanism preceding placental dysfunction (46).

The most effective contemporary screening process for early-onset pre-eclampsia involves assessment of maternal characteristics, biochemical markers (PAPP-A and PlGF), uterine artery Doppler PI and maternal mean arterial blood pressure at 11-13+6 weeks' gestation. Screening processes were discussed in more detail in *Chapter 1, section 1.12 Screening for pre-eclampsia*, but this test is most effective for early-onset disease predicting approximately 90% of cases (260, 477). When this is combined with preventative therapeutic intervention – (prescribing aspirin 150mg nocte) – rates of pre-eclampsia before 32 and 37 weeks' gestation are reduced 89% and 62% respectively (260, 478).

In contrast, this screening program only identifies 43% of term pre-eclamptics (478) and aspirin seems to be ineffective in this group, with there being only a modest 5% (not significant) reduction in prevalence of disease (242). Given the likely differences in aetiology of early and late-onset disease, involving other markers of maternal cardiac and endothelial function may improve screening efficacy, particularly for late-onset disease, and allow better targeting of therapeutic intervention.

The aims of this study were;

1. To evaluate maternal characteristics, pregnancy and birth outcomes in women deemed either low-risk or high-risk following screening for early-onset pre-eclampsia using a first trimester screening algorithm.

2. To compare and contrast maternal cardiac function and structure at 14 weeks of pregnancy in cohorts of women screened either low-risk or high-risk for early-onset pre-eclampsia using this test - prior to commencement of aspirin.

4.2 Methods

This was a prospective study of maternal cardiac structure and function in singleton pregnancies involving two cohorts of women; women who were high-risk for developing early-onset pre-eclampsia and women who were low-risk for developing the disease based on the FMF screening algorithm (195). Women were defined as high-risk when their risk was 2% or greater, or low-risk when their risk was less than 2%. Forty-eight women who had screened as low-risk for ePE and 105 women screened as high-risk for ePE were recruited into the study. The study excluded women with pre-existing cardiac disease or hypertension, multiple pregnancy, or a pregnancy with a major fetal anomaly. Women recruited into the study underwent an echocardiogram, blood pressure assessment and weight and height measurements at 14 weeks' gestation. Specific echocardiography and blood pressure protocols are detailed in *Chapter 3: Methodology, Sections 3.3 and 3.5,* while Figure 32 outlines the screening methodology.

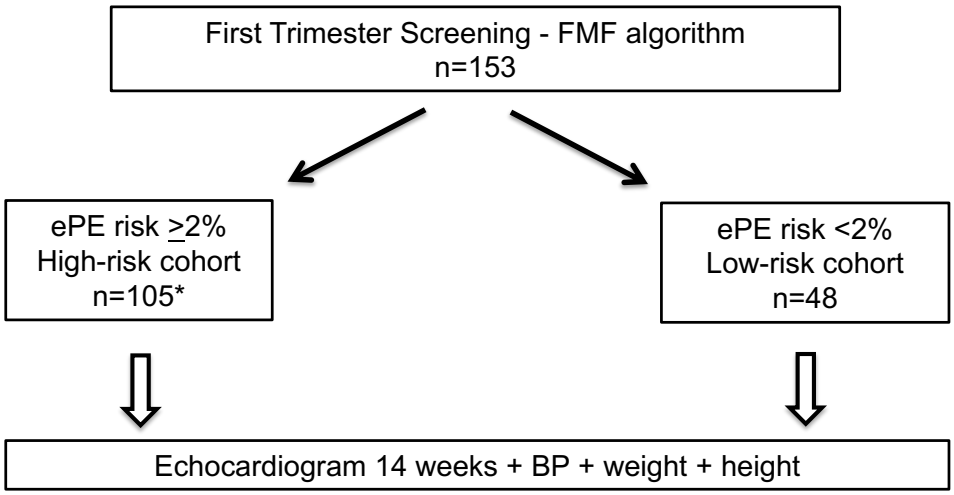


Figure 32. Methodology outline study 1

Women stratified as high-risk and low-risk based on first trimester screening for early-onset pre-eclampsia

BP: Blood pressure, ePE: Early-onset pre-eclampsia, FMF: Fetal Medicine Foundation.

*2 essential hypertension cases excluded.

A normal pregnancy outcome was defined as a normotensive pregnancy with term delivery (≥37 weeks' gestation) and a normal fetal birthweight (≥10th centile for gestational age) according to gender specific growth charts constructed from the local population (461). An abnormal outcome was the presence of gestational hypertension, pre-eclampsia, eclampsia, small for gestational age fetus (<10th centile) or preterm birth (<37 weeks' gestation).

4.2.1 Statistical analysis

Data was analysed using SPSS software version 25 (IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp). Normality of distribution was assessed using the Kolmogorov-Smirnov test as well as visual assessment of box-plots and histograms. Non-normally distributed data were analysed using the Mann Whitney U test to assess for differences between the two groups. These

data were displayed as medians with interquartile ranges or percentages as appropriate. Chi-square and Fisher exact tests were used to evaluate the categorical variables, ethnicity, parity and specific adverse outcomes. A Chi-square test was also used to assess the association of risk and subsequent pregnancy outcome. A two-tailed value of $p<0.05$ was considered statistically significant for all tests.

4.3 Results

Of the 48 women who screened low-risk for ePE, 24 were nulliparous and 24 were multiparous. In this low-risk group, 40 women (83.3%) subsequently had a normal pregnancy outcome. Eight women (16.7%) had an adverse pregnancy outcome due to the development of late pre-eclampsia (n = 2), preterm delivery (n = 3; 2 PPROM and one iatrogenic delivery for suspected FGR), fetal demise (n = 1; 15 weeks' gestation), or low infant birthweight (n = 2).

Of the 103 women who screened high-risk for early-onset pre-eclampsia, there were 65 nulliparous and 38 multiparous women. In this high-risk group, 62 high-risk women (60%) subsequently had a normal pregnancy outcome, and 41 women (40%) had an adverse pregnancy outcome. Within the adverse outcome subgroup there were no cases of early-onset pre-eclampsia. In those with an adverse pregnancy outcome; eight developed late-onset pre-eclampsia, eight developed gestational hypertension, 20 had an infant with a low birthweight, five experienced a preterm delivery and two women developed hypertension before 20 weeks' gestation. Two women who developed essential hypertension were excluded as the study was designed to only include asymptomatic women. As expected, there were more women with an adverse pregnancy outcome in the high-risk group compared to women in the low-risk group ($\chi^2 = 22.2$, $p < 0.001$).

The two groups did not differ at baseline in terms of maternal age, weight, body mass index and body surface area, although the low-risk women were slightly taller than the high-risk women measuring, 1.67m (1.62m - 1.69m) versus 1.64m (1.59m - 1.67m), $p = 0.05$. In terms of parity, 50% of women screened low-risk were nulliparous compared to 63% in the high-risk group. There was a significant

difference between the low-risk and high-risk cohorts in regard to ethnicity, (χ^2 = 10.6, p = 0.001) reflecting the known association of non-Caucasian women having a higher risk of pre-eclampsia. The low-risk cohort were primarily Caucasian women (83%) with the remaining 17% south-east Asian. In the high-risk cohort, 41% of women were south-east Asian and 56% were Caucasian. The maternal characteristics, pregnancy and birth outcomes for women screened low-risk and high-risk are summarised in Tables 12 and 13.

Table 12. Maternal characteristics of women stratified as low-risk and high-risk for early-onset pre-eclampsia

	Low-risk	High-risk	p-value
	(n=48)	(n=103)	
Maternal age (years)	33 (30 - 35)	32 (28.5 - 35)	0.13
Height (cm)	167 (162.1 - 169.9)	164 (159.3 - 167.3)	**0.03**
Weight (kg)	63.9 (58.5 - 76.4)	65.4 (58.5 - 73.0)	0.75
BSA at 14 weeks	1.74 (1.63 - 1.86)	1.70 (1.63 - 1.82)	0.32
BMI at 14 weeks	23.7 (21.2 - 27.2)	23.63 (21.4 - 27.6)	0.61
Ethnicity			**0.001**
Caucasian	40 (83.3%)	58 (56.3%)	
East Asian	6 (12.5%)	23 (22.3%)	
South Asian	2 (4.2%)	19 (18.4%)	
Black	0	2 (1.9%)	
Aboriginal	0	1 (1.0%)	
Nulliparous	24 (50%)	65 (63.1%)	**< 0.001**

All data values are median with interquartile range or n (%)

BSA: body surface area (weight$^{0.425}$ x height$^{0.725}$) x 0.007184 (470), BMI: body mass index (kg/m^2)

Table 13. Pregnancy and birth outcomes of women stratified as low-risk and high-risk for early-onset pre-eclampsia

	Low-risk	High-risk	p-value
	(n=48)	(n=103)	
Normal outcome	40 (83.3%)	62 (60.2%)	**0.03**
Adverse outcome	8 (16.7%)	41 (39.8%)	**<0.001**
Pre-eclampsia	2 (4.2%)	8 (7.6%)	
Gestational Hypertension	0	8 (7.6%)	
Small for Gestational Age	2 (4.2%)	20 (19%)	
Preterm birth	3 (6.3%)	5 (4.8%)	
Fetal demise	1 (2.1%)	0	
Gestation at delivery (weeks)	39.9 (38.9 - 40.9)	39.1 (37.9 - 40.4)	**0.03**
Birthweight (grams)	3630 (3300 - 3892)	3135 (2804 - 3467)	**<0.001**
Birthweight (percentile)	68 (43 - 82)	38 (14.5 - 64)	**<0.001**

All data values are median with interquartile range or n (%)

The infants born to high-risk women had a significantly lower birthweight (3135 gm [2804 gm - 3467gm] versus 3630 gm [3300 gm - 3892 gm]; p = <0.0001) and birthweight centile (38 % [14.5 % - 64 %] versus 68 % [43 % - 82 %]; p = 0.001), compared to infants born to low-risk women. There was also a significant difference in the gestational age of delivery between the groups, with gestational age at delivery slightly earlier in the high-risk group (39.1 weeks [37.9 weeks - 40.4 weeks] versus 39.9 weeks [38.9 weeks - 40.9 weeks]; p = 0.03) (Table 13).

There were some significant differences in cardiovascular function between women who screened low-risk for pre-eclampsia, compared to women who screened high-risk. Although there was a statistically significant three day difference in gestational age at the time of the echocardiogram between these groups, realistically this is too small a time frame to expect to see differences in cardiovascular measures. The mean arterial pressure was significantly lower in the low-risk group (85 mmHg [79 mmHg - 89 mmHg] versus 90 mmHg [86 mmHg - 97 mmHg]; p < 0.001) contributing to the significantly higher total peripheral resistance in the high-risk women (1240 Dynes.s^{-1}cm^{-5} [1067 Dynes.s^{-1}cm^{-5} - 1394 Dynes.s^{-1}cm^{-5}] Dynes.s^{-1}cm^{-5} versus 1396 Dynes.s^{-1}cm^{-5} [1229 Dynes.s^{-1}cm^{-5} - 1586 Dynes.s^{-1}cm^{-5}]; p < 0.001) (Table 14).

At 14 weeks' gestation, cardiac output was similar between the two groups, measuring 5.5 L/min (4.8 L/min - 6.1 L/min) and 5.2 L/min (4.6 L/min - 5.8 L/min); p = 0.13, in the low-risk and high-risk women respectively, despite a significantly lower stroke volume in the high-risk group (76.1 ml [66.4 ml - 87.5 ml] versus 68.1 [61.6 ml - 80.8 ml]; p = 0.005). The high-risk women were able to preserve their cardiac output primarily through a higher (non-significant) heart rate which counteracted the lower stroke volume. Importantly, stroke volume remained significantly lower when this measure was indexed to body surface area, while the cardiac output result was unchanged with indexation. These variables are summarised in Table 14.

There were mixed results in longitudinal systolic function with no difference seen in the tissue Doppler velocity at the left ventricular septum, while the left ventricular lateral wall and right ventricular lateral wall systolic velocities were both significantly lower in the high-risk women; LV lateral wall (11.32 cm/s [10.15 cm/s - 13.54 cm/s] versus 13.11 cm/s [11.78 cm/s -14.05 cm/s]; p = 0.006) and

RV lateral wall (15.22 cm/s [14.03 cm/s -16.47 cm/s] versus 15.99 cm/s [14.88 cm/s - 17.14 cm/s]; p = 0.02). Left ventricular mass and its indexed measure were not significantly different between the women, nor were measures of transverse left ventricular contractility including ejection fraction and fractional shortening. Cardiac structure and systolic variables are summarised in Table 14.

At 14 weeks' gestation, the mitral valve inflow and tissue Doppler indices were comparable between the women screened low-risk and high-risk for ePE, with no significant differences with the exception of right ventricular wall peak *e* velocity which was higher in the low-risk women (19.11 cm/s [17.49 cm/s - 21.91 cm/s] versus 17.77 cm/s [15.14 cm/s - 19.95 cm/s]; p = 0.002). The diastolic data are summarised in Table 15.

Table 14. 14-week haemodynamic, systolic and structural data of women stratified low-risk and high-risk for early-onset pre-eclampsia

Variable	Low-risk		High-risk		p - value
	Median	**IQR**	**Median**	**IQR**	
GA at 14-week scan	100.5	94.3 - 104.8	102	97 - 107	**0.04**
LVOT (cm)	1.99	1.91 - 2.11	1.95	1.86 - 2.06	**0.04**
VTI (cm/s)	24.3	22.2 - 26.0	23.2	21.5 - 25.6	0.14
CO (L/min)	5.47	4.83 - 6.12	5.24	4.55 - 5.80	0.13
CI ($L/min/m^2$)	3.20	2.86 - 3.51	3.02	2.68 - 3.40	0.09
SV (ml)	76.1	66.4 - 87.5	68.6	61.6 - 80.8	**0.005**
SVI (ml/m^2)	43.5	39.8 - 49.5	40.1	36.0 - 46.3	**0.008**
HR (beats/min)	72.3	67.3 - 78.4	75.8	67.0 - 81.7	0.12
MAP (mmHg)	84.7	78.9 - 88.8	90.2	85.6 - 97.3	**<0.001**
TPR ($Dynes.s^{-1}cm^{-5}$)	1240	1067 - 1394	1396	1229 - 1586	**<0.001**
TPRI ($Dynes.s^{-1}cm^{-5}m^2$)	2104	1906 - 2385	2378	2143 - 2724	**<0.001**
EF (Simpson)	68.2	65.9 - 70.0	66.6	64.7 - 69.2	0.05
EF (M-mode)	67.4	64.6 - 70.0	66.9	63.7 - 68.8	0.36
FS (M-mode)	37.5	35.2 - 39.7	37.0	34.5 - 38.6	0.29
LVM (g)	122.7	103.3 - 146.8	121.4	105.1 - 135.1	0.38
LVMI (g/m^2)	71.2	63.0 - 78.6	70.3	63.6 - 78.0	0.59
TDI s wave Septal (cm/s)	9.70	9.23 - 10.47	9.56	8.91 - 10.86	0.60
TDI s wave LVLW (cm/s)	13.11	11.78 - 14.05	11.32	10.15 - 13.54	**0.006**
TDI s wave RVLW (cm/s)	15.99	14.88 - 17.14	15.22	14.03 - 16.47	**0.02**

Data are expressed as median and interquartile range (IQR). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, EF: ejection fraction, FS: fractional shortening, HR: heart rate, LVLW: left ventricular lateral wall, LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), LVOT: left ventricular outflow tract, MAP: mean arterial pressure: RVLW: right ventricular lateral wall, SV: stroke volume, SVI: stroke volume index (SV/BSA), TDI: tissue Doppler imaging, TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA), VTI: velocity time integral.

Table 15. 14-week diastolic data of women stratified as low-risk and high-risk for early-onset pre-eclampsia

Variable	Low-risk		High-risk		p - value
	Median	**IQR**	**Median**	**IQR**	
E velocity (cm/s)	86.6	78.9 - 97.7	85.9	75.4 - 95.8	0.69
A velocity (cm/s)	49.7	43.2 - 58.8	50.1	44.7 - 57.5	0.93
E/A ratio	1.70	1.40 - 2.04	1.66	1.45 - 1.95	0.80
DT (msec)	152	142 - 165	146	134 -165	0.14
IVRT (msec)	90	81 - 99	89.5	84 - 102	0.74
A wave duration (msec)	115	106 - 126	117	108 - 130	0.27
TDI e septal (cm/s)	15.79	12.97 - 17.38	14.70	12.96 - 16.57	0.17
TDI a septal (cm/s)	7.62	6.87 - 8.77	7.95	7.08 - 8.97	0.27
TDI e/a septal ratio	1.93	1.60 - 2.44	1.80	1.49 - 2.19	0.11
TDI e LVLW (cm/s)	18.36	16.56 - 20.94	18.23	16.15 - 20.13	0.42
TDI a LVLW (cm/s)	8.33	7.14 - 9.35	8.33	7.33 - 9.49	0.92
TDI e/a LVLW ratio	2.24	1.94 - 2.60	2.17	1.86 - 2.61	0.63
E/e septal	5.68	4.90 - 6.52	5.87	5.06 - 6.67	0.43
E/e LVLW (cm/s)	4.65	4.28 - 5.26	4.63	4.06 - 5.59	0.82
TDI e RVLW (cm/s)	19.11	17.49 - 21.91	17.77	15.14 - 19.95	**0.002**
TDI a RVLW (cm/s)	12.78	11.11 - 14.20	12.16	10.39 - 14.43	0.87
TDI e/a RVLW (cm/s)	1.53	1.36 - 1.77	1.46	1.22 - 1.70	0.13

Data are expressed as median and interquartile range (IQR). DT: deceleration time, IVRT: isovolumetric relaxation time, LVLW: left ventricular lateral wall, RVLW: right ventricular lateral wall, TDI: tissue Doppler Imaging.

4.4 Discussion

This prospective cohort study measured cardiovascular structure and function at 14 weeks' gestation in women characterised as low-risk and high-risk for ePE using the FMF screening algorithm. Of the one hundred and fifty-three women included, one hundred and five were screened high-risk and forty-eight were screened low-risk. Two women in the high-risk group were excluded due to essential hypertension. Interestingly, the impact of prescribing aspirin to high-risk women was evident in so far as there were no cases of early-onset pre-eclampsia. A high-risk screening result was associated with adverse outcomes including the development of a hypertensive disorder or birth of a small for gestational age infant. These high-risk women also had significantly smaller infants. There was a greater representation of Asian ethnicity amongst the high-risk women however, the women in both groups were similar in body size. From a cardiovascular perspective, high-risk women had a significantly different haemodynamic profile with lower stroke volume, higher mean arterial pressure and greater total peripheral resistance at 14 weeks' gestation.

The women in the high-risk group displayed well known risk factors for pre-eclampsia, including South Asian ethnicity and nulliparity (176, 177, 197, 218). Our study showed there was a higher prevalence of south-east Asian and nulliparous women in the high-risk cohort. There was no difference in weight, body mass index or body surface area at 14 weeks' gestation to suggest these women were physically that dissimilar, although women with a normal outcome were slightly taller. Late-onset pre-eclampsia has previously been associated with an increased BMI (177, 203, 204) however, in our study there were insufficient late-onset pre-eclampsia outcomes to strongly influence the median body measurements.

In terms of birth outcomes, high-risk women were associated with an adverse pregnancy complication compared to low-risk women. The association was evident for the development of a hypertensive disorder (17% versus 4%) and SGA births (20% versus 4%). This is not unexpected given pre-eclampsia and SGA share similar causes associated with placental impairment, with increased uterine artery resistance a common finding (275, 276, 278, 281, 479, 480).

The FMF screening algorithm has previously demonstrated its effectiveness at predicting early-onset pre-eclampsia but performed less well at predicting late-onset pre-eclampsia (195, 198, 259). In this study, the overwhelming majority of women screened low-risk for ePE had a normal pregnancy outcome (83%), indicating the FMF algorithm was quite effective at identifying this cohort of women. In terms of the high-risk cohort, 60% of high-risk women had a normal outcome, indicating the algorithm works less well in determining who is truly high-risk.

The FMF screening model was not specifically designed to identify women high-risk for developing SGA infants, however similar predictive models aimed at identifying women high-risk for growth restriction and small for gestational age fetuses have been developed (311, 481). Using the same investigative tools as the ePE screening test (311), Poon *et al* (2013) (311) reported that 56% and 44% of preterm SGA and term SGA pregnancies respectively, were identified. Unfortunately, there are no external reported studies validating this algorithm. Another group developed a screening algorithm for identifying women at risk of fetal growth restriction (FGR), however risk was characterised in terms of early-onset and late-onset FGR using 34 weeks' gestation as the cut-off. The algorithm used different biochemical markers to Poon *et al* (2010) (201), namely sFLT1 rather than PAPP-A, with detection rates of 86 % and 66% for early and late FGR respectively. This algorithm is also yet to undergo external validation, highlighting a need for further research in this area. In regard to preterm births, the rate was similar between women screened high-risk and low-risk.

The high-risk women delivered significantly smaller infants (68^{th} centile versus 38^{th} centile), suggesting placental function in women with a subsequent pregnancy complication is not comparative to women screened low-risk. There is evidence through higher resistance uterine artery Doppler that this is likely (482), however the placenta is only one part of the maternal cardiovascular system. The response of the cardiovascular system to pregnancy may in fact play a key role in the development of the placenta and whether this occurs normally, or alternatively, the demands of placentation may lead to inadequate adaptation of the cardiovascular system (46). These mechanisms are complex and not well understood with further investigation of the cardiovascular system and its adaptation in adverse pregnancy complications needed. The significant

difference in birth weight and birth weight centile found in our study between the low-risk and high-risk women may also be impacted by the proportion of parous women in each group. A first trimester study by Turan *et al* (2008) (483) found parous women had higher CO/CI compared to nulliparous women (483). In our study, there were 12% more nulliparous women in the high-risk cohort.

The most salient findings from this study are that at 14 weeks' gestation the stroke volume and stroke volume index are significantly lower in women screened high-risk for ePE compared to women screened low-risk for ePE. Cardiac output and cardiac index were slightly lower but not significantly different at this gestation due to a compensatory higher heart rate. The combined effect of the elevated MAP and lower CO/CI in high-risk women resulted in a significantly higher TPR/TPRI. A previous study at 11-14 weeks' gestation showed elevated TPR/TPRI associated with ePE prior to the onset of signs and symptoms, while these values were unchanged in lPE when compared to normotensive women (42). Our study shows that both TRP/TRPI are elevated in high-risk women, however this was a cohort with mixed pregnancy complications, so further work is needed to determine specifically how women with different adverse outcomes (pre-eclampsia, gestational hypertension, SGA and preterm birth) are affected. The only other study of cardiovascular function at this early gestation in women with subsequent pregnancy complications was by De Paco *et al* (2008) (43), however they did not assess TPR/TPRI. The group did find CO/CI was increased in women who developed pre-eclampsia or gestational hypertension and decreased in pregnancies complicated by SGA (43), which was in keeping with the Khaw study (42). Khaw *et al* (2008) (42) also reported higher SV/SVI for hypertensive disorders and lower values in pregnancies complicated by SGA. Although we cannot directly compare these findings to our study, our CO/CI values were lower in high-risk pregnancies. Again, these women need to be subdivided into specific adverse pregnancy outcomes to further assess these differences. Importantly, cardiovascular differences were identified prior to the commencement of aspirin.

A similar study assessing cardiac maternal function in women with a subsequent adverse pregnancy outcome, identified women as high-risk based on abnormal uterine artery Doppler velocimetry in the second trimester. This group showed 42% of women with an abnormal second trimester uterine artery Doppler had a

subsequent adverse outcome, which was in keeping with our findings. However, the study was small involving 21 women and there were no cases of pre-eclampsia, only SGA infants and gestational hypertension (482). The group concluded that abnormal cardiac function, primarily diastolic parameters, were associated with pregnancy complications and that the high resistance uterine artery flow reflecting abnormal placentation was the likely cause of the maladaptation in the cardiovascular system. Our study did not demonstrate any diastolic differences in cardiac function; however, it was undertaken at 14 weeks' gestation compared to their study at 24 weeks' gestation.

Another study that assessed cardiac function in women with abnormal uterine artery Doppler found an association of systolic dysfunction and poorer diastolic function at 11-14 weeks' gestation with higher resistance uterine artery flow (484). These cardiovascular changes were also associated with SGA infants, leading the authors to suggest a relationship exists between uterine artery flow and cardiac adaptation in pregnancy. Again, this was a small study involving 36 women, with no cases of pre-eclampsia or hypertension. A few of the cardiovascular variables assessed in this study were the same as ours, although a number of measures were different. In comparison to our results, the LV ejection fraction was similar, while LVMI and measures of diastolic function acquired through tissue Doppler imaging and conventional methods were different. Overall, the most significant finding, despite measures being within normal ranges, was the association of decline in diastolic function with higher uterine artery resistance flow at 14 weeks' gestation. The gestational stage of our study was identical, however women screened high-risk based on an algorithm in which uterine artery Doppler has a significant contribution to the overall risk (195), did not show any change in diastolic function.

A limitation of this study was that the FMF algorithm was designed to screen women for pre-eclampsia, and not other adverse pregnancy outcomes such as small for gestational age fetuses and preterm birth. Assessing the efficacy of the screening algorithm for these outcomes was not a primary measure in this study. Another limitation of this study was that maternal characteristics, birth outcomes and cardiovascular parameters were compared between cohorts of women based on their screening result. An evaluation based on pregnancy outcome will

add further insight into how the maternal cardiovascular system adapts in the presence of different pathologies.

The results of this study demonstrate the effectiveness of the screening algorithm in identifying women at risk of an adverse outcome in their pregnancy. A high proportion of the women screened high-risk will fortunately have a normal pregnancy outcome, however screening may lead to increased anxiety levels during pregnancy and the need for greater maternal and fetal surveillance in these women. The FMF first trimester screening outcome is primarily a test of placental function and therefore is not designed to consider other possible factors that may contribute to an adverse pregnancy outcome such as maternal haemodynamics. Differences in cardiovascular function between low-risk and high-risk women are evident at 14 weeks' gestation prior to the commencement of prophylactic aspirin. Further investigation is needed to determine whether specific adverse outcomes such as pre-eclampsia and SGA are associated with certain cardiovascular differences. This could then open the possibility of including cardiovascular measures such as TPR/TPRI or SV/SVI into the screening algorithm which may improve the predictive value of the screening test and reduce the false positive rate. By determining those who are truly high-risk for the development of pre-eclampsia or other pregnancy complications; maternal anxiety and the number of hospital visits and associated costs may be reduced.

Chapter 5

Study 2 - Assessment of cardiovascular function in high-risk women with normal and adverse pregnancy outcomes at 14 weeks' gestation

5.1 Introduction

The identification of women who are high-risk for pre-eclampsia early in pregnancy provides an opportunity for prophylactic therapeutic intervention aiming to reduce the prevalence of disease (30, 31, 33, 201, 242, 477, 485). It also facilitates a program of well managed antenatal surveillance and allows appropriately timed interventions for improved pregnancy outcomes. Potential screening strategies have been discussed in detail previously in *Chapter 1, Section 1.12 Screening for pre-eclampsia*. The model used within the Fetal Medicine Unit at the Royal Prince Alfred Hospital is the algorithm developed by the Fetal Medicine Foundation (FMF) (201) and has been validated for the local population (198). This model had a 92% detection rate for a 10% false positive rate for ePE in the local validation study (198), but performed poorly, with a detection rate of 36% for pre-eclampsia occurring >37 weeks' gestation.

The poor performance of the FMF algorithm with respect to late-onset pre-eclampsia may be due to the fact that measures of maternal cardiovascular function are poorly represented in the risk algorithm. There is good evidence, from previous studies, that women who develop late-onset PE have altered cardiovascular function preceding the onset of disease (37, 39-45, 48-50, 58, 59, 436). The inclusion of a direct marker of cardiovascular function, such as measurement of cardiac output or total peripheral resistance, may help to improve the screening algorithm for late-onset PE.

The aim of this study was to evaluate cardiovascular parameters measured using transthoracic echocardiography at 14 weeks' gestation, in women stratified as high-risk for the development of early-onset pre-eclampsia with either a subsequent normal or adverse pregnancy outcome. This echocardiogram assessment was made prior to starting prophylactic low dose aspirin therapy.

5.2 Methods

This was a prospective study of maternal cardiovascular structure and function in singleton pregnancies involving women who had screened high-risk for early-onset pre-eclampsia based on the FMF screening algorithm. Women were

defined as high-risk when their risk was 2% or greater. 105 women who had screened high-risk for ePE were included in the study. Women were excluded if they had pre-existing cardiac disease, chronic hypertension, a multiple pregnancy or a fetus with a major anomaly. A transthoracic echocardiogram was performed at 14 weeks' gestation, with blood pressure, height and weight measured at the time of the visit.

The echocardiographic assessment and blood pressure measures that were recorded are described in detail in *Chapter 3, Methodology, sections 3.3 and 3.5.* Systolic and diastolic measures were included, with stroke volume, cardiac output, left ventricular mass and total peripheral resistance indexed to BSA as per current ASE and EACVI guidelines.

Women who were recruited to the study on the basis of their high-risk for pre-eclampsia were later divided into two groups depending on their pregnancy outcome. One group included women with a normal pregnancy outcome defined as a normotensive pregnancy with term delivery (>37 weeks' gestation) and a normal birthweight (>10th centile for gestational age) according to gender specific growth charts constructed from the local population (461). The other group included women with an adverse pregnancy outcome, which was defined by the presence of gestational hypertension, pre-eclampsia, eclampsia, small for gestational age fetus (<10th centile) or preterm birth (<37 weeks' gestation).

5.2.1 Statistical analysis

Data was analysed using SPSS version 25 (IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp). Normality of distribution was assessed using the Kolmogorov-Smirnov test as well as visual assessment of box-plots and histograms. Non-normally distributed data were analysed using the Mann Whitney U test to assess for differences between the two groups. Measures of cardiovascular structure and function in both systole and diastole were evaluated, as well as an assessment of maternal characteristics and birth outcomes in the normal and adverse cohorts. These data were displayed as median with interquartile range or percentage as appropriate. A two-tailed value of $p<0.05$ was considered statistically significant.

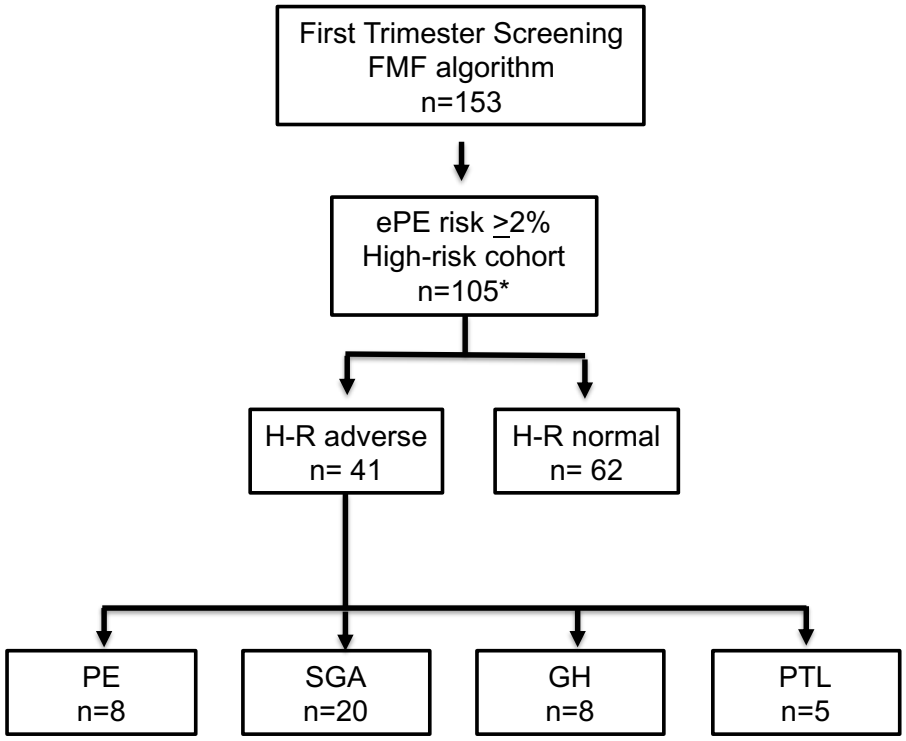


Figure 33. Methodology outline study 2

BP: blood pressure, ePE: early-onset pre-eclampsia, FMF: Fetal Medicine Foundation

* 2 essential hypertension cases excluded

5.3 Results

Of the 105 women who screened as high-risk for early pre-eclampsia, two women were excluded due to the existence of essential hypertension. These women developed hypertension prior to 20 weeks' gestation and were excluded on the basis they were symptomatic. Of the 103 women remaining, 62 had a normal outcome while 41 had an adverse outcome, including eight (19.5%) pre-eclamptic women, eight (19.5%) women with gestational hypertension, twenty (48.8%) small for gestational age infants and five (12.2%) preterm deliveries. The infants born to high-risk women with an adverse outcome were significantly smaller in birthweight (2745 gm [2415 gm – 3070 gm] versus 3330 gm [3109 gm – 3519 gm]; $p < 0.001$) and birthweight centile (9 % [4 % – 60 %] versus 44 % [32.3 % – 68.3 %]; $p < 0.001$) and were delivered 9 days earlier (38.3 weeks [36.4 weeks – 39.6 weeks] versus 39.6 weeks [38.7 weeks – 41 weeks]; $p < 0.001$) as

compared to the high-risk group with normal outcomes. Pregnancy outcomes and birth data are summarised in Table 16.

Table 16. Pregnancy and birth outcomes of women high-risk for early-onset pre-eclampsia with a subsequent normal or adverse outcome.

	High-risk Normal outcome	High-risk Adverse outcome	p-value
	n = 62	n = 41	
Risk of pre-eclampsia	7 (4 – 14)	8 (5 – 16)	0.4
Pre-eclampsia **Gestation Hypertension** **Small for Gestational Age** **Preterm birth**		8 (19.5%) 8 (19.5%) 20 (48.8%) 5 (12.2%)	
Gestation at delivery (weeks)	39.6 (38.7 – 41.0)	38.3 (36.4 – 39.6)	**<0.001**
Birthweight (grams)	3330 (3109 – 3519)	2745 (2415 – 3070)	**<0.001**
Birthweight (percentile)	44 (32 – 68)	9 (4 – 60)	**<0.001**

All data values are median with interquartile range or n (%)

Maternal weight, BMI and BSA were not significantly different between the groups of women at 14 weeks' gestation. Maternal height was significantly different, with slightly shorter women having an adverse outcome: 1.66m (1.6m - 1.69m) versus 1.63m (1.58m - 1.66m); p = 0.02. In terms of parity, 54 (87.1%) of high-risk women with a normal outcome were nulliparous compared to 31 (75.6%) of high-risk women with an adverse outcome. Approximately half the women with an adverse outcome were of South Asian and East Asian ethnicity (29.3% [12] and 19.5% [8] respectively) with the remaining 51.2% (21) Caucasian. The risk of ePE derived from the FMF screening algorithm was slightly higher in the cohort of high-risk women with an adverse outcome compared to those with a normal

outcome but this was not statistically significant. Maternal characteristics are summarised in Table 17.

The women with an adverse pregnancy outcome had a significantly lower cardiac output compared to those with a normal outcome (4.9 L/min [4.3 L/min - 5.6 L/min] versus 5.4 L/min [4.7 L/min - 6.1 L/min]; p = 0.02), a reduced stroke volume (65.1 ml [56.4 ml - 71.2 ml] versus 73.4 ml [63.0 ml - 84.4 ml]; p < 0.0001) and higher total peripheral resistance (1455 Dynes.s^{-1}cm^{-5} [1347 Dynes.s^{-1}cm^{-5} - 1640 Dynes.s^{-1}cm^{-5}] versus 1289 Dynes.s^{-1}cm^{-5} [1167 Dynes.s^{-1}cm^{-5} - 1533 Dynes.s^{-1}cm^{-5}]; p = 0.005). The indexed equivalent measures of cardiac output, stroke volume and total peripheral resistance paralleled the raw data changes and were all significantly different. The lower stroke volume in the adverse group was due to the combined effect of a significantly smaller left ventricular outflow tract (1.97 cm [1.91 cm - 2.10 cm] versus 1.91 cm [1.83 cm - 2.00 cm]; p = 0.01) and a lower velocity time integral (23.6 cm/s [21.8 cm/s - 26.6 cm/s] versus 22.7cm/s [20.1 cm/s - 25.0 cm/s]; p = 0.02). The heart rate was higher in the adverse group (78 bpm [67 bpm - 87 bpm] versus 74 bpm [67 bpm- 80 bpm]; p = 0.05), contributing to a lesser extent than SV to the overall lower CO. The mean arterial pressure did not contribute to the difference in TPR (90 mmHg [86 mmHg - 93 mmHg] versus 91 mmHg [84 mmHg - 99 mmHg]; p = 0.24), as the lower CO was the main contributing factor. Cardiovascular structure, systolic and haemodynamic data are summarised in Table 18.

Measures of systolic function, including Simpson's biplane ejection fraction, fractional shortening and s wave velocities were unchanged between the two groups, as were the left ventricular mass and left ventricular mass index. The left ventricular diastolic variables were also not significantly different between the two high-risk cohorts, with these data summarised in Table 19.

Table 17. Maternal characteristics of women high-risk for early-onset pre-eclampsia with a subsequent normal or adverse outcome.

	High-risk Normal outcome	High-risk Adverse outcome	p - value
	n = 62	n = 41	
Maternal age (years)	32 (29.0 - 35.0)	31 (27.5 - 35.0)	0.22
Height (cm)	1.66 (1.6 - 1.69)	1.63 (1.58 - 1.66)	**0.02**
Weight (kg)	64.5 (58.7 - 72.2)	65.6 (58.4 - 72.9)	0.9
BSA at 14 weeks	1.70 (1.64 - 1.84)	1.69 (1.61 - 1.79)	0.39
BMI at 14 weeks	23.3 (21.4 - 26.6)	24.6 (21.5 - 28.6)	0.37
Ethnicity			
Caucasian	37 (60.1%)	21 (51.2%)	
East Asian	15 (24.2%)	8 (19.5%)	
South Asian	7 (11.3%)	12 (29.3%)	
Black	2 (3.2%)	0	
Aboriginal	1 (1.6%)	0	
Nulliparous	54 (87.1%)	31 (75.6%)	**0.01**

All data values are median with interquartile range, or n (%). BSA: body surface area (weight$^{0.425}$ x height$^{0.725}$) x 0.007184 (Dubois and Dubois), BMI: body mass index (kg/m^2)

Table 18. 14-week haemodynamic, systolic and structural data of women high-risk for early-onset pre-eclampsia with a subsequent normal and adverse pregnancy outcome.

Variable	High-risk normal outcome		High-risk adverse outcome		p-value
	Median	IQR	Median	IQR	
GA at 14-week scan	104	97 - 107.5	100.5	96.3 - 106.8	0.13
LVOT (cm)	1.97	1.91 - 2.10	1.91	1.83 - 2.00	**0.01**
VTI (cm/s)	23.6	21.8 - 26.6	22.7	20.1 - 25.0	**0.02**
SV (ml)	73.4	63.0 - 84.4	65.1	56.4 - 71.2	**<0.001**
SVI (ml/m^2)	42.9	38.5 - 47.8	37.3	34.0 - 41.0	**<0.001**
HR (beats/min)	73.7	66.6 - 80.0	78.2	67.3 - 87.4	0.05
CO (L/min)	5.43	4.71 - 6.10	4.91	4.27 - 5.62	**0.02**
CI (L/min/m^2)	3.12	2.76 - 3.50	2.89	2.53 - 3.31	**0.04**
MAP (mmHg)	89.7	85.8 - 93.4	91.3	83.8 - 99.2	0.24
TPR (Dynes.$s^{-1}cm^{-5}$)	1289	1167 - 1533	1455	1347 - 1640	**0.005**
TPRI (Dynes.$s^{-1}cm^{-5}m^2$)	2253	2058 - 2606	2523	2275 - 2743	**0.007**
EF (Simpson)	67.4	65.0 - 69.9	66.1	64.1 - 68.4	0.09
EF (M mode)	67.0	63.7 - 69.0	66.9	64.4 - 69.1	0.91
FS (M mode)	37.2	34.6 - 38.7	36.9	34.8 - 38.6	0.86
LVM (g)	125.8	105.8 - 142.0	117.6	104.1 - 128.4	0.07
LVMI (g/m^2)	72.8	64.3 - 80.9	67.4	61.2 - 73.6	0.05
TDI s wave Septal	9.73	8.94 - 10.95	9.52	8.81 - 10.69	0.58
TDI s wave LVLW	11.62	10.15 - 13.57	11.22	10.03 - 12.83	0.39
TDI s wave RVLW	15.28	14.21 - 16.79	15.19	14.10 - 16.01	0.43

Data are expressed as median and interquartile range. BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, EF: ejection fraction, FS: fractional shortening, HR: heart rate, IQR: Interquartile range, LVLW: left ventricular lateral wall: LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), LVOT: left ventricular outflow tract, MAP: mean arterial pressure, RVLW: right ventricular lateral wall, SV: stroke volume, SVI: stroke volume index (SV/BSA), TDI: tissue Doppler imaging, TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA), VTI: velocity time integral.

Table 19. 14-week diastolic data of women high-risk for early-onset pre-eclampsia with a subsequent normal and adverse pregnancy outcome.

Variable	High-risk normal outcome		High-risk adverse outcome		p - value
	Median	IQR	Median	IQR	
E velocity (cm/s)	85.9	72.7 - 97.0	85.9	77.3 - 95.3	0.93
A velocity (cm/s)	49.1	44.4 - 54.5	52.8	43.4 - 62.7	0.23
E/A ratio	1.73	1.53 - 1.94	1.60	1.38 - 1.99	0.15
DT (msec)	148	135 - 166	144	134 - 165	0.50
IVRT (msec)	90	84 - 102	89	82 - 100	0.48
A wave duration (msec)	117	108 - 166	118	107 - 126	0.43
TDI e septal	14.52	13.23 - 16.15	14.84	12.58 - 16.98	0.89
TDI a septal	7.97	6.85 - 8.96	7.92	7.35 - 9.00	0.55
TDI e/a septal ratio	1.82	1.56 - 2.22	1.79	1.38 - 2.15	0.46
TDI e LVLW	18.84	16.28 - 21.32	17.63	15.43 - 19.38	0.07
TDI a LVLW	8.33	7.32 - 9.55	8.44	7.36 - 9.33	0.82
TDI e/a LVLW ratio	2.27	1.93 - 2.61	2.14	1.72 - 2.59	0.32
E/e septal	5.93	5.01 - 6.48	5.77	5.01 - 6.86	0.93
E/e LVLW	4.38	4.00 - 5.31	4.81	4.17 - 5.85	0.09
TDI e RVLW	17.57	15.41 - 19.13	17.93	13.98 - 20.57	0.95
TDI a RVLW	12.09	10.37 - 14.05	12.64	10.80 - 15.69	0.30
TDI e/a RVLW ratio	1.48	1.29 - 1.70	1.43	1.00 - 1.69	0.57

All data values are median with interquartile range. DT: deceleration time, IVRT: isovolumetric relaxation time, IQR: interquartile range, LVLW: left ventricular lateral wall, RVFW: right ventricular lateral wall, TDI: tissue Doppler Imaging.

5.4 Discussion

This prospective study evaluated cardiovascular structure and function at 14 weeks' gestation by transthoracic echocardiography, in women screened high-risk for early-onset PE using the FMF algorithm. Women were divided into two groups based on subsequent pregnancy outcome; women with a normal outcome, and those with an adverse outcome. The most significant finding of this study was that women destined to develop a hypertensive disorder, give birth to a small for gestational age infant or deliver preterm have a different cardiovascular profile to women with a subsequent normal pregnancy outcome. The women with an adverse outcome have a lower stroke volume and cardiac output despite a compensatory higher heart rate and the total peripheral resistance is a significantly higher.

The baseline characteristics of BMI, BSA and weight were the same between the two groups of women, with the exception of height. The women with an adverse outcome were slightly shorter. To normalise for differences in body size, indexation using body surface area was used as per ASE and EACVI guidelines (402). The impact of indexing did not change the results; stroke volume index and cardiac index were both significantly lower in women with an adverse outcome. Some groups have advocated indexing to height is more accurate than body surface area so the effects of obesity are preserved (486-489), while others suggest that indexing should be in relation to lean body mass (398). In theory, normalisation for body size is a reasonable approach, however all of these studies were based on non-pregnant populations. In terms of ethnicity, South-East Asian women made up approximately half the affected population in this study. Studies have shown ethnicity is an important risk factor for determining the likelihood of developing a hypertensive disorder, and that women of non-Caucasian ethnicity have an increased risk (177, 197, 219).

The cardiac output (5.4 L/min [4.7 L/min - 6.1 L/min]) and stroke volume (73.4 ml [63.0 ml - 84.4 ml]) for women with a subsequent normal pregnancy outcome were comparable to a number of studies that evaluated cardiac function using echocardiography at the same gestation (35, 329, 331, 358, 374, 416). One of the largest studies by Melchiorre *et al* (2016) (35) reported CO and SV at 5.7

L/min (5.1 L/min - 6.5 L/min) and 76 ml (66 ml - 87 ml) respectively, however the CI and SVI were markedly higher than our study, measuring 4.1 L/min/m^2 (3.5 L/min/m^2 - 4.6 L/min/m^2) versus 3.1L/min/m^2 (2.76 L/min/m^2 - 3.5 L/min/m^2) and 54 ml/m^2 (48 ml/m^2 - 61 ml/m^2) versus 42.9 ml/m^2 (38.5 ml/m^2- 47.8 ml/m^2). The heart rates were also comparative at 74 bpm (67 bpm- 80 bpm) versus 75 bpm (69 bpm- 82 bpm). Three other studies (42, 365, 416) reported comparative CI results to ours measuring 2.9L/min/m^2 (2.6 ml/m^2 - 3.3 ml/m^2), 3.1 L/min/m^2 and 3.0 L/min/m^2 (2.5 L/min/m^2 - 3.5 L/min/m^2) respectively, with comparative heart rates. In relation to the Melchiorre study, the same BSA indexing was applied as in our study, suggesting the population in the Melchiorre study were larger, despite excluding women with a BMI $\geq$30kg/m^2. The populations also differed in parity; our cohort involved nulliparous and multiparous women, with only nulliparous women in the Melchiorre study. Our results are in contrast to a number of studies that reported higher SV and CO values (44, 326, 328) including one study which reported CO to be 7.3 L/min in the first trimester (333).

In contrast to our findings, previous studies that have assessed cardiovascular function at 14 weeks' gestation in women who go on to develop late-onset pre-eclampsia found SV and CO were both increased (42, 43). Other groups have also demonstrated higher CO in the pre-clinical phase of the disease but at later gestations (39-41, 44, 50). Our results correlate with the study by Guy *et al* (2017) (53) which found SV and CO reduced in the preclinical phase of late-onset PE, however this was a third trimester study. The mid-gestation study by Melchiorre *et al* (2013) (36) also showed CO to be lower, but unlike our study, when indexed there was no difference between women with late-onset PE and a normal outcome. Despite the correlation of SV and CO results between the Guy study and ours, the contribution of heart rate and stroke volume to CO was different. Guy *et al* (2017) found the reduced CO was primarily due to a lower heart rate accompanied by a non-significant decrease in stroke volume in the pre-eclamptic women, while women destined to develop gestational hypertension had a decreased stroke volume. In our study, the lower CO in women with an adverse outcome was despite a higher heart rate, although this did not reach statistical significance. The heart rate and stroke volume differences between this study and ours may be attributed to different methodologies, including the gestational age at the time of the study. Our study population is high-risk, while other studies

compare to a low-risk population. Additionally, we did not differentiate between pre-eclampsia and gestational hypertension, SGA and preterm birth outcomes.

Our study also demonstrated that women destined to have a SGA infant had a lower SV and CO, including lower equivalent indexed values (SVI and CI). These findings are in keeping with a number of studies, however not all groups applied indexation (44, 437, 438, 441). The Melchiorre study also found that growth restricted fetuses have a lower CI but with a normal SVI due to a significantly higher heart rate. This result was in contrast to the study by Khaw *et al* (2008) (42), which showed women who subsequently gave birth to a SGA infants had significantly lower SV and normal heart rate compared to women with uncomplicated pregnancies; resulting in slightly lower CO and CI values that did not reach statistical significance. Importantly, this study was at 14 weeks' gestation compared to the forementioned studies which were undertaken late in the second trimester or third trimester.

In terms of total peripheral resistance, our values are similar to the Desai (329) and Valensise studies (358); 1289 Dynes.s^{-1}cm^{-5} (1167 Dynes.s^{-1}cm^{-5}- 1533 Dynes.s^{-1}cm^{-5}) versus 1214 Dynes.s^{-1}cm^{-5} (1051 Dynes.s^{-1}cm^{-5}- 1377 Dynes.s^{-1}cm^{-5}) and 1188 Dynes.s^{-1}cm^{-5} (989 Dynes.s^{-1}cm^{-5}- 1387 Dynes.s^{-1}cm^{-5}) respectively. Compared to a number of studies (35, 326, 331, 365), our TPR and TPRI results were relatively higher including the Melchiorre study (TPR; 1289 Dynes.s^{-1}cm^{-5} [1167 Dynes.s^{-1}cm^{-5}- 1533 Dynes.s^{-1}cm^{-5}] versus 1059 Dynes.s^{-1}cm^{-5} [936 Dynes.s^{-1}cm^{-5} - 1234 Dynes.s^{-1}cm^{-5}] and TPRI; 2253 Dynes.s^{-1}cm^{-5}m^2 [2058 Dynes.s^{-1}cm^{-5}m^2 - 2606 Dynes.s^{-1}cm^{-5}m^2] versus 1515 Dynes.s^{-1}cm^{-5}m^2 [1327 Dynes.s^{-1}cm^{-5}m^2 - 1768 Dynes.s^{-1}cm^{-5}m^2]). This difference is most likely due to our high-risk population having a higher MAP (89.7mmHg [85.8 mmHg - 93.4 mmHg] versus 77 mmHg [70 mmHg - 83 mmHg]). A number of studies also reported lower MAP and TPR values at the same gestation, but again the populations were not high-risk in these studies (326, 331, 334, 365).

TPR at 14 weeks' gestation was significantly increased in high-risk women who subsequently developed late-onset PE or delivered a SGA infant. This finding contradicts a number of studies that reflected the high CO / low TRP state in the preclinical phase of late-onset PE (39-42, 50), although only one study evaluated TPR at 14 weeks' gestation (42). Our results are in keeping with the study by Guy

et al (2017) (53) which reported increased TPR prior to the development of late-onset PE, however this was in the third trimester before clinical onset of disease. In regard to women who give birth to SGA infants, the study by Khaw at 14 weeks' gestation found TPR was increased, in keeping with our findings. This is also supported by the Bamfo study (437) which also found TPR increase in association with SGA pregnancies, however this was at 24 weeks' gestation.

TPR is dependent on many factors, including vascular tone and this may be compromised as early as 14 weeks in women destined to develop pre-eclampsia or a SGA infant, evidenced by increased TPR and TPRI values associated with these outcomes. Systemic vascular resistance normally decreases with a concomitant increase in arterial compliance secondary to a drop in arterial pressure. A possible pathway to the development of late-onset PE may be failure of the cardiovascular system to adequately adapt, resulting in elevated peripheral resistance and cardiac afterload. These events could be exacerbated by a hostile maternal environment resulting from underlying diseases such as diabetes and obesity or genetic susceptibility. The cardiovascular stress induced by maladaptation could impact endothelial function, leading to the onset of signs and symptoms of pre-eclampsia. Increased peripheral resistance has been shown to precede the clinical onset of disease in a study that investigated retinal microvasculature (58), while flow mediated-dilation studies also assessing vascular function prior to overt pre-eclampsia suggest dysfunction may contribute to its pathogenesis (59).

The EF, FS, LVM and LVMI values were all within normal ranges for gender specific reference charts on a non-pregnant population (402), with comparative values reported in pregnancy studies with a normal outcome (331, 334, 358, 365, 416). Geva *et al* (1997) (331) reported similar results to ours; EF: 69 % (64 % - 74 %), FS: 37 % (32 % - 42 %), LVM: 134.4 g (107.4 g - 161.4 g), LVMI: 80.6 g/m^2 (66.6 g/m^2 - 94.6 g/m^2) versus 67.4% (65.0 % - 69.9 %), 37.2% (34.6 %-38.7 %) and 125.8 g (105.8 g - 142.0 g) respectively. These values are also in keeping with Savu *et al* (2012) (334); EF: 63 % (60 % - 66 %), FS: 38 % (34 % - 42%), LVM:121 g (101 g - 140 g). We found no significant difference in the left ventricular mass between high-risk women with an adverse or normal outcome, unlike other studies that found altered LV geometry in hypertensive disorders. However, these findings in the preclinical phase have only been reported in

studies undertaken late in the second trimester or at term (36, 41) and not this early in pregnancy. In terms of s wave velocities, the Melchiorre study (36) used colour tissue Doppler, which is not comparative to pulsed-wave Doppler measures (435, 490). Our septal and lateral results are in keeping with the study by Fok *et al* (2006) (422); 9.1 cm/s (7.7 cm/s - 10.5 cm/s) versus 9.72 cm/s (8.94 cm/s - 10.95 cm/s) and 14.2 cm/s (11.8 cm/s - 16.6 cm/s) versus 11.62 cm/s (10.15 cm/s - 13.57cm/s).

The diastolic parameters of cardiac function were not significantly different between women with a subsequent normal or adverse pregnancy outcome at 14 weeks' gestation. The mitral valve inflow E and A peak velocities and E/A ratio in our study were comparative to both the Estensen *et al* (2013) (404) and Simmons *et al* (2002) (45) studies; E: 85.6 cm/s (72.7 cm/s - 97.0 cm/s) versus 0.8 m/s (0.6 m/s - 1.0 m/s) and 0.85 m/s (0.72 m/s - 0.98 m/s), A: 49.1 cm/s (44.4 cm/s - 54.5 cm/s) versus 0.50 m/s (0.40 m/s - 0.60 m/s) and 0.50 m/s (0.41 m/s - 0.59 m/s), E/A: 1.73 versus 1.6 and 1.7 respectively. Our E/A ratio was also similar to the Valensise study; 1.6 versus 1.73, despite their study measuring higher peak E and A mitral valve velocities. Both of these ratios are slightly lower compared to 1.88 reported in the Melchiorre study (35). The IVRT and DT times in our study were similar to a number of reports (35, 45, 358), while our A wave duration was slightly shorter than Valensise *et al* (2000) (358): 117 ms (108 ms - 166 ms) versus 138 ms (108 ms - 168 ms).

The septal and lateral *e/a* ratios in our study were 1.82 (1.56 - 2.22) and 2.21 (1.93 - 2.61) respectively, which are similar to the results of the Melchiorre and Fok studies (35, 422); septal *e/a*: 1.5 (1.1 - 1.9) and 1.6 (1.1 - 2.1), lateral *e/a*: 2.3 (1.5 - 3.0) and 2.0 (1.6 - 2.4) respectively, while Estensen *et al* (2013) (404) measured a mean of septal and lateral *e/a* measures (1.86 [1.44 - 2.28]). In terms of the septal and lateral E/*e* ratios our respective results of 5.93 (5.01 - 6.48) and 4.38 (4.00 - 5.31) are comparative to Melchiorre reporting an averaged septal and lateral E/*e* of 5.6 (4.3 - 6.5) and Fok reporting the lateral E/*e* of 5.9 (4.3 - 7.5). In terms of the septal E/e ratio, the Fok study reported a higher septal E/*e* ratio of 8.1 (5.9 - 10.3).

With respect to the left ventricular tissue Doppler measures, the ASE and EACVI outline four variables for identifying diastolic dysfunction with abnormal cut-off

values. This includes the annular e velocity: septal *e* < 7cm/s, lateral *e* < 10cm/s, average E/*e* ratio > 14 (420). In this study these values were well within normal reference ranges. Two other parameters recommended by the ASE and EACVI for the assessment of diastolic dysfunction are left atrial volume index and peak tricuspid regurgitation velocity > 2.8m/s, however LV diastolic function is normal if more than half of the available variables meet these cut-off values in women with normal LV EF% (420), which was the case in our study. The right ventricular diastolic tissue Doppler measures were also comparative between the two high-risk cohorts, however there are no pregnancy studies at 14 weeks' gestation to compare and contrast.

One of the strengths of this study was that the two high-risk cohorts were compared prior to the administration of low dose aspirin, so that the differences seen at 14 weeks' gestation were not due to therapeutic intervention. This is useful in terms of the potential to incorporate CO or TPR into a screening algorithm and as baseline measures for future longitudinal assessment of cardiovascular parameters prior to the clinical onset of signs and symptoms of disease. The major limitation of this study is that we did not differentiate pregnancy outcomes according to the development of late-onset pre-eclampsia, gestational hypertension or women with SGA infants.

An echocardiogram is a non-invasive, relatively quick examination to assess CO and TPR when combined with MAP measures. These cardiovascular parameters are significantly different at 14 weeks' gestation in a cohort of women screened high-risk for early-onset PE with a subsequent adverse outcome compared to those with a normal pregnancy outcome. To determine whether these markers are reliable, a longitudinal assessment of cardiovascular function parameters in normal pregnancy is essential. When normal physiological change is clearly established, pathological differences can be more readily identified. Although there are numerous studies assessing cardiovascular change in normal pregnancy, differences in methodology, equipment and measurement technique have led to a wide range of results, making it increasingly difficult to distinguish normal versus abnormal adaptation. With reliable markers, there is the potential to improve the sensitivity of the FMF screening algorithm, particularly in women destined to develop late-onset PE or a small for gestational age infant.

Chapter 6

Study 3 - Assessment of cardiovascular function in low and high-risk cohorts of women with subsequent normal pregnancy outcome from 14 - 30 weeks' gestation

6.1 Introduction

In pregnancy, modification of the cardiovascular system ensures adequate oxygen and nutrients are delivered to the meet the increased metabolic demand of the growing fetus. Significant increases in blood volume and cardiac output occur with a concomitant decrease in systemic vascular resistance to facilitate this adaptation (326-335, 350, 351, 362, 365, 367-369, 371, 399, 416, 418, 427). The magnitude and time course of change relating to stroke volume and cardiac output in normal pregnancy is inconsistently reported (367, 368) and confounded by numerous factors including maternal characteristics, study population, study design, different equipment and methodology.

Studies have shown that alterations in maternal cardiac structure and function occur in women destined to develop a hypertensive disorder and that these changes are evident prior to the clinical onset of symptoms and signs of disease (36, 42-44, 491, 492). Women with IUGR fetuses also demonstrate altered maternal cardiac structure and function (277, 440, 441). These studies suggest that IUGR and PE/GH pregnancy outcomes are associated with maternal cardiovascular maladaptation. In order to establish what constitutes pathological change, the physiological changes in normal pregnancy need to be clearly defined prior to the assessment of disease.

The aim of this study was to evaluate cardiovascular parameters measured using transthoracic echocardiography at 14, 20, 24 and 30 weeks' gestation, in women stratified as either low-risk or high-risk for the development of early-onset PE with a subsequent normal pregnancy outcome. A comparison between the two groups at each time point was also assessed.

6.2 Methods

This was a prospective study of maternal cardiovascular structure and function in singleton pregnancies involving women who had screened low-risk or high-risk for ePE based on the FMF screening algorithm. Women were defined as low-risk when their risk was less than 2%, with women defined as high-risk when their risk was 2% or greater. Forty-eight woman who had screened low-risk for ePE were

included in the study. Women were excluded if they had pre-existing cardiac disease, chronic hypertension, a multiple pregnancy or a fetus with a major anomaly. A transthoracic echocardiogram was performed at 14 weeks', 20 weeks', 24 weeks' and 30 weeks' gestation, with blood pressure and weight measured at the time of each visit. Maternal height was measured at the 14 week visit. Specific echocardiography and blood pressure protocols are detailed in *Chapter 3, Methodology, sections 3.3 and 3.5.*

A normal pregnancy outcome was defined as a normotensive pregnancy with term delivery ($\geq$37 weeks' gestation) and a normal fetal birthweight ($\geq 10^{th}$ centile for gestational age) according to gender specific growth charts constructed from the local population (461). An abnormal outcome was the presence of gestational hypertension, pre-eclampsia, eclampsia, small for gestational age fetus ($<10^{th}$ centile) or preterm birth (<37 weeks' gestation).

6.2.1 Statistical analysis

Data was analysed using Stata, version 15 (College Station, TX. StataCorp, LLC). All outcomes were continuous and approximately normally distributed. Means and standard deviations are presented for each time point by group. Comparison between groups was undertaken using linear regression models, with Generalised Estimating Equations to account for correlation between repeated measures on the same participant. For these analyses, due to the relatively small sample size, an exchangeable correlation structure was specified, which assumes that all observations within a cluster (participant) have equal covariance. However, robust variance estimation was used, which ensured valid inference even if the correlation structure was mis-specified. Estimates for the effect of time were derived from the same models as were used to compare high-risk normal / low-risk normal women at each time point. Estimates are the difference in means between each later time point and 14 weeks and are derived separately for each group. Measures of cardiovascular structure and function in both systole and diastole were evaluated, with BSA indexation applied to stroke volume, cardiac output, total peripheral resistance and left ventricular mass. Both unadjusted and adjusted analyses were performed, with parity and maternal age as covariates of the adjusted analyses. A two-tailed value of $p<0.05$ was considered statistically significant.

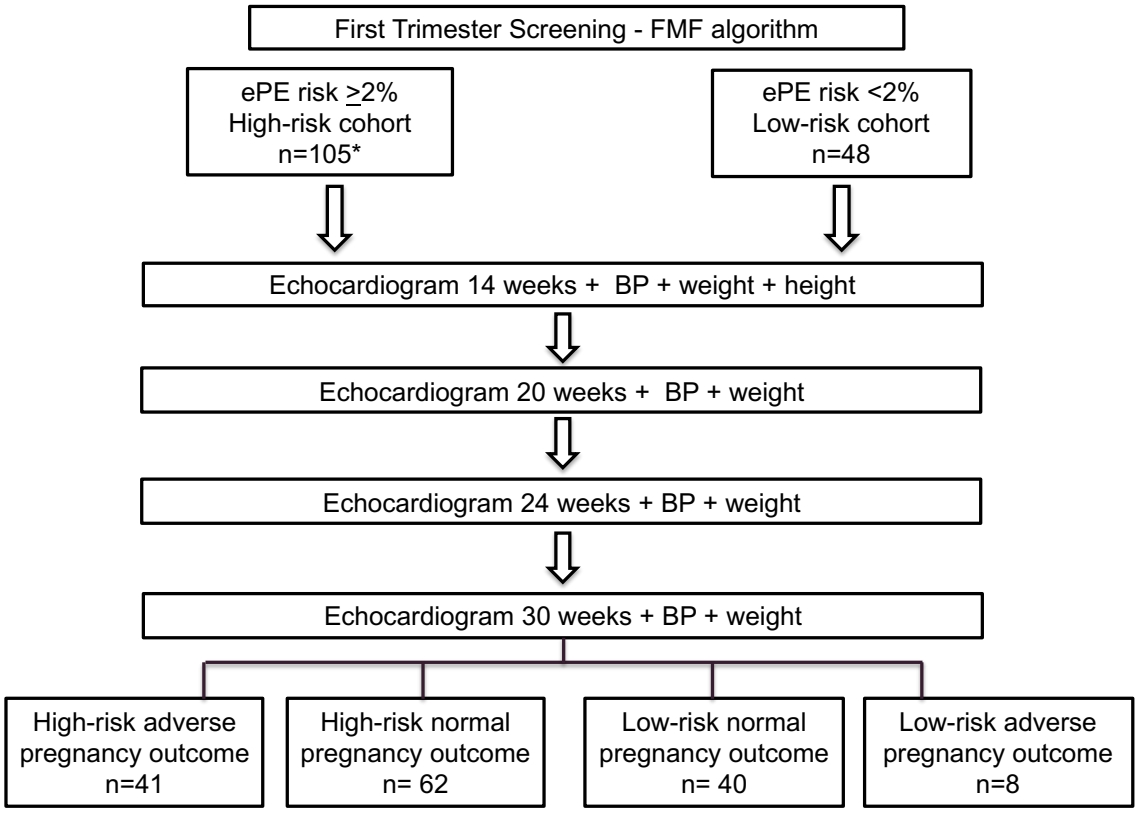


Figure 34. Methodology outline study 3

High-risk and low-risk women with subsequent pregnancy outcomes

BP: blood pressure, ePE: early-onset pre-eclampsia, FMF: Fetal Medicine Foundation

* 2 essential hypertension cases excluded

6.3 Results

Of the 48 women who screened low-risk for ePE, 40 women (83.3%) subsequently had a normal pregnancy outcome. Eight women (16.7%) had an adverse pregnancy outcome due to the development of late pre-eclampsia (2), preterm delivery (3), low infant birthweight (2) or fetal demise (1). The three preterm deliveries included two PPROM and one iatrogenic delivery for suspected FGR, while the fetal demise occurred at 15 weeks' gestation.

Of the 105 women who screened as high-risk for early pre-eclampsia, two women were excluded due to the existence of essential hypertension. Of the 103 women

remaining, 62 had a normal outcome while 41 had an adverse outcome including; 8 (19.5%) pre-eclamptic women, 8 (19.5%) women with gestational hypertension, 20 (48.8%) small for gestational age infants and 5 (12.2%) preterm deliveries. The five preterm deliveries included three PPROM and two spontaneous deliveries. Maternal characteristics and birth outcomes of both the low-risk and high-risk groups have previously been reported in *Chapter 5, Section 5.3 Results.*

6.3.1 Primary cardiovascular outcomes

In women stratified as low-risk for ePE with a normal pregnancy outcome, the stroke volume remained unchanged, measuring 77.5 ml (SD 14.5 ml) at 14 weeks' gestation, compared to 76.3 ml (SD 15.4 ml); p = 0.611 at 30 weeks' gestation. Women stratified as high-risk with a normal pregnancy outcome also showed no significant change in stroke volume between 14 and 30 weeks' gestation; 74.6 ml (SD 12.9 ml) to 72.4 ml (SD 12.6 ml); p = 0.364. There was also no significant difference in mean values between the two groups (p = 0.845).

The indexed equivalent measure, SVI, showed a significant decrease in this group measuring 44.4 ml/m^2 (SD 6.7 ml/m^2) and 41.5 ml/m^2 (SD 6.9 ml/m^2); p = 0.002, at 14 and 30 weeks' gestation respectively. A significant decline in SVI was also evident in the high-risk women measuring 43.3 ml/m^2 (SD 6.7 ml/m^2) and 40.2 ml/m^2 (SD 6.3ml/m^2); p = 0.001 at the same gestations, irrespective of adjustments for parity and maternal age. In terms of statistical difference between SVI mean values at each time point for the low-risk and high-risk groups of women, there was no significance in either the unadjusted or adjusted p - values. These data are summarised in Tables 20 and 23 and Figure 35.

Cardiac output increased between 14 - 30 weeks' gestation in the low-risk group; 5.58 L/min (SD 1.8 L/min) to 6.31 L/min (SD 1.2 L/min); p <0.001. This change was secondary to an increase in heart rate; 72.2 bpm (SD 7.9 bpm) to 83.3 bpm (SD 8.2 bpm); p <0.001. Women stratified as high-risk for ePE with a normal pregnancy outcome also showed a significant increase in cardiac output and heart rate respectively; 5.47 L/min (SD 1.09 L/min) to 5.82 L/min (SD 0.96 L/min); p = 0.005 and 73.3 bpm (SD 8.6 bpm) to 80.7 bpm (SD 10.6 bpm); p <0.001. At each time point the mean cardiac output values were not significantly different between the groups despite lower values in the high-risk group (p = 0.22). There was also no significant difference between groups in the mean heart rate values

at these time points. These data are summarised in Tables 20 and 23 and Figures 35 and 36.

The cardiac index of the low-risk women also increased across this time period from 3.19 L/min/m^2 (SD 0.52 L/min/m^2) to 3.43 L/min/m^2 (SD 0.52 L/min/m^2); p = 0.002, however the significant increase was from 14 to 20 weeks' gestation, with the mean values plateauing from this point. The high-risk women showed an increase in CI over 14 to 30 weeks' gestation, however this did not reach significance; 3.17 L/min/m^2 (SD 0.59 L/min/m^2) to 3.24 L/min/m^2 (SD 0.50 L/min/m^2); p = 0.293. At each time point, the CI was not significantly different between the groups of women (p = 0.281). These data are outlined in Tables 20 and 23 and Figure 35.

Mean arterial pressure was significantly higher in high-risk women with a normal pregnancy outcome at each time point compared to low-risk women; 14 weeks, 84.5mmHg (SD 6.0 mmHg) versus 89.4 mmHg (SD 7.2 mmHg); p <0.001, 20 weeks, 84.3 mmHg (SD 6.7 mmHg) versus 87.1 mmHg (SD 6.1 mmHg); p = 0.008, 24 weeks, 84.6 mmHg (SD 6.1 mmHg) versus 87.5 mmHg (SD 5.8 mmHg); p = 0.011 and 30 weeks', 84.9 mmHg (SD 6.0 mmHg) versus 89.4 mmHg (SD 6.5 mmHg); p <0.001. Between 14 and 30 weeks' gestation the MAP was unchanged in low-risk women; p = 0.738 and high-risk women; p = 0.842, however there was a statistically significant decrease in MAP at 20 and 24 weeks; p = 0.013, in the high-risk women. These data are summarised in Tables 20 and 23 and Figure 36.

Total peripheral resistance decreased over 14 - 30 weeks' gestation in the low-risk and high-risk groups respectively; 1253.5 Dynes.$s^{-1}cm^{-5}$ (SD 251.6 Dynes.$s^{-1}cm^{-5}$) to 1111.1 Dynes.$s^{-1}cm^{-5}$ (SD 210.2 Dynes.$s^{-1}cm^{-5}$); p <0.001 and 1356.1 Dynes.$s^{-1}cm^{-5}$ (SD 291.9 Dynes.$s^{-1}cm^{-5}$) to 1258.8 Dynes.$s^{-1}cm^{-5}$ (SD 216.9 Dynes.$s^{-1}cm^{-5}$); p = 0.002. The mean TPR values were not significantly different between the low-risk and high-risk women except at 20 weeks' gestation; 1145.0 Dynes.$s^{-1}cm^{-5}$ (SD 184.1 Dynes.$s^{-1}cm^{-5}$) versus 1290.5 Dynes.$s^{-1}cm^{-5}$ (SD 248.8 Dynes.$s^{-1}cm^{-5}$); p = 0.02. (Tables 20 and 23).

The total peripheral resistance index in the low-risk women decreased from 2162.6 Dynes.$s^{-1}cm^{-5}$ m^2 (SD 363.2 Dynes.$s^{-1}cm^{-5}$ m^2) at 14 weeks' gestation to 2021.7 Dynes.$s^{-1}cm^{-5}m^2$ (SD 323.4 Dynes.$s^{-1}cm^{-5}m^2$) at 30 weeks' gestation; p =

0.006, reaching nadir at 20 weeks'. This pattern was replicated in the high-risk women, decreasing from 2330.5 Dynes.s^{-1}cm^{-5}m^2 (SD 478.2 Dynes.s^{-1}cm^{-5}m^2) to 2261.6 Dynes.s^{-1}cm^{-5}m^2 (SD 405.1 Dynes.s^{-1}cm^{-5}m^2), with nadir reached at 24 weeks' gestation (p = 0.011). There was a significant difference in mean TPRI at 20 and 30 weeks' gestation respectively; 2005.9 Dynes.s^{-1}cm^{-5}m^2 (SD 248.3 Dynes.s^{-1}cm^{-5}m^2) versus 2233.0 Dynes.s^{-1}cm^{-5}m^2 (SD 416.0 Dynes.s^{-1}cm^{-5}m^2); p = 0.008 and 2021.7 Dynes.s^{-1}cm^{-5}m^2 (SD 323.4 Dynes.s^{-1}cm^{-5}m^2) versus 2261.6 (SD 405.1 Dynes.s^{-1}cm^{-5}m^2); p = 0.022. These data are summarised in Tables 20 and 23 and Figure 36.

The high-risk and low-risk women with a subsequent normal outcome both demonstrated the same cardiovascular changes; stable stroke volume, increasing cardiac output and heart rate with a concomitant decrease in total peripheral resistance. When these values were indexed this pattern of change largely persisted, however statistical significance with gestation was not always reached. The mean values were also not statistically different regardless of indexation, with the exception of higher mean TPR / TPRI values in the high-risk group. This was due to significantly higher MAP mean values in these women.

6.3.2 Secondary cardiovascular outcomes

Measures of systolic function in the low-risk women, including ejection fraction, fractional shortening and s wave velocities at the left ventricular septum and right ventricular wall were unchanged between 14 and 30 weeks' gestation. There was a significant decrease in the s wave velocity at left ventricular lateral wall measuring 12.92 cm/s (SD 2.18 cm/s) at 14 weeks' gestation and 11.76 cm/s (SD 1.92 cm/s); p value = 0.002, at 30 weeks' gestation. This decrease was not seen in the high-risk women, with values remaining unchanged. These systolic data measurements are summarised in Tables 21 and 24.

Ejection fraction and fractional shortening when measured using M-mode were unchanged between 14 and 30 weeks' gestation in both groups of women. The alternative Simpson's biplane method of calculating the ejection-fraction showed a small but significant decline in the high-risk women over this time period from 67.4 % (SD 3.7 %) to 66.3 % (SD 3.5 %); p = 0.04. Additionally, there was no

significant difference in mean values of M-mode EF and FS between the low-risk and high-risk groups. There was a small but significantly lower EF in the low-risk group using the Simpson's method at 24 and 30 weeks' gestation, measuring 67.3 % (SD 4.2 %) versus 65.6 % (SD 3.6 %); p = 0.023 and 67.7 % (SD 3.2 %) versus 66.3 % (SD 3.5 %); p = 0.008, respectively (Tables 21 and 24).

In the low-risk group there was a significant increase in LVM, measuring 123.2 g (SD 26.2 g) at 14 weeks' gestation compared to 138.0 g (SD 30.4 g); p <0.001 at 30 weeks' gestation. The equivalent indexed measure, LVMI, paralleled the raw data changes increasing from 70.7 g/m^2 (SD 11.7 g/m^2) to 75.1 g/m^2 (SD 12.5 g/m^2); p = 0.001, over the same gestation. The high-risk group also showed a significant increase in LVM, measuring 125.0 g (SD 25.0 g) to 130.8 g (SD 25.3 g); p = 0.001, however the LVMI was unchanged between 14 and 30 weeks' gestation (p = 0.52). At each time point there was no significant difference in both the LVM and LVMI mean measurements between the low-risk and high-risk women (Tables 21 and 24).

The TDI s wave velocities at the septum and left ventricular wall were the same at all time points, with the exception being at 14 weeks' gestation, whereby the left ventricular s wave velocity was less in the high-risk women compared to the low-risk women, measuring 12.92 cm/s (SD 2.2 cm/s) and 11.98 cm/s (SD 2.2 cm/s); p = 0.04, respectively. The mean right ventricular wall s velocity was the same between the two groups at 14 weeks' gestation, however this was statistically less in the high-risk women at 20, 24 and 30 weeks' gestation measuring, 17.00 cm/s (SD 1.9 cm/s) versus 16.24 cm/s (SD 2.2 cm/s); p = 0.049, 16.61cm/s (SD 2.8 cm/s) versus 15.56 cm/s (SD 1.8 cm/s); p = 0.046 and 16.75 cm/s (SD 2.2 cm/s) versus 15.67 cm/s (SD 1.7 cm/s); p = 0.015, respectively. These data are summarised in Tables 21 and 24.

In the low-risk women, the mitral inflow diastolic measures showed a decrease in E velocity (86.9 cm/s [SD 13.1 cm/s] to 81.5 cm/s [SD 11.8 cm/s]; p < 0.001) and an increase in A velocity (51.3 cm/s [SD 9.9 cm/s] to 56.2 cm/s [SD 7.6 cm/s]; p = 0.001, from 14 to 30 weeks' gestation. This resulted in a significant decline in the E/A ratio from 1.77 (SD 0.49) to 1.47 (SD 0.28); p < 0.001. In terms of deceleration time, isovolumetric relaxation time and A wave duration, there was no significant change in these mitral valve inflow measures (Tables 22 and 25).

The mitral valve diastolic E and A velocities in the high-risk women showed the same changes as seen in the low-risk women between 14 and 30 weeks' gestation; 85.9 cm/s (SD 13.9 cm/s) to 76.8 cm/s (SD 12.2 cm/s); $p < 0.001$ and 50.0 cm/s (SD 9.6 cm/s) to 52.4 cm/s (SD 8.6 cm/s); $p = 0.011$, respectively. The E/A ratio also declined significantly from 1.79 (SD 0.40) to 1.49 (SD 0.27); $p < 0.001$. The deceleration time and A-wave duration were not significantly different between 14 and 30 weeks' gestation in these women, while the IVRT increased from 92.2 msec (SD 12.2 msec) to 97.8 msec (SD 11.1 msec); $p = 0.007$. In terms of mean values for these measures, there was no significant difference between the low-risk and high-risk women with a normal pregnancy outcome (Tables 22 and 25).

The tissue Doppler imaging *e* and *a* velocities in the low-risk women mirrored the mitral flow measures at both the septal and left lateral wall sites, showing a decrease in *e* wave velocity (septal; 15.63 cm/s [SD 2.73 cm/s] to 14.08 cm/s [SD 9.49 cm/s]; $p < 0.001$, left lateral; 18.6 cm/s [SD 2.8 cm/s] to 16.41 cm/s [SD 3.2 cm/s]; $p <0.001$) and an increase in a wave velocity (septal; 8.08 cm/s [SD 1.94 cm/s] to 9.49 cm/s [SD 1.82 cm/s]; $p < 0.001$, left lateral; 8.58 cm/s [SD 1.9 cm/s] to 9.17 cm/s [SD 1.47 cm/s]; $p = 0.037$) from 14 to 30 weeks' gestation. The *e/a* ratio also decreased significantly at both the septal and left lateral sites respectively; 2.01 (SD 0.50) to 1.53 (SD 0.38); $p <0.001$ and 2.26 (SD 0.56) to 1.83 (SD 0.45); $p < 0.001$.The E/*e* ratios at both the septal and left lateral ventricle sites were unchanged (Tables 22 and 25).

The high-risk women demonstrated the same changes in septal and lateral wall velocities as the low-risk women, with the *e* velocity decreasing between 14 and 30 weeks' gestation from 14.86 cm/s (SD 2.41 cm/s) to 13.12 cm/s (SD 2.76 cm/s); $p < 0.001$ at the septum and 18.86 (SD 3.29 cm/s) to 17.02 cm/s (SD 2.88 cm/s); $p <0.001$, at the lateral wall. There was a concomitant *a* velocity increase over the same time period (septal; 8.06 cm/s [SD 1.62 cm/s] to 9.23 cm/s [SD 1.82 cm/s]; $p < 0.001$, left lateral; 8.46 cm/s [SD 1.67 cm/s] to 9.10 cm/s [SD 1.80 cm/s]; $p = 0.048$), resulting in a significant decline in the *e/a* ratio at both sites. The septal and lateral wall *e/a* ratios decreased from 1.91 (SD 0.49) to 1.49 (SD 0.43); $p < 0.001$ and 2.31 (SD 0.59) to 1.95 (SD 0.54); $p < 0.001$ from 14 to 30 weeks' gestation respectively. The E/*e* ratios were unchanged at both the septal and lateral sites (Tables 22 and 25).

In terms of mean *e*, *a e/a* and E/*e* values at the septum and left lateral wall there were no significant differences between the low-risk and high-risk women at any of the time points, with the exception of the septal *e* velocity measured at 20 and 24 weeks' gestation; 15.47 cm/s (SD 2.57 cm/s) versus 14.70 cm/s (SD 2.67 cm/s); p = 0.048 and 15.28 cm/s (SD 2.62cm/s) versus 14.06 cm/s (SD 2.33); p = 0.006, respectively.

In the low-risk women, tissue Doppler measures of the right ventricular free wall showed no change in the *e* velocity from 14 to 30 weeks' gestation, while the *a* velocity demonstrated a significant increase over this gestation from 12.50 cm/s (SD 2.27 cm/s) to 14.45 cm/s (SD 3.66 cm/s); p = 0.002. This resulted in a significantly lower right *e/a* ratio of 1.59 (SD 0.35) at 14 weeks' gestation compared to 1.36 (SD 0.40); p < 0.001 at 30 weeks' gestation. This pattern was replicated in the high-risk women with the *e* velocity unchanged, while *a* velocity increased from 12.55 cm/s (SD 2.83 cm/s) to 14.48 cm/s (SD 3.38 cm/s); p >0.001. The right *e/a* ratio also decreased from 1.47 (SD 0.41) at 14 weeks' gestation to 1.30 (SD 0.38); p = 0.001 at 30 weeks' gestation (Tables 22 and 25).

Overall, the mean values of secondary systolic cardiovascular measures (LVM, LVMI, VTI, LVOT, EF, FS and *s* velocities) were essentially unchanged between low-risk and high-risk women. In terms of diastolic function both groups demonstrated the expected adaptation to blood volume expansion with a shift in LV filling from early to late diastole, evidenced by an increased A velocity with a concomitant decline in E velocity. This was replicated in the TDI *e* and *a* velocities. Effectively, the trends and mean values were comparable between the two groups of women, with the exception of lower right ventricle *s* and *e* velocities in the high-risk group from 20-30 weeks' gestation and 14-24 weeks' gestation respectively, as well as lower septal *e* velocity between 20-24 weeks' gestation.

Table 20. Cardiovascular primary outcomes for low-risk and high-risk women with a subsequent normal pregnancy outcome

Outcome	L-R Normal Mean (SD)	H-R Normal Mean (SD)	Unadjusted Difference in Means (95% CI.)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
HR				0.209*		0.222*
- 14 weeks	72.2 (7.9)	73.3 (8.6)	0.92 (-2.37, 4.22)	0.583	1.75 (-1.51, 5.02)	0.292
- 20 weeks	76.2 (9.3)	74.1 (9.8)	-1.44 (-5.27, 2.39)	0.461	-0.57 (-4.48, 3.35)	0.777
- 24 weeks	79.0 (9.6)	77.5 (8.6)	-0.93 (-4.67, 2.82)	0.627	-0.07 (-3.87, 3.74)	0.972
- 30 weeks	83.3 (8.2)	80.7 (10.6)	-1.89 (-5.66, 1.89)	0.327	-1.01 (-4.84, 2.82)	0.605
SV				0.825*		0.845*
- 14 weeks	77.5 (14.5)	74.6 (12.9)	-2.72 (-8.24, 2.80)	0.334	-1.00 (-6.67, 4.67)	0.730
- 20 weeks	80.1 (15.9)	75.7 (14.1)	-4.62 (-10.77, 1.53)	0.141	-2.80 (-9.05, 3.44)	0.379
- 24 weeks	78.1 (15.7)	74.8 (13.4)	-3.10 (-9.01, 2.82)	0.305	-1.31 (-7.91, 5.29)	0.697
- 30 weeks	76.3 (15.4)	72.4 (12.6)	-3.26 (-9.04, 2.52)	0.269	-1.45 (-7.67, 4.77)	0.648
SVI				0.896*		0.901*
- 14 weeks	44.4 (6.7)	43.3 (6.7)	-0.99 (-3.67, 1.69)	0.469	-0.71 (-3.60, 2.18)	0.629
- 20 weeks	45.1 (6.7)	43.4 (6.7)	-1.83 (-4.56, 0.89)	0.187	-1.53 (-4.33, 1.27)	0.285
- 24 weeks	42.8 (6.8)	42.2 (6.3)	-0.92 (-3.65, 1.81)	0.508	-0.62 (-3.70, 2.45)	0.691
- 30 weeks	41.5 (6.9)	40.2 (6.3)	-1.13 (-3.87, 1.60)	0.416	-0.83 (-3.78, 2.13)	0.584
CO				0.192*		0.220*
- 14 weeks	5.58 (1.18)	5.47 (1.09)	-0.12 (-0.57, 0.34)	0.617	0.08 (-0.34, 0.49)	0.724
- 20 weeks	6.06 (1.20)	5.53 (0.98)	-0.47 (-0.93, -0.02)	0.040	-0.27 (-0.71, 0.17)	0.229
- 24 weeks	6.09 (1.00)	5.76 (1.05)	-0.28 (-0.68, 0.13)	0.179	-0.08 (-0.51, 0.35)	0.719
- 30 weeks	6.31 (1.20)	5.82 (0.96)	-0.41 (-0.86, 0.05)	0.078	-0.21 (-0.67, 0.26)	0.384
CI				0.253*		0.281*
- 14 weeks	3.19 (0.52)	3.17 (0.59)	-0.02 (-0.24, 0.20)	0.863	0.03 (-0.18, 0.25)	0.753
- 20 weeks	3.41 (0.45)	3.18 (0.48)	-0.21 (-0.40, -0.02)	0.029	-0.15 (-0.34, 0.04)	0.128
- 24 weeks	3.34 (0.40)	3.25 (0.49)	-0.10 (-0.28, 0.09)	0.298	-0.04 (-0.24, 0.16)	0.714
-30 weeks	3.43 (0.52)	3.24 (0.50)	-0.17 (-0.38, 0.04)	0.119	-0.11 (-0.33, 0.12)	0.344

Outcome	L-R Normal Mean (SD)	H-R Normal Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
MAP				0.352*		0.363*
- 14 weeks	84.5 (6.0)	89.4 (7.2)	4.8 (2.2, 7.3)	<0.001	5.4 (2.7, 8.0)	**<0.001**
- 20 weeks	84.3 (6.7)	87.1 (6.1)	2.9 (0.3, 5.6)	0.028	3.6 (1.0, 6.2)	**0.008**
- 24 weeks	84.6 (6.1)	87.5 (5.8)	2.8 (0.35, 5.3)	0.025	3.5 (0.8, 6.1)	**0.011**
- 30 weeks	84.9 (6.0)	89.4 (6.5)	4.2 (1.7, 6.8)	0.001	4.9 (2.3, 7.4)	**<0.001**
TPR				0.773*		0.798*
- 14 weeks	1253.5 (251.6)	1356.1 (291.9)	101.4 (-5.7, 208.5)	0.064	69.5 (-31.4, 170.3)	0.177
- 20 weeks	1145.0 (184.1)	1290.5 (248.8)	138.0 (52.4, 223.5)	0.002	103.4 (16.5, 190.3)	**0.020**
- 24 weeks	1137.1 (186.1)	1247.0 (204.7)	100.0 (22.2, 177.8)	0.012	66.4 (-17.2, 150.0)	0.119
- 30 weeks	1111.1 (210.2)	1258.8 (216.9)	125.1 (37.9, 212.2)	0.005	90.9 (-1.0, 182.7)	0.053
TPRI				0.670*		0.685*
- 14 weeks	2162.6 (363.2)	2330.5 (478.2)	161.6 (-3.7, 326.9)	0.055	137.9 (-28.3, 304.1)	0.104
- 20 weeks	2005.9 (248.4)	2233.0 (416.0)	217.8 (85.4, 350.3)	0.001	191.4 (49.4, 333.3)	**0.008**
- 24 weeks	2057.2 (320.6)	2194.9 (328.1)	137.7 (3.8, 271.6)	0.044	111.9 (-35.9, 259.7)	0.138
- 30 weeks	2021.7 (323.4)	2261.6 (405.1)	214.9 (66.3, 363.4)	0.005	187.9 (27.1, 348.7)	**0.022**

Data are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, HR: heart rate, LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), MAP: mean arterial pressure, SD: standard deviation, SV: stroke volume, SVI: stroke volume index (SV/BSA), TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA).

Table 21. Cardiovascular secondary systolic outcomes for low-risk and high-risk women with a normal pregnancy outcome

Outcome	L-R Normal Mean (SD)	H-R Normal Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
LVM				0.043*		0.045*
- 14 weeks	123.2 (26.2)	125.0 (25.0)	1.46 (-8.78, 11.70)	0.780	7.14 (-2.82, 17.10)	0.160
- 20 weeks	129.3 (29.4)	126.4 (25.1)	-2.05 (-13.03, 8.93)	0.714	3.75 (-7.20, 14.70)	0.503
- 24 weeks	137.9 (29.4)	128.2 (23.7)	-8.04 (-18.82, 2.74)	0.144	-2.31 (-13.51, 8.90)	0.686
- 30 weeks	138.0 (30.4)	130.8 (25.3)	-6.06 (-17.52, 5.40)	0.300	-0.27 (-11.73, 11.19)	0.963
LVMI				0.074*		0.079*
- 14 weeks	70.7 (11.7)	72.4 (12.3)	1.63 (-3.12, 6.37)	0.502	3.79 (-0.73, 8.32)	0.101
- 20 weeks	73.1 (13.1)	72.5 (11.9)	-0.26 (-5.28, 4.76)	0.919	1.98 (-2.94, 6.90)	0.431
- 24 weeks	75.7 (12.5)	72.3 (11.1)	-3.29 (-8.10, 1.52)	0.180	-1.08 (-6.00, 3.84)	0.666
- 30 weeks	75.1 (12.5)	72.4 (12.3)	-2.23 (-7.27, 2.81)	0.385	-0.00 (-5.04, 5.03)	0.999
VTI				0.956*		0.952*
- 14 weeks	24.4 (3.0)	24.1 (3.2)	-0.36 (-1.58, 0.87)	0.570	-0.49 (-1.82, 0.84)	0.470
- 20 weeks	24.8 (3.1)	24.2 (3.4)	-0.61 (-1.94, 0.71)	0.366	-0.76 (-2.13, 0.61)	0.279
- 24 weeks	23.9 (3.6)	23.9 (3.0)	-0.26 (-1.67, 1.15)	0.718	-0.40 (-1.92, 1.11)	0.603
- 30 weeks	23.4 (3.4)	22.9 (3.3)	-0.43 (-1.81, 0.95)	0.542	-0.58 (-2.02, 0.87)	0.435
LVOT				0.863*		0.876*
- 14 weeks	2.01 (0.14)	1.99 (0.13)	-0.02 (-0.07, 0.04)	0.507	0.01 (-0.04, 0.06)	0.691
- 20 weeks	2.02 (0.15)	1.99 (0.14)	-0.03 (-0.09, 0.03)	0.341	0.00 (-0.06, 0.06)	0.968
- 24 weeks	2.04 (0.14)	1.99 (0.13)	-0.03 (-0.08, 0.03)	0.321	0.00 (-0.06, 0.06)	0.959
- 30 weeks	2.03 (0.16)	2.00 (0.12)	-0.02 (-0.08, 0.04)	0.458	0.01 (-0.05, 0.06)	0.781
EF Simpson				0.324*		0.302*
- 14 weeks	67.9 (2.8)	67.4 (3.7)	-0.51 (-1.87, 0.85)	0.464	-0.92 (-2.21, 0.37)	0.161
- 20 weeks	67.7 (3.4)	68.1 (3.1)	0.17 (-1.26, 1.61)	0.814	-0.27 (-1.70, 1.16)	0.709
- 24 weeks	67.3 (4.2)	65.6 (3.6)	-1.49 (-3.27, 0.29)	0.101	-1.95 (-3.64, -0.27)	**0.023**
- 30 weeks	67.7 (3.2)	66.3 (3.5)	-1.35 (-2.79, 0.08)	0.064	-1.81 (-3.14, -0.48)	**0.008**

Outcome	L-R Normal Mean (SD)	H-R Normal Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
EF M-Mode				0.640*		0.639*
- 14 weeks	67.4 (4.6)	66.6 (3.6)	-0.73 (-2.41, 0.95)	0.392	-0.83 (-2.56, 0.90)	0.349
- 20 weeks	67.6 (4.3)	67.5 (4.6)	-0.13 (-1.94, 1.67)	0.884	-0.24 (-2.13, 1.65)	0.802
- 24 weeks	67.6 (5.3)	67.1 (3.8)	-0.58 (-2.53, 1.38)	0.562	-0.68 (-2.60, 1.23)	0.484
- 30 weeks	67.1 (5.6)	65.8 (4.2)	-1.37 (-3.45, 0.71)	0.197	-1.48 (-3.57, 0.61)	0.165
FS M-Mode				0.417*		0.414*
- 14 weeks	37.6 (3.6)	37.0 (3.0)	-0.59 (-1.94, 0.75)	0.387	-0.53 (-1.94, 0.87)	0.456
- 20 weeks	37.9 (3.6)	38.1 (3.4)	0.15 (-1.27, 1.56)	0.837	0.21 (-1.26, 1.67)	0.779
- 24 weeks	37.9 (4.2)	37.2 (3.0)	-0.65 (-2.18, 0.89)	0.407	-0.59 (-2.10, 0.92)	0.445
- 30 weeks	37.4 (4.4)	36.3 (3.1)	-1.13 (-2.74, 0.48)	0.169	-1.07 (-2.68, 0.53)	0.189
TDI s Sep				0.565*		0.565*
- 14 weeks	10.10 (1.49)	10.03 (1.59)	-0.13 (-0.74, 0.48)	0.681	-0.16 (-0.77, 0.44)	0.595
- 20 weeks	10.57 (1.78)	10.05 (1.34)	-0.54 (-1.21, 0.12)	0.109	-0.58 (-1.24, 0.08)	0.086
- 24 weeks	10.63 (1.79)	10.00 (1.25)	-0.63 (-1.31, 0.05)	0.068	-0.67 (-1.33, 0.00)	0.051
- 30 weeks	10.08 (1.35)	9.64 (1.28)	-0.46 (-1.01, 0.08)	0.096	-0.50 (-1.06, 0.06)	0.081
TDI s LVLW				0.468*		0.462*
- 14 weeks	12.92 (2.18)	11.98 (2.21)	-0.91 (-1.78, -0.04)	0.040	-0.98 (-1.91, -0.04)	**0.040**
- 20 weeks	12.47 (2.18)	11.96 (2.36)	-0.41 (-1.34, 0.51)	0.380	-0.48 (-1.46, 0.51)	0.343
- 24 weeks	12.27 (1.95)	11.97 (2.18)	-0.35 (-1.18, 0.49)	0.415	-0.41 (-1.29, 0.47)	0.360
- 30 weeks	11.76 (1.92)	11.43 (2.25)	-0.28 (-1.14, 0.59)	0.529	-0.33 (-1.28, 0.62)	0.492

Outcome	L-R Normal Mean (SD)	H-R Normal Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
TDI s RVLW				0.927*		0.930*
- 14 weeks	16.22 (2.24)	15.49 (1.95)	-0.76 (-1.60, 0.09)	0.078	-0.83 (-1.70, 0.05)	0.065
- 20 weeks	17.00 (1.92)	16.24 (2.16)	-0.81 (-1.66, 0.04)	0.061	-0.88 (-1.75, -0.00)	**0.049**
- 24 weeks	16.61 (2.77)	15.56 (1.77)	-1.00 (-2.01, 0.00)	0.050	-1.07 (-2.13, -0.02)	**0.046**
- 30 weeks	16.75 (2.22)	15.67 (1.73)	-1.01 (-1.84, -0.19)	0.016	-1.08 (-1.95, -0.21)	**0.015**

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). EF: ejection fraction, FS: fractional shortening, H-R: high-risk, LVFW: left ventricular lateral wall, LVOT: left ventricular outflow tract, L-R: low-risk, RVFW: right ventricular lateral wall, s: s wave velocity, Sep: septal, SD: standard deviation, TDI: tissue Doppler Imaging**,** VTI: velocity time integral.

Table 22. Cardiovascular diastolic outcomes for low-risk and high-risk women with a normal pregnancy outcome

Outcome	L-R Normal Mean (SD)	H-R Normal Mean (SD)	Unadjusted Difference in Means (95% CI)	Unadjusted p value	Adjusted Difference in Means (95% CI)	Adjusted p value
MV E				0.362*		0.366*
- 14 weeks	86.9 (13.1)	85.9 (13.9)	-0.99 (-6.30, 4.31)	0.713	-1.38 (-7.07, 4.32)	0.636
- 20 weeks	87.5 (14.1)	87.8 (15.2)	0.58 (-5.39, 6.55)	0.850	0.19 (-6.08, 6.45)	0.954
- 24 weeks	84.7 (13.7)	82.6 (14.8)	-2.54 (-8.44, 3.37)	0.400	-2.92 (-9.25, 3.41)	0.367
- 30 weeks	81.5 (11.8)	76.8 (12.2)	-3.83 (-8.68, 1.02)	0.122	-4.20 (-9.44, 1.03)	0.115
MV A				0.715*		0.718*
- 14 weeks	51.3 (9.9)	50.0 (9.6)	-1.22 (-5.09, 2.64)	0.535	-0.10 (-3.86, 3.67)	0.960
- 20 weeks	53.3 (9.3)	50.2 (7.8)	-2.33 (-5.90, 1.25)	0.202	-1.14 (-4.75, 2.47)	0.536
- 24 weeks	54.5 (8.6)	51.2 (8.3)	-2.68 (-6.16, 0.81)	0.132	-1.52 (-5.03, 1.99)	0.395
- 30 weeks	56.2 (7.6)	52.4 (8.6)	-3.49 (-6.82, -0.15)	0.041	-2.34 (-5.77, 1.08)	0.179
MV E/A				0.917*		0.923*
- 14 weeks	1.77 (0.49)	1.79 (0.40)	0.01 (-0.16, 0.19)	0.874	-0.04 (-0.22, 0.14)	0.684
- 20 weeks	1.71 (0.53)	1.80 (0.44)	0.07 (-0.13, 0.28)	0.472	0.02 (-0.19, 0.23)	0.854
- 24 weeks	1.58 (0.28)	1.66 (0.40)	0.05 (-0.10, 0.19)	0.535	-0.01 (-0.15, 0.14)	0.918
- 30 weeks	1.47 (0.28)	1.49 (0.27)	0.02 (-0.09, 0.13)	0.699	-0.03 (-0.15, 0.09)	0.605
IVRT				0.746*		0.732*
- 14 weeks	92.1 (14.4)	92.2 (12.2)	-0.07 (-5.49, 5.35)	0.980	0.84 (-4.84, 6.51)	0.773
- 20 weeks	88.0 (13.5)	90.7 (13.6)	2.45 (-3.25, 8.15)	0.399	3.46 (-2.32, 9.23)	0.241
- 24 weeks	93.0 (12.7)	94.5 (11.9)	1.65 (-3.54, 6.84)	0.533	2.60 (-2.89, 8.08)	0.353
- 30 weeks	94.0 (11.4)	97.8 (11.1)	2.75 (-1.93, 7.43)	0.249	3.68 (-1.43, 8.78)	0.158
DT				0.421*		0.415*
- 14 weeks	153.2 (19.3)	151.6 (26.5)	-1.50 (-10.39, 7.39)	0.741	-2.12 (-10.36, 6.12)	0.614
- 20 weeks	154.1 (19.6)	149.9 (15.9)	-4.75 (-12.19, 2.69)	0.211	-5.41 (-12.86, 2.05)	0.155
- 24 weeks	150.5 (17.7)	151.8 (19.2)	1.78 (-5.80, 9.37)	0.645	1.15 (-6.07, 8.38)	0.754
- 30 weeks	148.9 (20.5)	150.1 (19.2)	1.07 (-7.17, 9.30)	0.799	0.49 (-7.67, 8.66)	0.906

Outcome	L-R Normal Mean (SD)	H-R Normal Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
A Dur				0.592*		0.599*
- 14 weeks	116.6 (16.0)	120.7 (19.4)	3.80 (-3.10, 10.71)	0.280	4.36 (-2.66, 11.39)	0.223
- 20 weeks	114.4 (15.4)	116.9 (14.2)	1.77 (-4.39, 7.92)	0.574	2.38 (-3.86, 8.61)	0.455
- 24 weeks	118.6 (13.9)	118.9 (17.0)	0.30 (-5.98, 6.58)	0.924	0.89 (-5.49, 7.27)	0.784
- 30 weeks	116.7 (13.8)	117.7 (16.8)	-0.31 (-6.62, 6.00)	0.924	0.29 (-6.24, 6.82)	0.930
Sep e				0.691*		0.691*
- 14 weeks	15.63 (2.73)	14.86 (2.41)	-0.72 (-1.76, 0.32)	0.174	-0.88 (-1.94, 0.17)	0.101
- 20 weeks	15.47 (2.57)	14.70 (2.67)	-0.93 (-2.01, 0.15)	0.091	-1.09 (-2.17, -0.01)	**0.048**
- 24 weeks	15.28 (2.62)	14.06 (2.33)	-1.34 (-2.40, -0.29)	0.013	-1.50 (-2.57, -0.44)	**0.006**
- 30 weeks	14.08 (2.90)	13.12 (2.76)	-0.99 (-2.16, 0.19)	0.099	-1.14 (-2.33, 0.05)	0.060
Sep a				0.843*		0.846*
- 14 weeks	8.08 (1.94)	8.06 (1.62)	-0.11 (-0.84, 0.63)	0.779	0.11 (-0.62, 0.84)	0.775
- 20 weeks	8.34 (1.64)	8.29 (1.54)	-0.10 (-0.76, 0.56)	0.774	0.12 (-0.53, 0.78)	0.714
- 24 weeks	8.94 (1.55)	8.63 (1.35)	-0.37 (-0.98, 0.25)	0.245	-0.14 (-0.75, 0.46)	0.642
- 30 weeks	9.49 (1.82)	9.23 (1.82)	-0.33 (-1.09, 0.43)	0.400	-0.12 (-0.84, 0.61)	0.755
Sep e/a				0.913*		0.905*
- 14 weeks	2.01 (0.50)	1.91 (0.49)	-0.08 (-0.28, 0.12)	0.420	-0.14 (-0.34, 0.05)	0.149
- 20 weeks	1.90 (0.37)	1.84 (0.49)	-0.07 (-0.24, 0.10)	0.414	-0.13 (-0.29, 0.03)	0.111
- 24 weeks	1.75 (0.38)	1.67 (0.41)	-0.08 (-0.24, 0.08)	0.335	-0.14 (-0.29, 0.01)	0.076
- 30 weeks	1.53 (0.38)	1.49 (0.43)	-0.03 (-0.19, 0.14)	0.734	-0.09 (-0.24, 0.07)	0.274
Sep E/e				0.903*		0.901*
- 14 weeks	5.70 (1.11)	5.89 (1.17)	0.19 (-0.26, 0.64)	0.411	0.22 (-0.25, 0.69)	0.356
- 20 weeks	5.81 (1.10)	6.08 (1.16)	0.30 (-0.16, 0.76)	0.197	0.34 (-0.13, 0.80)	0.158
- 24 weeks	5.72 (1.19)	5.98 (1.11)	0.29 (-0.19, 0.77)	0.236	0.32 (-0.19, 0.84)	0.215
- 30 weeks	5.99 (1.23)	6.09 (1.47)	0.14 (-0.41, 0.70)	0.609	0.17 (-0.38, 0.73)	0.543

Outcome	L-R Normal Mean (SD)	H-R Normal Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
LVLW e				0.786*		0.777*
- 14 weeks	18.60 (2.76)	18.86 (3.29)	0.33 (-0.84, 1.51)	0.579	-0.08 (-1.25, 1.08)	0.892
- 20 weeks	18.28 (2.72)	18.56 (3.49)	0.07 (-1.16, 1.30)	0.910	-0.34 (-1.48, 0.81)	0.563
- 24 weeks	17.77 (3.39)	17.64 (3.48)	-0.10 (-1.48, 1.29)	0.892	-0.51 (-1.85, 0.83)	0.457
- 30 weeks	16.41 (3.17)	17.02 (2.88)	0.37 (-0.88, 1.62)	0.557	-0.02 (-1.30, 1.25)	0.971
LVLW a				0.621*		0.625*
- 14 weeks	8.58 (1.88)	8.46 (1.67)	-0.16 (-0.88, 0.56)	0.667	0.04 (-0.67, 0.74)	0.914
- 20 weeks	8.78 (1.80)	8.43 (1.44)	-0.44 (-1.14, 0.25)	0.212	-0.24 (-0.95, 0.47)	0.516
- 24 weeks	8.92 (1.95)	8.90 (1.76)	-0.00 (-0.76, 0.76)	0.998	0.20 (-0.56, 0.96)	0.602
- 30 weeks	9.17 (1.47)	9.10 (1.80)	-0.19 (-0.85, 0.48)	0.585	0.01 (-0.68, 0.71)	0.969
LVLW e/a				0.185*		0.180*
- 14 weeks	2.26 (0.56)	2.31 (0.59)	0.06 (-0.16, 0.29)	0.581	-0.03 (-0.25, 0.18)	0.753
- 20 weeks	2.15 (0.51)	2.27 (0.61)	0.12 (-0.10, 0.34)	0.293	0.02 (-0.19, 0.23)	0.867
- 24 weeks	2.09 (0.66)	2.05 (0.54)	-0.04 (-0.28, 0.21)	0.767	-0.14 (-0.37, 0.09)	0.243
- 30 weeks	1.83 (0.45)	1.95 (0.54)	0.13 (-0.06, 0.33)	0.182	0.04 (-0.16, 0.24)	0.726
LVLW E/e				0.536*		0.528*
- 14 weeks	4.77 (0.97)	4.65 (0.94)	-0.12 (-0.50, 0.26)	0.533	-0.03 (-0.44, 0.38)	0.887
- 20 weeks	4.92 (1.00)	4.81 (0.80)	-0.08 (-0.46, 0.29)	0.671	0.01 (-0.37, 0.39)	0.953
- 24 weeks	4.98 (1.21)	4.83 (1.13)	-0.18 (-0.67, 0.31)	0.476	-0.09 (-0.58, 0.41)	0.737
- 30 weeks	5.12 (1.15)	4.62 (0.97)	-0.42 (-0.86, 0.03)	0.066	-0.33 (-0.79, 0.13)	0.163
RVLW e				0.147*		0.138*
- 14 weeks	19.36 (2.91)	17.66 (3.10)	-1.66 (-2.85, -0.47)	0.006	-1.69 (-2.90, -0.49)	**0.006**
- 20 weeks	19.54 (2.84)	18.02 (3.03)	-1.68 (-2.88, -0.49)	0.006	-1.71 (-2.94, -0.47)	**0.007**
- 24 weeks	19.24 (3.32)	17.08 (2.91)	-2.19 (-3.51, -0.86)	0.001	-2.21 (-3.63, -0.78)	**0.002**
- 30 weeks	18.42 (3.47)	17.82 (3.76)	-0.48 (-1.97, 1.02)	0.531	-0.48 (-1.99, 1.02)	0.531

Outcome	L-R Normal Mean (SD)	H-R Normal Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
RVLW a				0.728*		0.733*
- 14 weeks	12.50 (2.27)	12.55 (2.83)	-0.04 (-1.04, 0.96)	0.941	0.23 (-0.81, 1.27)	0.664
- 20 weeks	13.44 (2.70)	12.73 (3.20)	-0.66 (-1.86, 0.53)	0.276	-0.40 (-1.74, 0.95)	0.564
- 24 weeks	13.74 (3.31)	13.71 (3.07)	-0.04 (-1.40, 1.31)	0.948	0.22 (-1.14, 1.58)	0.749
- 30 weeks	14.45 (3.66)	14.48 (3.38)	0.04 (-1.43, 1.50)	0.961	0.27 (-1.17, 1.71)	0.714
RVLW e/a				0.254*		0.243*
- 14 weeks	1.59 (0.35)	1.47 (0.41)	-0.10 (-0.25, 0.04)	0.168	-0.13 (-0.28, 0.02)	0.098
- 20 weeks	1.50 (0.32)	1.50 (0.42)	-0.02 (-0.16, 0.13)	0.824	-0.04 (-0.20, 0.12)	0.627
- 24 weeks	1.46 (0.32)	1.31 (0.35)	-0.15 (-0.29, -0.01)	0.032	-0.17 (-0.32, -0.03)	**0.021**
- 30 weeks	1.36 (0.40)	1.30 (0.38)	-0.05 (-0.21, 0.11)	0.529	-0.07 (-0.23, 0.09)	0.387

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). a: a wave velocity, A dur: A wave duration, DT: deceleration time, e: e wave velocity, H-R: high-risk; IVRT: isovolumetric relaxation time, L-R: low-risk, LVFW: left ventricular lateral wall, MV: mitral valve, RVFW: right ventricular lateral wall, Sep: septal, SD: standard deviation.

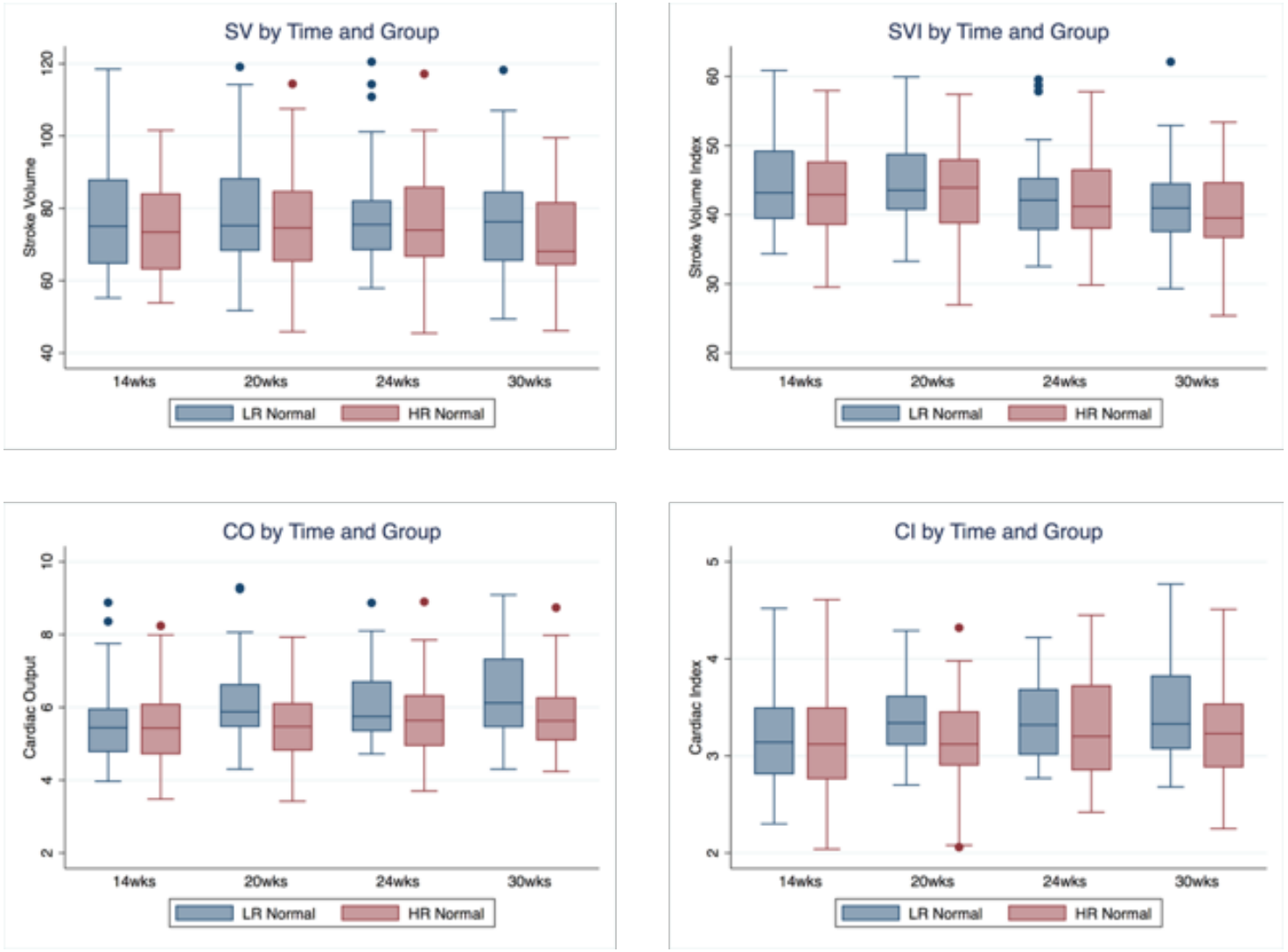


Figure 35. Stroke volume (SV), stroke volume index (SVI), cardiac output (CO) and cardiac index (CI) in low-risk (LR) and high-risk (HR) women with a subsequent normal pregnancy outcome

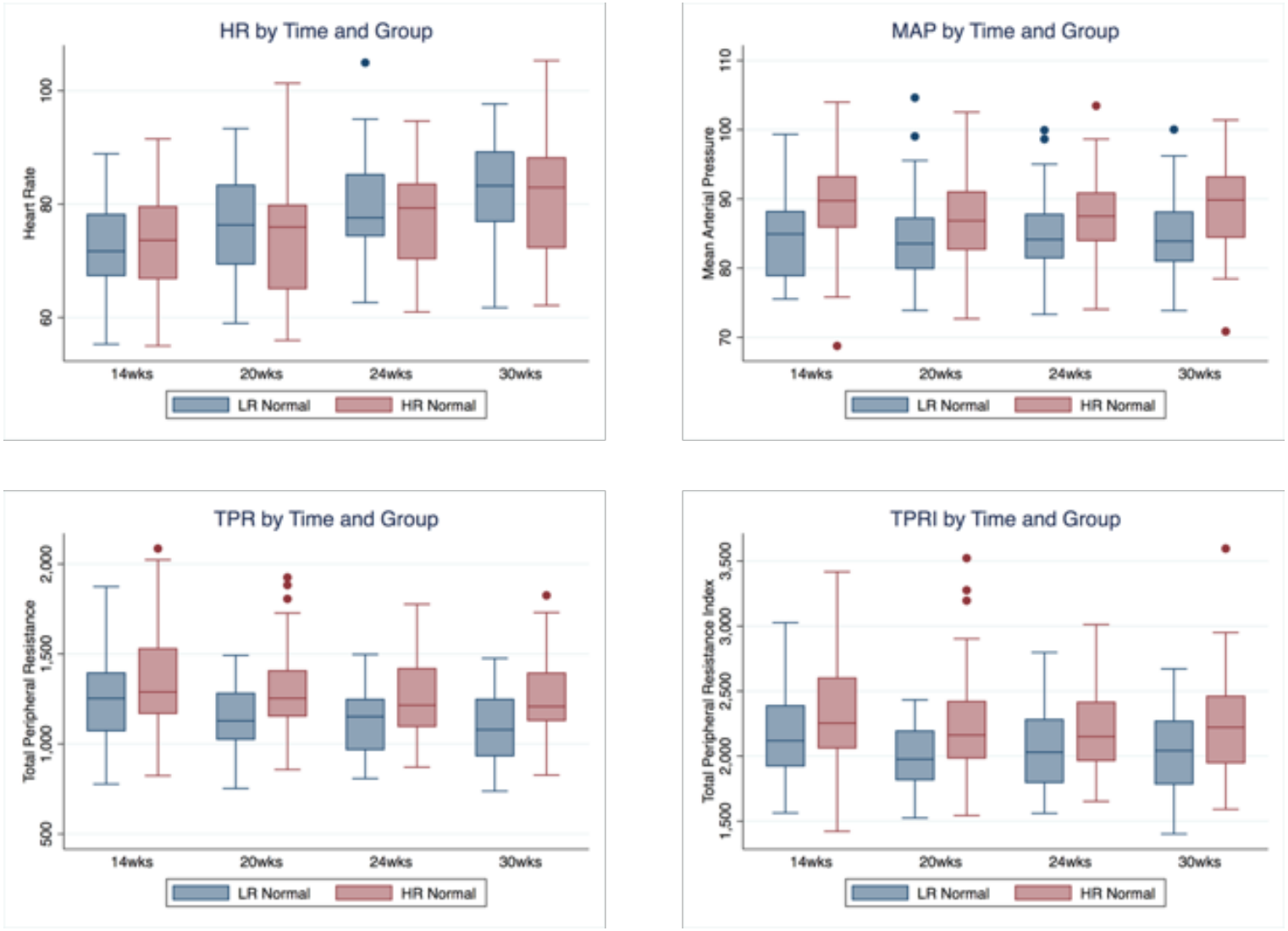


Figure 36. Heart rate (HR), mean arterial pressure (MAP), total peripheral resistance (TPR) and total peripheral resistance index (TPRI) in low-risk (LR) and high-risk (HR) women with a subsequent normal pregnancy outcome

Table 23. Primary cardiovascular variables over time in low-risk and high-risk women with a normal pregnancy outcome

Outcome - Time	L-R Mean (SD)	L-R Unadj. Diff vs 14wks (95% C.I)	L-R Unadj p value	L-R Adj Diff vs T1 (95% C.I)	L-R Adj p value	H-R Mean (SD)	H-R Unadj. Diff vs 14wks (95% C.I)	H-R Unadj p value	H-R Adj Diff vs T1 (95% C.I)	H-R Adj p value
HR - 14wks	72.2 (7.9)		.		.	73.3 (8.6)		0.209*		0.222*
- 20wks	76.2 (9.3)	3.6 (1.0, 6.2)	0.007	3.5 (0.9, 6.2)	**0.008**	74.1 (9.8)	1.2 (-0.8, 3.1)	0.230	1.2 (-0.7, 3.2)	0.219
- 24wks	79.0 (9.6)	6.2 (3.5, 9.0)	0.000	6.2 (3.4, 9.0)	**0.000**	77.5 (8.6)	4.4 (2.9, 5.8)	0.000	4.4 (3.0, 5.9)	**0.000**
- 30wks	83.3 (8.2)	10.8 (8.9, 12.7)	0.000	10.8 (8.9, 12.7)	**0.000**	80.7 (10.6)	8.0 (5.8, 10.2)	0.000	8.1 (5.9, 10.2)	**0.000**
SV - 14wks	77.5 (14.5)		.		.	74.6 (12.9)		0.825*		0.845*
- 20wks	80.1 (15.9)	3.5 (0.3, 6.8)	0.033	3.5 (0.3, 6.7)	**0.035**	75.7 (14.1)	1.6 (-0.9, 4.2)	0.209	1.7 (-0.9, 4.2)	0.192
- 24wks	78.1 (15.7)	1.0 (-2.8, 4.9)	0.600	1.0 (-2.9, 4.8)	0.614	74.8 (13.4)	0.7 (-2.4, 3.7)	0.678	0.7 (-2.4, 3.7)	0.666
- 30wks	76.3 (15.4)	-0.8 (-4.1, 2.4)	0.620	-0.9 (-4.1, 2.4)	0.611	72.4 (12.6)	-1.4 (-4.3, 1.6)	0.364	-1.3 (-4.3, 1.7)	0.387
SVI - 14wks	44.4 (6.7)		.		.	43.3 (6.7)		0.896*		0.901*
- 20wks	45.1 (6.7)	1.1 (-0.9, 3.0)	0.275	1.1 (-0.9, 3.0)	0.279	43.4 (6.7)	0.2 (-1.2, 1.6)	0.746	0.3 (-1.2, 1.7)	0.729
- 24wks	42.8 (6.8)	-1.1 (-3.3, 1.1)	0.336	-1.1 (-3.3, 1.1)	0.333	42.2 (6.3)	-1.0 (-2.7, 0.7)	0.251	-1.0 (-2.7, 0.7)	0.255
- 30wks	41.5 (6.9)	-2.8 (-4.5, -1.1)	0.002	-2.8 (-4.5, -1.1)	**0.002**	40.2 (6.3)	-2.9 (-4.6, -1.3)	0.001	-2.9 (-4.6, -1.2)	**0.001**
CO - 14wks	5.58 (1.18)		.		.	5.47 (1.09)		0.192*		0.220*
- 20wks	6.06 (1.20)	0.51 (0.27, 0.75)	0.000	0.50 (0.3, 0.8)	**0.000**	5.53 (0.98)	0.15 (-0.11, 0.41)	0.250	0.16 (-0.10, 0.41)	0.222
- 24wks	6.09 (1.00)	0.50 (0.19, 0.81)	0.002	0.49 (0.18, 0.81)	**0.002**	5.76 (1.05)	0.34 (0.07, 0.61)	0.015	0.34 (0.07, 0.61)	**0.014**
- 30wks	6.31 (1.20)	0.74 (0.46, 1.02)	0.000	0.74 (0.46, 1.01)	**0.000**	5.82 (0.96)	0.45 (0.14, 0.76)	0.005	0.45 (0.14, 0.77)	**0.004**
CI - 14wks	3.19 (0.52)		.		.	3.17 (0.59)		0.253*		0.281*
- 20wks	3.41 (0.45)	0.23 (0.08, 0.37)	0.002	0.22 (0.08, 0.37)	**0.002**	3.18 (0.48)	0.03 (-0.11, 0.18)	0.633	0.04 (-0.10, 0.18)	0.585
- 24wks	3.34 (0.40)	0.17 (-0.01, 0.34)	0.064	0.16 (-0.01, 0.34)	0.070	3.25 (0.49)	0.09 (-0.06, 0.24)	0.248	0.09 (-0.06, 0.24)	0.238
- 30wks	3.43 (0.52)	0.24 (0.09, 0.39)	0.002	0.24 (0.09, 0.39)	**0.002**	3.24 (0.50)	0.09 (-0.09, 0.27)	0.317	0.10 (-0.08, 0.27)	0.293

Outcome - Time	L-R Mean (SD)	L-R Unadj. Diff vs 14wks (95% C.I)	L-R Unadj p value	L-R Adj Diff vs T1 (95% C.I)	L-R Adj p value	H-R Mean (SD)	H-R Unadj. Diff vs 14wks (95% C.I)	H-R Unadj p value	H-R Adj Diff vs T1 (95% C.I)	H-R Adj p value
MAP - 14wks	84.5 (6.0)		.		.	89.4 (7.2)		0.352*		0.363*
- 20wks	84.3 (6.7)	-0.2 (-2.2, 1.8)	0.822	-0.2 (-2.2, 1.8)	0.821	87.1 (6.1)	-2.0 (-3.6, -0.5)	0.011	-2.0 (-3.6, -0.4)	**0.013**
- 24wks	84.6 (6.1)	-0.2 (-2.4, 1.9)	0.832	-0.2 (-2.4, 1.9)	0.827	87.5 (5.8)	-2.2 (-3.9, -0.5)	0.013	-2.2 (-3.9, -0.5)	**0.013**
- 30wks	84.9 (6.0)	0.3 (-1.6, 2.2)	0.738	0.3 (-1.6, 2.2)	0.735	89.4 (6.5)	-0.2 (-1.88, 1.50)	0.825	-0.2 (-1.9, 1.5)	0.842
TPR - 14wks	1253.5 (251.6)		.		.	1356.1 (291.9)		0.773*		0.798*
- 20wks	1145.0 (184.1)	-117.8 (-174.5, -61.0)	0.000	-116.4 (-173.3, -59.5)	**0.000**	1290.5 (248.8)	-81.2 (-143.7, -18.7)	0.011	-82.5 (-144.9, -20.0)	**0.010**
- 24wks	1137.1 (186.0)	-124.3 (-190.8, -57.)	0.000	-123.0 (-189.7, -56.2)	**0.000**	1247.0 (204.7)	-125.6 (-194.8, -56.5)	0.000	-126.0 (-195.3, -56.7)	**0.000**
- 30wks	1111.1 (210.2)	-147.0 (-206.8, -87.3)	0.000	-146.3 (-206.3, -86.3)	**0.000**	1258.8 (216.9)	-123.4 (-200.8, -46.0)	0.002	-124.9 (-202.4, -47.4)	**0.002**
TPRI - 14wks	2162.6 (363.2)		.		.	2330.5 (478.2)		0.670*		0.685*
- 20wks	2005.9 (248.3)	-167.2 (-268.3, -66.1)	0.001	-166.0 (-267.2, -64.9)	**0.001**	2233.0 (416.0)	-111.0 (-219.5, -2.5)	0.045	-112.5 (-221.2, -3.8)	**0.042**
- 24wks	2057.2 (320.6)	-127.5 (-249.3, -5.7)	0.040	-126.3 (-248.5, -4.1)	**0.043**	2194.9 (328.1)	-151.4 (-268.1, -34.7)	0.011	-152.3 (-269.1, -35.5)	**0.011**
- 30wks	2021.7 (323.4)	-146.2 (-249.1, -43.4)	0.005	-145.6 (-248.7, -42.5)	**0.006**	2261.6 (405.1)	-93.0 (-226.8, 40.8)	0.173	-95.6 (-230.1, 38.9)	0.164

Data are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, HR: heart rate, H-R: high-risk, LVM: left ventricular mass; LVMI: left ventricular mass index (LVM/BSA), L-R: low-risk, MAP: mean arterial pressure, SD: standard deviation, SV: stroke volume; SVI: stroke volume index (SV/BSA); TPR: total peripheral resistance; TPRI: total peripheral resistance index (TPR x BSA).

Table 24. Secondary systolic cardiovascular variables over time in low-risk and high-risk women with a normal pregnancy outcome

Outcome - Time	L-R Mean (SD)	L-R Unadj. Diff vs 14wks (95% C.I)	L-R Unadj p value	L-R Adj Diff vs T1 (95% C.I)	L-R Adj p value	H-R Mean (SD)	H-R Unadj. Diff vs 14wks (95% C.I)	H-R Unadj p value	H-R Adj Diff vs T1 (95% C.I)	H-R Adj p value
LVM - 14wks	123.2 (26.2)		.		.	125.0 (25.0)		0.043*		0.045*
- 20wks	129.3 (29.4)	7.1 (3.1, 11.1)	0.000	7.0 (3.0, 11.0)	**0.001**	126.4 (25.1)	3.6 (-0.1, 7.2)	0.057	3.6 (-0.04, 7.3)	0.053
- 24wks	137.9 (29.4)	14.9 (9.6, 20.3)	0.000	14.9 (9.5, 20.2)	**0.000**	128.2 (23.7)	5.4 (1.4, 9.5)	0.009	5.4 (1.4, 9.5)	**0.009**
- 30wks	138.0 (30.4)	15.5 (10.2, 20.9)	0.000	15.5 (10.1, 20.9)	**0.000**	130.8 (25.3)	8.0 (3.1, 12.9)	0.001	8.0 (3.2, 13.0)	**0.001**
LVMI - 14wks	70.7 (11.7)		.		.	72.4 (12.3)		0.074*		0.079*
- 20wks	73.1 (13.1)	2.8 (0.5, 5.1)	0.018	2.7 (0.5, 5.0)	**0.019**	72.5 (11.9)	0.9 (-1.2, 3.0)	0.405	0.9 (-1.2, 3.0)	0.383
- 24wks	75.7 (12.5)	5.7 (2.6, 8.8)	0.000	5.7 (2.56, 8.8)	**0.000**	72.3 (11.1)	0.8 (-1.4, 3.0)	0.490	0.8 (-1.4, 3.0)	0.485
- 30wks	75.1 (12.5)	4.7 (1.9, 7.4)	0.001	4.7 (1.9, 7.4)	**0.001**	72.4 (12.3)	0.8 (-1.8, 3.5)	0.544	0.9 (-1.8, 3.5)	0.522
VTI - 14wks	24.4 (3.0)		.		.	24.1 (3.2)		0.956*		0.952*
- 20wks	24.8 (3.1)	0.5 (-0.4, 1.5)	0.279	0.5 (-0.4, 1.5)	0.276	24.2 (3.4)	0.3 (-0.4, 1.0)	0.452	0.3 (-0.4, 0.9)	0.463
- 24wks	23.9 (3.6)	-0.3 (-1.1, 0.5)	0.486	-0.3 (-1.1, 0.5)	0.490	23.9 (3.0)	-0.2 (-1.1, 0.7)	0.664	-0.2 (-1.1, 0.7)	0.657
- 30wks	23.4 (3.4)	-1.0 (-1.8, -0.2)	0.020	-1.0 (-1.8, -0.2)	**0.020**	22.9 (3.3)	-1.0 (-1.8, -0.2)	0.010	-1.0 (-1.8, -0.3)	**0.009**
LVOT - 14wks	2.01 (0.14)		.		.	1.99 (0.13)		0.863*		0.876*
- 20wks	2.02 (0.15)	0.02 (0.00, 0.04)	0.039	0.02 (0.00, 0.04)	**0.040**	1.99 (0.14)	0.01 (-0.01, 0.03)	0.327	0.01 (-0.01, 0.03)	0.307
- 24wks	2.04 (0.14)	0.02 (-0.00, 0.05)	0.080	0.02 (-0.00, 0.05)	0.081	1.99 (0.13)	0.01 (-0.00, 0.03)	0.091	0.01 (-0.00, 0.03)	0.089
- 30wks	2.03 (0.16)	0.03 (0.01, 0.05)	0.015	0.03 (0.01, 0.05)	**0.015**	2.00 (0.12)	0.02 (0.00, 0.04)	0.015	0.02 (0.01, 0.04)	**0.013**
EF_SIMP - 14wks	67.9 (2.8)		.		.	67.4 (3.7)		0.324*		0.302*
- 20wks	67.7 (3.4)	-0.1 (-1.6, 1.3)	0.882	-0.1 (-1.6, 1.4)	0.893	68.1 (3.1)	0.6 (-0.6, 1.7)	0.316	0.6 (-0.6, 1.7)	0.336
- 24wks	67.3 (4.2)	-0.7 (-2.3, 1.0)	0.442	-0.6 (-2.3, 1.0)	0.456	65.6 (3.6)	-1.6 (-2.7, -0.6)	0.003	-1.7 (-2.72, -0.6)	**0.002**
- 30wks	67.7 (3.2)	-0.3 (-1.4, 0.9)	0.630	-0.3 (-1.5, 0.9)	0.627	66.3 (3.5)	-1.1 (-2.3, -0.01)	0.049	-1.2 (-2.3, -0.04)	**0.042**
EF_MMODE - 14wks	67.4 (4.6)		.		.	66.6 (3.6)		0.640*		0.639*
- 20wks	67.6 (4.3)	0.2 (-1.1, 1.5)	0.776	0.19 (-1.09, 1.47)	0.771	67.5 (4.6)	0.8 (-0.4, 1.9)	0.183	0.8 (-0.4, 1.9)	0.187
- 24wks	67.6 (5.3)	0.3 (-1.0, 1.6)	0.637	0.31 (-0.98, 1.60)	0.633	67.1 (3.8)	0.5 (-0.7, 1.6)	0.438	0.5 (-0.7, 1.6)	0.442
- 30wks	67.1 (5.6)	-0.3 (-2.0, 1.3)	0.710	-0.31 (-1.95, 1.34)	0.713	65.8 (4.2)	-1.0 (-2.0, 0.1)	0.087	-1.0 (-2.1, 0.1)	0.082

Outcome - Time	L-R Mean (SD)	L-R Unadj. Diff vs 14wks (95% C.I)	L-R Unadj p value	L-R Adj Diff vs T1 (95% C.I)	L-R Adj p value	H-R Mean (SD)	H-R Unadj. Diff vs 14wks (95% C.I)	H-R Unadj p value	H-R Adj Diff vs T1 (95% C.I)	H-R Adj p value
FS_MMODE - 14wks	37.6 (3.6)		.		.	37.0 (3.0)		0.417*		0.414*
- 20wks	37.9 (3.6)	0.3 (-0.7, 1.3)	0.587	0.3 (-0.7, 1.3)	0.584	38.07 (3.36)	1.0 (0.2, 1.8)	0.012	1.0 (0.2, 1.8)	**0.012**
- 24wks	37.9 (4.2)	0.4 (-0.7, 1.4)	0.508	0.4 (-0.7, 1.4)	0.506	37.23 (3.00)	0.3 (-0.6, 1.2)	0.538	0.3 (-0.6, 1.2)	0.539
- 30wks	37.4 (4.4)	-0.2 (-1.5, 1.1)	0.742	-0.2 (-1.5, 1.1)	0.746	36.28 (3.05)	-0.8 (-1.6, 0.06)	0.068	-0.8 (-1.6, 0.1)	0.066
SEP_s - 14wks	10.10 (1.49)		.		.	10.03 (1.59)		0.565*		0.565*
- 20wks	10.57 (1.78)	0.48 (-0.02, 0.98)	0.061	0.48 (-0.03, 0.98)	0.063	10.05 (1.34)	0.06 (-0.38, 0.50)	0.780	0.06 (-0.38, 0.50)	0.790
- 24wks	10.63 (1.79)	0.51 (-0.19, 1.22)	0.154	0.52 (-0.19, 1.22)	0.152	10.00 (1.25)	0.01 (-0.41, 0.44)	0.948	0.01 (-0.41, 0.43)	0.948
- 30wks	10.08 (1.35)	-0.04 (-0.49, 0.42)	0.870	-0.04 (-0.49, 0.42)	0.871	9.64 (1.28)	-0.37 (-0.76, 0.01)	0.058	-0.37 (-0.76, 0.01)	0.058
LVFW_s - 14wks	12.92 (2.18)		.		.	11.98 (2.21)		0.468*		0.462*
- 20wks	12.47 (2.18)	-0.53 (-1.30, 0.24)	0.179	-0.53 (-1.30, 0.24)	0.180	11.96 (2.36)	-0.03 (-0.49, 0.43)	0.898	-0.03 (-0.49, 0.43)	0.908
- 24wks	12.27 (1.95)	-0.57 (-1.18, 0.03)	0.065	-0.58 (-1.18, 0.03)	0.063	11.97 (2.18)	-0.01 (-0.47, 0.46)	0.976	-0.01 (-0.47, 0.45)	0.968
- 30wks	11.76 (1.92)	-1.13 (-1.86, -0.40)	0.002	-1.13 (-1.86, -0.40)	0.002	11.43 (2.25)	-0.50 (-1.11, 0.12)	0.113	-0.49 (-1.10, 0.13)	0.120
RV_s - 14wks	16.22 (2.24)		.		.	15.49 (1.95)		0.927*		0.930*
- 20wks	17.00 (1.92)	0.78 (0.19, 1.38)	0.010	0.78 (0.19, 1.38)	0.010	16.24 (2.16)	0.73 (0.22, 1.24)	0.005	0.73 (0.22, 1.24)	0.005
- 24wks	16.61 (2.77)	0.39 (-0.53, 1.30)	0.408	0.39 (-0.53, 1.31)	0.406	15.56 (1.77)	0.14 (-0.33, 0.61)	0.550	0.14 (-0.32, 0.61)	0.546
- 30wks	16.75 (2.22)	0.50 (-0.16, 1.15)	0.138	0.50 (-0.16, 1.15)	0.139	15.67 (1.73)	0.24 (-0.25, 0.74)	0.339	0.25 (-0.25, 0.74)	0.334

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). EF: ejection fraction; FS: fractional shortening; H-R: high-risk, LVFW: left ventricular free wall, LVOT: left ventricular outflow tract, L-R: low-risk, RV: right ventricle, Sep: septal, SIMP: Simpson's biplane method, VTI: velocity time integral.

Table 25. Diastolic cardiovascular variables over time in low-risk and high-risk women with a normal pregnancy outcome

Outcome - Time	L-R Mean (SD)	L-R Unadj. Diff vs 14wks (95% C.I)	L-R Unadj p value	L-R Adj Diff vs T1 (95% C.I)	L-R Adj p value	H-R Mean (SD)	H-R Unadj. Diff vs 14wks (95% C.I)	H-R Unadj p value	H-R Adj Diff vs T1 (95% C.I)	H-R Adj p value
MV_E - 14wks	86.85 (13.11)		.		.	85.86 (13.90)		0.362*		0.366*
- 20wks	87.54 (14.11)	0.70 (-2.18, 3.58)	0.635	0.69 (-2.18, 3.57)	0.636	87.84 (15.24)	2.27 (-1.04, 5.58)	0.179	2.26 (-1.05, 5.56)	0.180
- 24wks	84.71 (13.77)	-1.74 (-4.61, 1.14)	0.236	-1.74 (-4.61, 1.14)	0.237	82.60 (14.76)	-3.28 (-6.35, -0.21)	0.037	-3.28 (-6.35, -0.20)	**0.037**
- 30wks	81.54 (11.80)	-5.85 (-9.11, -2.59)	0.000	-5.85 (-9.11, -2.60)	**0.000**	76.75 (12.23)	-8.69 (-11.73, -5.64)	0.000	-8.68 (-11.75, -5.62)	**0.000**
MV_A - 14wks	51.26 (9.90)		.		.	49.98 (9.56)		0.715*		0.718*
- 20wks	53.30 (9.26)	1.91 (-0.93, 4.75)	0.187	1.91 (-0.94, 4.75)	0.189	50.20 (7.80)	0.81 (-1.38, 2.99)	0.470	0.86 (-1.32, 3.04)	0.438
- 24wks	54.52 (8.56)	2.84 (-0.20, 5.88)	0.067	2.83 (-0.22, 5.87)	0.069	51.18 (8.30)	1.39 (-0.80, 3.58)	0.214	1.40 (-0.80, 3.59)	0.212
- 30wks	56.22 (7.61)	5.15 (2.01, 8.30)	0.001	5.18 (2.03, 8.32)	**0.001**	52.43 (8.62)	2.89 (0.63, 5.15)	0.012	2.93 (0.67, 5.18)	**0.011**
MV_EA - 14wks	1.77 (0.49)		.		.	1.79 (0.40)		0.917*		0.923*
- 20wks	1.71 (0.53)	-0.06 (-0.21, 0.10)	0.471	-0.06 (-0.21, 0.10)	0.473	1.80 (0.44)	0.00 (-0.09, 0.10)	0.954	0.00 (-0.09, 0.09)	0.993
- 24wks	1.58 (0.28)	-0.17 (-0.30, -0.04)	0.011	-0.17 (-0.30, -0.04)	**0.011**	1.66 (0.40)	-0.14 (-0.22, -0.06)	0.001	-0.14 (-0.22, -0.06)	**0.001**
- 30wks	1.47 (0.28)	-0.31 (-0.45, -0.17)	0.000	-0.31 (-0.45, -0.17)	**0.000**	1.49 (0.27)	-0.30 (-0.38, -0.22)	0.000	-0.30 (-0.38, -0.22)	**0.000**
IVRT - 14wks	92.14 (14.38)		.		.	92.23 (12.23)		0.746*		0.732*
- 20wks	88.01 (13.51)	-4.35 (-8.72, 0.01)	0.051	-4.38 (-8.75, -0.02)	0.049	90.69 (13.62)	-1.83 (-5.52, 1.86)	0.331	-1.76 (-5.45, 1.93)	0.349
- 24wks	93.03 (12.67)	0.49 (-3.71, 4.69)	0.820	0.43 (-3.76, 4.62)	0.840	94.46 (11.85)	2.21 (-1.28, 5.69)	0.214	2.19 (-1.30, 5.68)	0.218
- 30wks	94.03 (11.37)	1.98 (-2.56, 6.53)	0.393	1.96 (-2.58, 6.51)	0.398	97.84 (11.05)	4.80 (1.34, 8.27)	0.007	4.80 (1.34, 8.27)	**0.007**
DT - 14wks	153.22 (19.25)		.		.	151.55 (26.46)		0.421*		0.415*
- 20wks	154.11 (19.55)	1.61 (-4.66, 7.89)	0.614	1.61 (-4.68, 7.90)	0.616	149.89 (15.89)	-1.63 (-7.47, 4.20)	0.583	-1.67 (-7.53, 4.18)	0.575
- 24wks	150.47 (17.72)	-2.55 (-9.10, 4.00)	0.446	-2.52 (-9.11, 4.07)	0.453	151.78 (19.17)	0.73 (-4.80, 6.27)	0.795	0.75 (-4.76, 6.27)	0.789
- 30wks	148.91 (20.50)	-3.94 (-11.38, 3.50)	0.299	-3.94 (-11.40, 3.51)	0.300	150.05 (19.24)	-1.37 (-8.36, 5.61)	0.700	-1.33 (-8.31, 5.65)	0.709
A_DUR - 14wks	116.59 (15.95)		.		.	120.73 (19.38)		0.592*		0.599*
- 20wks	114.43 (15.42)	-1.72 (-6.03, 2.58)	0.432	-1.74 (-6.04, 2.56)	0.427	116.92 (14.17)	-3.76 (-7.87, 0.34)	0.072	-3.73 (-7.83, 0.37)	0.074
- 24wks	118.63 (13.85)	2.32 (-1.95, 6.60)	0.287	2.30 (-1.96, 6.57)	0.290	118.90 (17.02)	-1.18 (-5.60, 3.24)	0.602	-1.17 (-5.58, 3.24)	0.603
- 30wks	116.71 (13.82)	0.42 (-4.30, 5.14)	0.861	0.41 (-4.31, 5.13)	0.864	117.68 (16.79)	-3.69 (-8.75, 1.36)	0.152	-3.66 (-8.71, 1.39)	0.156

Outcome - Time	L-R Mean (SD)	L-R Unadj. Diff vs 14wks (95% C.I)	L-R Unadj p value	L-R Adj Diff vs T1 (95% C.I)	L-R Adj p value	HR Mean (SD)	H-R Unadj. Diff vs 14wks (95% C.I)	H-R Unadj p value	H-R Adj Diff vs T1 (95% C.I)	H-R Adj p value
SEP_e - 14wks	15.63 (2.73)		.		.	14.86 (2.41)		0.691*		0.691*
- 20wks	15.47 (2.57)	0.02 (-0.85, 0.89)	0.966	0.01 (-0.86, 0.88)	0.978	14.70 (2.67)	-0.19 (-0.81, 0.43)	0.546	-0.20 (-0.82, 0.42)	0.532
- 24wks	15.28 (2.62)	-0.19 (-1.02, 0.63)	0.645	-0.19 (-1.02, 0.63)	0.650	14.06 (2.33)	-0.82 (-1.45, -0.18)	0.012	-0.81 (-1.45, -0.18)	**0.012**
- 30wks	14.08 (2.90)	-1.43 (-2.23, -0.64)	0.000	-1.43 (-2.23, -0.64)	**0.000**	13.12 (2.76)	-1.70 (-2.34, -1.05)	0.000	-1.69 (-2.33, -1.05)	**0.000**
SEP_a - 14wks	8.08 (1.94)		.		.	8.06 (1.62)		0.843*		0.846*
- 20wks	8.34 (1.64)	0.27 (-0.29, 0.82)	0.346	0.27 (-0.28, 0.82)	0.338	8.29 (1.54)	0.28 (-0.09, 0.64)	0.139	0.29 (-0.08, 0.65)	0.125
- 24wks	8.94 (1.55)	0.85 (0.25, 1.44)	0.005	0.84 (0.24, 1.43)	**0.006**	8.63 (1.35)	0.59 (0.19, 0.98)	0.004	0.58 (0.18, 0.98)	**0.004**
- 30wks	9.49 (1.82)	1.41 (0.73, 2.09)	0.000	1.41 (0.72, 2.09)	**0.000**	9.23 (1.82)	1.19 (0.69, 1.69)	0.000	1.18 (0.68, 1.69)	**0.000**
SEP_e/a - 14wks	2.01 (0.50)		.		.	1.91 (0.49)		0.913*		0.905*
- 20wks	1.90 (0.37)	-0.11 (-0.22, 0.01)	0.075	-0.11 (-0.22, 0.01)	0.071	1.84 (0.49)	-0.09 (-0.19, 0.01)	0.071	-0.09 (-0.20, 0.01)	0.065
- 24wks	1.75 (0.38)	-0.25 (-0.37, -0.14)	0.000	-0.25 (-0.36, -0.14)	**0.000**	1.67 (0.41)	-0.25 (-0.35, -0.14)	0.000	-0.25 (-0.35, -0.14)	**0.000**
- 30wks	1.53 (0.38)	-0.48 (-0.60, -0.36)	0.000	-0.48 (-0.61, -0.36)	**0.000**	1.49 (0.43)	-0.43 (-0.55, -0.31)	0.000	-0.43 (-0.55, -0.31)	**0.000**
SEP_E/e - 14wks	5.70 (1.11)		.		.	5.89 (1.17)		0.903*		0.901*
- 20wks	5.81 (1.10)	0.10 (-0.23, 0.44)	0.542	0.11 (-0.23, 0.44)	0.536	6.08 (1.16)	0.22 (-0.08, 0.51)	0.146	0.22 (-0.07, 0.51)	0.141
- 24wks	5.72 (1.19)	-0.00 (-0.30, 0.30)	0.975	-0.01 (-0.31, 0.30)	0.971	5.98 (1.11)	0.10 (-0.19, 0.38)	0.499	0.10 (-0.19, 0.38)	0.505
- 30wks	5.99 (1.23)	0.24 (-0.15, 0.64)	0.230	0.24 (-0.15, 0.64)	0.229	6.09 (1.47)	0.20 (-0.20, 0.60)	0.333	0.20 (-0.21, 0.60)	0.340
LVLW_e - 14wks	18.60 (2.76)		.		.	18.86 (3.29)		0.786*		0.777*
- 20wks	18.28 (2.72)	-0.14 (-0.79, 0.50)	0.662	-0.16 (-0.80, 0.49)	0.635	18.56 (3.49)	-0.41 (-1.02, 0.21)	0.199	-0.41 (-1.03, 0.20)	0.188
- 24wks	17.77 (3.39)	-0.83 (-1.69, 0.02)	0.056	-0.83 (-1.68, 0.02)	0.057	17.64 (3.48)	-1.26 (-1.96, -0.56)	0.000	-1.26 (-1.96, -0.56)	**0.000**
- 30wks	16.41 (3.17)	-2.05 (-2.85, -1.24)	0.000	-2.05 (-2.86, -1.24)	**0.000**	17.02 (2.88)	-2.01 (-2.75, -1.26)	0.000	-2.00 (-2.74, -1.25)	**0.000**
LVLW_a - 14wks	8.58 (1.88)		.		.	8.46 (1.67)		0.621*		0.625*
- 20wks	8.78 (1.80)	0.28 (-0.28, 0.83)	0.326	0.28 (-0.27, 0.83)	0.322	8.43 (1.44)	-0.01 (-0.46, 0.45)	0.982	0.01 (-0.45, 0.46)	0.981
- 24wks	8.92 (1.95)	0.29 (-0.24, 0.83)	0.282	0.29 (-0.25, 0.82)	0.292	8.90 (1.76)	0.45 (-0.01, 0.92)	0.057	0.45 (-0.02, 0.92)	0.058
- 30wks	9.17 (1.47)	0.58 (0.04, 1.12)	0.036	0.58 (0.04, 1.12)	**0.037**	9.10 (1.80)	0.55 (0.00, 1.10)	0.048	0.55 (0.01, 1.10)	**0.048**
LVLW_e/a - 14wks	2.26 (0.56)		.		.	2.31 (0.59)		0.185*		0.180*
- 20wks	2.15 (0.51)	-0.11 (-0.23, 0.01)	0.082	-0.11 (-0.23, 0.01)	0.078	2.27 (0.61)	-0.05 (-0.18, 0.07)	0.389	-0.06 (-0.18, 0.07)	0.366
- 24wks	2.09 (0.66)	-0.17 (-0.31, -0.02)	0.022	-0.17 (-0.31, -0.02)	**0.023**	2.05 (0.54)	-0.27 (-0.39, -0.15)	0.000	-0.27 (-0.39, -0.15)	**0.000**
- 30wks	1.83 (0.45)	-0.42 (-0.55, -0.30)	0.000	-0.42 (-0.55, -0.30)	**0.000**	1.95 (0.54)	-0.35 (-0.50, -0.20)	0.000	-0.35 (-0.50, -0.20)	**0.000**

Outcome - Time	L-R Mean (SD)	L-R Unadj. Diff vs 14wks (95% C.I)	L-R Unadj p value	L-R Adj Diff vs T1 (95% C.I)	L-R Adj p value	HR Mean (SD)	H-R Unadj. Diff vs 14wks (95% CI.)	H-R Unadj p value	H-R Adj Diff vs T1 (95% C.I)	H-R Adj p value
LVLW_E/e - 14wks	4.77 (0.97)		.		.	4.65 (0.94)		0.536*		0.528*
- 20wks	4.92 (1.00)	0.15 (-0.10, 0.40)	0.249	0.15 (-0.10, 0.40)	0.245	4.81 (0.80)	0.19 (0.00, 0.37)	0.046	0.19 (0.01, 0.37)	**0.040**
- 24wks	4.98 (1.21)	0.24 (-0.06, 0.53)	0.115	0.23 (-0.06, 0.53)	0.119	4.83 (1.13)	0.18 (-0.07, 0.42)	0.151	0.18 (-0.07, 0.42)	0.153
- 30wks	5.12 (1.15)	0.31 (-0.05, 0.67)	0.088	0.31 (-0.05, 0.67)	0.087	4.62 (0.97)	0.02 (-0.23, 0.26)	0.892	0.02 (-0.23, 0.26)	0.896
RV_e - 14wks	19.36 (2.91)		.		.	17.66 (3.10)		0.147*		0.138*
- 20wks	19.54 (2.84)	0.35 (-0.44, 1.14)	0.386	0.34 (-0.45, 1.13)	0.400	18.02 (3.03)	0.33 (-0.40, 1.05)	0.379	0.33 (-0.40, 1.05)	0.378
- 24wks	19.24 (3.32)	0.08 (-0.98, 1.13)	0.889	0.07 (-0.99, 1.13)	0.894	17.08 (2.91)	-0.45 (-1.25, 0.35)	0.271	-0.44 (-1.24, 0.36)	0.281
- 30wks	18.42 (3.47)	-0.90 (-2.14, 0.34)	0.155	-0.90 (-2.14, 0.33)	0.153	17.82 (3.76)	0.28 (-0.68, 1.25)	0.564	0.31 (-0.65, 1.28)	0.528
RV_a - 14wks	12.50 (2.27)		.		.	12.55 (2.83)		0.728*		0.733*
- 20wks	13.44 (2.70)	0.92 (0.00, 1.84)	0.050	0.93 (0.02, 1.84)	0.045	12.73 (3.20)	0.29 (-0.47, 1.05)	0.453	0.30 (-0.46, 1.07)	0.438
- 24wks	13.74 (3.31)	1.21 (0.07, 2.35)	0.037	1.20 (0.06, 2.33)	**0.038**	13.71 (3.07)	1.20 (0.50, 1.90)	0.001	1.19 (0.49, 1.89)	**0.001**
- 30wks	14.45 (3.66)	1.93 (0.68, 3.18)	0.002	1.93 (0.69, 3.18)	**0.002**	14.48 (3.38)	2.01 (1.13, 2.89)	0.000	1.97 (1.09, 2.86)	**0.000**
RV_e/a - 14wks	1.59 (0.35)		.		.	1.47 (0.41)		0.254*		0.243*
- 20wks	1.50 (0.32)	-0.08 (-0.19, 0.03)	0.154	-0.08 (-0.20, 0.03)	0.145	1.50 (0.42)	0.01 (-0.07, 0.08)	0.889	0.01 (-0.07, 0.08)	0.892
- 24wks	1.46 (0.32)	-0.12 (-0.22, -0.02)	0.021	-0.12 (-0.22, -0.02)	**0.021**	1.31 (0.35)	-0.17 (-0.25, -0.08)	0.000	-0.16 (-0.25, -0.08)	**0.000**
- 30wks	1.36 (0.40)	-0.23 (-0.36, -0.10)	0.000	-0.23 (-0.36, -0.11)	**0.000**	1.30 (0.38)	-0.18 (-0.29, -0.07)	0.001	-0.18 (-0.28, -0.07)	**0.001**

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). a: a wave velocity, A dur: A wave duration, DT: deceleration time, e: e wave velocity, H-R: high-risk, IVRT: isovolumetric relaxation time: LR: low-risk, LVFW: left ventricular lateral wall, MV: mitral valve, RV: right ventricle, SEP: septal.

6.4 Discussion

This prospective longitudinal study evaluated cardiovascular structure and function at 14, 20, 24 and 30 weeks' gestation, in women screened 'low-risk' and 'high-risk' for early-onset PE using the FMF algorithm with a subsequent normal pregnancy outcome. Forty low-risk women with a normal pregnancy outcome had a significant increase in their CO, CI and HR from 14 to 30 weeks' gestation, while MAP was unchanged and TPR/TPRI declined.

These changes were in keeping with previous studies; however, the most salient finding was that the major contribution towards the increased CO/CI was a rise in HR without an increase in SV. When SV was indexed, there was a significant decrease over this time period. This is in contrast to previously held beliefs that SV and therefore SVI increases during pregnancy despite very few studies actually applying indexation to SV. The majority of studies that did report indexed values, only applied indexation to CO and not SV (42, 327, 329, 330, 350, 365, 399, 404, 406, 483).

In regard to the 62 high-risk women with a normal pregnancy outcome, there was also a significant increase in their CO and HR, with mean values comparable to the low-risk women. Despite a small increase in CI between 14 and 30 weeks' gestation this was not statistically significant in the high-risk women, unlike the low-risk group. In keeping with the low-risk women, the SV was unchanged while the SVI decreased significantly. The TPR and TPRI also declined in keeping with the low-risk women, however the TPRI only reached statistical significance between 14 - 24 weeks' gestation. This was directly related to the changes in MAP, with values decreasing over the same time period and rising again slightly at 30 weeks' gestation.

It is well accepted that a healthy pregnancy requires physiological adaptation of the cardiovascular system to support fetal growth and development whilst maintaining maternal well-being. The blood volume expansion that begins early in pregnancy leads to an increase in preload with a concomitant decrease in afterload, secondary to a reduction in systemic vascular resistance. The TPR / TPRI decrease in both groups within our study between 14 and 30 weeks' gestation, reflected the reduction in afterload and is in keeping with numerous

studies (35, 332, 334, 358, 362, 363). There is, however, considerable variation in published values, relating to differences in CO / CI and MAP values. A recently published meta-analysis suggested that TPR decreased in the first half of pregnancy, with a small significant rise late in the second trimester followed by a continual decline to term (368). Our low-risk and high-risk women both reflected a continual decline from the second to third trimesters.

The MAP was essentially stable in low-risk women between 14 and 30 weeks' gestation in keeping with numerous studies (331, 332, 351, 358, 364, 365), however there was a subtle drop at 20 weeks' gestation which was not statistically significant. The high-risk women showed this decline at 20 and 24 weeks' gestation, reaching statistical significance. A number of previous studies have reported a mid-gestation drop in MAP (45, 330, 333, 334, 368). This may reflect the lower resistance in the uterine vasculature bed, resulting from further vasodilatation of the uterine arteries at this gestation. A notable difference between the low-risk and high-risk women with a subsequent normal pregnancy, was the MAP was significantly higher in the women stratified as high-risk. The mean values were also markedly higher than other studies (35, 45, 334, 350, 351, 368).

Heart rate increased steadily over 14 - 30 weeks' gestation in both groups, consistent with the literature (35, 44, 45, 326, 328, 330-332, 334, 351, 362, 368, 374, 416). The significant rise in heart rate was solely responsible for the changes in CO / CI, whereas previous studies have reported increased stroke volume as the main determinant (328, 329, 331, 332, 362, 416).

Our study showed SV did not change from 14 - 30 weeks' gestation in contrast to a number of studies which found stroke volume continually increased with gestation (328, 329, 331, 332, 409). Other groups showed SV peaked in the second trimester and then plateaued (334, 348, 358, 365, 399), while a few studies reported that SV declined near term (330, 333, 416). The gestation of the SV measurements in these studies were not identical to our time points and therefore the SV changes could have occurred prior to 14 weeks' gestation or after 30 weeks' gestation. Two studies have demonstrated a marked increase in stroke volume during the first 8 weeks of pregnancy (326, 351), while Mabie *et al* (1994) (328) reported a higher SV at 8 - 11 weeks compared to 12 - 15 weeks.

There are only a few longitudinal studies that commenced pre-conception with small subject numbers (326, 351, 374), while other studies used post-partum values or non-pregnant controls to determine SV changes during pregnancy. It is quite reasonable that SV would increase prior to 14 weeks' gestation, given it is widely accepted that blood volume increases during the first trimester. The effect of this volume expansion results in an increase in preload and therefore contractility, consequently increasing SV prior to 14 weeks' gestation.

In regard to a potential rise in SV beyond 30 weeks' gestation, the study by Schannwell *et al* (2002) (362) found SV was not significantly different between non-pregnant controls and women at 24 weeks' gestation, however there was a significant increase from 24 to 33 weeks' gestation. The meta-analysis by Meah *et al* (2016) (368) showed SV only contributed a small proportion to the overall increase in CO with gestation, with a drop during the late second trimester. An explanation for this observation was that while blood volume remained relatively stable during the second trimester, there is a further increase in capacity of the venous compartment (secondary to further vasodilation of the uterine arteries and other organ systems) resulting in a decrease in venous return (368).

In terms of SVI, our values were significantly less at 30 weeks' gestation compared to 14 weeks' gestation, in keeping with the studies by Melchiorre *et al* (2016) (35) and Mone *et al* (1996) (330). Melchiorre showed a significant decline in SVI from the first to the third trimester but did not provide comment on this result; instead, they commented on the results between the first and second trimesters, which showed there was no change in SVI. Mone reported that the fall in SVI corresponded to the fall in FS, suggesting this was related to a decline in contractility, in contrast to the load independent measures that showed contractility was preserved in normal pregnancy. This does not adequately explain their observation. This result brings into question the impact normalising measurements for body size can have on the validity of these data and whether BSA is an appropriate method of indexation in pregnancy. It is also possible that the decline in SVI may be due to excess or inappropriate weight gain unduly influencing the BSA.

The CO increase from the start of the second trimester to early in the third trimester was in keeping with a number of studies (326, 328, 331, 332, 334, 351, 364, 365, 409) and a meta-analysis by Meah *et al* (2016) (368). The meta-analysis was compiled from studies of which the majority were longitudinal in design using echocardiography derived measurements of CO. The results were comparable to our study; 5.7 L/min - 6.48 L/min versus 5.58 L/min - 6.31 L/min (low-risk women) and 5.47 L/min - 5.82 L/min (high-risk women). A subsequent study by Melchiorre *et al* (2016) (35) also reported similar results with the median CO increasing from 5.7 L/min in the first trimester to 6.4 L/min in the third trimester. In terms of CI, this group found no change over the same time period (4.1 L/min/m^2 - 4.0 L/min/m^2). The CI in our low-risk women increased significantly from 14 to 20 weeks' gestation and then plateaued, while our mean values were substantially lower (3.19 L/min/m^2 - 3.43 L/min/m^2). The high-risk women showed CI increased marginally (3.17 L/min/m^2 - 3.24 L/min/m^2), however remained statistically unchanged. The Melchiorre group used the same body surface area indexation method as our study, which would infer their cohort had smaller BSA. This is unsurprising given the Melchiorre study excluded women with a prepregnancy BMI > 30kg/m^2 and we did not. Other studies have reported that CO/CI declined late in the third trimester (330, 333, 340, 374) which may correlate to a concomitant increase in MAP, however this is beyond the scope of our study.

Indexation of cardiac output is widely accepted to normalise for differences in body size, however the method of indexation is not consistent across studies. A number of studies derived CI using the Dubois BSA formula (35, 37, 328, 331, 365, 406, 416), while Mone *et al* (1996) (330) used the Haycock BSA formula. These groups all used BSA derived from actual weight. The study by Simmons *et al* (2002) (45) also used the Dubois formula, however the BSA calculation was derived from weight measured at 12 weeks' post-partum, termed the 'ideal BSA'. The group used the 'ideal BSA' so as not to overestimate the CI from weight gained in pregnancy. The limitation with this approach is that it does not account for the amount of weight gain of the individual and the increased metabolic demand with advancing gestation. Both of these factors have a significant impact on cardiac output. One of the largest longitudinal studies by Bosio *et al* (1991) (40) adjusted CO with BMI, while the study by De Paco *et al* (2008) (43) indexed

CO to height raised to the 1.83 exponent. The lack of standardisation with cardiac output indexation has confounded the variability in results and potentially led to different conclusions regarding cardiovascular adaptation in normal pregnancy.

The majority of the secondary systolic outcomes (ejection fraction, fractional shortening and s wave velocities) showed no change between 14 and 30 weeks' gestation, in keeping with the literature (327, 331, 332, 363-365, 404, 409). The majority of secondary measurements also showed no difference in mean values between the two groups. There were a few exceptions, notably the Simpson's ejection fraction in the high-risk women was lower at 24 and 30 weeks' gestation, while the s wave velocity at the left lateral wall in the low-risk women was higher only at 14 weeks' gestation. Additionally, the s wave velocities in the right lateral wall were significantly lower in the high-risk group between 20 and 30 weeks' gestation.

In regard to the s wave velocities, only the low-risk women showed a significant decrease at the left lateral wall between 14 and 30 weeks' gestation. This was not evident at the septum, however changes in velocity using TDI are often observed in the left lateral wall prior to the septum in certain conditions. There have only been a few studies that have reported s wave velocities in normal pregnancy, with mixed results in regard to an increase from the first to second trimesters versus no change (404, 409, 422). The s wave velocities at the right lateral wall were also significantly less in the high-risk women between 20 and 30 weeks' gestations. There is very limited data of right lateral TDI velocities, with Melchiorre *et al* (2016) (35) the only group to study this measure. The group used colour TDI, which is not comparable to PW Doppler in terms of absolute values, however the group showed no change between the first, second and third trimesters (35).

The Simpson's biplane method of calculating ejection-fraction showed a small but significant decline in the high-risk women, with a significant difference the mean values at 24 and 30 weeks compared to low-risk women. As this was not replicated in the M-mode method, the result may be due to technical difficulties with measuring the LV chamber, as the endocardium can be difficult to identify, especially when confounded by advancing gestation. However, two studies have shown a decrease in EF and FS from the second to third trimesters (369, 416).

Cardiac remodelling secondary to an increase in circulating volume during pregnancy was evidenced in both groups of women by an increase in LVM and between 14 to 30 weeks' gestation, consistent with the majority of reports (35, 45, 326, 328, 330, 332, 334, 362, 368, 374, 404). In terms of LVMI, the high-risk women showed no change, while low-risk women demonstrated LVMI increased. The study by Melchiorre *et al* 2016(35) also showed no change in LVMI between 14 and 30 weeks' gestation in nulliparous women with a normal pregnancy outcome. This is in contrast to other studies that have shown LVMI increases during normal pregnancy (45, 328, 329, 331, 332). This discrepancy in results suggests potential indexation issues, with the method of indexation not always reported.

The alterations in left ventricular diastolic function were in keeping with the expected changes that are well reported secondary to blood volume expansion during pregnancy (358, 404, 409, 427). The blood volume increase resulted in a shift in left ventricular filling from early to late diastole, reflected in both the transmitral inflow Doppler and tissue Doppler imaging waveforms. This is evidenced by a decrease in peak E and e wave velocities with a concomitant increase in A and *a* wave velocities from the first to third trimesters. The E/A ratio and *e/a* ratios at both the septal and left lateral ventricle sites in all women consequently decreased, which is consistent with the literature (35, 362, 404, 409, 416, 422). The septal and left lateral E/*e* ratios were unchanged in both groups at all time points (with the exception of the lateral E/*e* ratio at 20 weeks' gestation in the high-risk women), in keeping with a number of studies at the same gestation (35, 404, 416, 427). The diagnosis and classification of diastolic dysfunction as recommended jointly by the ASE and EACVI relies on a number of indices and should be interpreted in a wider context with other 2D or Doppler parameters (420). Despite significant changes in left ventricular diastolic function from 14 - 30 weeks' gestation, none of the women in this study with a normal pregnancy outcome had impaired LV relaxation. However, the parameters for defining diastolic dysfunction are applicable to non-pregnant individuals and have not been validated in pregnancy (420).

There are very limited data on right ventricular diastolic function in pregnancy (35, 334). Melchiorre *et al* (2016) (35) assessed right diastolic function using colour TDI and found the *e/a* ratio was significantly higher in the first trimester compared

to non-pregnant controls and that this ratio significantly declined with gestation to term. In conjunction with strain rate data, the group inferred right diastolic dysfunction was more frequent at term in women with a normal pregnancy. The ASE have guidelines and reference ranges for diagnosing right diastolic dysfunction, of which the measurement criteria differ to those used in the Melchiorre study (493). Our study found that the right ventricular *a* wave velocity using PW TDI increased with gestation, resulting in a significant decrease in the *e/a* ratio, despite the *e* wave velocity remaining stable. Assessment of right ventricular diastolic function was not a primary outcome measure of this study and cannot be determined from the TDI measures alone. Additionally, colour and PW tissue Doppler values are not interchangeable (435, 490) and therefore a direct comparison of values with our data could not be made.

This study demonstrates normal cardiovascular adaptation from 14 to 30 weeks' gestation in women stratified as low-risk and high-risk for ePE with a subsequent normal pregnancy outcome. The cardiovascular changes seen in pregnancy were fairly consistent between the two groups of women without a significant difference in mean values, except in regard to MAP and TPR. The significantly higher MAP in the high-risk women elevated TPR/TPRI. In terms of heart rate, stroke volume and cardiac output and their indexed equivalent measures, the values were all lower, however significance was not reached. These findings may suggest that women stratified as high-risk with a normal pregnancy outcome do not exhibit the same degree of cardiovascular adaptation as women stratified as low-risk for early-onset PE, similar to a recent study by Ling *et al* (2018) (494). This group demonstrated normotensive women screen-positive for preterm PE exhibited pathological cardiovascular adaptation in pregnancy compared to screen-negative women. Future application of these parameters to help differentiate the likelihood of normal versus an abnormal pregnancy outcome will need to be performed with consideration to what appropriately represents 'normal' population data.

The study was limited to 30 weeks' gestation as the primary interest was to identify changes early in pregnancy prior to any onset of signs and symptoms of pre-eclampsia that potentially could be included in screening for late-onset disease either in the first trimester or as a second tier of screening at a later gestation. To determine the validity and inclusion of potential cardiovascular

markers, an accurate evaluation in women with a normal pregnancy outcome should be established to help clearly differentiate physiological from pathological changes. There are conflicting reports of some of these cardiovascular measures, namely the time course and magnitude of change in CO and SV with gestation. For the time period observed, the increase in CO / CI was in keeping with the majority of studies. In terms of SV and SVI our results were consistent with more recent studies, while conflicting with older data.

An important consideration when evaluating these data is the application of indexation, which is generally an acceptable method for adjusting for differences in body size. In pregnancy, indexation is complex and problematic due to the highly metabolic fetus and placental mass influencing maternal weight and body shape and therefore BSA and BMI. Inappropriate indexation could potentially give rise to erroneous or misleading results and undermine differentiating physiological and pathological changes. These issues therefore impact the potential use of cardiovascular parameters as a screening marker.

Chapter 7

Study 4 - Longitudinal assessment of cardiovascular function in high-risk women with subsequent adverse pregnancy outcomes

7.1 Introduction

The cardiovascular system undergoes significant structural and functional change in pregnancy to accommodate maternal demand and the rapidly growing fetus. A number of studies have assessed these haemodynamic changes in women with a subsequent normal pregnancy outcome and I reported my findings in this context in *Chapter 6, section 6.3 Results*.

Studies have shown maladaptation of the cardiovascular system is associated with the development of both ePE and lPE, gestational hypertension and fetal growth restriction, with different haemodynamic profiles reported for these pathologies (36-41, 44, 45, 47-49, 51, 53, 54, 56, 419, 437, 438, 495). A proposed theory is that pre-eclamptic women have a hyperdynamic circulation prior to the onset of symptoms and signs of pre-eclampsia which changes to a low cardiac output / high resistance profile when disease becomes overt. This theory has not been adequately investigated, with only a handful of studies supporting the concept (39-44, 50, 496).

Maternal endothelial dysfunction has been consistently demonstrated during pre-eclampsia and may provide a potential mechanistic link between the condition and possibly maladaptive changes in cardiac structure and function (27, 46, 58). This raises the question of whether some women destined to develop pre-eclampsia have undetected endothelial dysfunction manifesting prior to the rise in blood pressure, and that this is the cause and not the consequence of late-onset disease. (46, 138, 186, 188).

Current screening methods to identify women at risk of developing pre-eclampsia using the FMF algorithm have an excellent detection rate of 93% for a fixed false positive rate of 5% for early-onset disease (195), however the algorithm works less well for late-onset disease with a detection rate of up to 47% for a fixed false positive rate of 10% (259, 260). The FMF algorithm incorporates markers related to placentation, namely PAPP-A, PlGF and uterine artery Doppler PI with low PAPP-A / PlGF and high uterine artery PI both strongly associated with early-onset PE. These features support the concept of a placental phenotype of pre-eclampsia. In terms of late-onset disease, this association is weaker, suggesting that in the first half of pregnancy, placentation is not initially affected and that

other factors such as maladaptation of the cardiovascular system may have an important role in the development of a maternal phenotype of pre-eclampsia. Exploring potential cardiovascular markers in the preclinical phase of disease may help to identify those truly at risk of late-onset PE.

The aim of this study was to describe cardiovascular parameters of women stratified as high-risk for the development of early-onset pre-eclampsia who went on to have an adverse pregnancy outcome and compare these findings to high-risk women who had a normal pregnancy outcome.

7.2 Methods

This was a prospective study of maternal cardiac structure and function in singleton pregnancies involving 105 women screened high-risk for pre-eclampsia based on the FMF screening algorithm. Women were excluded if they had either pre-existing cardiac disease or hypertension, or developed essential hypertension, a multiple pregnancy or a fetus with a major anomaly. An echocardiogram was performed four times in their pregnancy at 14, 20, 24 and 30 weeks' gestation, with blood pressure and weight measured at each visit. A normal outcome was defined as a normotensive pregnancy with term delivery (greater than 37 weeks' gestation) and a normal birthweight (greater than 10th centile for gestational age) according to gender specific growth charts constructed from the local population (461). Cardiovascular structure and function at 14, 20, 24 and 30 weeks' gestation in women screened high-risk for pre-eclampsia was assessed, with a comparison between those who had a normal pregnancy outcome and those who experienced an adverse outcome. This included women who developed pre-eclampsia or gestational hypertension, delivered a small for gestational age infant or had a preterm birth. The primary cardiovascular parameters of the study were HR, SV, SVI, CO, CI, TRP and TPRI, with structural, systolic and diastolic measures secondary parameters. Specific echocardiography and blood pressure protocols are detailed in *Chapter 3, Methodology, sections 3.3 and 3.5.* Figure 37 outlines the methodology of this study.

7.2.1 Statistical analysis

Table 26 outlines baseline characteristics of each pregnancy outcome group (normal, pre-eclampsia, gestational hypertension, SGA, and preterm birth) for women stratified as high-risk. Continuous variables were characterised in terms of mean and standard deviation, or median and interquartile range if the distributions were highly skewed. Categorical variables are described as number and percentage.

A comparison of baseline characteristics between groups was done in two ways: firstly, comparing each adverse outcome group individually against the normal outcome group and secondly, performing an 'omnibus' test for any differences between all groups.

For normally distributed continuous outcomes, linear regression was used to test for differences in means between groups. For skewed continuous outcomes, the Wilcoxon (rank sum) test was used to test for differences in medians between normal outcome and each individual adverse outcome, while a Kruskal-Wallis test was used for the omnibus test of any difference between groups. For categorical variables, chi-square tests were used to test for differences between groups.

All cardiovascular variables were continuous and approximately normally distributed. Means and standard deviations are presented for each time point by group. A comparison between groups was undertaken using linear regression models, with Generalised Estimating Equations to account for correlation between repeated measures on the same participant and a time-by-group interaction term. For these analyses, due to the relatively small sample size, an exchangeable correlation structure was specified, which assumes that all observations within a cluster (participant) have equal covariance. However, robust variance estimation was used, which ensured valid inference even if the correlation structure was mis-specified. Measures of cardiovascular structure and function in both systole and diastole were evaluated, with BSA indexation applied to stroke volume, cardiac output and total peripheral resistance. Both unadjusted and adjusted analyses were performed, with parity and maternal age as covariates in the adjusted analyses. A two-tailed value of $p<0.05$ was considered statistically significant.

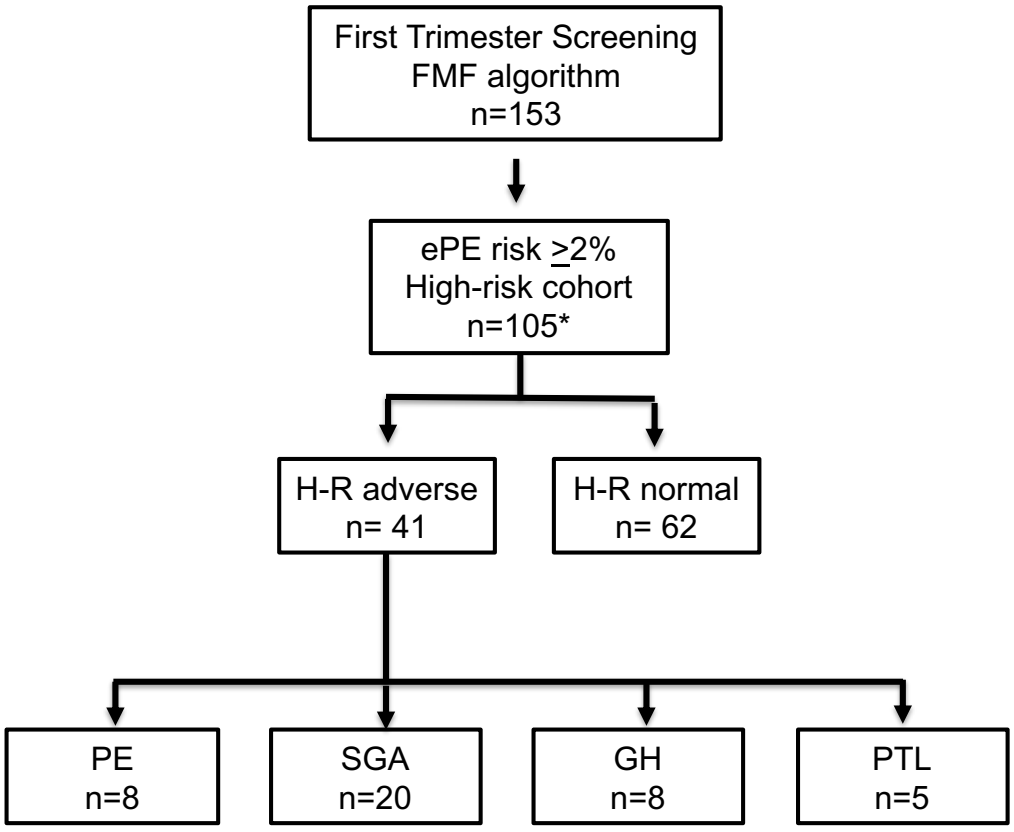


Figure 37. Methodology outline study 4

High-risk women with subsequent normal and adverse pregnancy outcomes

*2 cases excluded due to the existence of essential hypertension.

ePE: early-onset pre-eclampsia; FMF: Fetal Medicine Foundation; GH: gestational hypertension; HR: high-risk; PTL: preterm birth; SGA: small for gestational age.

7.3 Results

Forty-one (39%) of the 153 women defined as high-risk using the FMF screening algorithm subsequently had an adverse outcome, which included 8 (7.6 %) pre-eclamptic women, 8 (7.6 %) women with gestational hypertension, 20 (19 %) small for gestational age infants and 5 (4.8 %) preterm deliveries. With respect to baseline maternal characteristics, women with a normal pregnancy outcome were not significantly different in age compared to those with an adverse

pregnancy outcome, however there were some significant differences in body size.

For women who developed pre-eclampsia, height, weight, BSA and BMI were not statistically different compared to women with a normal pregnancy outcome respectively; 160.2 cm (SD 7.3 cm) versus 164.7 cm (SD 6.1 cm), p = 0.05; 66.3 kg (SD 10.6 kg) versus 66.3 kg (SD 9.2 kg), p = 0.98; 1.69 (SD 0.14) versus 1.72 (SD 0.13), p = 0.55 and 25.9 (SD 3.2) versus 24.5 (SD 4.0), p = 0.37. Women who had a preterm birth did not show statistically different maternal characteristics to women with a normal pregnancy outcome despite BSA of 1.84 (SD 0.10) compared to 1.72 (SD 0.13), p = 0.07. In regard to ethnicity, women who delivered SGA infants had greater representation of South Asian women (45% versus 11%), and less Caucasian women (35% versus 60%) compared to the normal group, while women who developed gestational hypertension had greater representation of Caucasian women (88% versus 60%). Table 26 outlines these results.

Weight, BSA and BMI in women who developed GH was significantly higher compared to women with a normal pregnancy outcome respectively; 77.6 kg (SD 16.6 kg) versus 66.3 kg (SD 10.6 kg), p = 0.007; 1.83 (SD 0.17) versus 1.72 (SD 0.13), p = 0.034 and 24.5 (SD 4.0) versus 29.0 (SD 6.1), p = 0.004. Women who gave birth to SGA infants were significantly shorter, weighed less and had a lower BSA compared to women with a normal outcome respectively; 159.8 cm (SD 5.4 cm) versus 164.7 cm (SD 6.1 cm), p = 0.002; 59.9 kg (SD 9.6 kg) versus 66.3 kg (SD 10.6 kg), p = 0.026 and 1.61 (SD 0.12) versus 1.72 (SD 0.13), p = 0.002. The BMI was, however, no different, measuring 23.5 (SD 4.1) in the SGA group compared to 24.5 (SD 4.0), p = 0.389 in the normal group. These data are summarised in Table 26 and Figure 38.

Pre-eclamptic women had infants with significantly lower birthweight and birthweight centile and delivered earlier than women with a normal pregnancy outcome respectively; 2859 gm (SD 619 gm) versus 3397 gm (SD 432 gm), p = 0.002; 19 % (IQR 10 %, 32 %) versus 44 % (IQR 32 %, 68 %) p = 0.002 and 266 days (IQR 259 days, 284 days) versus 277 days (IQR 271 days, 287 days), p = 0.045 (Table 26 and Figure 38).

Infants born to women with SGA had significantly lower birthweight and birthweight centile compared to infants born to women with a normal pregnancy outcome respectively; 2434 gm (SD 446 gm) versus 3397 gm (SD 432 gm), p < 0.001 and 4 % (IQR 2 %, 5 %) versus 44 % (IQR 32 %, 68 %), p < 0.001. These women with SGA infants also delivered slightly earlier at 274 days (IQR 261 days, 279 days) compared to 277 days (IQR 271 days, 278 days); p = 0.016 (Table 26 and Figure 38).

The birthweight and birthweight centiles for infants of women who developed gestational hypertension were similar to infants born to women with a normal pregnancy outcome; 3225 gm (SD 394 gm) versus 3397 gm (SD 432 gm) p = 0.319 and 70 % (IQR 43 %, 79 %) versus 44 % (IQR 32 %, 68 %), p = 0.914. The gestational age at delivery for GH women was, however, earlier at 268 days (IQR 261 days, 275 days) p = 0.006 compared to 277 days (IQR 271 days, 287 days) for women with a normal pregnancy outcome (Table 26 and Figure 38).

As expected, women who delivered preterm had an earlier gestational age at birth; 249 days (IQR 247 days, 258 days), compared to women with a normal pregnancy outcome; 277 days (IQR 271 days, 287 days), p <0.001. Subsequently, these infants were of significantly lower birthweight but no different in birthweight percentile; 2862 gm (SD 629 gm) versus 3397 gm (SD 432 gm), p = 0.014 and 70 % (IQR 58 %, 85 %) versus 44 % (IQR 32 %, 68 %), p = 0.985 (Table 26 and Figure 38).

The women who developed pre-eclampsia were all nulliparous, while the rate for women with a normal pregnancy outcome was 74%, comparative to the percentage of nulliparous women in the SGA group (80%). Nulliparous rates were 50% and 60% for women who developed gestational hypertension and had a preterm birth respectively. There was variation in the stratified percentage risk for the different outcome groups compared to high-risk women with a normal pregnancy outcome, however, there was not statistical significance. These data are summarised in Table 26 and Figure 38.

Table 26. Maternal and birth characteristics by pregnancy outcome

Characteristic	Normal	Pre-eclampsia	Gestational hypertension	SGA	Preterm	Omnibus
Maternal Age (years): Mean (SD)	31.90 (4.36)	32.00 (5.37) p=0.955	29.25 (5.09) p=0.123	30.60 (4.90) p=0.267	32.20 (2.39) p=0.889	0.490
Height (cm): Mean (SD)	164.69 (6.10)	160.19 (7.30) p=0.045	163.69 (4.34) p=0.653	159.80 (5.36) p=0.002	168.80 (4.56) p=0.136	**0.003**
Weight (kg): Mean (SD)	66.26 (10.56)	66.34 (9.20) p=0.983	77.55 (16.55) p=0.007	59.86 (9.62) p=0.026	73.78 (8.94) p=0.137	**0.002**
BSA: Mean (SD)	1.72 (0.13)	1.69 (0.14) p=0.545	1.83 (0.17) p=0.034	1.61 (0.12) p=0.002	1.84 (0.10) p=0.066	**0.001**
Ethnicity: N (%) - White - East Asian - South Asian - Aboriginal - Black - Black/White	 37 (59.7) 15 (24.2) 7 (11.3) 1 (1.6) 1 (1.6) 1 (1.6)	 5 (62.5) 0 (0.0) 3 (37.5) 0 (0.0) 0 (0.0) 0 (0.0) p=0.332	 7 (87.5) 1 (12.5) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) p=0.763	 7 (35.0) 4 (20.0) 9 (45.0) 0 (0.0) 0 (0.0) 0 (0.0) p=0.041	 2 (40.0) 3 (60.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) p=0.650	0.234
BMI: Mean (SD)	24.48 (3.95)	25.86 (3.19) p=0.372	28.98 (6.14) p=0.004	23.54 (4.06) p=0.389	25.94 (3.34) p=0.445	**0.028**
Parity ≥ 1: N (%)	16/62 (25.81%)	0/8 (0.00%) p=0.102	4/8 (50.00%) p=0.154	4/20 (20.00%) p=0.599	2/5 (40.00%) p=0.491	0.186
Birthweight (g): Mean (SD)	3396.68 (432.02)	2859.25 (618.52) p=0.002	3224.62 (394.04) p=0.319	2434.45 (445.99) p=0.000	2862.40 (629.03) p=0.014	**<0.001**
Birthweight Centile: Median (IQR)	44.0 (32.0, 68.0)	19.0 (10.0, 31.5) p=0.002	69.5 (43.0, 78.5) p=0.914	4.0 (2.0, 5.0) p=0.000	70.0 (58.0, 85.0) p=0.985	**<0.001**
GA at Delivery (days): Median (IQR)	277.0 (271.0, 287.0)	265.5 (259.0, 284.0) p=0.045	268.0 (261.0, 274.5) p=0.006	274.0 (261.0, 279.0) p=0.016	249.0 (247.0, 258.0) p=0.000	**<0.001**
Risk of ePE (%): Median (IQR)	5.50 (2.00, 13.00)	13.50 (7.50, 26.00) p=0.987	13.00 (4.00, 22.50) p=0.915	7.50 (5.00, 12.50) p=0.916	6.00 (3.00, 8.00) p=0.382	0.091

Data expressed as mean (SD) or median (IQR). BMI: body mass index, BSA: body surface area, ePE: early-onset pre-eclampsia, GA: gestational age, IQR: interquartile range, SGA: small for gestational age, SD: standard deviation.

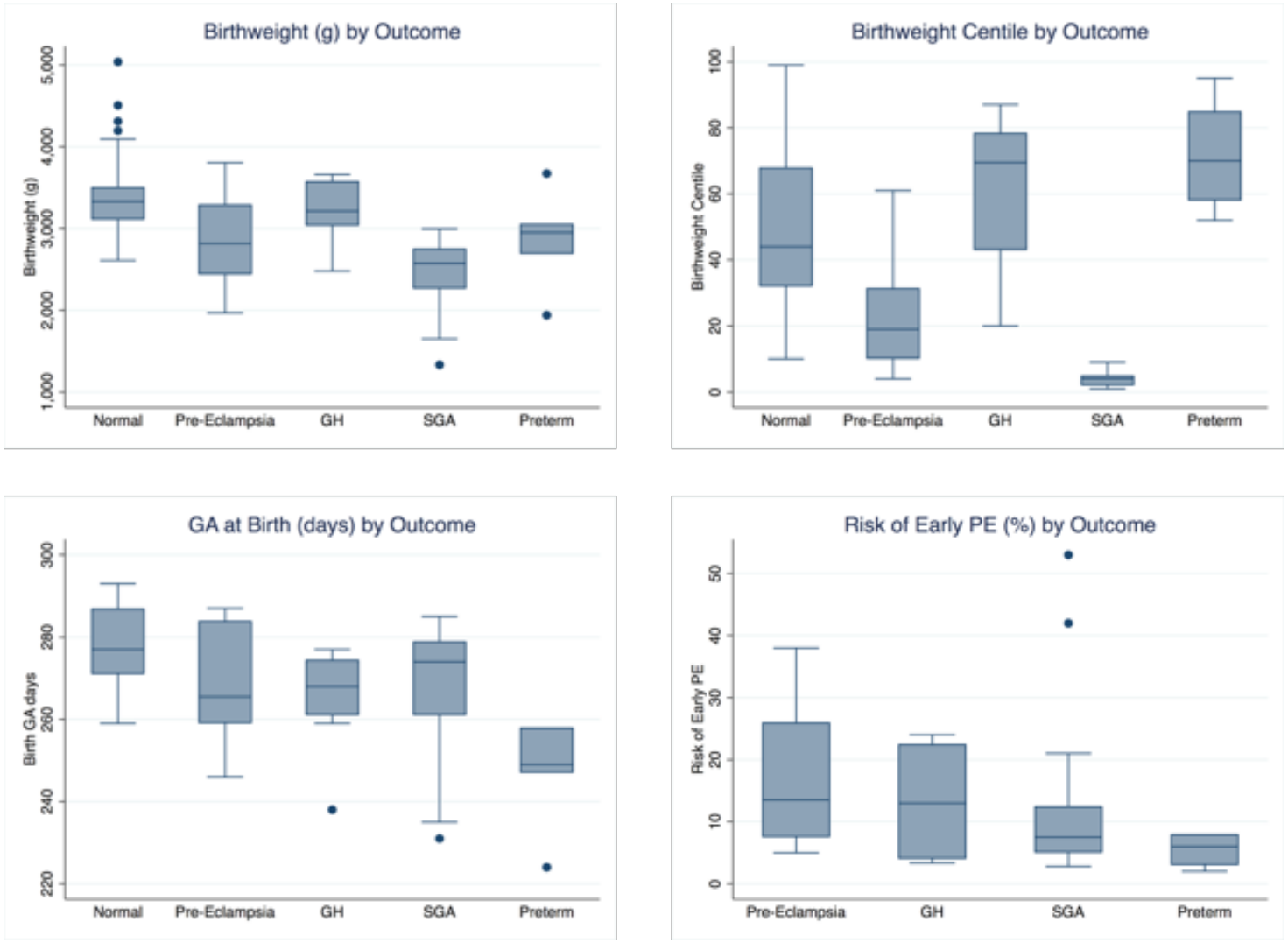


Figure 38. Birth characteristics by pregnancy outcome

Normal represents women stratified as high-risk with a normal pregnancy outcome. GH: gestational hypertension, SGA: small for gestational age.

7.4 Primary Cardiovascular Outcomes

7.4.1 Pre-eclampsia primary cardiovascular outcomes

Women stratified as high-risk for ePE who developed pre-eclampsia, did not augment their stroke volume between 14 and 30 weeks' gestation, measuring 64 ml (SD 17 ml) at 14 weeks' gestation and 66 ml (SD 19 ml); p = 0.439, at 30 weeks' gestation. There was no significant difference in mean values between the women who developed pre-eclampsia and those high-risk with a normal pregnancy outcome, despite lower mean values in the pre-eclampsia group (Table 27, Figure 42). SVI mean values were also lower in the pre-eclampsia group however statistical significance was also not reached. Between 14 and 30 weeks' gestation SVI was unchanged in women who developed pre-eclampsia; 37.4 ml/m^2 (SD 7.7 ml/m^2) to 37.1 ml/m^2 (SD 9.0 ml/m^2); p = 0.823, in contrast to the high-risk women with a normal outcome where SVI decreased significantly from 43.4 ml/m^2 (SD 6.7 ml/m^2) to 40.2 ml/m^2 (SD 6.8 ml/m^2); p = 0.001 (Table 28 and Figure 43).

Cardiac output increased secondary to a significant increase in heart rate from 73 bpm (SD 12 bpm) at 14 weeks to 78 bpm (SD 14 bpm) at 30 weeks' gestation; p = 0.036 (Table 27 and Figures 39 and 41). There was, however, no difference in mean values compared to high-risk women with a normal pregnancy outcome (Table 23). CO showed a non-significant increase from 4.6 L/min (SD 0.8 L/min) at 14 weeks' gestation to 5.0 L/min (SD 1.0 L/min) at 30 weeks' gestation; p = 0.075. (Table 28 and Figures 40 and 44) in women who developed pre-eclampsia. These values were all significantly lower compared to women with a subsequent normal pregnancy outcome at each time point (Table 27).

In high-risk women who developed pre-eclampsia, cardiac index increased between 14 and 24 weeks' gestation, plateauing to 30 weeks' gestation. All mean CI values were significantly lower compared to high-risk women with a normal pregnancy outcome between 14 to 30 weeks' gestation respectively; 3.2 L/min/m^2 (SD 0.6 L/min/m^2) versus 2.7 L/min/m^2 (SD 0.4 L/min/m^2); p = 0.004 and 3.2 L/min/m^2 (SD 0.5 L/min/m^2) versus 2.8 L/min/m^2 (SD 0.5 L/min/m^2) p = 0.023 (Tables 27 and 28 and Figures 40 and 45).

Between 14 and 30 weeks' gestation, the mean arterial pressure was unchanged in women who developed pre-eclampsia, as was seen in high-risk women with a normal outcome. The MAP mean values were significantly higher in women who developed pre-eclampsia compared to high-risk women with a normal pregnancy outcome between 14 and 24 weeks' gestation respectively; 89 mmHg (SD 7 mmHg) versus 94 mmHg (SD 8 mmHg); p = 0.025 and 88 mmHg (SD 6 mmHg) versus 94 mmHg (SD 6 mmHg); p = 0.001 (Tables 27 and 28 and Figures 39 and 46). This contributed to significantly higher TPR and TPRI mean values over the same time period in the women who developed pre-eclampsia compared to those with a normal pregnancy outcome (Table 27 and Figures 39, 47 and 48).

TPR decreased significantly from 1694 Dynes.s^{-1}cm^{-5} (SD 356 Dynes.s^{-1}cm^{-5}) at 14 weeks' gestation to 1446 Dynes.s^{-1}cm^{-5} (SD 159 Dynes.s^{-1}cm^{-5}) at 24 weeks' gestation; p = 0.002, followed by a mild rise to 1525 Dynes.s^{-1}cm^{-5} (SD 399 Dynes.s^{-1}cm^{-5}), replicating the trend seen in high-risk normal women with a normal pregnancy outcome (Table 27 and Figures 39 and 47). TPRI also decreased significantly from 2839 Dynes.s^{-1}cm^{-5}m^{2} (SD 467 Dynes.s^{-1}cm^{-5}m^{2}) to 2510 Dynes.s^{-1}cm^{-5}m^{2} (SD 239 Dynes.s^{-1}cm^{-5}m^{2}); p = 0.008 between 14 and 24 weeks' gestation, rising slightly to 2683 Dynes.s^{-1}cm^{-5}m^{2} (SD 644 Dynes.s^{-1}cm^{-5}m^{2}) at 30 weeks' gestation (Table 28 and Figures 39 and 48). This pattern of change is consistent with high-risk women who had a normal outcome.

Effectively, women who subsequently develop pre-eclampsia have a significantly lower CO/CI and significantly higher TPR/TPRI compared to high-risk women with a normal pregnancy outcome, secondary to a lower SV (non-significant) and higher MAP respectively.

Table 27. Pre-eclampsia primary cardiovascular outcomes

Outcome	Normal Mean (SD)	PE Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
HR				0.177*		0.175*
- 14 weeks	73.3 (8.6)	73.7 (12.2)	0.31 (-7.95, 8.56)	0.942	0.79 (-7.71, 9.29)	0.855
- 20 weeks	74.1 (9.8)	74.4 (15.6)	-0.23 (-10.72, 10.25)	0.965	0.24 (-10.44, 10.91)	0.965
- 24 weeks	77.5 (8.6)	79.8 (12.3)	1.96 (-6.36, 10.28)	0.644	2.44 (-6.00, 10.88)	0.571
- 30 weeks	80.7 (10.6)	78.1 (14.1)	-3.37 (-13.02, 6.27)	0.493	-2.91 (-12.62, 6.80)	0.557
SV				0.506*		0.513*
- 14 weeks	74.6 (12.9)	63.9 (16.9)	-10.50 (-22.01, 1.00)	0.074	-8.45 (-19.91, 3.01)	0.148
- 20 weeks	75.7 (14.1)	65.51 (18.7)	-10.51 (-23.22, 2.20)	0.105	-8.52 (-21.19, 4.16)	0.188
- 24 weeks	74.8 (13.4)	67.5 (14.9)	-7.54 (-17.82, 2.73)	0.150	-5.52 (-15.66, 4.62)	0.286
- 30 weeks	72.4 (12.6)	66.1 (18.9)	-6.96 (-19.71, 5.79)	0.285	-4.98 (-17.72, 7.77)	0.444
SVI				0.316*		0.321*
- 14 weeks	43.3 (6.7)	37.4 (7.7)	-5.77 (-11.07, -0.47)	0.033	-5.26 (-10.56, 0.03)	0.052
- 20 weeks	43.4 (6.7)	37.9 (9.0)	-5.57 (-11.65, 0.52)	0.073	-5.09 (-11.26, 1.09)	0.106
- 24 weeks	42.2 (6.3)	38.6 (6.7)	-3.65 (-8.30, 1.01)	0.125	-3.15 (-7.71, 1.42)	0.177
- 30 weeks	40.2 (6.3)	37.1 (9.0)	-3.21 (-9.31, 2.90)	0.303	-2.72 (-8.78, 3.34)	0.379
CO				0.086*		0.082*
- 14 weeks	5.47 (1.09)	4.59 (0.78)	-0.87 (-1.45, -0.29)	0.003	-0.70 (-1.28, -0.12)	**0.018**
- 20 weeks	5.53 (0.98)	4.65 (0.48)	-0.95 (-1.36, -0.55)	<0.001	-0.79 (-1.19, -0.39)	**<0.001**
- 24 weeks	5.76 (1.05)	5.23 (0.35)	-0.56 (-0.91, -0.21)	0.002	-0.39 (-0.73, -0.04)	**0.027**
- 30 weeks	5.82 (0.96)	5.02 (0.96)	-0.88 (-1.56, -0.20)	0.011	-0.72 (-1.39, -0.04)	**0.037**

Outcome	Normal Mean (SD)	PE Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
CI				0.045*		**0.042***
- 14 weeks	3.17 (0.59)	2.71 (0.37)	-0.46 (-0.74, -0.18)	0.001	-0.41 (-0.69, -0.13)	**0.004**
- 20 weeks	3.18 (0.48)	2.72 (0.29)	-0.49 (-0.72, -0.26)	<0.001	-0.44 (-0.67, -0.21)	**<0.001**
- 24 weeks	3.25 (0.49)	3.01 (0.13)	-0.25 (-0.40, -0.10)	0.001	-0.20 (-0.35, -0.05)	**0.010**
- 30 weeks	3.24 (0.50)	2.83 (0.47)	-0.43 (-0.77, -0.10)	0.011	-0.39 (-0.72, -0.05)	**0.023**
MAP				0.103*		0.107*
- 14 weeks	89.4 (7.2)	94.4 (7.8)	5.15 (-0.28, 10.57)	0.063	5.49 (0.69, 10.29)	**0.025**
- 20 weeks	87.1 (6.1)	95.3 (10.9)	8.10 (0.80, 15.40)	0.030	8.40 (1.78, 15.02)	**0.013**
- 24 weeks	87.5 (5.8)	94.1 (6.3)	6.99 (2.62, 11.37)	0.002	7.34 (3.02, 11.66)	**0.001**
- 30 weeks	89.4 (6.5)	91.8 (12.8)	2.72 (-5.77, 11.22)	0.530	3.06 (-5.11, 11.23)	0.463
TPR				0.197*		0.187*
- 14 weeks	1356.1 (291.9)	1694.4 (356.1)	335.34 (91.48, 579.21)	0.007	301.04 (63.78, 538.29)	**0.013**
- 20 weeks	1290.5 (248.8)	1672.0 (281.8)	365.7 (162.27, 569.12)	<0.001	335.13 (143.12, 527.13)	**0.001**
- 24 weeks	1247.0 (204.7)	1445.9 (158.8)	211.9 (95.69, 328.18)	<0.001	178.39 (65.43, 291.36)	**0.002**
- 30 weeks	1258.8 (216.9)	1524.9 (398.8)	288.4 (21.58, 555.20)	0.034	256.57 (-3.41, 516.54)	0.053
TPRI				0.228*		0.223*
- 14 weeks	2330.5 (478.2)	2839.05 (466.67)	507.42 (179.69, 835.15)	0.002	479.40 (153.10, 805.71)	**0.004**
- 20 weeks	2233.0 (416.0)	2844.33 (501.53)	590.85 (231.98, 949.71)	0.001	566.24 (214.10, 918.39)	**0.002**
- 24 weeks	2194.9 (328.1)	2510.10 (239.06)	330.32 (152.99, 507.66)	<0.001	303.30 (122.09, 484.50)	**0.001**
- 30 weeks	2261.6 (405.1)	2683.32 (643.75)	445.37 (11.04, 879.70)	0.044	420.08 (-9.86, 850.03)	0.055

Data are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, HR: heart rate, LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), MAP: mean arterial pressure, PE: pre-eclampsia, SD: standard deviation, SV: stroke volume, SVI: stroke volume index (SV/BSA), TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA).

Table 28. Pre-eclampsia primary cardiovascular outcomes with gestation

Outcome (Time)	Normal: Mean (SD)	Normal: Unadj. Estimate (95% C.I)	Norm: unadj. p value	Normal: Adj. Estimate (95% C.I)	Norm: Adj. p value	PE: Mean (SD)	PE: Unadj. Estimate (95% C.I)	PE: Unadj. p value	PE: Adj. Estimate (95% C.I)	PE: p value
HR - 14wks	73.3 (8.6)		.		.	73.7 (12.2)		0.177*		0.175*
- 20wks	74.1 (9.8)	1.2 (-0.7, 3.2)	0.220	1.2 (-0.7, 3.2)	0.218	74.4 (15.6)	0.7 (-5.9, 7.3)	0.839	0.7 (-5.9, 7.3)	0.839
- 24wks	77.5 (8.6)	4.4 (2.9, 5.9)	<0.001	4.4 (3.0, 5.9)	<0.001	79.8 (12.3)	6.1 (2.9, 9.2)	<0.001	6.1 (2.9, 9.2)	**<0.001**
- 30wks	80.7 (10.6)	8.1 (5.9, 10.3)	<0.001	8.1 (5.9, 10.3)	<0.001	78.1 (14.1)	4.4 (0.3, 8.5)	0.036	4.4 (0.3, 8.5)	**0.036**
SV - 14wks	74.6 (12.9)		.		.	63.9 (16.9)		0.506*		0.513*
- 20wks	75.7 (14.1)	1.7 (-0.9, 4.2)	0.201	1.7 (-0.8, 4.2)	0.183	65.5 (18.7)	1.7 (-3.7, 7.0)	0.543	1.6 (-3.7, 7.0)	0.543
- 24wks	74.8 (13.4)	0.7 (-2.4, 3.8)	0.668	0.7 (-2.4, 3.8)	0.656	67.5 (14.9)	3.6 (0.2, 7.1)	0.037	3.6 (0.2, 7.1)	**0.037**
- 30wks	72.4 (12.6)	-1.3 (-4.3, 1.6)	0.379	-1.3 (-4.2, 1.7)	0.404	66.1 (18.9)	2.2 (-3.4, 7.8)	0.439	2.2 (-3.4, 7.8)	0.439
SVI - 14wks	43.3 (6.7)		.		.	37.4 (7.7)		0.316*		0.321*
- 20wks	43.4 (6.7)	0.3 (-1.2, 1.7)	0.730	0.3 (-1.2, 1.7)	0.700	37.9 (9.0)	0.5 (-2.7, 3.6)	0.773	0.5 (-2.7, 3.6)	0.773
- 24wks	42.2 (6.3)	-1.0 (-2.7, 0.7)	0.255	-1.0 (-2.7, 0.7)	0.261	38.6 (6.7)	1.1 (-0.9, 3.1)	0.267	1.1 (-0.9, 3.1)	0.267
- 30wks	40.2 (6.3)	-2.9 (-4.6, -1.2)	0.001	-2.9 (-4.6, -1.2)	0.001	37.1 (9.0)	-0.3 (-3.4, 2.7)	0.823	-0.3 (-3.4, 2.7)	0.823
CO - 14wks	5.47 (1.09)		.		.	4.59 (0.78)		0.086*		0.082*
- 20wks	5.53 (0.98)	0.14 (-0.11, 0.40)	0.272	0.15 (-0.10, 0.41)	0.235	4.65 (0.48)	0.06 (-0.51, 0.63)	0.836	0.06 (-0.51, 0.63)	0.836
- 24wks	5.76 (1.05)	0.33 (0.06, 0.61)	0.016	0.34 (0.07, 0.61)	0.015	5.23 (0.35)	0.65 (0.33, 0.96)	<0.001	0.65 (0.33, 0.96)	**<0.001**
- 30wks	5.82 (0.96)	0.44 (0.13, 0.75)	0.006	0.45 (0.14, 0.76)	0.005	5.02 (0.96)	0.43 (-0.04, 0.90)	0.075	0.43 (-0.04, 0.90)	0.075
CI - 14wks	3.17 (0.59)		.		.	2.71 (0.37)		0.045*		0.042*
- 20wks	3.18 (0.48)	0.03 (-0.11, 0.18)	0.633	0.04 (-0.10, 0.18)	0.578	2.72 (0.29)	0.01 (-0.32, 0.34)	0.952	0.01 (-0.32, 0.34)	0.952
- 24wks	3.25 (0.49)	0.09 (-0.06, 0.24)	0.249	0.09 (-0.06, 0.24)	0.241	3.01 (0.13)	0.30 (0.11, 0.50)	0.003	0.30 (0.11, 0.50)	**0.003**
- 30wks	3.24 (0.50)	0.09 (-0.09, 0.27)	0.317	0.09 (-0.08, 0.27)	0.299	2.83 (0.47)	0.12 (-0.14, 0.38)	0.371	0.12 (-0.14, 0.38)	0.371

Outcome (Time)	Normal: Mean (SD)	Normal: Unadj. Estimate (95% C.I)	Norm: unadj. p value	Normal: Adj. Estimate (95% C.I)	Norm: Adj. p value	PE: Mean (SD)	PE: Unadj. Estimate (95% C.I)	PE: Unadj. p value	PE: Adj. Estimate (95% C.I)	PE: p value
MAP - 14wks	89.4 (7.2)		.		.	94.4 (7.8)		0.103*		0.107*
- 20wks	87.1 (6.1)	-2.1 (-3.6, -0.5)	0.011	-2.0 (-3.6, -0.4)	0.013	95.3 (10.9)	0.9 (-1.5, 3.3)	0.460	0.91 (-1.50, 3.32)	0.460
- 24wks	87.5 (5.8)	-2.2 (-3.9, -0.4)	0.014	-2.2 (-3.9, -0.5)	0.013	94.1 (6.3)	-0.3 (-4.6, 4.0)	0.889	-0.31 (-4.61, 4.00)	0.889
- 30wks	89.4 (6.5)	-0.2 (-1.9, 1.5)	0.826	-0.2 (-1.9, 1.5)	0.832	91.8 (12.8)	-2.6 (-10.7, 5.5)	0.527	-2.61 (-10.70, 5.48)	0.527
TPR - 14wks	1356.1 (291.9)		.		.	1694.4 (356.1)		0.197*		0.187*
- 20wks	1290.5 (248.8)	-80.7 (-143.3, -18.1)	0.012	-82.1 (-144.9, -19.3)	0.010	1672.0 (281.8)	-50.3 (-282.0, 181.4)	0.670	-48.0 (-279.4, 183.4)	0.684
- 24wks	1245.0 (204.7)	-125.1 (-194.4, -55.9)	<0.001	-125.9 (-195.4, -56.4)	<0.001	1445.9 (158.8)	-248.5 (-403.2, -93.9)	0.002	-248.5 (-403.2, -93.9)	**0.002**
- 30wks	1258.8 (216.9)	-122.6 (-200.1, -45.1)	0.002	-125.1 (-203.0, -47.2)	0.002	1524.86 (398.7)	-169.5 (-359.2, 20.1)	0.080	-169.5 (-359.2, 20.1)	0.080
TPRI - 14wks	2330.5 (478.2)		.		.	2839.1 (466.7)		0.228*		0.223*
- 20wks	2233.0 (416.0)	-111.4 (-220.2, -2.6)	0.045	-112.9 (-222.3, -3.5)	0.043	2844.33 (501.5)	-28.0 (-436.0, 380.0)	0.893	-26.1 (-433.9, 381.8)	0.900
- 24wks	2194.9 (328.1)	-151.9 (-268.9, -34.9)	0.011	-152.8 (-270.1, -35.6)	0.011	2510.10 (239.1)	-329.0 (-571.6, -86.3)	0.008	-329.0 (-571.6, -86.3)	**0.008**
- 30wks	2261.6 (405.1)	-93.7 (-227.9, 40.5)	0.171	-96.4 (-231.8, 39.0)	0.163	2683.32 (643.8)	-155.7 (-498.3, 186.0)	0.373	-155.7 (-498.3, 186.9)	0.373

Data are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, HR: heart rate, LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), MAP: mean arterial pressure, PE: pre-eclampsia, SD: standard deviation, SV: stroke volume, SVI: stroke volume index (SV/BSA), T1: first trimester, TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA).

7.4.2 Gestational hypertension primary cardiovascular outcomes

Heart rate increased with gestation in women who subsequently developed gestational hypertension, although this was not statistically significant; 85 bpm (SD 8 bpm) to 91 bpm (SD 13 bpm); p = 0.057. The mean heart rate values were higher compared to women with a normal pregnancy outcome, reaching significance between 14 and 24 weeks' gestation respectively; 73 bpm (SD 9 bpm) versus 85 bpm (SD 8 bpm); p = 0.001 and 78 bpm (SD 9 bpm) versus 93 bpm (SD 16 bpm); p = 0.014 (Table 29 and 30 and Figures 39 and 41).

Stroke volume was unchanged between 14 and 30 weeks' gestation; (67.39 ml [SD 4.72 ml] to 66.24 ml [SD 7.98 ml]; p = 0.547), while SVI decreased slightly in women who developed GH; 36.90 ml/m^2 (SD 1.70 ml/m^2) at 14 weeks' to 34.74 ml/m^2 (SD 3.42 ml/m^2); p = 0.017 at 30 weeks' gestation, with significantly lower mean values at all time points compared to high-risk women with a normal pregnancy outcome (Table 29 and 30 and Figures 40, 42 and 43).

In women who developed GH, there was a non-significant increase in CO and CI between 14 and 30 weeks' gestation respectively; 5.71 L/min (SD 0.70 L/min) to 6.39 L/min (SD 1.59 L/min); p = 0.137 and 3.12 L/min/m^2 (SD 0.32 L/min/m^2) to 3.36 L/min/m^2 (SD 0.88 L/min/m^2); p = 0.33, in contrast to high-risk women with a normal pregnancy outcome, which showed a statistically significant increase over this time period. In terms of CO and CI between the two outcome groups, there was no significant difference at any of the time points, despite lower mean values in the high-risk normal women (Table 29 and Figures 40,44 and 45).

The mean arterial pressure mean values were significantly higher between 14 and 30 weeks' gestation in high-risk women who developed GH compared to those with a normal outcome; 101 mmHg (SD 5 mmHg) versus 89 mmHg (SD 7 mmHg) versus; p < 0.001 and 103 mmHg (SD 11 mmHg) versus 89 mmHg (SD 7 mmHg); p < 0.001, respectively. The MAP remained constant over this time period in women who developed GH, in keeping with high-risk women who had a normal pregnancy outcome. The significant drop in MAP seen in the normal high-risk women at 20 weeks' gestation was not evident in women who developed GH (Table 30 and Figures 39 and 46).

No significant difference in TPR was found between the two groups of women, despite higher mean values in the women who developed GH. There was a non-significant decline in TPR between 14 and 30 weeks' gestation, in contrast to high-risk women with a normal pregnancy outcome. The TPRI mean values were also higher in women who developed GH, with statistical significance reached at 14 and 20 weeks' gestation respectively; 2608.37 Dynes.s^{-1}cm^{-5}m^2 (SD 332.36 Dynes.s^{-1}cm^{-5}m^2) versus 2330.50 Dynes.s^{-1}cm^{-5}m^2 (SD 405.09 Dynes.s^{-1}cm^{-5}m^2); p = 0.011 and 2560.43 Dynes.s^{-1}cm^{-5}m^2 (SD 532.69 Dynes.s^{-1}cm^{-5}m^2) versus 2233.03 Dynes.s^{-1}cm^{-5}m^2 (SD 416.02 Dynes.s^{-1}cm^{-5}m^2); p = 0.02. There was no significant decline in TPRI in women who developed GH between 14 and 30 weeks' gestation, in keeping with high-risk women with a normal pregnancy outcome. These data are summarised in Table 29 and 30, and Figures 39, 47 and 48.

Women who subsequently develop GH had significantly higher heart rate and lower SV/SVI compared to high-risk women with a normal pregnancy outcome. This resulted in higher CO/CI in the GH group, however statistical significance was only reached at 24 weeks' gestation. The MAP, TPR and TPRI were also higher in women who developed GH compared to those with a normal outcome at most time points.

Table 29. Gestational hypertension primary cardiovascular outcomes

Outcome	Normal Mean (SD)	GH Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
HR				0.177*		**0.181***
- 14 weeks	73.3 (8.6)	84.7 (8.0)	11.28 (5.66, 16.91)	<0.001	10.17 (4.02, 16.32)	**0.001**
- 20 weeks	74.1 (9.8)	90.4 (11.2)	15.59 (8.22, 22.95)	<0.001	14.45 (6.61, 22.28)	**<0.001**
- 24 weeks	77.5 (8.6)	92.6 (16.3)	14.82 (3.99, 25.65)	0.007	13.70 (2.77, 24.63)	**0.014**
- 30 weeks	80.7 (10.6)	91.2 (13.0)	9.77 (0.86, 18.68)	0.032	8.63 (-0.24, 17.51)	0.057
SV				0.521*		0.501*
- 14 weeks	74.6 (12.9)	67.4 (4.7)	-6.98 (-11.44, -2.52)	0.002	-8.67 (-14.61, -2.73)	**0.004**
- 20 weeks	75.7 (14.1)	65.1 (7.8)	-9.92 (-16.53, -3.32)	0.003	-11.75 (-19.40, -4.10)	**0.003**
- 24 weeks	74.8 (13.4)	66.6 (3.4)	-8.41 (-12.43, -4.38)	<0.001	-10.12 (-15.48, -4.76)	**<0.001**
- 30 weeks	72.4 (12.6)	66.2 (8.0)	-6.77 (-12.94, -0.59)	0.032	-8.52 (-15.92, -1.13)	**0.024**
SVI				0.440*		0.432*
- 14 weeks	43.3 (6.7)	36.9 (1.7)	-6.31 (-8.31, -4.31)	<0.001	-6.63 (-8.94, -4.31)	**<0.001**
- 20 weeks	43.4 (6.7)	35.9 (3.7)	-7.73 (-10.75, -4.72)	<0.001	-8.11 (-11.43, -4.79)	**<0.001**
- 24 weeks	42.2 (6.3)	35.6 (3.2)	-6.57 (-9.19, -3.94)	<0.001	-6.90 (-9.78, -4.02)	**<0.001**
- 30 weeks	40.2 (6.3)	34.7 (3.4)	-5.54 (-8.34, -2.75)	<0.001	-5.89 (-8.81, -2.97)	**<0.001**
CO				0.090*		0.078*
- 14 weeks	5.47 (1.09)	5.71 (0.70)	0.26 (-0.28, 0.79)	0.346	0.06 (-0.57, 0.70)	0.848
- 20 weeks	5.53 (0.98)	5.88 (0.98)	0.31 (-0.36, 0.97)	0.367	0.09 (-0.59, 0.78)	0.788
- 24 weeks	5.76 (1.05)	6.75 (1.59)	0.96 (-0.11, 2.04)	0.079	0.76 (-0.32, 1.84)	0.166
- 30 weeks	5.82 (0.96)	6.39 (1.59)	0.49 (-0.58, 1.56)	0.367	0.29 (-0.78, 1.36)	0.600

Outcome	Normal Mean (SD)	GH Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
CI				0.102*		0.094*
- 14 weeks	3.17 (0.59)	3.12 (0.32)	-0.04 (-0.30, 0.21)	0.743	-0.11 (-0.38, 0.16)	0.435
- 20 weeks	3.18 (0.48)	3.24 (0.49)	-0.00 (-0.34, 0.34)	0.992	-0.08 (-0.42, 0.27)	0.667
- 24 weeks	3.25 (0.49)	3.61 (0.90)	0.35 (-0.25, 0.95)	0.250	0.28 (-0.31, 0.87)	0.344
- 30 weeks	3.24 (0.50)	3.36 (0.88)	0.10 (-0.49, 0.69)	0.737	0.03 (-0.55, 0.61)	0.918
MAP				0.119*		0.117*
- 14 weeks	89.4 (7.2)	100.8 (5.0)	11.56 (7.82, 15.30)	<0.001	11.62 (7.60, 15.64)	**<0.001**
- 20 weeks	87.1 (6.1)	101.3 (8.3)	13.49 (7.78, 19.21)	<0.001	13.50 (8.50, 18.50)	**<0.001**
- 24 weeks	87.5 (5.8)	103.1 (6.5)	15.97 (11.47, 20.46)	<0.001	16.02 (11.77, 20.27)	**<0.001**
- 30 weeks	89.4 (6.5)	103.3 (10.9)	14.24 (6.94, 21.54)	<0.001	14.28 (7.33, 21.23)	**<0.001**
TPR				0.321*		0.278*
- 14 weeks	1356.1 (291.9)	1435.8 (231.2)	76.58 (-91.34, 244.51)	0.371	121.52 (-59.10, 302.14)	0.187
- 20 weeks	1290.5 (248.8)	1422.1 (335.1)	126.04 (-97.37, 349.45)	0.269	173.87 (-50.44, 398.17)	0.129
- 24 weeks	1247.0 (204.7)	1280.0 (318.9)	47.10 (-167.59, 261.79)	0.667	92.60 (-122.45, 307.65)	0.399
- 30 weeks	1258.8 (216.9)	1362.8 (379.6)	127.91 (-126.72, 382.53)	0.325	174.66 (-83.05, 432.37)	0.184
TPRI				0.489*		0.460*
- 14 weeks	2330.5 (478.2)	2608.4 (332.4)	276.59 (28.29, 524.89)	0.029	329.02 (75.84, 582.20)	**0.011**
- 20 weeks	2233.0 (416.0)	2560.4 (532.7)	350.98 (-1.52, 703.49)	0.051	405.85 (60.38, 751.31)	**0.021**
- 24 weeks	2194.9 (328.1)	2396.3 (566.9)	217.99 (-161.55, 597.52)	0.260	271.05 (-95.18, 637.28)	0.147
- 30 weeks	2261.6 (405.1)	2580.0 (644.0)	344.55 (-89.97, 779.08)	0.120	399.15 (-25.14, 823.45)	0.065

Data are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, GH: gestational hypertension, HR: heart rate, LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), MAP: mean arterial pressure; SD: standard deviation, SV: stroke volume, SVI: stroke volume index (SV/BSA), TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA).

Table 30. Gestational hypertension primary cardiovascular outcomes with gestation

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	GH Mean (SD)	GH Unadj. Diff vs T1 (95% C.I)	GH Unadj p value	GH Adj Diff vs T1 (95% C.I)	GH Adj p value
HR - 14wks	73.3 (8.6)		.		.	84.7 (8.0)		0.177*		0.181*
- 20wks	74.1 (9.8)	1.2 (-0.7, 3.2)	0.220	1.2 (-0.7, 3.2)	0.218	90.4 (11.2)	5.5 (0.5, 10.5)	0.031	5.5 (0.5, 10.5)	**0.032**
- 24wks	77.5 (8.6)	4.4 (2.9, 5.9)	<0.001	4.4 (3.0, 5.9)	<0.001	92.6 (16.3)	7.9 (0.3, 15.6)	0.042	**7.9 (0.3, 15.6)**	**0.042**
- 30wks	80.7 (10.6)	8.1 (5.9, 10.3)	<0.001	8.1 (5.9, 10.3)	<0.001	91.2 (13.0)	6.5 (-0.7, 13.7)	0.075	6.5 (-0.7, 13.7)	0.075
SV - 14wks	74.6 (12.9)		.		.	67.4 (4.7)		0.521*		0.501*
- 20wks	75.7 (14.1)	1.7 (-0.9, 4.2)	0.201	1.7 (-0.8, 4.2)	0.183	65.1 (7.9)	-1.3 (-4.9, 2.3)	0.470	-1.4 (-5.0, 2.2)	0.446
- 24wks	74.8 (13.4)	0.7 (-2.4, 3.8)	0.668	0.7 (-2.4, 3.8)	0.656	66.6 (3.4)	-0.8 (-4.2, 2.6)	0.657	-0.8 (-4.2, 2.6)	0.657
- 30wks	72.4 (12.6)	-1.3 (-4.3, 1.6)	0.379	-1.3 (-4.2, 1.7)	0.404	66.2 (8.0)	-1.2 (-4.9, 2.6)	0.547	-1.2 (-4.9, 2.6)	0.547
SVI - 14wks	43.3 (6.7)		.		.	36.9 (1.7)		0.440*		0.432*
- 20wks	43.4 (6.7)	0.3 (-1.2, 1.7)	0.730	0.3 (-1.2, 1.7)	0.700	35.9 (3.7)	-1.18 (-3.11, 0.75)	0.231	-1.20 (-3.14, 0.73)	0.222
- 24wks	42.2 (6.3)	-1.0 (-2.7, 0.7)	0.255	-1.0 (-2.7, 0.7)	0.261	35.6 (3.2)	-1.27 (-2.99, 0.46)	0.151	-1.27 (-2.99, 0.46)	0.151
- 30wks	40.2 (6.3)	-2.9 (-4.6, -1.2)	0.001	-2.9 (-4.6, -1.2)	0.001	34.7 (3.4)	-2.16 (-3.92, -0.39)	0.017	-2.16 (-3.92, -0.39)	**0.017**
CO - 14wks	5.47 (1.09)		.		.	5.71 (0.70)		0.090*		0.078*
- 20wks	5.53 (0.98)	0.14 (-0.11, 0.40)	0.272	0.15 (-0.10, 0.41)	0.235	5.88 (0.98)	0.20 (-0.22, 0.61)	0.353	0.19 (-0.24, 0.61)	0.390
- 24wks	5.76 (1.05)	0.33 (0.06, 0.61)	0.016	0.34 (0.07, 0.61)	0.015	6.75 (1.59)	1.04 (0.16, 1.92)	0.020	**1.04 (0.16, 1.92)**	**0.020**
- 30wks	5.82 (0.96)	0.44 (0.13, 0.75)	0.006	0.45 (0.14, 0.76)	0.005	6.39 (1.59)	0.68 (-0.22, 1.57)	0.137	0.68 (-0.22, 1.57)	0.137
CI - 14wks	3.17 (0.59)		.		.	3.12 (0.32)		0.102*		0.094*
- 20wks	3.18 (0.48)	0.03 (-0.11, 0.18)	0.633	0.04 (-0.10, 0.18)	0.578	3.24 (0.49)	0.08 (-0.12, 0.28)	0.446	0.07 (-0.13, 0.28)	0.475
- 24wks	3.25 (0.49)	0.09 (-0.06, 0.24)	0.249	0.09 (-0.06, 0.24)	0.241	3.61 (0.90)	0.49 (0.03, 0.95)	0.039	0.49 (0.03, 0.95)	**0.039**
- 30wks	3.24 (0.50)	0.09 (-0.09, 0.27)	0.317	0.09 (-0.08, 0.27)	0.299	3.36 (0.88)	0.24 (-0.24, 0.72)	0.330	0.24 (-0.24, 0.72)	0.330

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	GH Mean (SD)	GH Unadj. Diff vs T1 (95% C.I)	GH Unadj p value	GH Adj Diff vs T1 (95% C.I)	GH Adj p value
MAP - 14wks	89.4 (7.2)		.		.	100.84 (5.02)		0.119*		0.117*
- 20wks	87.1 (6.1)	-2.1 (-3.6, -0.5)	0.011	-2.0 (-3.6, -0.4)	0.013	101.30 (8.34)	-0.11 (-5.17, 4.95)	0.966	-0.1 (-5.2, 4.9)	0.963
- 24wks	87.5 (5.8)	-2.2 (-3.9, -0.4)	0.014	-2.2 (-3.9, -0.5)	0.013	103.09 (6.48)	2.25 (-1.38, 5.87)	0.225	2.3 (-1.4, 5.9)	0.225
- 30wks	89.4 (6.5)	-0.2 (-1.9, 1.5)	0.826	-0.2 (-1.9, 1.5)	0.832	103.33 (10.87)	2.49 (-3.47, 8.44)	0.413	2.5 (-3.5, 8.4)	0.413
TPR - 14wks	1356.1 (291.9)		.		.	1435.8 (231.2)		0.321*		0.278*
- 20wks	1290.5 (248.8)	-80.7 (-143.3, -18.1)	0.012	-82.1 (-144.9, -19.3)	0.010	1422.1 (335.1)	-32.4 (-147.1, 82.3)	0.579	-30.1 (-145.8, 85.6)	0.610
- 24wks	1245.0 (204.7)	-125.1 (-194.4, -55.9)	<0.001	-125.9 (-195.4, -56.4)	<0.001	1280.0 (318.9)	-155.8 (-313.0, 1.3)	0.052	-155.8 (-313.0, 1.3)	0.052
- 30wks	1258.8 (216.9)	-122.6 (-200.1, -45.1)	0.002	-125.1 (-203.0, -47.2)	0.002	1362.8 (379.6)	-73.1 (-231.8, 85.7)	0.367	-73.1 (-231.8, 85.7)	0.367
TPRI - 14wks	2330.5 (478.2)		.		.	2608.4 (332.4)		0.489*		0.460*
- 20wks	2233.0 (416.0)	-111.4 (-220.2, -2.6)	0.045	-112.9 (-222.3, -3.5)	0.043	2560.4 (532.7)	-38.7 (-233.3, 156.0)	0.697	-36.3 (-231.4, 158.7)	0.715
- 24wks	2194.9 (328.1)	-151.9 (-268.9, -34.9)	0.011	-152.8 (-270.1, -35.6)	0.011	2396.3 (566.9)	-212.1 (-495.7, 71.4)	0.143	-212.1 (-495.7, 71.4)	0.143
- 30wks	2261.6 (405.1)	-93.7 (-227.9, 40.5)	0.171	-96.4 (-231.8, 39.0)	0.163	2580.0 (644.0)	-28.3 (-324.5, 267.8)	0.851	-28.3 (-324.5, 267.8)	0.851

Data are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, GH: gestational hypertension, HR: heart rate, LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), MAP: mean arterial pressure, SD: standard deviation, SV: stroke volume; SVI: stroke volume index (SV/BSA): T1: first trimester, TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA).

7.4.3 SGA primary cardiovascular outcomes

There was a significant increase in heart rate between 14 and 30 weeks' gestation in women who delivered small for gestational age infants; 75 bpm (SD 10 bpm) to 82 bpm (SD 8 bpm); $p < 0.001$, as was seen in high-risk women with a normal pregnancy outcome. The mean values between the two groups of women were only significantly different at 20 weeks' gestation; 74 bpm (SD 10 bpm) versus 80 bpm (SD 11 bpm); $p = 0.042$ (Tables 31 and 32 and Figures 39 and 41).

Stroke volume was unchanged between 14 and 30 weeks' gestation; 61.6 ml (SD 12.7 ml) to 61.7 ml (SD 9.0 ml); $p = 0.763$, in keeping with results seen in high-risk women with a normal pregnancy outcome. SVI decreased slightly during this time period, following the same trend as the high-risk women with a normal pregnancy outcome, however significance was not reached; 38.2 ml/m^2 (SD 7.8 ml/m^2) to 36.4 ml/m^2 (SD 4.9 ml/m^2); $p = 0.176$. In women who delivered a SGA infant, the mean values of both SV and SVI were all significantly lower between 14 and 30 weeks' gestation (Tables 31 and 32 and Figures 40, 42 and 43).

In women who delivered a SGA infant, the CO followed the same pattern of change as high-risk women with a normal pregnancy, increasing significantly between 14 and 30 weeks' gestation; 4.58 L/min (SD 1.06 L/min) to 5.43 L/min (SD 1.54 L/min); $p = 0.009$. CI also increased over this time period; however, statistical significance was not reached; 2.83 L/min/m^2 (SD 0.62 L/min/m^2) to 3.19 L/min/m^2 (SD 0.08 L/min/m^2); $p = 0.074$. The mean CO values were significantly lower compared to high-risk women with a normal pregnancy outcome at 14 and 24 weeks' gestation respectively; 4.58 L/min (SD 1.06 L/min) versus 5.47 L/min (SD 0.98L/min); $p = 0.001$ and 5.13 L/min (SD 1.26 L/min) versus 5.76 L/min (SD 1.05 L/min); $p = 0.021$. The mean values of the indexed equivalent CI were only statistically lower at 14 weeks' gestation; 2.83 L/min/m^2 (SD 0.62 L/min/m^2) versus 3.17 L/min/m^2 (SD 0.59 L/min/m^2); p 0.037. These data are summarised in Tables 31 and 32 and Figures 40,44 and 45.

The MAP was stable between 14 and 30 weeks' gestation in women who delivered a SGA infant; 87 mmHg (SD 8 mmHg) to 89 mmHg (SD 7 mmHg); $p = 0.196$, with mean values comparable to women with a normal pregnancy outcome (Table 27 and Figure 41). The TPR decreased significantly across this

time period; 1619.21 Dynes.s^{-1}cm^{-5} (SD 520.60 Dynes.s^{-1}cm^{-5}) to 1375.82 Dynes.s^{-1}cm^{-5} (SD 278.82 Dynes.s^{-1}cm^{-5}); p = 0.025, with mean values all significantly higher than high-risk women with a normal pregnancy outcome (Table 31 and Figures 39 and 47).

The mean TPRI values of women who delivered a SGA infant were slightly higher than high-risk women with a normal pregnancy outcome between 14 and 30 weeks' gestation, however statistical significance was not reached (Table 32 and Figures 39 and 48). Despite a decline in TPRI over this time period, significance was not reached in keeping with the trend seen in high-risk women with a normal pregnancy outcome (Table 32, Figures 39 and 48).

Effectively, women who delivered a SGA infant had significantly lower SV/SVI compared to high-risk women with a normal pregnancy outcome. This resulted in lower CO, with CI lower at just 14 weeks' gestation. The TPR was also significantly higher in these women, while TPRI changes and mean values were consistent to those with a normal outcome.

Table 31. Small for gestational age primary cardiovascular outcomes

Outcome	Normal Mean (SD)	SGA Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
HR				0.091*		0.091*
- 14 weeks	73.3 (8.6)	74.6 (9.6)	1.55 (-3.12, 6.22)	0.515	1.63 (-2.83, 6.09)	0.474
- 20 weeks	74.1 (9.8)	80.3 (11.0)	5.31 (-0.09, 10.72)	0.054	5.36 (0.20, 10.52)	**0.042**
- 24 weeks	77.5 (8.6)	81.4 (12.5)	3.75 (-2.06, 9.56)	0.206	3.81 (-1.72, 9.35)	0.177
- 30 weeks	80.7 (10.6)	81.5 (8.2)	0.13 (-4.35, 4.62)	0.954	0.17 (-3.92, 4.26)	0.934
SV				0.772*		0.782*
- 14 weeks	74.6 (12.9)	61.6 (12.7)	-13.11 (-19.48, -6.75)	<0.001	-12.66 (-19.09, -6.23)	**<0.001**
- 20 weeks	75.7 (14.1)	65.0 (11.8)	-12.39 (-19.02, -5.76)	<0.001	-12.01 (-18.64, -5.39)	**<0.001**
- 24 weeks	74.8(13.4)	61.4 (11.8)	-14.74 (-21.22, -8.26)	<0.001	-14.31 (-20.81, -7.82)	**<0.001**
- 30 weeks	72.4 (12.6)	61.7 (9.0)	-12.47 (-18.02, -6.92)	<0.001	-12.09 (-17.56, -6.63)	**<0.001**
SVI				0.751*		0.757*
- 14 weeks	43.3 (6.7)	38.2 (7.8)	-5.15 (-8.93, -1.38)	0.007	-4.99 (-8.80, -1.18)	**0.010**
- 20 weeks	43.4 (6.7)	39.7 (7.5)	-4.45 (-8.29, -0.60)	0.023	-4.32 (-8.20, -0.43)	**0.029**
- 24 weeks	42.2 (6.3)	36.9 (7.3)	-5.83 (-9.53, -2.12)	0.002	-5.68 (-9.41, -1.95)	**0.003**
- 30 weeks	40.2 (6.3)	36.4 (4.9)	-4.43 (-7.33, -1.53)	0.003	-4.29 (-7.16, -1.41)	**0.003**
CO				0.414*		0.438*
- 14 weeks	5.47 (1.09)	4.58 (1.06)	-0.89 (-1.42, -0.36)	0.001	-0.84 (-1.36, -0.33)	**0.001**
- 20 weeks	5.53 (0.98)	5.21 (1.11)	-0.52 (-1.09, 0.06)	0.078	-0.48 (-1.01, 0.05)	0.079
- 24 weeks	5.76 (1.05)	5.13 (1.26)	-0.74 (-1.36, -0.12)	0.020	-0.69 (-1.28, -0.10)	**0.021**
- 30 weeks	5.82 (0.96)	5.43 (1.54)	-0.57 (-1.30, 0.17)	0.131	-0.53 (-1.22, 0.17)	0.135

Outcome	Normal Mean (SD)	SGA Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
CI				0.354*		0.377*
- 14 weeks	3.17 (0.59)	2.83 (0.62)	-0.34 (-0.65, -0.04)	0.028	-0.32 (-0.63, -0.02)	**0.037**
- 20 weeks	3.18 (0.48)	3.16 (0.62)	-0.10 (-0.41, 0.21)	0.531	-0.09 (-0.39, 0.22)	0.572
- 24 weeks	3.25 (0.49)	3.07 (0.70)	-0.22 (-0.56, 0.11)	0.192	-0.21 (-0.54, 0.12)	0.218
- 30 weeks	3.24 (0.50)	3.19 (0.80)	-0.12 (-0.50, 0.27)	0.552	-0.10 (-0.48, 0.27)	0.589
MAP				0.217*		0.239*
- 14 weeks	89.4 (7.2)	87.2 (7.6)	-1.62 (-5.42, 2.18)	0.403	-1.08 (-4.57, 2.42)	0.546
- 20 weeks	87.1 (6.1)	88.2 (8.2)	1.29 (-2.60, 5.19)	0.516	1.76 (-1.78, 5.29)	0.330
- 24 weeks	87.5 (5.8)	86.7 (7.4)	-0.08 (-3.64, 3.48)	0.966	0.42 (-2.94, 3.79)	0.805
- 30 weeks	89.4 (6.5)	89.2 (7.6)	0.45 (-3.27, 4.18)	0.812	0.94 (-2.72, 4.61)	0.614
TPR				0.782*		0.797*
- 14 weeks	1356.1 (291.9)	1619.2 (520.6)	268.68 (30.74, 506.62)	0.027	264.95 (33.49, 496.40)	**0.025**
- 20 weeks	1290.5 (248.8)	1413.5 (304.7)	187.02 (17.08, 356.97)	0.031	183.81 (24.91, 342.70)	**0.023**
- 24 weeks	1247.0 (204.7)	1410.6 (285.3)	217.44 (59.99, 374.90)	0.007	212.61 (65.02, 360.20)	**0.005**
- 30 weeks	1258.7 (216.9)	1375.8 (278.8)	182.57 (24.82, 340.32)	0.023	180.36 (36.66, 324.07)	**0.014**
TPRI				0.778*		0.791*
- 14 weeks	2330.5 (478.2)	2589.7 (753.7)	271.96 (-78.09, 622.01)	0.128	272.26 (-71.60, 616.12)	0.121
- 20 weeks	2233.0 (416.0)	2318.2 (481.9)	167.98 (-96.06, 432.03)	0.212	169.86 (-82.96, 422.67)	0.188
- 24 weeks	2194.9 (328.1)	2348.4 (472.0)	225.26 (-24.00, 474.52)	0.077	225.83 (-14.52, 466.18)	0.066
- 30 weeks	2261.6 (405.1)	2316.2 (422.3)	138.75 (-104.89, 382.39)	0.264	142.10 (-89.57, 373.77)	0.229

Data are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, HR: heart rate, LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), MAP: mean arterial pressure, SD: standard deviation: SGA: small for gestational age, SV: stroke volume, SVI: stroke volume index (SV/BSA), TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA).

Table 32. SGA primary cardiovascular outcomes with gestation

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	SGA Mean (SD)	SGA Unadj. Diff vs T1 (95% C.I)	SGA Unadj p value	SGA Adj Diff vs T1 (95% C.I)	SGA Adj p value
HR - 14wks	73.3 (8.6)		.		.	74.59 (9.58)		0.091*		0.091*
- 20wks	74.1 (9.8)	1.2 (-0.7, 3.2)	0.220	1.2 (-0.7, 3.2)	0.218	80.30 (10.96)	4.97 (1.43, 8.51)	0.006	4.97 (1.44, 8.50)	**0.006**
- 24wks	77.5 (8.6)	4.4 (2.9, 5.9)	<0.001	4.4 (3.0, 5.9)	<0.001	81.43 (12.50)	6.59 (2.75, 10.44)	0.001	6.59 (2.74, 10.45)	**0.001**
- 30wks	80.7 (10.6)	8.1 (5.9, 10.3)	<0.001	8.1 (5.9, 10.3)	<0.001	81.46 (8.18)	6.63 (3.26, 9.99)	0.000	6.63 (3.26, 9.99)	**0.000**
SV - 14wks	74.6 (12.9)		.		.	61.59 (12.71)		0.772*		0.782*
- 20wks	75.7 (14.1)	1.7 (-0.9, 4.2)	0.201	1.7 (-0.8, 4.2)	0.183	65.03 (11.78)	2.34 (-2.47, 7.15)	0.341	2.33 (-2.48, 7.13)	0.342
- 24wks	74.8 (13.4)	0.7 (-2.4, 3.8)	0.668	0.7 (-2.4, 3.8)	0.656	61.40 (11.79)	-0.98 (-5.58, 3.61)	0.675	-0.99 (-5.57, 3.60)	0.674
- 30wks	72.4 (12.6)	-1.3 (-4.3, 1.6)	0.379	-1.3 (-4.2, 1.7)	0.404	61.68 (9.04)	-0.74 (-5.64, 4.16)	0.767	-0.75 (-5.65, 4.15)	0.763
SVI - 14wks	43.3 (6.7)		.		.	38.24 (7.81)		0.751*		0.757*
- 20wks	43.4 (6.7)	0.3 (-1.2, 1.7)	0.730	0.3 (-1.2, 1.7)	0.700	39.67 (7.48)	0.95 (-2.04, 3.94)	0.533	0.94 (-2.05, 3.93)	0.538
- 24wks	42.2 (6.3)	-1.0 (-2.7, 0.7)	0.255	-1.0 (-2.7, 0.7)	0.261	36.93 (7.29)	-1.68 (-4.65, 1.29)	0.267	-1.69 (-4.66, 1.28)	0.264
- 30wks	40.2 (6.3)	-2.9 (-4.6, -1.2)	0.001	-2.9 (-4.6, -1.2)	0.001	36.43 (4.85)	-2.20 (-5.40, 1.00)	0.178	-2.21 (-5.41, 0.99)	0.176
CO - 14wks	5.47 (1.09)		.		.	4.58 (1.06)		0.414*		0.438*
- 20wks	5.53 (0.98)	0.14 (-0.11, 0.40)	0.272	0.15 (-0.10, 0.41)	0.235	5.21 (1.11)	0.52 (0.10, 0.95)	0.016	0.53 (0.10, 0.95)	**0.015**
- 24wks	5.76 (1.05)	0.33 (0.06, 0.61)	0.016	0.34 (0.07, 0.61)	0.015	5.13 (1.26)	0.49 (0.06, 0.92)	0.025	0.49 (0.07, 0.92)	**0.023**
- 30wks	5.82 (0.96)	0.44 (0.13, 0.75)	0.006	0.45 (0.14, 0.76)	0.005	5.43 (1.54)	0.77 (0.18, 1.35)	0.010	0.77 (0.19, 1.35)	**0.009**
CI - 14wks	3.17 (0.59)		.		.	2.83 (0.62)		0.354*		0.377*
- 20wks	3.18 (0.48)	0.04 (-0.11, 0.18)	0.606	0.04 (-0.10, 0.19)	0.548	3.16 (0.62)	0.28 (0.02, 0.54)	0.032	0.28 (0.02, 0.53)	**0.032**
- 24wks	3.25 (0.49)	0.09 (-0.06, 0.24)	0.246	0.09 (-0.06, 0.24)	0.235	3.07 (0.70)	0.21 (-0.05, 0.47)	0.120	0.21 (-0.05, 0.47)	0.118
- 30wks	3.24 (0.50)	0.09 (-0.08, 0.27)	0.301	0.10 (-0.08, 0.28)	0.279	3.19 (0.80)	0.32 (-0.03, 0.67)	0.075	0.32 (-0.03, 0.67)	0.074

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	SGA Mean (SD)	SGA Unadj. Diff vs T1 (95% C.I)	SGA Unadj p value	SGA Adj Diff vs T1 (95% C.I)	SGA Adj p value
MAP - 14wks	89.37 (7.16)		.		.	87.2 (7.6)		0.217*		0.239*
- 20wks	87.12 (6.08)	-2.0 (-3.6, -0.5)	0.012	-1.99 (-3.58, -0.41)	0.014	88.2 (8.2)	0.88 (-1.38, 3.14)	0.447	0.84 (-1.43, 3.12)	0.468
- 24wks	87.46 (5.84)	-2.2 (-3.9, -0.5)	0.013	-2.17 (-3.87, -0.46)	0.013	86.7 (7.4)	-0.63 (-2.94, 1.68)	0.594	-0.66 (-3.00, 1.67)	0.576
- 30wks	89.39 (6.50)	-0.2 (-1.9, 1.5)	0.813	-0.19 (-1.89, 1.51)	0.827	89.2 (7.6)	1.87 (-0.90, 4.63)	0.185	1.83 (-0.95, 4.61)	0.196
TPR - 14wks	1356.1 (291.9)		.		.	1619.2 (520.6)		0.782*		0.797*
- 20wks	1290.5 (248.8)	-79.1 (-141.5, -16.8)	0.013	-81.6 (-144.0, -19.2)	0.010	1413.5 (304.7)	-160.8 (-330.8, 9.2)	0.064	-162.7 (-334.3, 8.8)	0.063
- 24wks	1245.0 (204.7)	-123.5 (-192.6, -54.5)	<0.001	-124.6 (-194.0, -55.3)	<0.001	1410.6 (285.3)	-174.7 (-352.8, 3.2)	0.054	-177.0 (-356.3, 2.4)	0.053
- 30wks	1258.8 (216.9)	-120.2 (-197.5, -43.0)	0.002	-123.5 (-201.1, -45.9)	0.002	1375.8 (278.8)	-206.3 (-386.6, -26.1)	0.025	-208.1 (-389.5, -26.7)	**0.025**
TPRI - 14wks	2330.5 (478.2)		.		.	2589.7 (753.7)		0.778*		0.791*
- 20wks	2233.0 (416.0)	-110.1 (-218.7, -1.6)	0.047	-112.4 (-221.4, -3.43)	0.043	2318.2 (481.9)	-214.1 (-488.9, 60.7)	0.127	-214.8 (-489.7, 60.1)	0.126
- 24wks	2194.9 (328.1)	-150.5 (-267.2, -33.8)	0.011	-151.9 (-268.9, -34.9)	0.011	2348.4 (472.0)	-197.2 (-479.6, 85.2)	0.171	-198.3 (-480.7, 84.0)	0.169
- 30wks	2261.6 (405.1)	-91.6 (-225.5, 42.4)	0.180	-95.3 (-230.3, 39.7)	0.166	2316.2 (422.3)	-224.8 (-519.3, 69.8)	0.135	-225.5 (-519.7, 68.7)	0.133

Data are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, HR: heart rate, LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), MAP: mean arterial pressure, SD: standard deviation, SGA: small for gestational age: SV: stroke volume, SVI: stroke volume index (SV/BSA), T1: first trimester, TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA).

7.4.4 Preterm birth primary cardiovascular outcomes

In women who delivered preterm, CO and CI both increased significantly with gestation between 14 and 30 weeks' respectively; 5.39 L/min (SD 1.59 L/min) to 6.44 L/min (SD 1.41 L/min); $p < 0.001$ and 2.92 L/min/kg^2 (SD 0.78 L/min/kg^2) to 3.30 L/min/ kg^2 (SD 0.61 L/min/kg^2); $p = 0.011$, with no significant difference in mean values at each time point compared to high-risk women with a normal pregnancy outcome (Tables 29 and 30 and Figures 42, 46 and 47). Heart rate also increased significantly with gestation from 81 bpm (SD 11 bpm) to 89 bpm (SD 5 bpm); $p = 0.028$, with higher mean values at all time points reaching significance between 20 to 30 weeks' gestation (Tables 33 and 34 and Figures 39 and 41).

Stroke volume and stroke volume index were unchanged over the gestation studied, with no significant difference in SV mean values compared to the high-risk normal women. Women who delivered preterm had lower SVI compared to high-risk women with a normal pregnancy outcome, reaching statistical significance at 14 and 20 weeks' gestation respectively; 43.30 ml/kg^2 (SD 6.65 ml/m^2) versus 37.82 ml/m^2 (SD 2.23 ml/m^2); $p < 0.001$ and 43.42 ml/m^2 (SD 6.67 ml/m^2) 39.08 ml/m^2 (SD 5.30 ml/m^2); $p = 0.027$. These data are summarised in Tables 33 and 34 and Figures 40, 42 and 43.

The MAP was stable between 14 and 30 weeks' gestation; 90 mmHg (SD 11 mmHg) to 92 mmHg (6 mmHg); $p = 0.345$, with TPR significantly decreasing over this time period, replicating the same pattern of change seen in the high-risk women with a normal pregnancy outcome; 1451.5 Dynes.s^{-1}cm^{-5} (SD 524.9 Dynes.s^{-1}cm^{-5}) to 1167.9 Dynes.s^{-1}cm^{-5} (SD 192.1 Dynes.s^{-1}cm^{-5}); $p = 0.043$. The TPRI also decreased, however statistical significance was not reached, in keeping with the high-risk women with a normal outcome. TPRI; 2662.2 Dynes.s^{-1}cm^{-5}m^2 (SD 949.8 Dynes.s^{-1}cm^{-5}m^2) to 2264.4 Dynes.s^{-1}cm^{-5}m^2 (SD 332.8 Dynes.s^{-1}cm^{-5}m^2); $p = 0.796$. In terms of mean values; MAP, TPR and TPRI were not significantly different between the high-risk women with a normal pregnancy outcome and those who delivered preterm. MAP, TPR and TPRI data are summarised in Tables 33 and 34 and Figures 39, 46, 47 and 48).

The cardiovascular changes between 14 and 30 weeks' gestation in women who delivered preterm were in keeping with high-risk women who had a normal pregnancy outcome. CO/CI increased secondary to an increase in heart rate, while stable MAP coupled with elevated cardiac output decreased total peripheral resistance over this gestation.

Table 33. Preterm primary cardiovascular outcomes

Outcome	Normal Mean (SD)	PTL Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
HR				<0.001*		<0.001*
- 14 weeks	73.3 (8.6)	80.6(11.3)	7.15 (-2.04, 16.34)	0.127	6.94 (-2.36, 16.23)	0.143
- 20 weeks	74.1 (9.8)	89.4 (10.5)	14.64 (6.71, 22.58)	<0.001	14.38 (6.43, 22.33)	**<0.001**
- 24 weeks	77.5 (8.6)	89.9 (11.4)	11.97 (3.41, 20.53)	0.006	11.70 (3.25, 20.16)	**0.007**
- 30 weeks	80.7 (10.6)	89.2 (4.5)	7.59 (3.79, 11.38)	<0.001	7.31 (3.30, 11.32)	**<0.001**
SV				0.388*		0.472*
- 14 weeks	74.6 (12.9)	69.7 (7.7)	-4.70 (-11.59, 2.19)	0.181	-5.80 (-12.00, 0.41)	0.067
- 20 weeks	75.7 (14.1)	73.9 (13.8)	-2.32 (-13.77, 9.13)	0.691	-3.74 (-13.62, 6.14)	0.458
- 24 weeks	74.8(13.4)	72.9 (17.0)	-2.40 (-16.62, 11.83)	0.741	-3.78 (-17.16, 9.61)	0.580
- 30 weeks	72.4 (12.6)	72.0 (13.6)	-1.32 (-12.61, 9.96)	0.819	-2.74 (-13.78, 8.30)	0.627
SVI				0.319*		0.363*
- 14 weeks	43.3 (6.7)	37.8 (2.2)	-5.39 (-7.81, -2.97)	<0.001	-5.68 (-8.13, -3.24)	**<0.001**
- 20 weeks	43.4 (6.7)	39.1 (5.3)	-4.36 (-9.04, 0.32)	0.068	-4.79 (-9.02, -0.55)	**0.027**
- 24 weeks	42.2 (6.3)	37.8 (7.2)	-4.36 (-10.62, 1.91)	0.173	-4.76 (-10.81, 1.29)	0.123
- 30 weeks	40.2 (6.3)	36.9 (5.5)	-3.41 (-8.20, 1.39)	0.164	-3.82 (-8.59, 0.95)	0.117
CO				0.093*		0.100*
- 14 weeks	5.47 (1.09)	5.39 (1.59)	-0.06 (-1.34, 1.22)	0.924	-0.15 (-1.44, 1.14)	0.816
- 20 weeks	5.53 (0.98)	6.60 (1.48)	1.00 (-0.17, 2.17)	0.094	0.87 (-0.10, 1.84)	0.077
- 24 weeks	5.76 (1.05)	6.70 (2.43)	0.91 (-1.01, 2.84)	0.353	0.79 (-1.03, 2.61)	0.395
- 30 weeks	5.82 (0.96)	6.44 (1.41)	0.55 (-0.51, 1.61)	0.311	0.42 (-0.60, 1.44)	0.417

Outcome	Normal Mean (SD)	PTL Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
CI				0.148*		0.159*
- 14 weeks	3.17 (0.59)	2.92 (0.78)	-0.25 (-0.88, 0.39)	0.446	-0.27 (-0.91, 0.37)	0.404
- 20 weeks	3.18 (0.48)	3.48 (0.57)	0.29 (-0.18, 0.76)	0.229	0.25 (-0.15, 0.64)	0.225
- 24 weeks	3.25 (0.49)	3.46 (1.09)	0.22 (-0.66, 1.10)	0.629	0.18 (-0.67, 1.02)	0.680
- 30 weeks	3.24 (0.50)	3.30 (0.61)	0.05 (-0.43, 0.53)	0.828	0.01 (-0.46, 0.48)	0.961
MAP				0.855*		0.836*
- 14 weeks	89.4 (7.2)	90.7 (11.1)	1.41 (-7.52, 10.34)	0.757	1.03 (-7.00, 9.07)	0.801
- 20 weeks	87.1 (6.1)	91.2 (8.4)	1.69 (-6.10, 9.48)	0.671	1.15 (-6.20, 8.50)	0.760
- 24 weeks	87.5 (5.8)	88.6 (5.3)	-0.74 (-6.70, 5.23)	0.809	-1.24 (-7.14, 4.67)	0.681
- 30 weeks	89.4 (6.5)	91.7 (6.4)	0.31 (-6.08, 6.70)	0.923	-0.20 (-5.79, 5.38)	0.943
TPR				0.622*		0.646*
- 14 weeks	1356.1 (291.9)	1451.5 (524.9)	92.55 (-328.56, 513.67)	0.667	105.64 (-332.57, 543.85)	0.637
- 20 weeks	1290.5 (248.8)	1133.3 (193.3)	-188.46 (-386.43, 9.51)	0.062	-167.84 (-344.95, 9.26)	0.063
- 24 weeks	1247.0 (204.7)	1146.5 (335.4)	-130.88 (-404.61, 142.85)	0.349	-111.01 (-376.85, 154.83)	0.413
- 30 weeks	1258.8 (216.9)	1167.9 (192.1)	-112.20 (-269.44, 45.04)	0.162	-91.10 (-257.06, 74.86)	0.282
TPRI				0.634*		0.647*
- 14 weeks	2330.5 (478.2)	2662.2 (949.8)	330.56 (-429.33, 1090.45)	0.394	338.11 (-428.78, 1104.99)	0.388
- 20 weeks	2233.0 (416.0)	2117.8 (241.6)	-179.67 (-469.62, 110.28)	0.225	-167.94 (-453.60, 117.72)	0.249
- 24 weeks	2194.9 (328.1)	2184.4 (598.3)	-72.69 (-566.76, 421.37)	0.773	-61.37 (-551.25, 428.51)	0.806
- 30 weeks	2261.6 (405.1)	2264.4 (332.8)	-51.00 (-334.06, 232.07)	0.724	-38.75 (-332.08, 254.58)	0.796

Data are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, HR: heart rate, LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), MAP: mean arterial pressure, PTL: preterm birth, SD: standard deviation, SV: stroke volume, SVI: stroke volume index (SV/BSA), TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA).

Table 34. Preterm birth primary cardiovascular outcomes with gestation

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	Preterm Mean (SD)	Preterm Unadj. Diff vs T1 (95% C.I)	Preterm Unadj p value	Preterm Adj Diff vs T1 (95% C.I)	Preterm Adj p value
HR - 14wks	73.3 (8.6)		.		.	80.6 (11.3)		<0.001*		<0.001*
- 20wks	74.1 (9.8)	1.2 (-0.7, 3.2)	0.223	1.2 (-0.7, 3.2)	0.220	89.4 (10.5)	8.7 (4.8,12.6)	<0.001	8.7 (4.8, 12.6)	**<0.001**
- 24wks	77.5 (8.6)	4.4 (2.9, 5.9)	<0.001	4.4 (3.0, 5.9)	<0.001	89.9 (11.4)	9. (4.8, 13.6)	<0.001	9.2 (4.8, 13.5)	**<0.001**
- 30wks	80.7 (10.6)	8.1 (5.9, 10.3)	<0.001	8.1 (5.9, 10.3)	<0.001	89.2 (4.5)	8.5 (1.0, 16.0)	0.027	8.5 (0.9, 16.0)	**0.028**
SV - 14wks	74.6 (12.9)		.		.	69.7 (7.7)		0.388*		0.472*
- 20wks	75.7 (14.1)	1.7 (-0.9, 4.2)	0.208	1.7 (-0.8, 4.2)	0.187	73.9 (13.8)	4.0 (-2.4, 10.4)	0.218	3.8 (-2.5, 10.0)	0.239
- 24wks	74.8 (13.4)	0.7 (-2.4, 3.8)	0.677	0.7 (-2.4, 3.8)	0.664	72.9 (17.0)	3.0 (-7.7, 13.6)	0.586	2.7 (-7.9, 13.3)	0.615
- 30wks	72.4 (12.6)	-1.3 (-4.3, 1.6)	0.368	-1.3 (-4.2, 1.7)	0.393	72.0 (13.6)	2.0 (-5.4, 9.4)	0.593	1.77 (-5.6, 9.2)	0.639
SVI - 14wks	43.3 (6.7)		.		.	37.8 (2.2)		0.319*		0.363*
- 20wks	43.4 (6.7)	0.3 (-1.2, 1.7)	0.740	0.3 (-1.2, 1.7)	0.703	39.1 (5.3)	1.3 (-2.1, 4.6)	0.457	1.2 (-2.1, 4.5)	0.486
- 24wks	42.2 (6.3)	-1.0 (-2.7, 0.7)	0.253	-1.0 (-2.7, 0.7)	0.260	37.8 (7.2)	0.0 (-5.3, 5.3)	0.993	-0.07 (-5.4, 5.2)	0.978
- 30wks	40.2 (6.3)	-2.9 (-4.6, -1.2)	0.001	-2.9 (-4.6, -1.2)	0.001	36.9 (5.5)	-0.9 (-4.5, 2.6)	0.607	-1.0 (-4.6, 2.5)	0.570
CO - 14wks	5.47 (1.09)		.		.	5.4 (1.6)		0.093*		0.100*
- 20wks	5.53 (0.98)	0.14 (-0.11, 0.40)	0.254	0.15 (-0.10, 0.41)	0.224	6.60 (1.48)	1.21 (0.13, 2.29)	0.028	1.18 (0.12, 2.24)	**0.029**
- 24wks	5.76 (1.05)	0.33 (0.06, 0.61)	0.015	0.34 (0.07, 0.61)	0.015	6.70 (2.43)	1.31 (0.35, 2.27)	0.007	1.28 (0.34, 2.23)	**0.008**
- 30wks	5.82 (0.96)	0.44 (0.13, 0.75)	0.005	0.45 (0.14, 0.76)	0.004	6.44 (1.41)	1.06 (0.55, 1.56)	<0.001	1.03 (0.53, 1.52)	**<0.001**
CI - 14wks	3.17 (0.59)		.		.	2.92 (0.78)		0.148*		0.159*
- 20wks	3.18 (0.48)	0.04 (-0.11, 0.18)	0.610	0.04 (-0.10, 0.19)	0.564	3.48 (0.57)	0.57 (0.00, 1.14)	0.048	0.56 (-0.00, 1.12)	0.050
- 24wks	3.25 (0.49)	0.09 (-0.06, 0.24)	0.247	0.09 (-0.06, 0.24)	0.240	3.46 (1.09)	0.55 (0.09, 1.02)	0.020	0.54 (0.08, 1.00)	**0.020**
- 30wks	3.24 (0.50)	0.09 (-0.08, 0.27)	0.304	0.10 (-0.08, 0.27)	0.291	3.30 (0.61)	0.39 (0.10, 0.68)	0.008	0.38 (0.09, 0.67)	**0.011**

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	PTL Mean (SD)	PTL Unadj. Diff vs T1 (95% C.I)	PTL Unadj p value	PTL Adj Diff vs T1 (95% C.I)	PTL Adj p value
MAP - 14wks	89.4 (7.2)		.		.	90.7 (11.1)		0.855*		0.836*
- 20wks	87.1 (6.1)	-2.0 (-3.6, -0.5)	0.012	-1.99 (-3.58, -0.41)	0.014	91.2 (8.4)	-1.8 (-6.5, 2.9)	0.461	-1.9 (-6.5, 2.7)	0.425
- 24wks	87.5 (5.8)	-2.2 (-3.9, -0.5)	0.013	-2.15 (-3.86, -0.45)	0.013	88.6 (5.3)	-4.3 (-10.1, 1.5)	0.143	-4.4 (-10.2, 1.3)	0.132
- 30wks	89.4 (6.5)	-0.2 (-1.9, 1.5)	0.823	-0.17 (-1.87, 1.53)	0.847	91.7 (6.4)	-1.3 (-4.4, 1.8)	0.413	-1.4 (-4.3, 1.5)	0.345
TPR - 14wks	1356.1 (291.9)		.		.	1451.5 (524.9)		0.622*		0.646*
- 20wks	1290.5 (248.8)	-80.2 (-142.8, -17.7)	0.012	-81.6 (-144.4, -18.8)	0.011	1133.3 (193.3)	-361.2 (-828.4, 106.0)	0.130	-355.1 (-821.6, 111.5)	0.136
- 24wks	1245.0 (204.7)	-124.4 (-193.9, -55.4)	<0.001	-125.3 (-194.7, -55.8)	<0.001	1146.5 (335.4)	-348.1 (-680.4, -15.7)	0.040	-341.9 (-674.2, -9.7)	**0.044**
- 30wks	1258.8 (216.9)	-121.9 (-199.4, -44.4)	0.002	-123.7 (-201.6, -45.8)	0.002	1167.9 (192.1)	-326.6 (-635.8, -17.4)	0.038	-320.5 (-630.8, -10.1)	0.043
TPRI - 14wks	2330.5 (478.2)		.		.	2662.2 (949.8)		0.634*		0.647*
- 20wks	2233.0 (416.0)	-111.2 (-220.0, -2.4)	0.045	-112.2 (-221.7, -2.7)	0.045	2117.8 (241.6)	-621.4 (-1462.6, 219.8)	0.148	-618.2 (-1461.4, 225.0)	0.151
- 24wks	2194.9 (328.1)	-151.6 (-268.6, -34.6)	0.011	-152.2 (-269.4, -34.9)	0.011	2184.4 (598.3)	-554.8 (-1180.0, 70.4)	0.082	-551.6 (-1179.0, 75.7)	0.085
- 30wks	2261.6 (405.1)	-93.3 (-227.5, 40.9)	0.173	-94.8 (-230.2, 40.6)	0.170	2264.4 (332.8)	-474.8 (-1046.2, 96.6)	0.103	-471.6 (-1046.5, 103.2)	0.108

Data are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). BSA: body surface area, CI: cardiac index (CO/BSA), CO: cardiac output, HR: heart rate, LVM: left ventricular mass, LVMI: left ventricular mass index (LVM/BSA), MAP: mean arterial pressure, PTL: preterm birth, SD: standard deviation, SV: stroke volume, SVI: stroke volume index (SV/BSA); T1: first trimester, TPR: total peripheral resistance, TPRI: total peripheral resistance index (TPR x BSA).

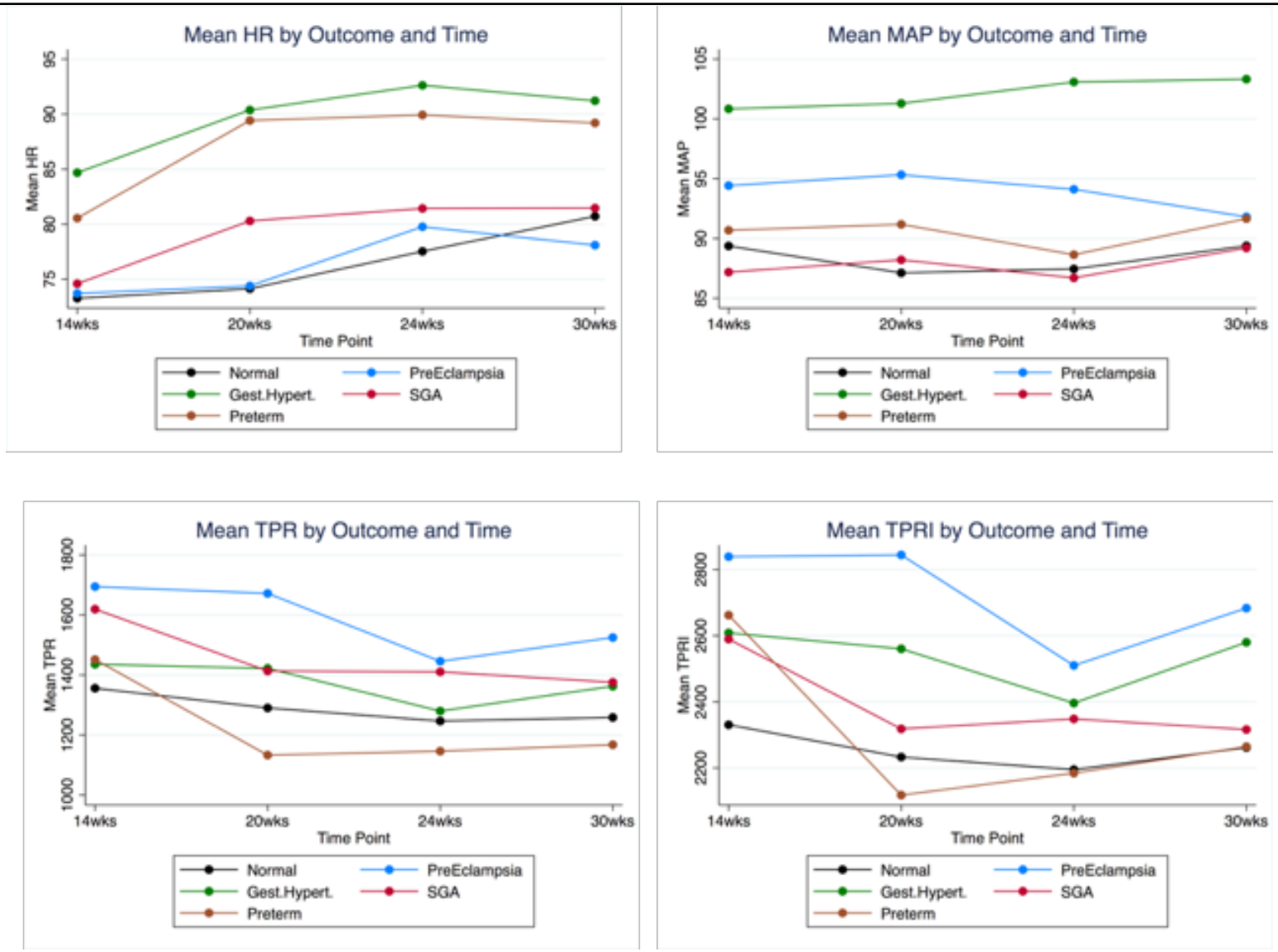


Figure 39. Primary cardiovascular variables HR, MAP, TPR and TPRI by pregnancy outcomes and time

HR: heart rate; MAP: mean arterial pressure, SGA: small for gestational age, TPR: total peripheral resistance, TPRI: total peripheral resistance index.

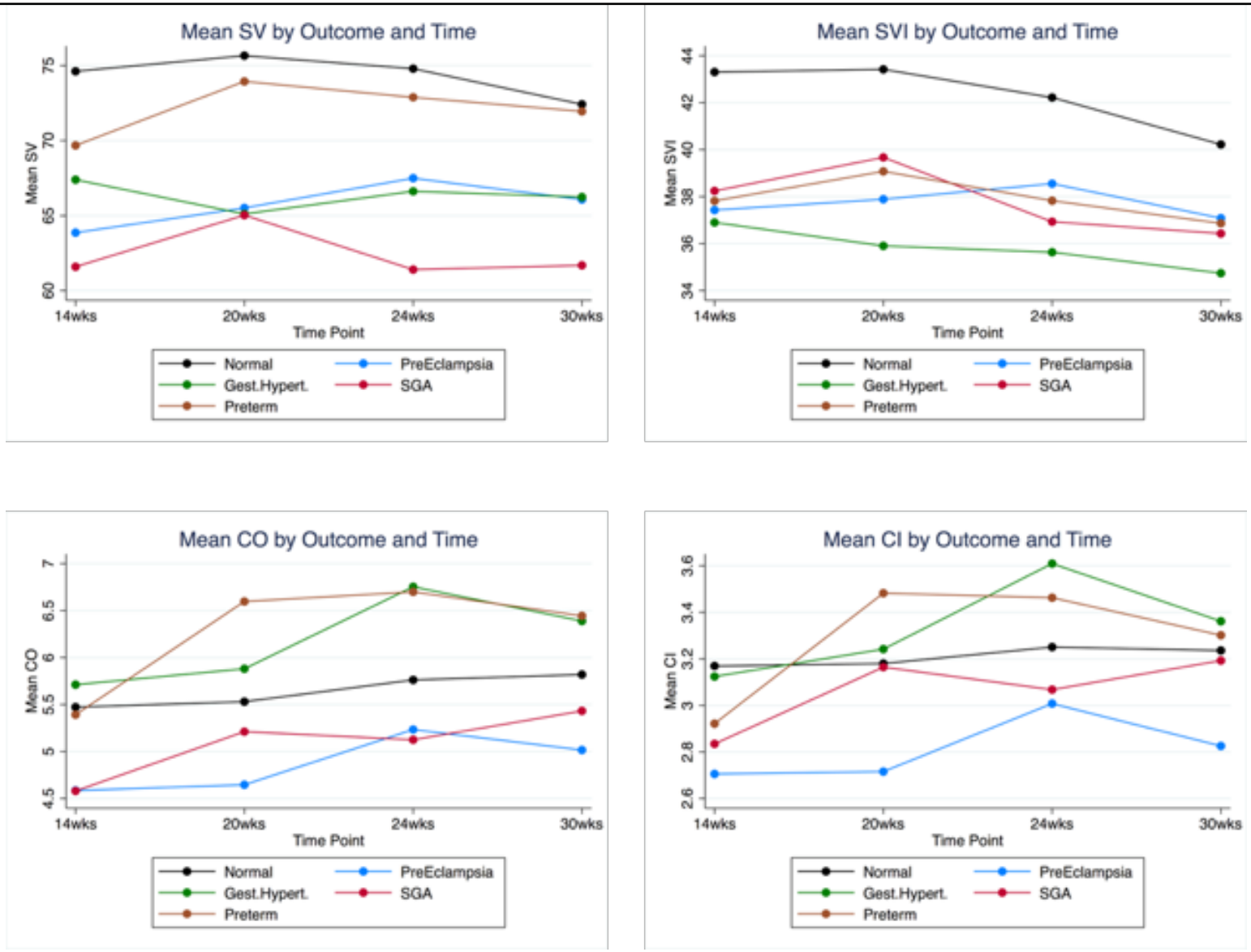


Figure 40. Primary cardiovascular variables SV, SVI, CO and CI by pregnancy outcomes and time

CI: cardiac index; CO: cardiac output, SGA: small for gestational age, SV: stroke volume, SVI: stroke volume index.

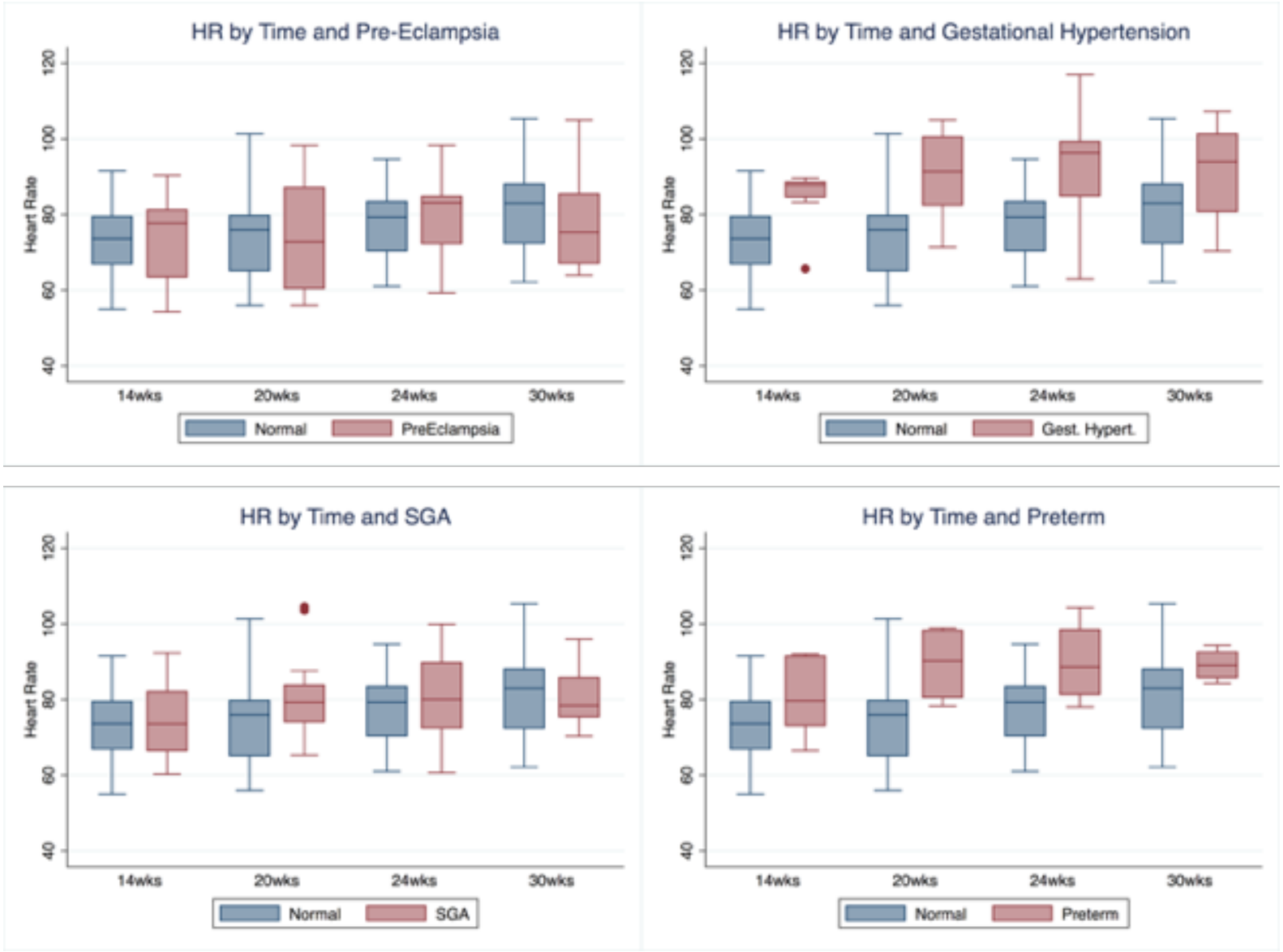
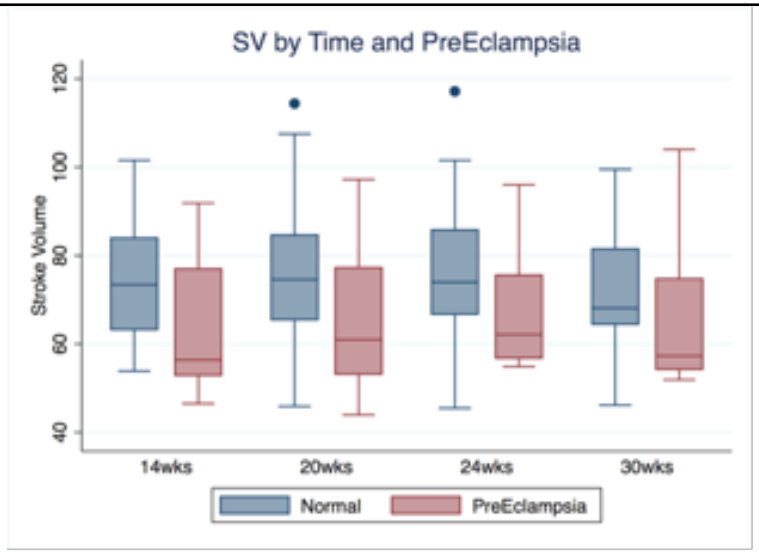
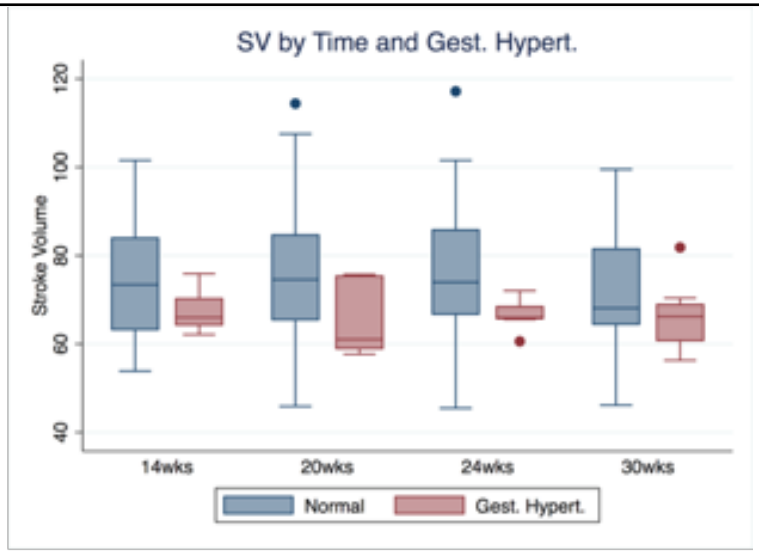
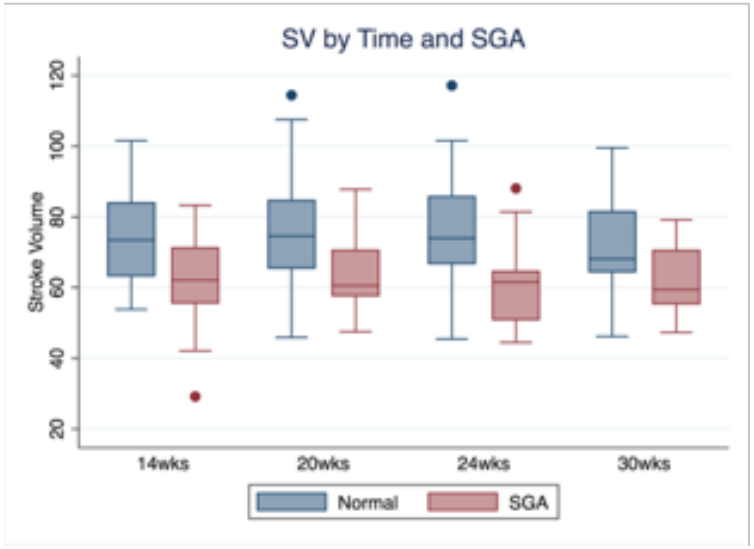


Figure 41. Heart rate with gestation and by pregnancy outcome

HR: heart rate, SGA: small for gestational age.







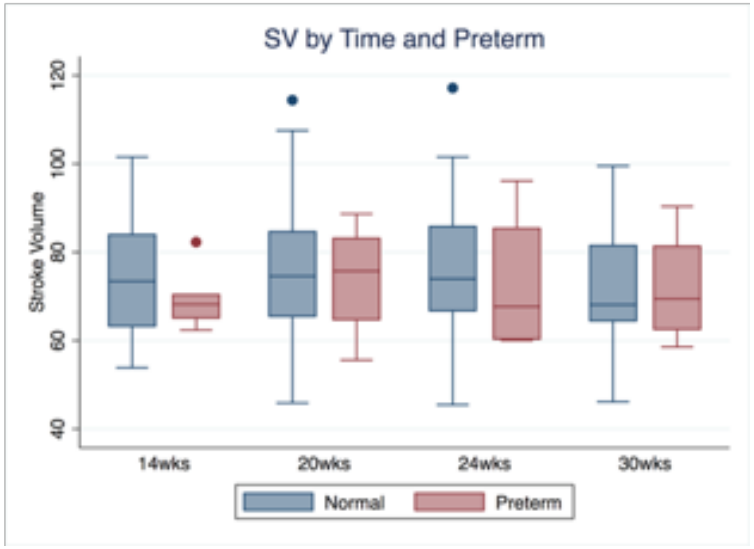


Figure 42. SV with gestation and by pregnancy outcome

Gest. Hypert: gestational hypertension; SGA: small for gestational age; SV: stroke volume.

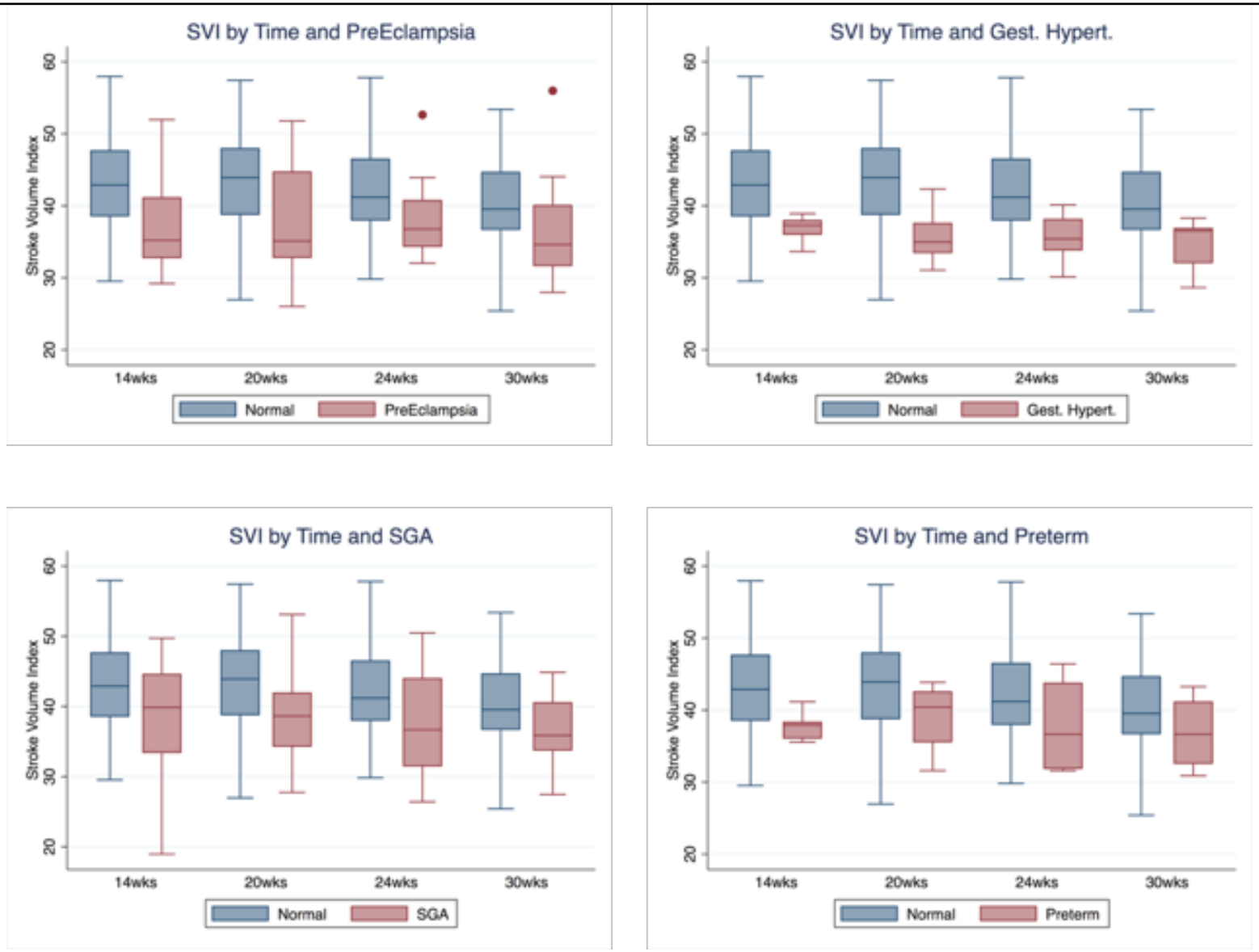


Figure 43. SVI with gestation and by pregnancy outcome

Gest. Hypert: gestational hypertension, SGA: small for gestational age, SVI: stroke volume index.

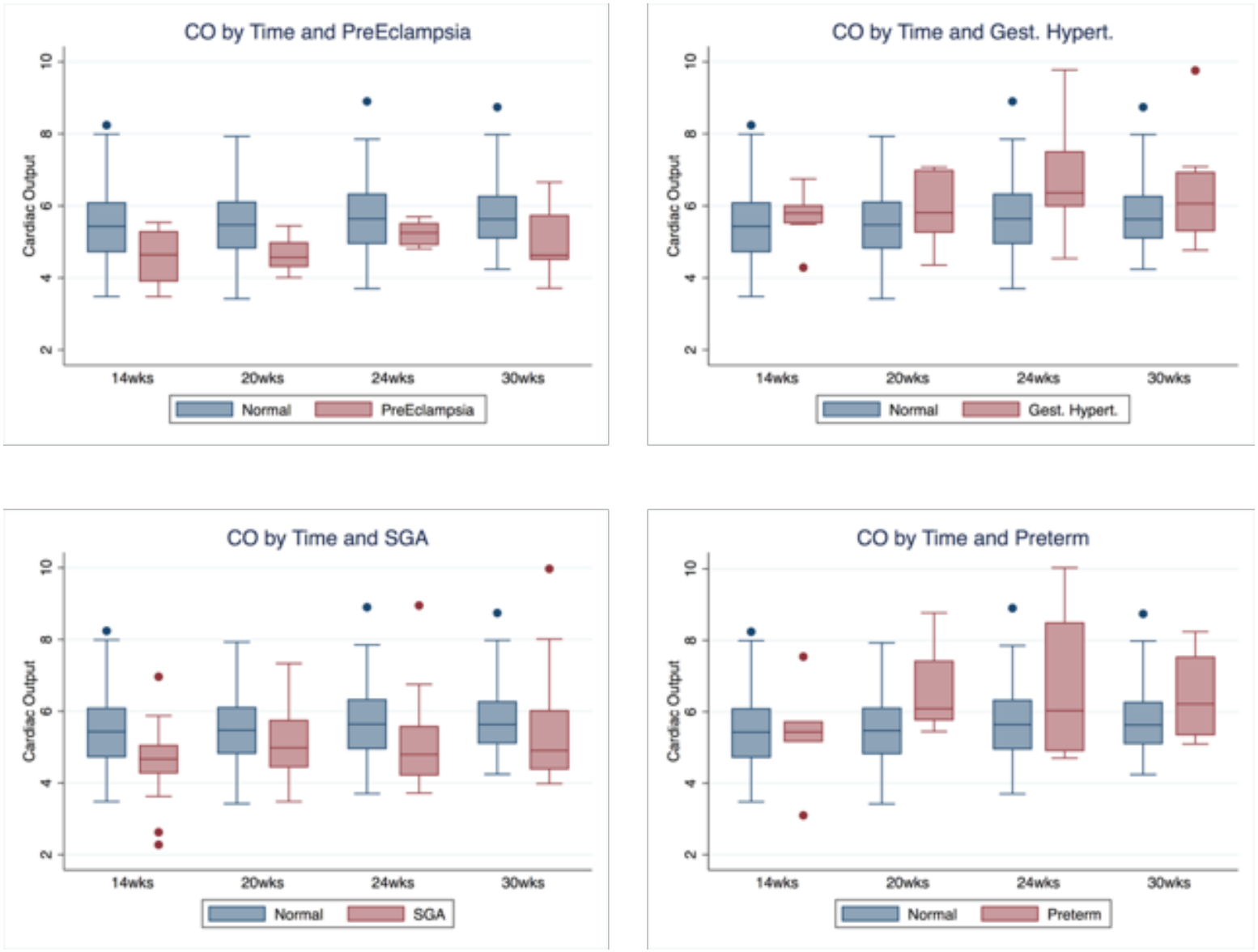


Figure 44. CO with gestation and by pregnancy outcome

CO: cardiac output, Gest. Hypert: gestational hypertension, SGA: small for gestational age

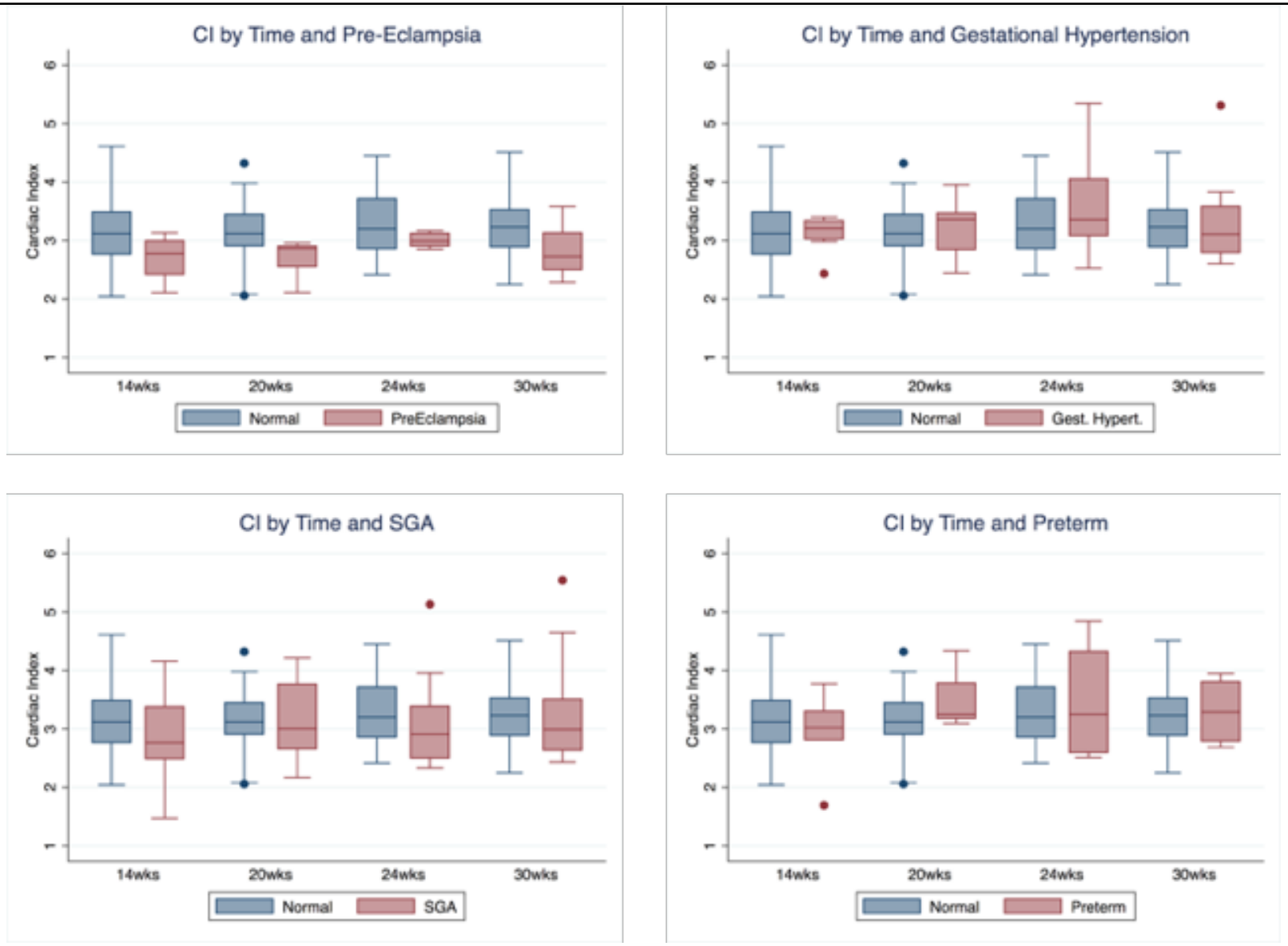


Figure 45. CI with gestation and by pregnancy outcome

CI: cardiac output, Gest. Hypert: gestational hypertension, SGA: small for gestational age

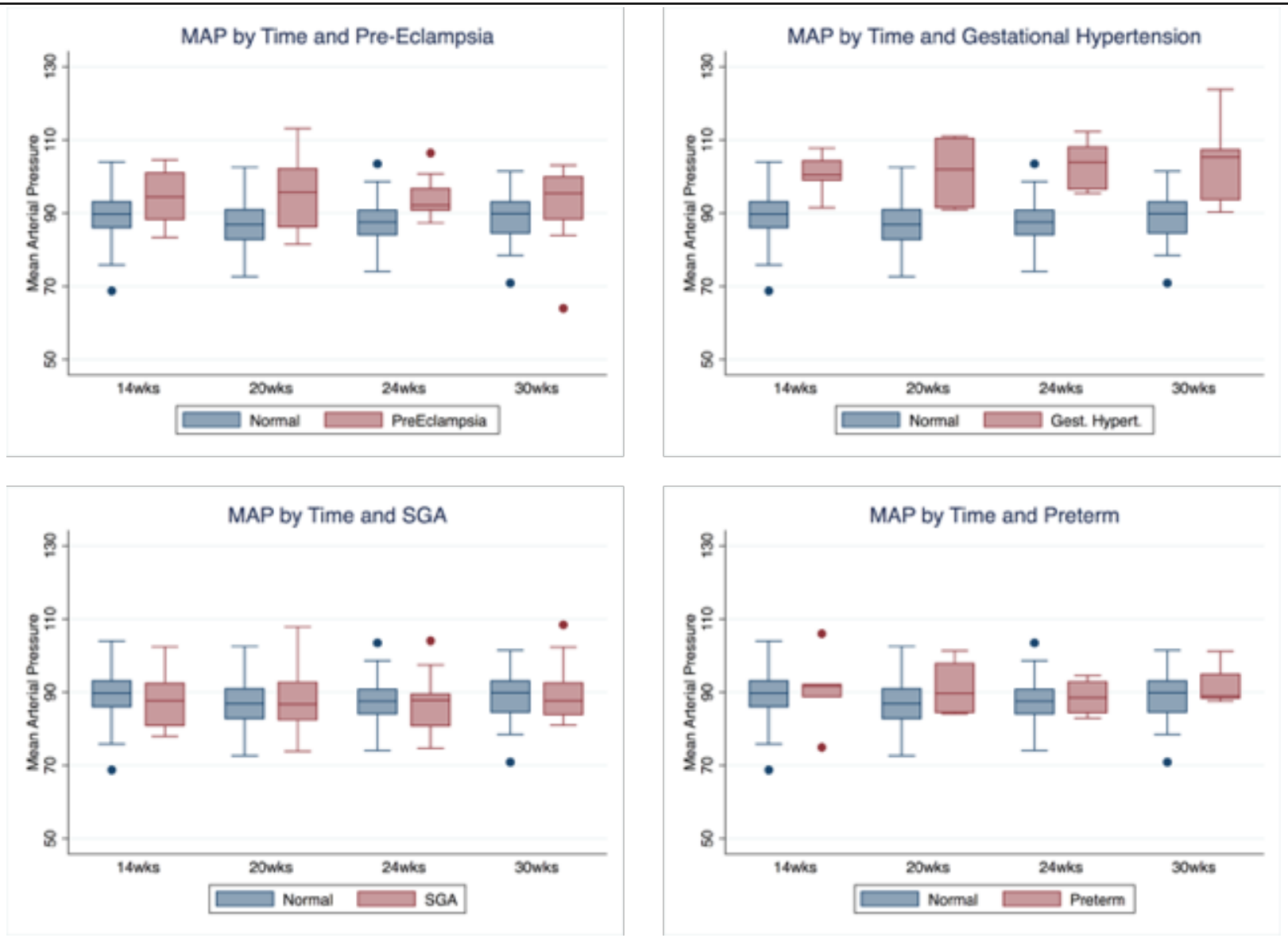


Figure 46. MAP with gestation and by pregnancy outcome

MAP: mean arterial pressure, SGA: small for gestational age.

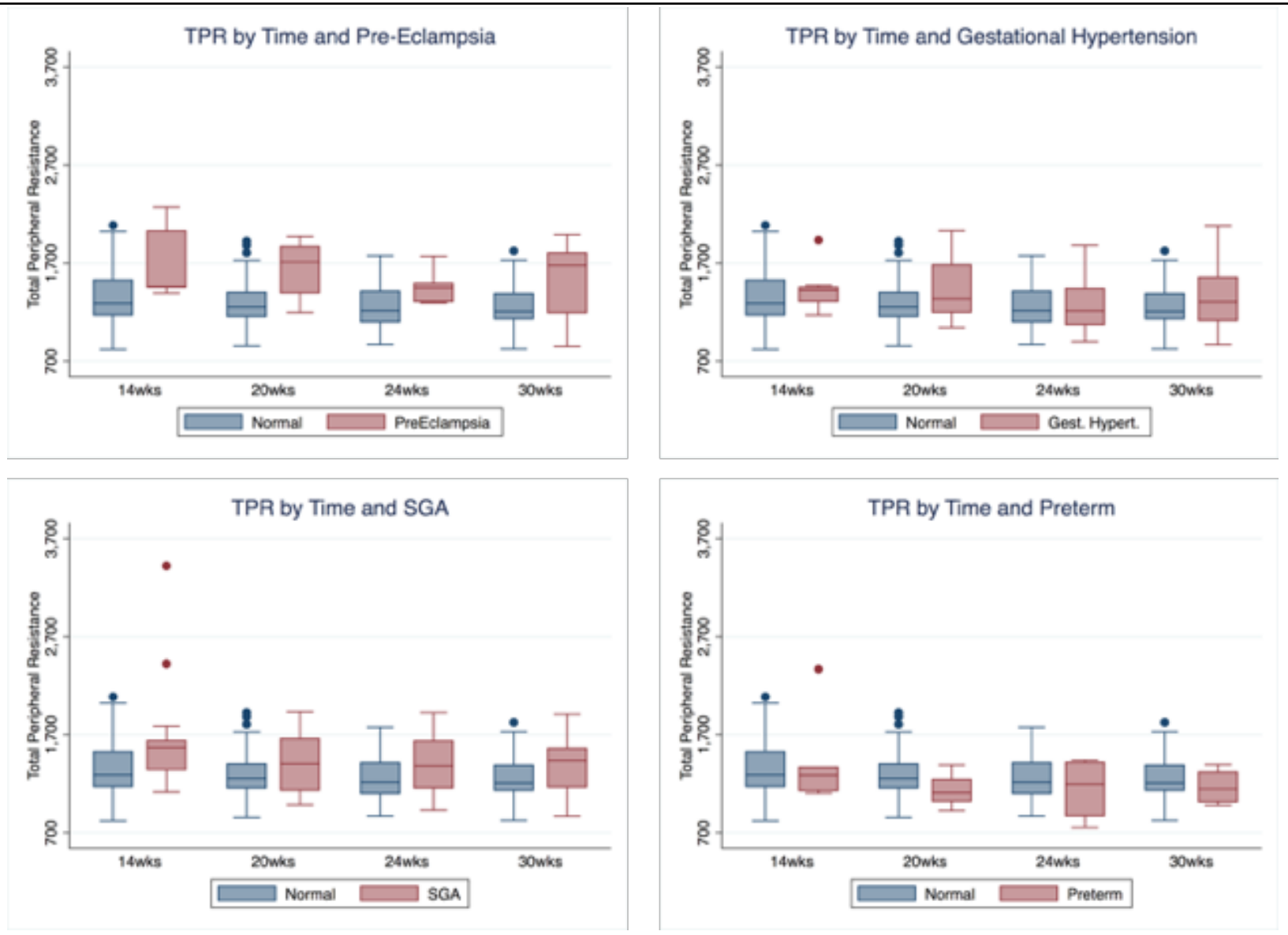
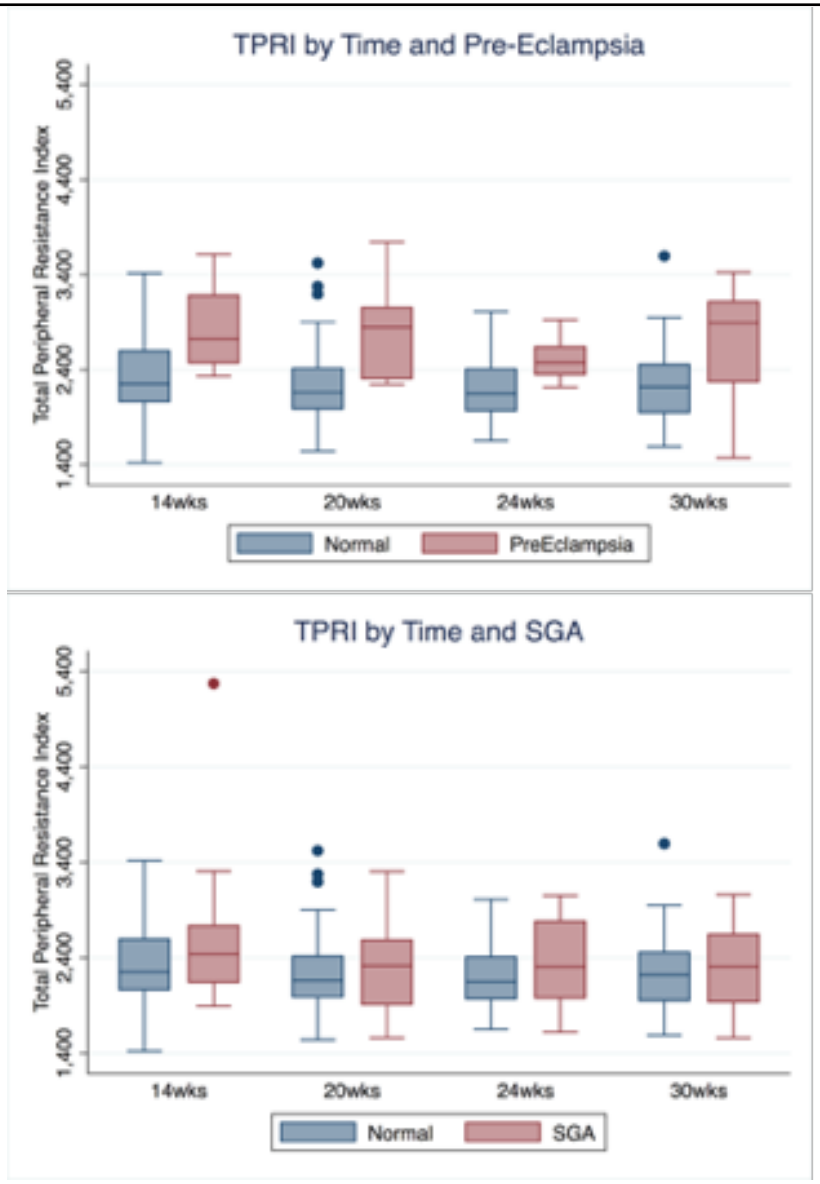


Figure 47. TPR with gestation and by pregnancy outcome

SGA: small for gestational age, TPR: total peripheral resistance



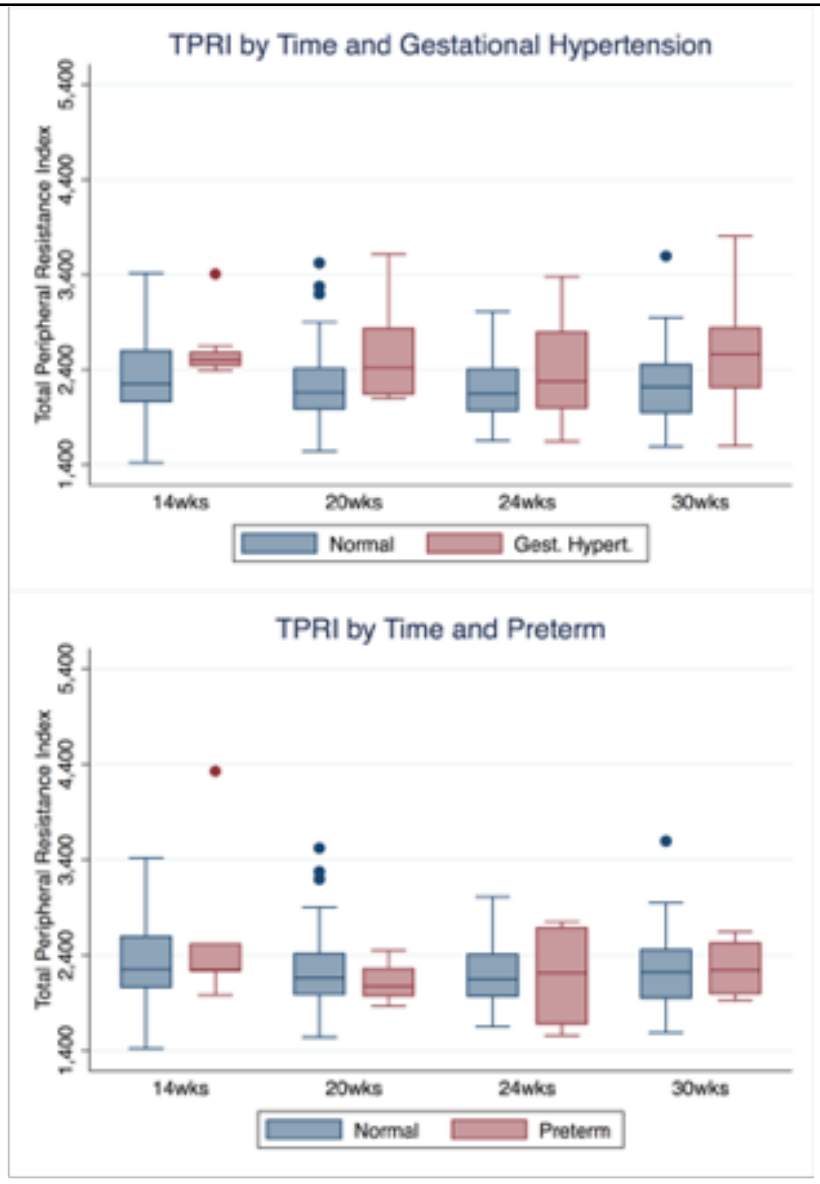


Figure 48. TPRI with gestation and by pregnancy outcome

SGA: small for gestational age, TPRI: total peripheral resistance index

7.5 Secondary Cardiovascular Outcomes

7.5.1 Pre-eclampsia secondary cardiovascular outcomes

The left ventricular mass of women who developed pre-eclampsia increased significantly between 14 and 30 weeks' gestation; 122.8 g (SD 33.5 g) to 132.8 g (SD 29.5 g); p <0.001, with no significant difference in mean values compared to high-risk women with a normal pregnancy outcome. The LVMI mean values were also unchanged between the two groups, however women who developed PE showed a mild non-statistical increase in LVMI in contrast to the high-risk women with a normal pregnancy outcome who did not.

Ejection fraction and fractional shortening were generally no different between women who developed pre-eclampsia and those with a normal pregnancy outcome, with the exception of Simpson's EF at 14 weeks' gestation. The mean value for women who developed pre-eclampsia was lower; 65.2 % (SD 2.7 %) compared to high-risk women with a normal outcome; 67.4 % (3.7%). This was not replicated in the M-Mode EF measure.

The *s* wave velocities were different between the two groups of women, with mean values lower in the women who developed pre-eclampsia reaching significance at 30 weeks' gestation at the septum; 9.64 cm/s (SD 1.28 cm/s) versus 8.39 cm/s (SD 1.32 cm/s); p = 0.006 and at all time points at the left ventricular lateral wall. At the right ventricular lateral wall, the *s* wave velocities were also lower in the women who developed pre-eclampsia, reaching significance at 20 and 24 weeks' gestation respectively; 14.67 cm/s (SD 1.88 cm/s) versus 16.24 cm/s (SD 2.16 cm/s);p = 0.034 and 13.89 cm/s (SD 1.19 cm/s) versus 15.56 cm/s (SD 1.77 cm/s); p < 0.001.

With respect to the diastolic mitral valve inflow velocity measures E, A and E/A ratio between the high-risk women who developed pre-eclampsia and those with a normal pregnancy outcome, there was no difference in mean values from 14 to 30 weeks' gestation. The DT also showed no difference, with the IVRT only significantly higher at 20 weeks' gestation in the women who developed pre-eclampsia; 90.7 ms (SD 13.6 ms) versus 98.9 ms (SD 9.4 ms); p = 0.031. The A wave duration was significantly longer at 30 weeks' gestation in the women who

developed pre-eclampsia, measuring 124.3 ms (SD 8.0 ms) compared to 117.7 ms (SD 16.8 ms); p = 0.038 in the women with a normal pregnancy outcome.

In women who developed pre-eclampsia, the diastolic tissue Doppler *e* velocity at the septum decreased between 14 and 30 weeks' gestation from 13.44 cm/s [SD 2.56 cm/s] to 11.12 cm/s [SD 2.49 cm/s]; p < 0.001, with a concomitant decline in the *e/a* ratio (1.58 [SD 0.44] to 1.29 [SD 0.35]; p = 0.006), in keeping with the trends seen in the high-risk normal group. However, this occurred when the *a* velocity in the PE group was static, in contrast to the high-risk normal group which showed an increase; 8.06 cm/s (SD 1.62 cm/s) to 9.23 cm/s (SD 1.82); p < 0.001 versus 8.69 cm/s (SD 1.27 cm/s) to 8.83 cm/s (SD 1.50 cm/s); p = 0.650, respectively. The *e* velocity and *e/a* ratio mean values were lower in the pre-eclampsia group compared to the high-risk normal group, reaching statistical significance at 20 and 30 weeks' gestation respectively; 13.18 ms (1.86 ms) versus 14.70 ms (2.67 ms): p = 0.035 and 13.12 ms (2.76 ms) versus 11.12 ms (2.49 ms); p = 0.023.

The equivalent lateral wall velocities between 14 and 30 weeks' gestation in women who developed pre-eclampsia showed the same statistically significant decrease in *e* wave velocity (16.91 cm/s [SD 3.50 cm/s] to 15.04 cm/s [SD 3.32 cm/s], p = 0.029) and *e/a* ratio (2.08 [SD 0.63] to 1.89 [SD 0.62], p = 0.001), with the *a* wave velocity unchanged over the same time period (8.34 cm/s [SD 1.07] to 8.26cm/s [SD 1.66 cm/s], p = 0.823). This was in contrast to the high-risk women with a normal outcome who showed *a* wave velocity increase. The left lateral wall mean values were significantly lower in the women who developed pre-eclampsia measuring, 16.00 cm/s (SD 2.41 cm/s) versus 18.56 cm/s (SD 3.49 cm/s); p = 0.004 at 20 weeks' gestation and 15.72 cm/s (SD 2.96 cm/s) versus 17.64 cm/s (SD 3.48 cm/s); p = 0.041 at 24 weeks' gestation. There was no significant difference in the E/*e* ratios at the septum or left lateral wall.

In terms of the right lateral wall *e* and *a* velocities, there was no significant difference in mean values between the high-risk normal women and those that developed pre-eclampsia, with the exception of the *a* wave velocity at 14 weeks' gestation which was significantly higher in the women who developed pre-eclampsia; 15.07 cm/s (SD 3.20 cm/s) versus 12.55 cm/s (SD 2.83 cm/s); p = 0.023. The right *e/a* ratio was also consistently higher in the high-risk normal

women compared to those that subsequently developed pre-eclampsia, however statistical significance was not reached.

Women who developed pre-eclampsia compared to high-risk women with a normal outcome had similar diastolic changes, with one notable difference in *a* wave velocity. At all three tissue Doppler sites (septum, left lateral wall and right lateral wall), *a* wave velocity was unchanged in women who developed pre-eclampsia while women with a normal pregnancy outcome showed a marked increase. The finding was also seen in the mitral valve inflow A wave velocity. The data for all of these outcomes can be seen in Appendices A and E.

7.5.2 Gestational hypertension secondary cardiovascular outcomes

Left ventricular mass and LVMI were unchanged between 14 and 30 weeks' gestation in women who developed GH respectively; 131.5 g (SD 26.3 g) to 133.2 g (SD 49.1 g); p 0.890 and 71.1g/m^2 (SD 11.4 g/m^2) to 68.9 g/m^2 (SD 19.9 g/m^2); p = 0.662. This is in contrast to women with a normal pregnancy outcome which showed a significant increase.

In women who developed GH, VTI was unchanged between 14 and 30 weeks' gestation; 22.91 cm/s (SD 1.02 cm/s) to 22.32 cm/s (SD 1.87 cm/s); p = 0.325. This is in contrast to women with a normal pregnancy outcome which showed VTI decrease over the same time period. VTI mean values were also significantly lower in the GH group at 20 and 24 weeks' gestation respectively; 22.01cm/s (SD 1.57 cm/s) versus 24.21 cm/s (SD 3.38 cm/s); p = 0.011 and 21.59 cm/s (SD 1.17 cm/s) versus 23.87 cm/s (SD 3.01 cm/s); p = 0.001. There was no change in LVOT with gestation in keeping with high-risk women with a normal outcome, however the mean diameter was lower in the GH women at 20 and 30 weeks' gestation respectively; 1.94 cm (0.07 cm) versus 1.99 cm (0.14 cm); p = 0.044 and 1.94 cm (0.08 cm) versus 2.00 cm (0.12 cm); p = 0.010. The combination of lower VTI and LVOT resulted in lower SV/SVI values.

Fractional shortening was unchanged between 14 and 30 weeks' gestation; 37.0 % (SD 4.9 %) to 38.2 % (SD 6.4 %); p = 0.253, consistent with the results seen in high-risk women with a normal pregnancy outcome. There was also no difference in mean values. Ejection fraction was also essentially unchanged, with

differences in mean values seen only at one time point using both the M-mode and Simpson methods.

The *s* velocities at the septum, left lateral wall and right lateral wall were all in keeping with the mean values of high-risk women who had a normal pregnancy outcome with the exception of lower *s* velocities at both the left and right lateral wall sites at 20 weeks' gestation respectively; 10.63 cm/s (SD 1.67 cm/s) versus 11.97 cm/s (SD 10.63 cm/s); p = 0.007 and 15.72 cm/s (SD 1.14 cm/s) versus 16.25 cm/s (SD 3.00 cm/s); p = 0.035. In keeping with high-risk women with a normal pregnancy outcome, there was no change with gestation in these measures.

In women who developed GH, the mitral valve E velocity decreased significantly between 14 and 30 weeks' gestation; 89.99 cm/s (SD 13.12 cm/s) to 79.49 cm/s (SD 13.58 cm/s); p = 0.038, in keeping with the changes seen in women with a normal pregnancy outcome. There was a concomitant A velocity increase from 61.66 cm/s (SD 13.24 cm/s) to 68.20 cm/s (SD 16.83 cm/s), however significance was not reached; p = 0.185. This resulted in a significant *e/a* ratio decline from 1.50 (SD 0.27) to 1.21 (SD 0.26); p = 0.027, again consistent with the changes seen in high-risk women with a normal pregnancy outcome. The mean E velocity between the two outcome groups was not significantly different between 14 and 30 weeks' gestation, while the A velocity was significantly higher in women who developed GH at all time points. The mean E/A ratio values were also all significantly lower in the GH groups.

The remaining traditional diastolic indices (IVRT, DT and A duration) showed no significant change between 14 and 30 weeks' gestation in women who developed GH. There was also no significant difference in mean values between women who developed GH and those with a normal pregnancy outcome, with the exception of DT at 24 weeks' lower in the GH group; 133.4 ms (SD 26.6 ms) versus 151.8 ms (19.2 ms); p = 0.043.

The mean septal tissue Doppler *e* and *a* velocities were comparative to high-risk women with a normal pregnancy outcome. Septal *e* velocity decreased between 14 and 30 weeks' gestation, however significance was not reached; 15.68 cm/s (SD 3.20 cm/s) to 14.71 cm/s (SD 3.10 cm/s); p = 0.473, while *a* velocity remained unchanged over this time period. The *e/a* ratio significantly declined from 1.74

(SD 0.27) at 14 weeks' gestation to 1.40 (SD 0.46); p = 0.019 at 24 weeks' gestation in keeping with the trend seen in high-risk women with a normal pregnancy outcome.

The left lateral wall *e* and *a* velocities in women who developed GH followed the same trend as seen at the septum with *e* velocity decreasing from 17.45 cm/s (SD 2.80 cm/s) to 15.93 cm/s (SD 3.05 cm/s), however statistical significance was not reached; p = 0.218. The mean *e* velocity was also lower in women who developed GH at 20 and 24 weeks' gestation respectively; 16.76 cm/s (3.04 cm/s) versus 18.56 cm/s (3.49 cm/s); p = 0.013 and 15.74 cm/s (2.04 cm/s) versus 17.64 cm/s (3.48 cm/s); p = 0.002. The *a* velocity was unchanged, with a mild non-significant decrease in *e/a* ratio from 14 to 30 weeks' gestation; 1.94 (0.34) to 1.88 (0.43); p = 0.236. The E/*e* ratio at the septum and left lateral wall was comparative between the two groups of women at each time point, with the exception of the left lateral wall ratio at 24 weeks' gestation higher in the GH women; 5.43 (SD 1.83) versus 4.83 (SD 1.13).

At the right lateral wall, the *e* velocity decreased significantly between 14 and 30 weeks' gestation; 19.88 cm/s (SD 3.27 cm/s) to 17.34 cm/s (SD 5.42 cm/s); p = 0.018, while *a* velocity remained unchanged over the same time period; 13.91 cm/s (SD 2.56 cm/s) to 13.71 cm/s (SD 4.10 cm/s); p = 0.896. Effectively, the *e/a* ratio decreased significantly from 1.50 (SD 0.52) to 1.11 (SD 0.52); p = 0.004 at 24 weeks' gestation, followed by a slight increase to 1.37 (0.52) at 30 weeks' gestation. The mean *e* and *a* velocities values were not significantly different between women who developed GH and those with a normal pregnancy outcome with the exception of higher *a* velocity measured at 24 weeks' gestation in the GH group; 17. 34 cm/s (5.10 cm/s) versus 13.71 cm/s (3.07 cm/s); p = 0.018.

High-risk women who developed GH compared to high-risk women with a normal outcome showed the same diastolic changes with gestation in both the mitral inflow and tissue Doppler measurements, with minor differences in some of the mean values. The measures of systolic function were also comparative between the two groups. Differences in VTI measurements underpinned the lower SV and SVI values seen in women who developed GH compared to high-risk women with a normal pregnancy outcome. The data for all of these outcomes can be seen in Appendices B and F.

7.5.3 SGA secondary cardiovascular outcomes

Left ventricular mass increased significantly between 14 and 30 weeks' gestation; 104.7 g (SD 17.9 g) to 119.8 g (SD 21.2 g); $p < 0.001$, following the same trend as high-risk women with a normal pregnancy outcome. LVM mean values were all significantly lower between 14 and 30 weeks' gestation in women who delivered a SGA infant compared to high-risk women with a normal pregnancy outcome.

LVMI increased significantly between 14 and 30 weeks' gestation, in contrast to high-risk women who had a normal pregnancy outcome. The LVMI mean values were also significantly lower in women who delivered a SGA infant between 14 and 24 weeks' gestation compared to high-risk women with a normal pregnancy outcome respectively; 64.7 g/m^2 (SD 8.6 g/m^2) versus 72.4 g/m^2 (SD 12.3 g/m^2); $p = 0.006$ and 66.9 g/m^2 (SD 8.3 g/m^2) versus 72.3 g/m^2 (SD 11.1 g/m^2); $p = 0.009$.

VTI was unchanged between 14 and 30 weeks' gestation in women who delivered a SGA infant; 22.82 cm/s (SD 3.30 cm/s) to 22.38 cm/s (SD 2.96); $p = 0.532$, while high-risk women with a normal pregnancy outcome showed a decline in VTI over the same time period; 24.09 cm/s (SD 3.19 cm/s) to 22.94 cm/s (SD 3.32 cm/s); $p = 0.015$. VTI was only significantly lower in the SGA group compared to the high-risk normal group at 24 weeks' gestation; 21.96 cm/s (3.87 cm/s) versus 23.87 cm/s (3.01); $p = 0.033$.

Measurements of LVOT at each time point were consistently smaller in women who delivered a SGA infant compared to high-risk women with a normal pregnancy outcome; 14 weeks' gestation; 1.85 cm (0.16 cm) versus 1.99 cm (0.13 cm); $p = 0.001$ and 30 weeks' gestation; 1.88 cm (0.14 cm) versus 2.00 cm (0.12 cm); $p < 0.001$.

The systolic variables ejection fraction and fractional shortening were unchanged between 14 and 30 weeks' gestation. There was also no significant difference in mean values between high-risk women who delivered a SGA infant and those with a normal pregnancy outcome, with the exception of a lower EF (M-Mode) at 24 weeks' gestation in the SGA group; 64.9 % (SD 4.2 %) versus 67.1 % (3.8 %); $p = 0.041$. Between 14 and 30 weeks' gestation there was no change in *s*

velocities measured at all 3 sites (septum, left lateral wall and right lateral wall). This result is consistent with high-risk women who had a normal pregnancy outcome.

The mitral valve inflow measures E, A and E/A showed no difference in mean values between women who delivered a SGA infant and those with a normal pregnancy outcome. There was a significant E velocity decrease and A velocity increase between 14 and 30 weeks' gestation respectively; 88.17 cm/s (SD 16.61 cm/s) to 80.35 cm/s (SD 12.69 cm/s); p = 0.022 and 48.40 cm/s (SD 13.47 cm/s) to 54.85 cm/s (SD 13.03 cm/s); p = 0.02, mirroring the changes with gestation seen in high-risk women with a normal pregnancy outcome. DT, IVRT and A wave duration mean values were not significantly different, with the exception of a shorter A wave duration at 24 weeks' gestation in women who delivered a SGA infant; 112.0 ms (SD 11.3 ms) versus 119.0 ms (SD 17.0 ms); p = 0.033.

In women who delivered a SGA infant, the TDI indices at the septum and left lateral wall showed no difference in mean values compared to high-risk women with a normal pregnancy outcome, with the exception of a lower septal *a* velocity at 30 weeks' gestation; 8.27 cm/s (SD 1.37 cm/s) versus 9.23 cm/s (SD 1.82 cm/s); p = 0.017. At the septum, the *e* velocity decreased significantly between 14 and 30 weeks' gestation; 14.90 cm/s (SD 3.47 cm/s) to 12.35 cm/s (SD 2.47 cm/s); p < 0.001, while *a* velocity increased slightly, however significance was not reached; 7.66 cm/s (SD 1.08 cm/s) to 8.27cm/s (SD 1.37 cm/s); p = 0.165. This resulted in a significant decline in *e/a* ratio; 2.00 (SD 0.63) to 1.53 (SD 0.38); p <0.001. The lateral wall showed *e* and *a* velocities were unchanged over this time period, with a non-significant decrease in *e/a* ratio from 2.34 (SD 0.77) to 2.00 (SD 0.45); p = 0.057.

The right lateral wall *e* and *a* velocities and *e/a* ratio between the two groups showed no significant difference in mean values. The *e* velocity was essentially unchanged between 14 and 30 weeks' gestation; 17.08 cm/s (SD 3.96 cm/s) to 16.54 cm/s (SD 3.47 cm/s) with *a* velocity increasing slightly; 12.18 cm/s (2.78 cm/s) to 13.29 cm/s (3.16 cm/s); p = 0.118, however, statistical significance was not reached. This resulted in a non-significant decrease in *e/a* ratio over the same time period; 1.50 (0.58) to 1.28 (0.28); p = 0.064, reflecting the same trend seen in high-risk women with a normal pregnancy outcome.

Women who give birth to a SGA infant had lower LVM and LVMI mean values compared to high-risk women with a normal pregnancy outcome. LVOT measurements were also smaller in the SGA group, while the VTI remained unchanged, resulting in the lower SV and SVI reported in Section 7.4.3. The changes seen in diastole were in keeping with the high-risk women with a normal outcome. The data for all of these outcomes can be seen in Appendices C and G.

7.5.4 Preterm birth secondary cardiovascular outcomes

The majority of the secondary systolic measures (ejection fraction, fractional shortening and *s* velocities) were unchanged between 14 and 30 weeks' gestation, with no significant difference in mean values except for a higher left lateral wall *s* velocity in the preterm women measured at 24 weeks' gestation; 13.07 cm/s (SD 0.62 cm/s) versus 11.96 cm/s (SD 2.36 cm/s); p = 0.014.

VTI at 14 weeks' gestation was significantly lower in women who delivered preterm; 24.09 cm/s (SD 3.19 cm/s) versus 21.27 cm/s (SD 1.77 cm/s); p = 0.001, with no significant change between 14 and 30 weeks' gestation in contrast to the high-risk women with a normal outcome, which showed VTI declined significantly. The LVOT measurements were comparable between high-risk women with a normal outcome and those that delivered preterm.

Women who delivered preterm, showed a non-significant rise in E velocity and a concomitant A velocity increase, with both indices reaching significance between 14 and 30 weeks' gestation respectively; 82.28 cm/s (SD 11.36 cm/s) to 87.11 cm/s (SD 23.36 cm/s); p = 0.429 and 53.62 cm/s (SD 9.24 cm/s) to 63.74 cm/s (16.27 cm/s); p = 0.03. This resulted in a mild reduction in E/A ratio which did not reach statistical significance, in contrast to high-risk women with a normal outcome which showed a significant E/A ratio decline. There was no difference in mean values between these groups of women, with the exception of E velocity at 20 weeks' gestation; 87.84 cm/s (SD 15.24 cm/s) versus 81.81 cm/s (SD 6.93 cm/s); p = 0.043. The IVRT, DT and A wave duration mean values showed no significant difference between 14 and 30 weeks' gestation compared to the high-risk normal group.

In terms of tissue Doppler indices, *e* velocity, *a* velocity and *e/a* ratio at the septum showed no difference in mean values between 14 and 30 weeks' gestation with the exception of *a* velocity at 24 weeks'; 8.63 cm/s (SD 1.35 cm/s) versus 10.93 cm/s (SD 2.3 cm/s); p = 0.025. These indices replicated the changes seen with gestation in high-risk women with a normal outcome; an increase in *a* velocity from 8.81 cm/s (SD 1.99 cm/s) to 11.51 cm/s (SD 2.89 cm/s); p < 0.001, with a concomitant decrease in *e* velocity and *e/a* ratio over this time period respectively; 16.24 cm/s (SD 2.12 cm/s) to 12.94 cm/s (SD 2.93 cm/s); p <0.001 and 1.90 (SD 0.37) to 1.20 (SD 0.43); p < 0.001.

At the lateral wall, there was a non-significant *e* velocity decrease between 14 and 30 weeks' gestation; 17.08 cm/s (SD 2.56 cm/s) to 15.87 cm/s (SD 1.27 cm/s); p = 0.264, with *a* velocity increasing significantly; 8.17 cm/s (SD 1.17 cm/s) to 10.27 cm/s (SD 1.01 cm/s); p = 0.009. This resulted in a significant decline in *e/a* ratio from 2.15 (SD 0.15) to 1.55 (SD 0.17); p = 0.014. These patterns of change with gestation were seen in high-risk women with a normal pregnancy outcome. In terms of mean values between women with a normal pregnancy outcome and those that delivered preterm, there was no significant difference with the exception of a lower *a* velocity at 24 weeks' gestation in women who delivered preterm; 8.90 cm/s (SD 1.76 cm/s) versus 10.65 cm/s (SD 0.92 cm/s); p = 0.002 and a lower *e/a* ratio reaching statistical significance at 20 and 24 weeks' gestation; 2.27 (SD 0.61) versus 1.82 (SD 0.42) and 2.05 (SD 0.54) versus 1.52 (SD 0.12); p = 0.001. The E/*e* ratio at the septum and left lateral wall were not significantly different between the two groups with the exception of the septal E/*e* at 14 weeks' gestation; 5.89 (1.17) versus 5.10 (0.68); p = 0.014.

The mean values of the right lateral wall *e* and *a* velocities were consistent between the two groups of women, with no change in *e* velocity and a significant increase in *a* wave velocity between 14 and 30 weeks' gestation respectively; 17.14 cm/s (SD 4.60 cm/s) to 16.17 cm/s (SD 3.59 cm/s) p = 0.845 and 12.39 cm/s (SD 3.96 cm/s) to 16.10 cm/s (SD 3.37 cm/s); p = 0.007. This resulted in a decline in *e/a* ratio over the same time period; 1.54 (SD 0.71) to 1.05 (SD 0.32) in keeping with changes seen in the high-risk women with a normal pregnancy outcome. The mean *e/a* ratio values were also not significantly different.

Women who delivered preterm had a lower VTI than high-risk women with a normal pregnancy outcome, resulting in the lower SV and SVI mean values reported in section 7.4.4. Systolic function was preserved, with diastolic changes in keeping with high-risk women with a normal pregnancy outcome. The data for all of these outcomes can be found in Appendices D and H.

7.6 Discussion

This prospective longitudinal study evaluated cardiovascular structure and function between 14 and 30 weeks' gestation in 105 women screened high-risk for early-onset pre-eclampsia using the FMF algorithm. Forty-one women subsequently had an adverse pregnancy outcome which included, 8 late-onset pre-eclampsia, 8 gestational hypertension, 20 SGA infants and 5 preterm deliveries.

One of the most important findings of this study was that the cardiovascular profiles of women who developed pre-eclampsia, gestational hypertension or delivered a SGA infant, differed in some respects to high-risk women with a normal pregnancy outcome in the preclinical phase of the disease. While maladaptation of the cardiovascular system with these pathologies is recognised, there are limited studies, with variable results in regard to hypertensive disorders (36-40, 42, 43, 45, 53, 56, 437, 497).

In our study, the cardiovascular profile of women who subsequently developed pre-eclampsia showed a reduced cardiac output coupled with a high total peripheral resistance, which does not fit with the widely accepted view that women destined to develop late-onset pre-eclampsia have a hyperdynamic circulation (elevated CO and low TPR), prior to the signs and symptoms of disease (40-43, 50, 496, 498). Our results are in keeping with the late third trimester study by Guy *et al* (2017) (53) and mid trimester study by Melchiorre et al (2013) (36), which did not show a hyperdynamic circulation in women who subsequently developed late-onset pre-eclampsia.

In regard to the cardiovascular profile of women who delivered SGA infants, the low CO/CI and high TPR/TPRI results were consistent with previous studies (42, 44, 419, 437, 438, 441) .

7.6.1 Maternal characteristics and birth outcomes

Women who developed pre-eclampsia were nulliparous and had a body habitus similar to high-risk women with a normal pregnancy outcome, with no significant difference in weight, BMI or BSA. Our study showed pre-eclampsia is associated with primiparity, in keeping with previous studies (176, 177). Late-onset pre-eclampsia is also associated with an increased body mass (197, 202, 204) however, we did not find this in our study, which is consistent with the meta-analysis by Cnossen *et al* (2007) which found BMI was only weakly associated with pre-eclampsia (203).

Women who developed gestational hypertension had increased weight, BMI and BSA compared to women with a normal outcome, in keeping with previous studies (109, 197, 499). For women who delivered a SGA infant, their weight and BSA were both significantly lower than those with a normal pregnancy outcome, consistent with other studies (500, 501), while the maternal characteristics of women who delivered preterm were no different to those with a normal pregnancy outcome. Women of South-Asian ethnicity were over represented in the group who developed PE, which is consistent with the study by Poon *et al* 2010 (197).

The birthweight and birthweight centiles of infants born to women who developed pre-eclampsia were markedly lower compared to infants born to women with a normal pregnancy outcome. The association of lower birthweight and early-onset pre-eclampsia is well established, given the disease is related to poor placentation (4, 6, 7, 23, 502). In terms of late-onset pre-eclampsia, a number of studies have shown infants with birthweight comparable to those born to normotensive mothers (503, 504), while a more recent study demonstrated a bimodal distribution of birthweight with both LGA and SGA infants (502). This group suggested that there are two types of late-onset pre-eclampsia to account for this finding. Our study showed infants born to mothers who developed late-onset pre-eclampsia had lower birthweight compared to infants born to high-risk women with a normal outcome, in agreement with the study by Odegard *et al* 2000 (80). This raises the possibility that the response of the cardiovascular system due to the higher MAP and TPR in early pregnancy essentially restricts maximal SV and CO from being achieved. This inappropriate adaptation subsequently results in placentation not reaching its full potential and therefore

smaller babies compared to those that adapt properly. Unsurprisingly, all adverse outcome groups delivered earlier than women with a normal pregnancy outcome.

7.6.2 Stroke volume

Stroke volume and SVI remained relatively stable between 14 and 30 weeks' gestation in women who developed pre-eclampsia. The pre-eclamptic women also had lower mean SV and SVI values compared to women with a normal pregnancy outcome, however significance was not reached. This finding is comparable to the Melchiorre *et al* (2013) (36) and Guy *et al* (2017) (53) studies, while the majority of other studies that have assessed late-onset PE in the pre-clinical phase found SV increased (39, 41, 42, 44, 50).

The PW Doppler echocardiography study at 20-23 weeks' gestation by Melchiorre *et al* (2013) also involved high-risk women, however these women were identified by uterine artery Doppler PI above the 95th centile. The group found SV and SVI were not significantly different in women who subsequently developed term pre-eclampsia compared to high-risk women with an uneventful outcome, although the median values were lower. The third trimester study by Guy *et al* (2017) used an unselected population and also reported lower SV, however statistical significance was not reached, in keeping with our results. Furthermore, a recent systematic review by Castleman *et al* (2016) (505), found stroke volume was decreased in women with pre-eclampsia.

Stroke volume was higher in the longitudinal study by Easterling *et al* (1990) (39) in women who subsequently developed PE compared to normotensive women, although statistical significance was not reached. The group utilised an automated cardiac output monitor to determine stroke volume in contrast to our echocardiographic Doppler method, with a small sample of nine women. In this study, the women who developed PE had significantly greater BSA and weight compared to women with a normal outcome, however indexation was not applied.

The study by Rang *et al* (2008) (44) of women who subsequently developed term PE, reported SV increased during the first 20 weeks of pregnancy, followed by a small decline after this time point, however PE outcomes were grouped together with women who developed gestational hypertension and involved only 5 women. The group also utilised a different method to our study (continuous finger arterial

pressure waveform registration, Modelflow), validating the technique with a comparison to echocardiography in a small study of 16 pregnant women. Rang *et al* (2007) (506) concluded the random 30% variation seen in Modelflow compared to Doppler echocardiography was the same variation seen when comparing Doppler echocardiography to thermodilution and therefore deemed the technique valid.

The study by Khaw *et al* (2008) (42) measured SV using the same PW Doppler technique as our study with the same number of PE cases, however it was a cross-sectional study assessing women at just 14 weeks' gestation. The group found SV was significantly higher, which is in contrast to our finding, with no SVI calculated. The women who developed PE were taller and heavier compared to the women in our study, although BMI and BSA were unreported. This finding may partially explain the difference in stroke volume between our studies. The study by Valensise *et al* (2008) (41) also reported significantly higher SV at 24 weeks' gestation in women who developed PE compared to women with a normal outcome using PW Doppler. Like the Khaw study, the PE women were heavier, with a greater prepregnancy BMI of 28 kg/m^2 compared to 25.9 kg/m^2 in our study.

The SV and SVI results of women who developed GH showed the same trend with gestation as women with a normal pregnancy; SV stable and SVI decreasing significantly. The mean SV/SVI values were also significantly lower in the GH group, which is in contrast to the study by Valensise *et al* (2006) (492) at 24 weeks' gestation, which showed SV was significantly higher. Our results were in keeping with the study by Guy *et al* (2017) (53). They also found a lower SV in GH, although their study was at a later gestation (35 - 37 weeks). The study by Rang *et al* (2008) (44) grouped GH and PE outcomes together, while Bosio *et al* (1999) (40) did not report these values.

High-risk women who subsequently delivered a SGA fetus also had significantly lower SV/SVI mean values compared to women with a normal pregnancy outcome, consistent with the literature (42, 44, 419, 437, 438, 441). The mean SV/SVI values were stable between 14 and 30 weeks' gestation, consistent with the trend seen in high-risk women with a normal pregnancy outcome. The women who gave birth to SGA infants were smaller in stature, with significantly lower

weight, BSA and BMI at 14 weeks' gestation. It is therefore unsurprising that the SV was significantly lower in this group given organ size is relative to body size (507), however, indexing SV with BSA still resulted in lower values compared to those with a normal outcome. This also raises the possibility that BSA indexation may not necessarily be the most appropriate scaling method to account for differences in body size during pregnancy (398, 487, 488, 508).

7.6.3 Heart rate

Heart rate increased between 14 and 30 weeks' gestation in all outcome groups. Mean values in women who developed PE or delivered a SGA fetus were consistent with those who had an uncomplicated pregnancy, in keeping with the study by Khaw *et al* (2008) (42) at 14 weeks' gestation and the study by Rang *et al* (2008) (44) up to 32 weeks' gestation, although this group combined with GH and PE outcomes together. This is in contrast to Valensise *et al* (2008) (41) and Melchiorre *et al* (2013) (36) who found heart rate higher in women who developed PE compared to normotensive controls and high-risk women with a normal outcome respectively.

In terms of women who developed gestational hypertension, our study found mean heart-rate values were significantly higher compared to women with a normal outcome between 14 and 24 weeks' gestation, while at 30 weeks' gestation heart rate was not significantly different. These observations are comparable to the two Valensise studies at 28 - 32 weeks' gestation (491, 492) and the Guy *et al* (2017) (53) study at 35 - 37 weeks' gestation. This suggests that heart rate in women who develop GH is higher in the first two trimesters but not during the third trimester. Heart rate was significantly higher in women who delivered preterm, however with only five women in this group the significance of this finding is questionable.

7.6.4 Cardiac output and cardiac index

Cardiac output and CI were significantly lower in women who subsequently developed late-onset pre-eclampsia, in agreement with the late third trimester

study by Guy *et al* (2017) (53). These results were secondary to lower SV/SVI, while the Guy study showed a lower heart rate also contributed to the lower CO/CI. This finding is in contrast to a number of studies that found CO elevated in the latent phase of the disease (39-44, 50, 498), while the mid gestational study by Melchiorre *et al* (2013) (36) showed CO/CI unchanged in high-risk women who developed late-onset PE compared to high-risk women with a normal pregnancy outcome.

The majority of these studies did not correct for body size despite significantly greater BMI or weight in the PE group compared to controls (39-41), while the study by Kazerooni *et al* (2006) (50) did not report any body size indices. Bosio *et al* (1999) (40) adjusted for the disparity in BMI between heavier pre-eclamptic women and normotensive women, however, as they found haemodynamic differences were maintained, they chose not to report the indexed values. The group postulated that the magnitude of the physiological increase in CO obscured the effect of maternal size on cardiac output, based on the estimations of Easterling *et al* (1990) (39), which found poor correlation between BSA and CO in pregnancy.

The studies that reported elevated CO in women who subsequently developed pre-eclampsia also had different study designs with inherent limitations. A number of these studies were conducted at one time point (41-43) compared to the longitudinal design of this study which consistently demonstrated a lower CO/CI at all time points. Furthermore, the study by Bosio et al (1999) (40) calculated VTI using continuous wave Doppler which does not enable an accurate velocity measurement specifically at the LVOT. This is technically incorrect and can result in an overestimation of SV and therefore CO (401). The cross-sectional study by Valensise et al (2008) (41) was performed on two different machines with an unknown number of operators, factors that can compound variation in results unlike this study. Finally, the study by Tay et al (2018) (498) used inert gas breathing to calculate CO which has not been validated in pregnancy (509).

Women who developed gestational hypertension showed significantly higher heart rate and lower SV/SVI between 14 and 30 weeks' gestation compared to women with a normal pregnancy outcome. This resulted in non-significantly

higher CO/CI mean values compared to the normal outcome group. Of the few studies that investigated CO/CI in women who subsequently developed gestational hypertension, the majority reported CO/CI was elevated (40, 43, 44, 492).

Women who delivered a SGA infant had lower CO between 14 and 30 weeks' gestation, reaching significance at 14 and 24 weeks' gestation. In terms of CI, the mean values in our study were comparative to high-risk women with a normal pregnancy outcome except at 14 weeks' gestation. At this time point CI was significantly lower. A number of studies have demonstrated that reduced CO is associated with fetal growth restriction (437, 441, 498, 510) and that the association is also evident with SGA infants (43, 510). This is in contrast to the study by Khaw *et al* (2008) (42) which found CO and CI in women who delivered SGA infants comparable to women with an uncomplicated pregnancy. There are a few studies that have assessed cardiac function in relation to SGA and FGR and have found CO is significantly lower in women who subsequently deliver a growth restricted infant compared to women who deliver SGA infants (438, 440). Given our cardiac index results, it could be inferred that a number of these infants may have been constitutionally small.

7.6.5 Mean arterial pressure

High-risk women who developed PE had a significantly higher MAP compared to those with a normal outcome between 14 and 30 weeks' gestation, in keeping with the majority of previous studies (36, 42, 50, 53, 491, 492, 495). This in in contrast to one study by Valensise *et al* (2008) (41) which found MAP at 24 weeks' gestation in asymptomatic women who subsequently developed late-onset PE, comparable to those with a normal pregnancy outcome.

In regard to gestational hypertension outcomes, these women also had significantly higher MAP between 14 and 30 weeks' gestation compared to women with a normal pregnancy outcome, in keeping with the late third trimester study by Guy *et al* (2017) (53). This is in contrast to the study by Valensise *et al* (2001) (482) which showed MAP was not significantly different at 24 weeks' gestation in women who subsequently developed GH, although this study grouped the 12 GH outcomes with 3 SGA outcomes. In terms of women who

delivered SGA infants or preterm, MAP was comparative to women with a normal pregnancy outcome.

7.6.6 Total peripheral resistance

In women who developed pre-eclampsia, the combined effect of a significantly higher MAP between 14 and 24 weeks' gestation and lower CO/CI resulted in significantly elevated TPR/TPRI across this time period. The mid gestational study by Melchiorre *et al* (2013) (36) also showed higher TPR/TPRI values in women who developed term pre-eclampsia compared to high-risk women with a normal outcome, however this was not statistically significant, with significance only reached when compared to low-risk women with a normal outcome.

Our results were in contrast to a number of studies that have shown TPR is lower in women who develop late-onset pre-eclampsia compared to those with a normal outcome in the pre-clinical phase of the disease (39-41). The study by Valensise et al (2008) (41) did not index TPR despite a significant difference in prepregnancy BMI between the two groups of women. The longitudinal study by Easterling *et al* (1990) (39) also reported lower TPR in the latent phase of disease with no indexed value, despite significantly greater BSA in the women who developed pre-eclampsia. Indexation may not have altered the conclusion of a hyperdynamic circulation in either of these studies, as the TPR data was also in contrast to our study.

7.6.7 Left ventricular mass

Left ventricular mass increased between 14 and 30 weeks' gestation in women who developed pre-eclampsia. In our study, the mean values were comparable to high-risk women with a normal pregnancy outcome, while Valensise *et al* (2008) (41) showed both early and late-onset pre-eclampsia associated with a greater increase in LVM and LVMI during the pre-clinical phase of the disease compared to normotensive women (41). Importantly, this study was only at one time point, compared to our longitudinal study at multiple gestations, and

prepregnancy BMI was also significantly different between these groups of women.

In terms of LVMI, we showed no change over the same time period, consistent with the mid-gestational study by Melchiorre *et al* (2013) (36), suggesting an appropriate response to the change in loading conditions in the second trimester and early third trimester. There is significantly more evidence when women become pre-eclamptic that both LVM/LVMI are increased to a greater extent compared to women with a normal pregnancy outcome (37, 38, 45, 456), with a strong association with concentric remodelling (37, 45). Our study was limited to 30 weeks' gestation, prior to the signs and symptoms of pre-eclampsia, to enable an assessment of this observation.

Women who developed gestational hypertension also showed LVM increase between 14 and 30 weeks' gestation, with mean values comparable to high-risk women with a normal pregnancy outcome. LVMI remained unchanged over this time period, with limited studies of LVM/LVMI prior to the onset of gestational hypertension reported in the literature available for comparison. One study by Valensise *et al* 2001 (491) at 24 weeks' gestation found LVM and LVMI mean values both significantly greater than women with a normal outcome, in contrast to our study. The group did not report any measures of body size except height, which was the same. In our study, the GH women had significantly larger body stature, with greater weight, BSA and BMI compared to high-risk women with a normal pregnancy outcome, despite no significant difference in height.

Indexation is intended to remove the variation between individuals attributable to body size and body composition. In theory the principle of indexing is more than reasonable, however choosing which method should be used in this population is debatable, with minimal evidence to support what is appropriate in pregnancy. Demographic factors such as sex, age, ethnicity, body size and composition are known to affect cardiac structure and function and have been investigated in a variety of adult and paediatric populations (398, 486-489, 511-514).

In non-pregnant populations numerous studies have shown that indexing LVM to height or lean body mass is an appropriate method to account for variation due to adiposity (398, 515). The ASE have published reference ranges for LVM based on gender including height, height$^{2.7}$ and body surface area (BSA) (402), with the

organisation stating that correcting LVM with height preserves the effects of obesity, whereas obesity related LV hypertrophy will not be detected when indexing with BSA (402). There are conflicting reports of LVM in women with gestational hypertension; some have shown no change (516, 517), while the majority of others have found LVM and LVMI significantly increased (505, 518, 519). It is therefore unsurprising that there are mixed reports of LVM and LVMI in women with pre-eclampsia or gestational hypertension, given the difficulties with indexation, which is confounded by pregnancy and obesity.

In terms of women who delivered an SGA infant, LVM and LVMI both increased with gestation, however mean values were both significantly lower compared to women with a normal pregnancy outcome. It was unsurprising that LVM was lower in this group of women as their body habitus (BMI, BSA and weight) was significantly smaller compared to high-risk women with a normal pregnancy outcome, as LVM is relative to body size (488). The fact that LVMI also increased with gestation in contrast to women with a normal pregnancy outcome may reflect that the indexation applied may not be appropriate for small stature women, or that these infants may be constitutionally small and not pathologically growth-restricted fetuses. One study showed that LVM and LVMI were both significantly lower in women who delivered growth restricted fetuses however the comparison was women with SGA infants with no control group (440).

7.6.8 Secondary systolic cardiovascular parameters

The systolic measures of left ventricular ejection fraction, fractional shortening and s velocity were largely unremarkable in each of the adverse outcome groups during the gestation period studied, suggesting these indices were not useful in differentiating normal and pathological differences.

7.6.9 Diastolic cardiovascular parameters

Diastolic function is difficult to interpret in the context of pregnancy due to chronic volume overload, despite technological advances of TDI overcoming some of the issues related to loading conditions. It is well established that diastolic function is compromised in women with pre-eclampsia and especially in early-onset or severe disease (37, 51, 456, 505, 520, 521), although there is limited evidence in the pre-clinical phase (36). Changes in diastolic function during pregnancy

were expected due to the increased circulating blood volume that occurs in pregnancy, evidenced by a reduction in mitral inflow E wave velocity, an increase in A wave velocity and a concomitant decrease in E/A ratio. These adaptive changes were also seen in the tissue Doppler indices (*e*, *a* and *e/a*), reflecting the increased stroke volume filling that needs to occur during late diastole, in order to maintain cardiac output.

In this study, the changes that occurred during diastole between 14 and 30 weeks' gestation in women with a subsequent adverse pregnancy outcome, generally followed the same pattern as women who had a normal pregnancy outcome, with the exception of women who developed pre-eclampsia. The women who subsequently developed pre-eclampsia showed mitral A wave velocity and tissue Doppler *a* velocity at the septum, left and right lateral walls remained unchanged, while the high-risk normal outcome group showed an increase in all of these indices with gestation, marking the shift in left ventricular filling from early to late diastole. This infers that women with a normal outcome adapted to the changing cardiovascular conditions, whilst the women who developed pre-eclampsia seemed not to adapt.

It is well accepted that left ventricular mass increases in normal pregnancy to counteract the wall stress exerted by the expanding blood volume and this was clearly evident in our study. In normal pregnancy, afterload decreases secondary to a decline in total peripheral resistance and this impacts LV compliance. Lower TPR effectively reduces the pressure that the LV needs to contract against to push the increased LV blood volume out into the circulation. In women who developed pre-eclampsia, total peripheral resistance was higher, resulting in greater afterload and decreased compliance of the LV wall. The compensatory increased SV filling that should occur during late diastole, did not follow. Consequently, this maladaptation may contribute to the lower cardiac output seen in women who develop late-onset pre-eclampsia compared to women with a normal pregnancy outcome.

7.6.10 Limitations

One of the limitations of this study was women who delivered SGA infants were predominantly of East-Asian and South-Asian ethnicity which may relate more to their small body size than ethnicity. While birthweight charts derived from the

local population were used to classify SGA infants (461), the inclusion of these women may mask the true cardiovascular outcomes of the group. The study by Hanley *et al* (2013) (522) showed ethnicity-specific birthweight distributions improved the identification of SGA newborns at risk of short-term morbidity versus those that were constitutionally small compared to traditional birthweight charts. Alternatively, the use of birthweight percentile charts for maternal height could be considered for future work, given a recent study by Rochow *et al* (2018) (523) found maternal height had a greater influence on birthweight than maternal ethnicity.

A further limitation of this study was the method of indexation applied to left ventricular mass, stroke volume, cardiac output and total peripheral resistance. Indexation to normalise for differences in body size is routinely performed in the paediatric and adult populations with reference ranges specific for age and gender (395, 402). With respect to pregnant women, there is no consensus or recommendations from leading international cardiac societies as to what is the most appropriate method of indexation. Only one study has validated BSA indexation in pregnancy using the Dubois-Dubois formula (470), however this was through modelling rather than through prospective data collection and analysis (524) and only included women in their third trimester.

A potential problem with indexation using BSA, is that relations between body size and the dimensions or functions of organs are often non-linear, so use of BSA may not provide a fair representation of functional load (507). This raises the possibility that BSA indexation may not necessarily be the most appropriate scaling method to account for differences in body size (398, 487, 488, 508).

Alternative methods of indexation in the non-pregnant population include allometric scaling, typically using an individual's height (not impacted by adiposity) raised to exponents in the range of 1.7 - 2.7 (486, 488, 489). Whilst these research groups differed in their conclusions about the most appropriate height exponent to use, they all found that indexing LVM relative to height was more accurate than BSA. Data related to CO and SV are more limited; height and BSA seem to be of equivalent value in normal-weight individuals but 'ideal' BSA or height raised to an age specific power appear to be more accurate in obese individuals (487). An alternative approach to account for variation due to adiposity

involves measurement and indexing on the basis of height and lean body mass. This has been shown to correlate well for LVM, CO and SV (398, 515), however measurement of lean body mass in pregnancy is complicated by the presence of highly metabolic placental tissue and ametabolic amniotic fluid.

7.6.11 Summary

In our study, we found a low CO/CI and high TPR/TPRI profile in the pre-clinical phase of late-onset PE, which is in contrast to the widely held belief that these women have a hyperdynamic circulation. These results are consistent with the studies by Melchiorre *et al* (2013) (36) and Guy *et al* (2013) (53). Our work does not support the crossing over theory from a high CO - low TPR haemodynamic profile to a low CO - high TPR haemodynamic profile when women show signs and symptoms of pre-eclampsia (39-41). A limitation of our study was that we did not assess women when they developed the clinical disease to fully evaluate this theory.

Our study supports the concept that women who subsequently develop pre-eclampsia have inadequate adaptation of their cardiovascular system, evidenced by low CO and high TPR, which is also apparent in women with untreated disease (37, 52, 54, 56, 455, 520). Furthermore, diastolic dysfunction has been shown in women with pre-eclampsia, especially those with early-onset disease, suggesting additional cardiac compromise (37, 456, 520).

The study of haemodynamic cardiovascular function in pre-eclamptic women by Dennis *et al* (2012) (38) is in contrast to the majority of reports. This group found cardiac output markedly increased in untreated pre-eclamptic women with both early and late-onset disease, while most studies have found cardiac output decreased or consistent with normotensive women (37, 39, 40, 54, 449, 455, 460, 525). The increased cardiac output in the Dennis study was secondary to increased stroke volume, with the group claiming the results were consistent with the proposed hyperdynamic model, despite demonstrating a greater CO when symptomatic. They also suggested the increased CO was due to increased inotropy (relating to increased fractional shortening) and not due to the larger BMI in this group, without applying indexation. Differences in study design and methodologies may account for some disparity between studies, however the rationale of their results lacks consistency.

In terms of gestational hypertension there are limited studies, with some groups evaluating GH and PE outcomes together (44, 526) and others finding they have similar cardiovascular profiles (40, 527). The results from our study show these pathologies have different profiles (that can be distinguished from each other), giving potential to cardiovascular measures such as SV, HR, CO or TPR to be used as screening tools in women stratified as high-risk in the first trimester.

One of the primary issues confounding the interpreting of cardiac output, TPR and other cardiac parameters is that pre-eclampsia outcomes in early papers investigating cardiovascular adaptation were grouped as one entity and not assessed in terms of early and late-onset disease (39, 40). Furthermore, the definition and diagnostic criteria of pre-eclampsia varied between studies with the potential for women to be incorrectly categorised as pre-eclamptic or simply hypertensive. Other studies have also grouped women who develop gestational hypertension and pre-eclampsia under the collective outcome of hypertensive disorders, which may be misleading (44, 526). Despite these disorders sharing the major symptom of hypertension, there are different pathophysiological processes occurring, with endothelial dysfunction the underlying pathology differentiating pre-eclampsia from gestational hypertension. Our longitudinal study supports this distinction, with the identification of different cardiovascular profiles observed. Table 35 summarises these profiles. Also, of interest is the difference in heart rate results between women who developed late-onset pre-eclampsia and those that developed gestational hypertension between 14 and 30 weeks' gestation. Future studies warrant investigating this finding, as the potential to determine a threshold in which these pathologies may be differentiated would have important clinical utility as this measurement is easily accessible and inexpensive.

Women who subsequently developed pre-eclampsia had significantly lower CO and CI compared to women with a normal outcome, while women who developed gestational hypertension had higher CO and CI, although significance was not reached. This finding was consistent between 14 and 30 weeks' gestation and primarily the result of a significantly higher heart rate in women who developed gestational hypertension, with both pathologies demonstrating lower SV and SVI and higher TPRI. This is an important finding moving forward to enable the early

identification of women who are truly at risk of developing late-onset pre-eclampsia and reassure those who are not.

Table 35. Primary cardiovascular variables summarised for adverse pregnancy outcomes in comparison to a high-risk normal pregnancy outcome

	SV	SVI	HR	CO	CI	MAP	TPR	TPRI
Pre-eclampsia	lower	lower	unchanged	lower*	lower*	higher**	higher**	higher**
Gestational hypertension	lower*	lower*	higher**	higher^^^^	higher^^^^	higher*	unchanged	higher***
SGA	lower*	lower*	^^^higher	lower^^	lower^	unchanged	higher*	higher
Preterm	unchanged	lower**	higher****	unchanged	unchanged	unchanged	unchanged	unchanged

*significance at 14-30 weeks, **significance at 14-24 weeks, *** significance at 14-20 weeks, ****significance at 20-30 weeks, ^significance at 14 weeks, ^^significance at 14 and 24 weeks, ^^^significance at 20 weeks, ^^^^significance at 24 weeks. CI: cardiac index, CO: cardiac output, HR: heart rate, MAP: mean arterial pressure, TPR: total peripheral resistance, TPRI: total peripheral resistance index.

Chapter 8

Study 5 - Potential cardiovascular markers for second tier pre-eclampsia screening

8.1 Introduction

The current FMF screening strategy is highly successful at identifying women at risk of developing early-onset pre-eclampsia, with an Australian study validating the algorithm with a detection rate of 92% for a fixed false positive rate of 10% (198). The algorithm works less well for late-onset disease with a detection rate of 35% (198). Therapeutic low-dose aspirin has significantly reduced the prevalence of early-onset pre-eclampsia, however aspirin remains ineffective at reducing the prevalence of late-onset disease and gestational hypertension (31, 34, 241, 242, 478). As I have shown in Chapter 7, the cardiovascular profile of women who develop late-onset pre-eclampsia is different compared to studies of women who develop early-onset disease (36). This profile also differs to women who develop gestational hypertension. As early-onset pre-eclampsia is a relatively rare condition (prevalence 0.4%) compared to late-onset pre-eclampsia (3 - 5%), the positive predictive value of current screening tools is relatively low, with significant limitations.

The primary aim of this study was to determine the ability of maternal cardiovascular parameters, assessed using echocardiography, to predict an adverse pregnancy outcome as a secondary screening tool, in women stratified as high-risk for early-onset pre-eclampsia. A further aim was to determine the ability of maternal cardiovascular parameters to predict specific adverse pregnancy outcomes, including pre-eclampsia, gestational hypertension, small for gestational age fetus and preterm birth in this high-risk group. The identification of such cardiovascular parameters would reduce the false positive rate of the initial screening test and improve the positive predictive value of those truly at high-risk. The implementation of a secondary screening tool could reduce maternal anxiety, improve targeted therapeutic intervention and potentially reduce health costs associated with increased surveillance.

8.2 Methods

A comparison of cardiovascular parameters at 14, 20, 24 and 30 weeks' gestation in women screened high-risk for early-onset pre-eclampsia between those who

did and did not experience a range of adverse pregnancy outcomes, including pre-eclampsia, gestational hypertension, small for gestational age fetus and preterm birth was assessed in Chapter 7. Based on the findings of this study, the cardiovascular parameters LVM, LVMI, HR, SV, SVI, CO, CI, TRP and TPRI were evaluated using univariate logistic regression models for each cardiac variable to determine the area under the receiver operating characteristics (ROC) curve using Stata, version 15 (College Station, TX: Statacorp, LLC). The ROC curves were created by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity), with a threshold of 50% used to identify what parameters required further consideration (528). The first analysis included all four time points while the second analysis included only the 14 and 20 week measurements. An area of 0.90-1 was considered outstanding; 0.80-0.90, excellent; 0.80-0.70, acceptable/fair; 0.70-0.60, poor; 0.60-0.50, fail (529).

8.3 Results

Univariate logistic regression analysis demonstrated that certain cardiovascular parameters were associated with adverse pregnancy outcomes in women stratified as high-risk for early-onset pre-eclampsia. The most significant findings were evident when the adverse outcomes were evaluated separately in terms of the development of pre-eclampsia, gestational hypertension, delivery of a small for gestational age infant and preterm birth and not when combined into one adverse group. Similar results were seen in most instances when the assessment included just the 14 and 20 week measurements and not all time points.

8.3.1 Pre-eclampsia

Mean arterial pressure, cardiac output, cardiac index, total peripheral resistance and total peripheral resistance index were the best performing cardiovascular parameters for the prediction of pre-eclampsia. The ROC area under the curve (AUC) for MAP was 0.85 (0.73 - 0.93) for all time points, dropping to 0.72 (0.58 - 0.82) when only 14 and 20 week measurements were included. The AUC for CO was essentially the same at 0.80 (0.67 - 0.90) and 0.81 (0.69 - 0.90) for all time points and the early gestation time points respectively. CI results were slightly

better at all time points; 0.83 (0.70 - 0.92), while there was no difference to CO with the 14 and 20 week measures. In terms of TPR and TPRI the test worked equally well when just the early measures were included compared to all time points, with AUC equal to 0.84 (0.71 - 0.93) for both TPR tests, 0.86 (0.74 - 0.94) and 0.85 (0.75 - 0.94) for TPRI at all time points and 14 and 20 week time points respectively. LVM and LVMI were overall not useful while the HR, SV and SVI performed fairly. These results are outlined in Table 36 with ROC curves displayed in Figures 49 and 50.

8.3.2 Gestational hypertension

The most significant finding was that MAP performed very well, with an outstanding AUC result of 0.98 (0.90 - 1.00) at all time points and 0.94 (0.83 - 0.98) at the combined 14 and 20 week time point. This is perhaps not surprising given that hypertension is defined in terms of measurement of blood pressure. Despite these results the TPRI AUC tests were only fair; 0.72 (0.58 - 0.84) in both analyses, while the TPR AUC was poorer at 0.70 (0.56 - 0.83) and 0.61 (0.47 - 0.73) for all time points and the earlier time points respectively. Heart rate was determined to be an excellent predictor with AUCs of 0.87 (0.74 - 0.94) and 0.86 (0.75 - 0.94), while SVI also performed very well. The AUC for SVI was 0.87 at all time points and 0.86 at the earlier gestations, outperforming stroke volume. CO and CI worked reasonably well at all time points with AUCs of 0.78 and 0.77 but were not useful at just the earlier gestations; 0.59 and 0.57 for CO and CI respectively. In terms of left ventricular mass, only the indexed equivalent LVMI at all points performed fairly with an AUC of 0.71. A summary of the AUCs and ROC curves are shown Table 36 and Figure 51.

8.3.3 Small for gestational age

The cardiovascular AUC results for women who delivered SGA infants were not particularly useful, with only a few parameters showing a fair performance as predictors. This included, LVM, LVMI, SV, SVI at all time points and the earlier gestations. MAP and HR were also only fair at all time points with both variables having an AUC of 0.71. The AUC for LVM was 0.72 and 0.74 for all time points and earlier gestations respectively, with no improvement in AUC when LVM was indexed; 0.71 (all time points) and 0.70 (14 and 20 week time points). SV was reasonable at all time points; AUC = 0.77 but worked less well at the early

gestation period (AUC = 0.72) and when indexed at all time points; AUC = 0.70. The variables CO, CI, TPR and TPRI did not perform well. Table 36 outlines the AUC results.

8.3.4 Preterm birth

The most significant cardiovascular marker for the prediction of preterm birth was heart rate, with an outstanding AUC = 0.97 at all time points, and AUC = 0.89 at the earlier gestations only. SV did not perform well (AUC = 0.58 for both tests) but improved substantially when indexed (SVI); AUC = 0.76 for all time points and the earlier gestation times. CO performed reasonably well with an AUC = 0.78 for all time points and AUC = 0.80 for 14 and 20 week time points. When this variable was indexed, the tests did not perform as well; AUC = 0.77 at all time points versus AUC = 0.75 at the early times alone. MAP was not useful as a predictor while TPR performed quite well; AUC = 0.79 at all time points and AUC = 0.71 for 14 and 20 week time points. There was minimal change when TPR was indexed (TPRI); AUC = 0.72 for all time points versus AUC = 0.70 at the early times alone. LVM and LVMI at all time points also performed reasonably well with AUC = 0.76 and AUC = 0.74 respectively. The AUC results and ROC curves are outlined in Table 36 and Figure 52.

8.3.5 High-risk adverse outcomes

Collectively, high-risk women with an adverse pregnancy outcome did not demonstrate any cardiovascular parameters that would be highly useful as a predictive marker (with results summarised in Table 36). The test worked fairly for heart rate at all time points (AUC = 0.72), SV at all time points (AUC = 0.72) and the early times alone (AUC = 0.72) while the SVI performed slightly better at all time points (AUC = 0.75) versus early time alone (AUC = 0.73). MAP was the only other variable that worked reasonably well, however this was only at all time points; AUC = 0.71. CO, CI, TPR, TPRI, LVM and LVMI were not at all useful tools.

Table 36. Summary of ROC analyses

Cardiac variable		Pre-eclampsia	Gestational hypertension	Small for gestational age	Preterm birth	All adverse outcomes
		AUC	AUC	AUC	AUC	AUC
LVM	All time points	0.55 (0.41 - 0.68)	0.67 (0.54 - 0.80)	0.72 (0.59 - 0.82)	0.76 (0.63 - 0.87)	0.62 (0.51 - 0.73)
	14 + 20 weeks	0.50 (0.38 - 0.64)	0.59 (0.46 - 0.72)	0.74 (0.63 - 0.84)	0.69 (0.57 - 0.82)	0.63 (0.52 - 0.73)
LVMI	All time points	0.57 (0.42 - 0.70)	0.71 (0.58 - 0.83)	0.71 (0.59 - 0.82)	0.74 (0.60 - 0.86)	0.64 (0.53 - 0.75)
	14 + 20 weeks	0.51 (0.38 - 0.64)	0.68 (0.54 - 0.79)	0.70 (0.57 - 0.79)	0.69 (0.57 - 0.82)	0.65 (0.54 - 0.75)
HR	All time points	0.75 (0.62 - 0.86)	0.87 (0.74 - 0.94)	0.71 (0.58 - 0.82)	0.97 (0.86 - 1.00)	0.72 (0.60 - 0.81)
	14 + 20 weeks	0.53 (0.40 - 0.66)	0.86 (0.75 - 0.94)	0.66 (0.54 - 0.78)	0.89 (0.78 - 0.96)	0.69 (0.57 - 0.78)
SV	All time points	0.72 (0.58 - 0.83)	0.76 (0.61 - 0.86)	0.77 (0.65 - 0.87)	0.58 (0.42 - 0.71)	0.72 (0.61 - 0.82)
	14 + 20 weeks	0.73 (0.60 - 0.84)	0.73 (0.60 - 0.84)	0.72 (0.60 - 0.83)	0.58 (0.45 - 0.72)	0.70 (0.60 - 0.80)
SVI	All time points	0.75 (0.62 - 0.86)	0.87 (0.74 - 0.94)	0.70 (0.57 - 0.81)	0.76 (0.61 - 0.87)	0.75 (0.64 - 0.84)
	14 + 20 weeks	0.74 (0.62 - 0.85)	0.86 (0.75 - 0.94)	0.67 (0.54 - 0.78)	0.76 (0.64 - 0.87)	0.73 (0.62 - 0.82)
CO	All time points	0.80 (0.67 - 0.90)	0.78 (0.65 - 0.89)	0.65 (0.52 - 0.77)	0.78 (0.65 - 0.90)	0.66 (0.54 - 0.76)
	14 + 20 weeks	0.81 (0.69 - 0.90)	0.59 (0.46 - 0.72)	0.66 (0.53 - 0.77)	0.80 (0.66 - 0.89)	0.58 (0.47 - 0.69)
CI	All time points	0.83 (0.70 - 0.92)	0.77 (0.63 - 0.87)	0.55 (0.42 - 0.68)	0.77 (0.63 - 0.88)	0.68 (0.56 - 0.77)
	14 + 20 weeks	0.81 (0.69 - 0.90)	0.57 (0.42 - 0.69)	0.59 (0.46 - 0.70)	0.75 (0.60 - 0.85)	0.58 (0.47 - 0.69)
MAP	All time points	0.85 (0.73 - 0.93)	0.98 (0.90 - 1.00)	0.71 (0.58 - 0.81)	0.68 (0.53 - 0.80)	0.71 (0.60 - 0.81)
	14 + 20 weeks	0.72 (0.58 - 0.82)	0.94 (0.83 - 0.98)	0.68 (0.56 - 0.79)	0.69 (0.55 - 0.81)	0.66 (0.55 - 0.76)
TPR	All time points	0.84 (0.71 - 0.93)	0.70 (0.56 - 0.83)	0.62 (0.48 - 0.74)	0.79 (0.65 - 0.90)	0.64 (0.52 - 0.75)
	14 + 20 weeks	0.84 (0.73 - 0.93)	0.61 (0.47 - 0.73)	0.65 (0.52 - 0.76)	0.71 (0.57 - 0.82)	0.67 (0.55 - 0.76)
TPRI	All time points	0.86 (0.74 - 0.94)	0.72 (0.58 - 0.84)	0.52 (0.38 - 0.65)	0.72 (0.58 - 0.85)	0.65 (0.52 - 0.75)
	14 + 20 weeks	0.85 (0.75 - 0.94)	0.72 (0.59 - 0.83)	0.57 (0.45 - 0.69)	0.70 (0.57 - 0.82)	0.67 (0.56 - 0.77)

Data in parentheses are 95 % confidence interval. AUC: area under receiver-operating characteristics curve; CI: cardiac index, CO: cardiac output, HR: heart rate, LVM: left ventricular mass, LVMI: left ventricular mass index, MAP: mean arterial pressure, SVI: stroke volume index, SV: stroke volume, TPR: total peripheral resistance, TPRI: total peripheral resistance index.

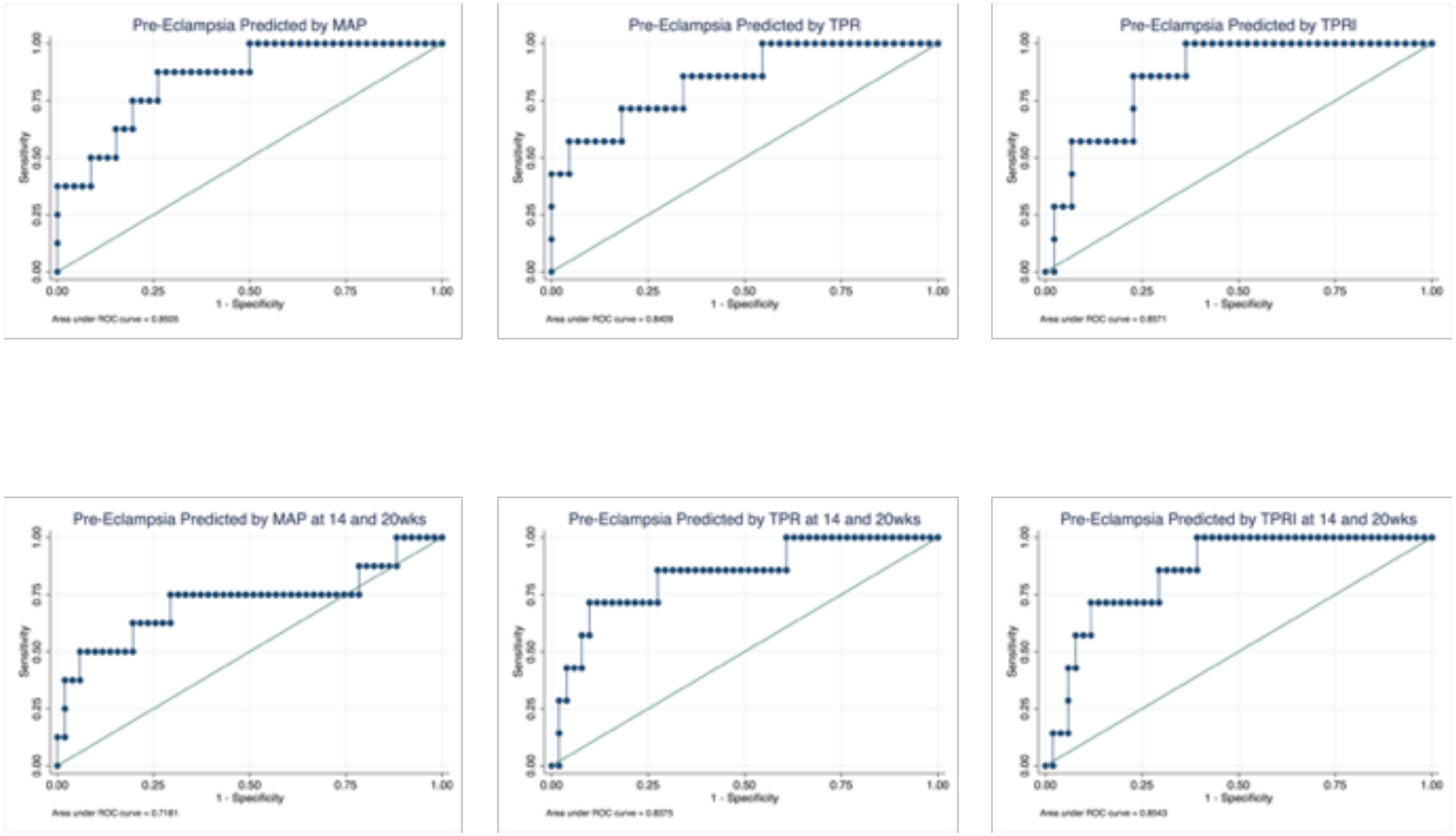


Figure 49. Pre-eclampsia ROC curves for mean arterial pressure, total peripheral resistance and total peripheral resistance index

All time points included unless specified. MAP: mean arterial pressure, TPR: total peripheral resistance, TPRI: total peripheral resistance index; wks: weeks. The diagonal line is a reference line, representing AUC of 0.5 which indicates no predictive value.

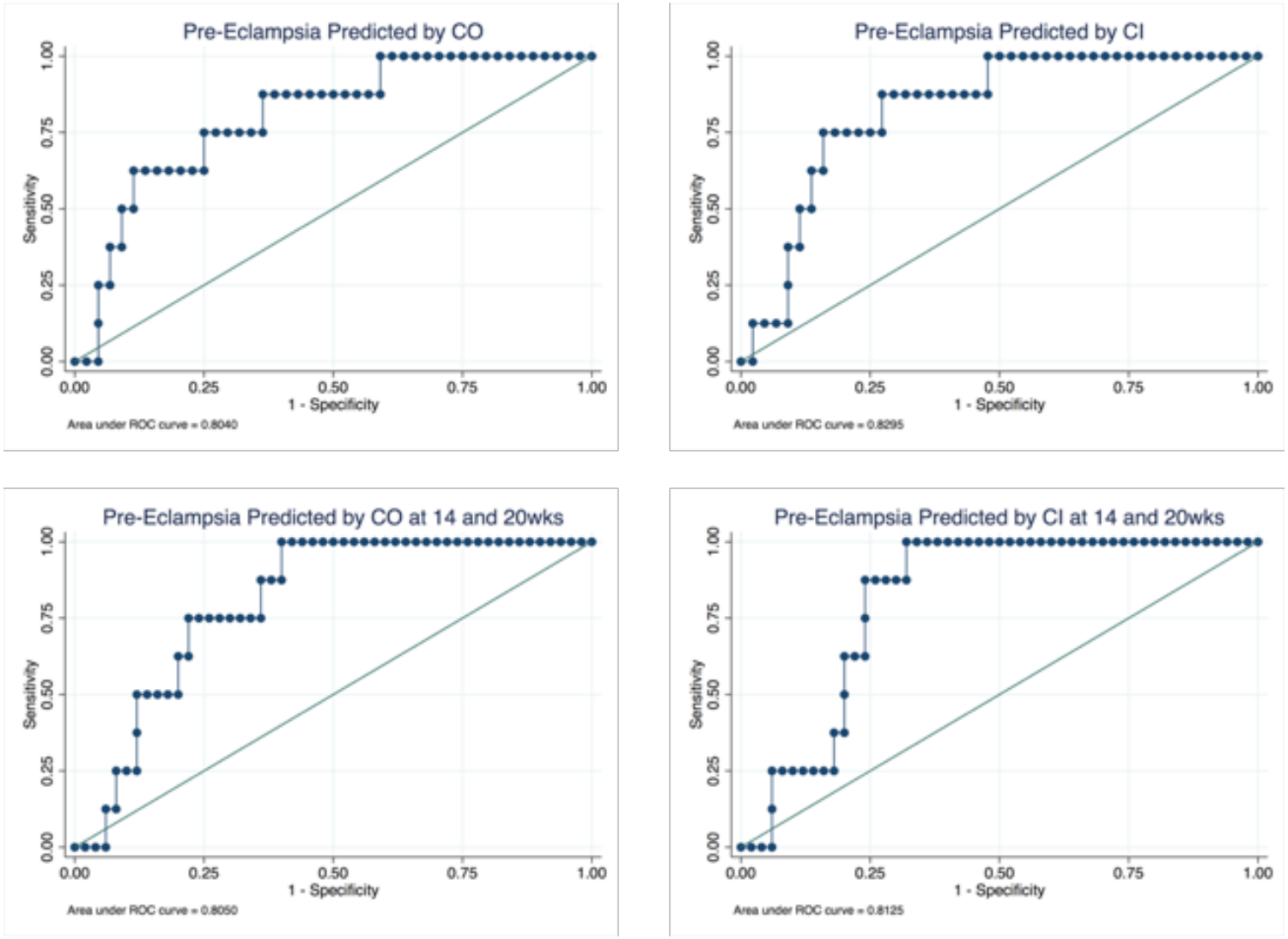


Figure 50. Pre-eclampsia receiver-operating characteristics curves for cardiac output and cardiac index

All time points included unless specified. CI: cardiac index, CO: cardiac output, wks: weeks. The diagonal line is a reference line, representing AUC of 0.5 which indicates no predictive value.

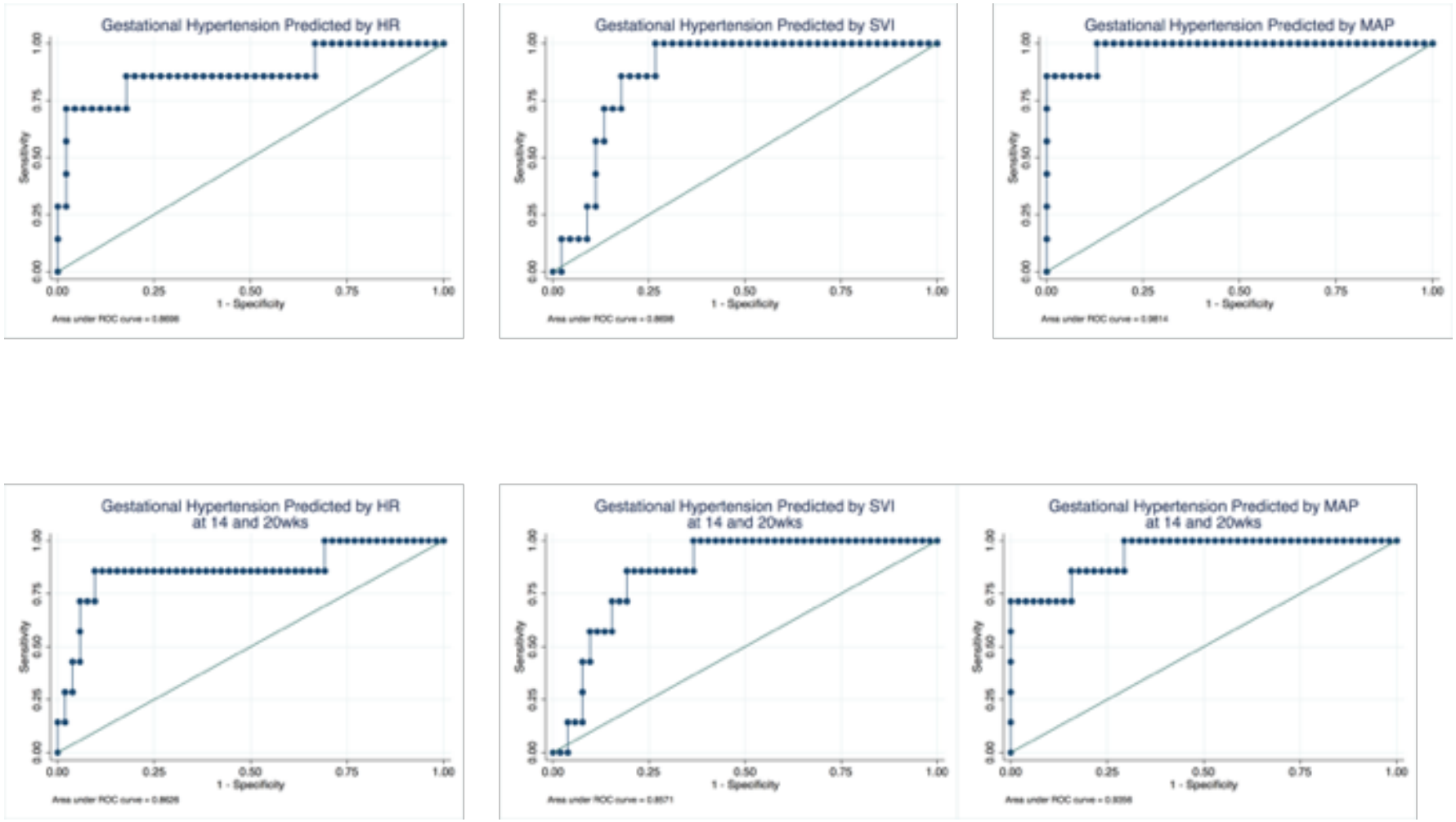


Figure 51. Gestational hypertension receiver-operating characteristics curves for heart rate, stroke volume index and mean arterial pressure

All time points included unless specified. HR: heart rate, MAP: mean arterial pressure, SVI: stroke volume index, wks: weeks. The diagonal line is a reference line, representing AUC of 0.5 which indicates no predictive value.

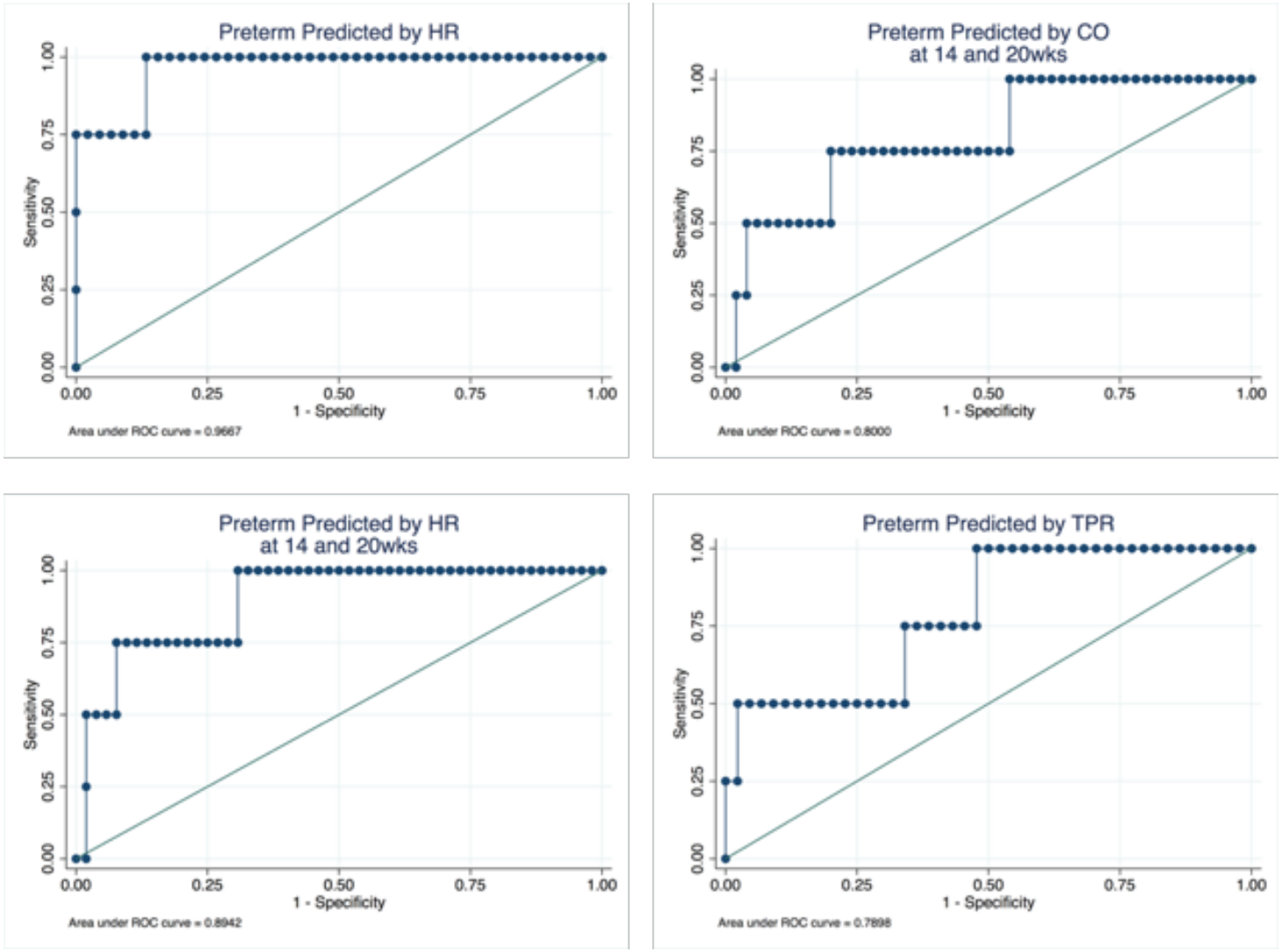


Figure 52. Preterm receiver-operating characteristics curves for heart rate, cardiac output and total peripheral resistance

All time points included unless specified. CO: cardiac output, HR: heart rate, TPR: total peripheral resistance, wks: weeks. The diagonal line is a reference line, representing AUC of 0.5 which indicates no predictive value.

8.4 Discussion

This study demonstrates that specific cardiovascular variables assessed in the second trimester could potentially be used as secondary screening tools for women who have been classified as screen-positive for early-onset pre-eclampsia. This will facilitate the identification of those truly high-risk for the development of late-onset pre-eclampsia, gestational hypertension and preterm birth. One of the most salient findings was that heart rate was a very strong marker. Unsurprisingly, mean arterial pressure was also determined to be quite significant in terms of the development of hypertensive disorders. In general, indexed measures also slightly outperformed raw data measures as predictive markers, and of those markers that did perform well, they did so equally, but only at the earlier gestations compared to all time points. There was one notable exception to this in regard to pre-eclampsia; MAP worked very well at all time points but not at the early gestation times. Cardiac output, total peripheral resistance and their indexed equivalent measures were also excellent predictors of pre-eclampsia, while MAP, HR and SVI were excellent to outstanding predictors of gestational hypertension. When these cardiovascular parameters were assessed in terms of all adverse pregnancy outcomes together, the findings were not especially remarkable. This likely indicates that these are a heterogenous group of conditions that cannot be predicted using one tool, but rather should be considered individually when predicting risk.

In our modest sample size, mean arterial pressure was an outstanding predictor of gestational hypertension regardless of gestation, with 100% detection rate for a 12.5% false positive rate when all time points are considered, dropping to 100% DR for a 30% FPR when only the 14 and 20 week time points were included. MAP also performed well as a screening tool for pre-eclampsia, however this was only when all time points were included and not the early gestations alone. Our findings are in keeping with a recent study by Guy *et al* 2017 (53) which assessed cardiovascular parameters at 35-37 weeks' gestation to screen for term pre-eclampsia, however they used an unselected population whereas our study involved women stratified as high-risk for early-onset pre-eclampsia. This group found the performance of pre-eclampsia and gestational hypertension screening was improved by the inclusion of MAP late in the third trimester. In regard to

women who delivered a small for gestational age infant or had a preterm birth, MAP was not particularly useful as a predictor of these conditions.

The MAP results for hypertensive disorders are unsurprising given elevated blood pressure is diagnostic for these conditions. However, an important difference was that MAP was an excellent predictor for gestation hypertension but only performed fairly as a predictor for pre-eclampsia in the second trimester. When we consider what we have previously shown in Chapter 7 – that women who develop late-onset pre-eclampsia have a different cardiovascular profile compared to women with a subsequent normal pregnancy outcome or those that develop gestational hypertension – these findings support the idea that endothelial dysfunction precedes hypertension in women who develop late-onset pre-eclampsia.

In women who develop gestational hypertension, the cardiovascular system has the ability to adapt to the increased vascular resistance associated with hypertension and maintain their endothelial health, while women who develop late-onset pre-eclampsia possibly have underlying poor endothelial function, (confounded by underlying maternal co-morbidities) that subsequently becomes dysfunctional with pregnancy and gives rise to hypertension late in the pregnancy. This proposed endothelial dysfunction could potentially impact the placental vasculature with vasoconstriction and hypoxia ensuing. This could explain why women with late-onset pre-eclampsia generally have appropriately sized infants, and why aspirin is largely ineffective in this group.

Furthermore, despite women who develop late-onset pre-eclampsia having appropriately sized infants, they remain significantly lower in birthweight and birthweight centile compared to women with a normal pregnancy outcome, suggesting that elevated MAP and TRP due to a failure of normal adaptive endothelial function and arterial stiffness may inhibit normal blood volume expansion (339). Consequently, maladaptation of the cardiovascular system secondary to increased afterload may result in the placental not reaching its full potential as opposed to primary placental failure.

Stroke volume and stroke volume index were fair predictors of pre-eclampsia, with improved prediction following the inclusion of heart rate, as seen by an increase in the ROC AUC for CO and CI. CI also performed slightly better when

all time points were included. When only the early time points were used, there was no difference in the performance of CO and CI as a predictor for pre-eclampsia. In keeping with our findings, the study by Ling *et al* (2017) (494) also found the addition of heart rate improved the detection of late-onset pre-eclampsia. TPR and TPRI were the most promising tools for the prediction of late-onset pre-eclampsia, with TPRI performing slightly better than TPR. One of the most useful findings is that the TPR worked equally well at just the early gestations compared to all time points.

Heart rate alone was an excellent predictor for gestational hypertension, performing just as well when only the early gestation measures were included, compared to all time points. SVI was also a very good predictor, outperforming SV convincingly. Interestingly, CO and CI, which are reflective of a combination of these variables together, performed less well, most notably at the early gestation times alone. This is in contrast to the Guy study which found CO improved the detection rate of gestational hypertension (53).

For women who delivered a SGA infant, SV and SVI were fair predictors, with SV at all time points showing the best result. The ROC AUC for SV was equivalent to heart rate at all time points and LVM/LVMI, however none of these tools were particularly strong predictors. CO, CI, TPR and TPRI were poor predictors of SGA. Studies including our own have shown lower CO/CI and higher TPR/TPRI associated with SGA and IUGR (42, 44, 49, 437, 438, 510), however only one study evaluated cardiovascular parameters for the prediction of SGA. This was a late third trimester cross-sectional study by Guy *et al* (2017b) (530) which found screening by maternal characteristics and fetal biometry was not improved by the inclusion of these parameters, despite a significant positive association with CO and HR.

In terms of LVM and LVMI, these variables did not perform well for the prediction of an adverse outcome, and in particular, pre-eclampsia and gestational hypertension. For women who delivered a SGA infant, LVM and LVMI performed fairly, with LVM marginally better than LVMI. There was little difference when just the early gestations were included compared to all time points.

One of the limitations of this study was the small number of cases for each of the specific adverse outcomes. Echocardiography requires highly skilled operators

and can be a time-consuming scan compared to similar tests. Future work could be directed towards automated machines that do not require the intensive training of echocardiographers, although caution regarding the validation and reliability of this equipment is needed with studies showing these platforms cannot be used interchangeably (383, 384, 389).

In terms of screening for an adverse pregnancy outcome, none of the cardiovascular parameters assessed in our study performed well as predictors. For the prediction of late-onset pre-eclampsia, TPR/TPRI and to a slightly lesser extent CO/CI were very good and may be useful second tier screening tools. For the prediction of gestational hypertension, TPR/TPRI performed fairly, with CO and CI only marginally better when measurements over a greater gestation time were included. HR and SVI were very good predictors for gestational hypertension, with MAP the standout tool with excellent prediction, performing equally well at just the early gestation times.

This study shows quite clearly that there are some highly useful predictors for these hypertensive disorders and that there is potential for them to be differentiated early in the second trimester of pregnancy. In regard to SGA, none of the cardiac variables were particularly impressive as predictors. One of the most important, yet surprising findings was the excellent performance of heart rate for the prediction of preterm birth. Despite the small numbers in the group, this result warrants further investigation.

Chapter 9 Summary

9.1 Summary

Cardiovascular maladaptation in pregnancy is a relatively new theory in relation to the development of pre-eclampsia and it is also a contentious issue with many believing that pre-eclampsia is purely a disease of placental origin (46, 138, 188, 531-533). While abnormal placentation is a key factor in the development of early-onset pre-eclampsia, this aetiology does not fit well for late-onset pre-eclampsia.

Current screening strategies identify women who are high-risk for the development of early-onset pre-eclampsia using a multiple logistic regression algorithm (201, 256, 261). Risk is predicted based on the population rate of pre-eclampsia, maternal demographic factors, mean arterial blood pressure, pregnancy associated plasma protein A and uterine artery Doppler PI, collated at the routine 12-week ultrasound. The models predict early-onset eclampsia in 95% of women at a 10% false positive rate (256), and has been validated by an Australian study involving over 3000 women, yielding a detection rate of 91.7% at a false positive rate of 10% (198). In terms of all cases of pre-eclampsia, the FMF model works less well, with a detection rate of 40.1% at a 10% false positive rate (256). The efficacy of screening for early-onset pre-eclampsia is high as it is essentially a screening test for placental disease. It is unsurprising that screening for late-onset pre-eclampsia does not perform well using this algorithm, considering it is not strongly associated with inadequate placentation, thereby necessitating other maternal criterion to improve sensitivity.

The current screening strategy for late-onset pre-eclampsia may be improved by including maternal cardiovascular parameters, given the recognised haemodynamic changes that occur in women with this disease (37, 54, 56, 455, 520). The design of this research project was developed to address the paucity of maternal haemodynamic longitudinal data prior to the development of signs and symptoms of pre-eclampsia, with the primary aim to investigate what cardiovascular parameters may be useful markers of cardiovascular maladaptation in pregnancy and whether any of these parameters had the potential to improve the sensitivity of screening women at risk of developing the disease.

In general terms, this research clearly demonstrated that cardiovascular adaptation was altered in women who develop late-onset pre-eclampsia prior to symptoms and signs of disease, in keeping with one of the major aims of this thesis. The findings of reduced cardiac output and increased total peripheral resistance were suggestive of maladaptation and these results were evident at more than one time point; however, this was in contrast to the widely held view that women destined to develop late-onset pre-eclampsia have a hyperdynamic circulation. Importantly, the haemodynamic profile of women who subsequently developed late-onset pre-eclampsia was different to those with other adverse outcomes such as gestational hypertension and the birth of a small of gestational age fetus, highlighting the potential of specific cardiovascular markers: stroke volume, heart rate, cardiac output and total peripheral resistance, could make the current screening algorithm more specific for the prediction of pre-eclampsia, which was the second major aim of this thesis.

This research was divided into five main studies: i) to assess pregnancy and birth outcomes and cardiovascular parameters based on screening outcome prior to the commencement of aspirin in screen positive women; ii) to evaluate cardiac function and structure at 14 weeks' gestation in high-risk women with subsequent normal and adverse pregnancy outcomes (including the development of gestational hypertension, pre-eclampsia, birth of a small for gestational age fetus or premature birth); iii) to evaluate cardiac function and structure in low-risk and high-risk women between 14 and 30 weeks' gestation with a subsequent normal pregnancy outcome; iv) to assess cardiovascular function in high-risk women with subsequent adverse pregnancy outcomes; and v) evaluate what cardiovascular parameters may be useful predictors of late-onset pre-eclampsia or other adverse outcomes.

In the first Study (Chapter 4), the primary aim was to validate the FMF algorithm to select high-risk women. During this process I recruited 153 women, including 105 women high-risk for early-onset pre-eclampsia and 48 low-risk controls for serial assessment of cardiovascular function. I reported maternal characteristics, pregnancy and birth outcomes in women defined as low-risk or high-risk using the FMF first trimester screening algorithm and showed women screened high-risk were more likely to have an adverse pregnancy outcome, including the development of a hypertensive disorder or birth of a small for gestational age

infant compared to women screened low-risk. These women also delivered earlier and had significantly smaller infants. These results support the use of the FMF algorithm to assess risk.

The second aim of this study was to evaluate cardiac function and structure at 14 weeks' gestation prior to the administration of aspirin. This study showed high-risk women had a lower stroke volume and stroke volume index compared to women stratified as low-risk. The cardiac output and cardiac index values were slightly lower; however, significance was not reached. As expected, the mean arterial pressure was significantly higher in the screen positive group compared to the screen negative group, (as it is a marker within the screening algorithm). The combination of cardiac output and mean arterial pressure resulted in significantly higher total peripheral resistance and total peripheral resistance index values in the high-risk women, thereby suggesting the inclusion of these cardiovascular parameters could potentially improve the screening algorithm, or alternatively be used as a second-tier screening tool to determine those truly at high-risk.

In Study two (Chapter 5), I sought to determine whether cardiovascular parameters at 14 weeks' gestation in women stratified as high-risk with a normal or adverse pregnancy outcome were different. In this study, I demonstrated that women destined to develop pre-eclampsia, gestational hypertension or delivery of a small for gestational age fetus did have a different cardiovascular profile compared to women with a subsequent normal outcome. The most important findings were that women with an adverse outcome had a significantly lower cardiac output compared to those with a normal outcome (4.91 L/min [4.27 L/min - 5.62 L/min] versus 5.43 L/min [4.71 L/min - 6.12 L/min]; p = 0.02), a reduced stroke volume (65.1ml [56.4ml - 71.2ml] versus 73.4ml [63.0ml - 84.4ml]; p<0.001) and higher total peripheral resistance (1455 Dynes.s^{-1}cm^{-5} [1347 Dynes.s^{-1}cm^{-5} - 1640 Dynes.s^{-1}cm^{-5}] versus 1289 Dynes.s^{-1}cm^{-5} [1167 Dynes.s^{-1}cm^{-5} - 1533 Dynes.s^{-1}cm^{-5}]; p = 0.005). The indexed equivalent measures of cardiac index, stroke volume index and total peripheral resistance index, paralleled the raw data changes and were all significantly different. These findings were in contrast to some earlier studies at the same gestation which showed either elevated cardiac output or a hyperdynamic circulation (high CO / low TPR) in women who developed late-onset pre-eclampsia, while the profile

fitted well for women who delivered a SGA infant (39-44, 49, 50). This finding was not unexpected for SGA, as these infants and growth restriction fetuses are both associated with poor placentation secondary to failure of the uterine arteries to adequately dilate (273, 437, 534). At this early gestation, other systolic or diastolic measures were unchanged between women with a normal and adverse pregnancy outcome and were not considered useful markers.

An important consideration was whether the cardiovascular parameters SV, CO and TRP identified at 14 weeks' gestation, would be reliable markers for screening. This necessitated a longitudinal assessment of these cardiovascular parameters in normal pregnancy, to establish what constituted physiological change, so they could be differentiated from pathological change identified in pregnancies with an adverse outcome. Although numerous studies have looked at normal cardiovascular adaptation in pregnancy, there are conflicting reports on the magnitude and timing of cardiac output change, confounded by different measurement techniques and methodologies (35, 44, 45, 326, 328-333, 341, 350, 351, 358, 362-365, 368, 369, 372, 374, 387, 399, 404, 449, 535).

Study three (Chapter 6), was therefore undertaken to assess cardiovascular parameters longitudinally between 14 and 30 weeks' gestation, in women stratified as either high-risk or low-risk for early-onset pre-eclampsia with a subsequent normal pregnancy outcome. This study was performed as it was important to establish what constituted a normal cardiovascular profile in these populations, which were corrected for maternal age and parity. In this study I showed that both low-risk and high-risk women with a normal pregnancy outcome, increased their cardiac output/cardiac index and heart rate between 14 and 30 weeks' gestation in keeping with previous work (35, 326, 328, 331, 332, 334, 351, 362, 364, 365, 368, 409).

In terms of both groups of women, the most salient finding was that the rise in cardiac output / cardiac index was secondary to an increased heart rate, while stroke volume remained unchanged. In the women stratified as low-risk, cardiac output increased from 5.58 L/min (SD 1.8 L/min) at 14 weeks' gestation to 6.31 L/min (SD 1.2 L/min) at 30 weeks' gestation; $p < 0.001$, while the cardiac index increased from 3.19 L/min/m^2 (SD 0.52 L/min/m^2) to 3.43 L/min/m^2 (SD 0.52 L/min/m^2); $p = 0.002$. However, the significant increase in CI was from 14 to 20

weeks' gestation, with the mean values plateauing from this point. Heart rate also increased from 72 bpm (SD 8 bpm) to 83 bpm (SD 8 bpm); $p < 0.001$.

High-risk women also showed a significant increase in cardiac output and heart rate respectively; 5.47 L/min (SD 1.09 L/min) to 5.82 L/min (SD 0.96 L/min); $p = 0.005$ and 73 bpm (SD 9 bpm) to 81 bpm (SD 11 bpm); $p < 0.001$, while the cardiac index was essentially unchanged; 3.17 L/min/m^2 (SD 0.59 L/min/m^2) to 3.24 L/min/m^2 (SD 0.50 L/min/m^2); $p = 0.293$. The increase in cardiac output with gestation in high-risk women was not as marked compared to low-risk women, suggesting these women did not undergo the same degree of physiological expansion, although statistically there was no significant difference in mean CO values at any of the time points.

One of the most interesting findings in both low-risk and high-risk women with a normal pregnancy outcome, was that stroke volume remained stable between 14 and 30 weeks' gestation, while a significant decline in stroke volume index was seen. These results were in keeping with one large study (35) and a recent meta-analysis (368) while in contrast to a number of studies which reported SV increased during this time period in women with a normal pregnancy outcome (328, 329, 331, 362, 409, 416). This difference may be attributed in part to study design, as previous studies measured stroke volume at different gestations to our study. Additionally, an increase in stroke volume may have occurred prior to 14 weeks' gestation or after 30 weeks' gestation. Blood volume expansion is well recognised to occur from as early as 5 weeks' gestation, which consequently increases preload and stroke volume (337, 340, 347, 536, 537). In terms of stroke volume index, most studies did not report this value, despite indexing cardiac output. One study that did report stroke volume index also showed a decline from the first to third trimesters, in keeping with our results. With respect to indexation, a variety of methods have been used, further confounding the results, in addition to the different mean BMI of the populations studied. The decline in SVI in women with a normal pregnancy outcome also raises the issue regarding how appropriate body surface area indexation is in pregnancy, considering the significant body and size changes that occur and the lack of validation of the Dubois and Dubois formula in pregnancy.

As expected, the mean arterial pressure was unchanged in the low-risk group, so both the total peripheral resistance and indexed equivalent ultimately decreased between 14 and 30 weeks' gestation, secondary to the rise in cardiac output. Total peripheral resistance and total peripheral resistance index decreased between 14 - 30 weeks' gestation respectively; 1253.5 Dynes.s^{-1}cm^{-5} (SD 251.6 Dynes.s^{-1}cm^{-5}) to 1111.1 Dynes.s^{-1}cm^{-5} (SD 210.2 Dynes.s^{-1}cm^{-5}); p <0.001 and 2162.6 Dynes.s^{-1}cm^{-5} m^2 (SD 363.2 Dynes.s^{-1}cm^{-5} m^2) to 2021.7 Dynes.s^{-1}cm^{-5}m^2 (SD 323.4 Dynes.s^{-1}cm^{-5}m^2); p = 0.006, reaching a nadir at 20 weeks' gestation. These changes were in keeping with expected cardiovascular adaptation in normal pregnancy.

The mean arterial pressure was significantly higher in the high-risk women with a normal outcome compared to the low-risk risk women with a normal outcome at each time point, resulting in mildly higher total peripheral resistance values in high-risk women. This difference was not statistically significant, with the same pattern of change in TPR and TPRI seen in low-risk women observed, decreasing from 1356.1 Dynes.s^{-1}cm^{-5} (SD 291.9 Dynes.s^{-1}cm^{-5}) to 1258.8 Dynes.s^{-1}cm^{-5} (SD 216.9 Dynes.s^{-1}cm^{-5}); p = 0.002 and 2330.5 Dynes.s^{-1}cm^{-5}m^2 (SD 478.2 Dynes.s^{-1}cm^{-5}m^2) to 2261.6 Dynes.s^{-1}cm^{-5}m^2 (SD 405.1 Dynes.s^{-1}cm^{-5}m^2); p = 0.011, respectively. One of the most important differences between the two groups of women with a normal pregnancy outcome was that the MAP and TPRI values were significantly higher in the women screened high-risk at most time points, suggesting the change in vascular tone was not to the same extent as that seen in low-risk women. These values were also higher than other studies, however our results represented a selected population. In regard to additional measures of cardiac function, the systolic results were largely unremarkable, with diastolic changes in keeping with increased blood volume for both groups of women. Assessment of the cardiovascular data in women with a normal pregnancy outcome was important in order to determine normal physiological adaption in pregnancy, however as we have shown in regard to MAP, TPR and TPRI, consideration as to what represents 'normal' depends on the population studied. This study highlights that the cardiovascular adaptation of women stratified as high-risk for early-onset pre-eclampsia may be mildly inhibited by elevated resistance of the systemic vascular system and that this increase in

afterload could potentially prevent an appropriate augmentation in stroke volume and cardiac output.

In Study 4 (Chapter 7), I aimed to evaluate cardiovascular parameters with respect to specific adverse outcomes, namely pre-eclampsia, gestational hypertension, delivery of a small for gestational age infant or preterm birth, with a comparison to women with a normal pregnancy outcome. In this study, I clearly demonstrated that women who were destined to develop late-onset pre-eclampsia had significantly lower SV, SVI, CO and CI and higher MAP, TPR and TPRI compared to high-risk women with a normal pregnancy outcome. Despite the increase in cardiac output, this was not statistically significant between 14 and 30 weeks' gestation; 4.6 L/min (SD 0.8 L/min) to 5.0 L/min (SD 1.0 L/min); p = 0.075, in contrast to high-risk women with a normal outcome; 5.47 L/min (SD 1.1 L/min) to 5.82 L/min (SD 1.0 L/min); p = 0.005, suggesting inadequate expansion of the normal cardiac output. This is supported by the cardiac index results, which were all lower in the women who developed pre-eclampsia; 2.7 L/min/m^2 (SD 0.4 L/min/m^2) versus 3.2 L/min/m^2 (SD 0.6 L/min/m^2); p = 0.004, at 14 weeks' gestation and 2.8 L/min/m^2 (SD 0.5 L/min/m^2) versus 3.2 L/min/m^2 (SD 0.5 L/min/m^2); p = 0.023, at 30 weeks' gestation.

The significantly higher MAP in women who developed pre-eclampsia resulted in higher TPR/TPRI values in these women compared to those with a normal pregnancy outcome; 1694 Dynes.$s^{-1}cm^{-5}$ (SD 356 Dynes.$s^{-1}cm^{-5}$) versus 1356 Dynes.$s^{-1}cm^{-5}$ (SD 292 Dynes.$s^{-1}cm^{-5}$); p = 0.013 at 14 weeks' gestation and 1446 Dynes.$s^{-1}cm^{-5}$ (SD 159 Dynes.$s^{-1}cm^{-5}$) versus 1247 Dynes.$s^{-1}cm^{-5}$ (SD 206 Dynes.$s^{-1}cm^{-5}$); p = 0.002 at 24 weeks' gestation. These findings were replicated in the TPRI results; 2839 Dynes.$s^{-1}cm^{-5}m^2$ (SD 467 Dynes.$s^{-1}cm^{-5}m^2$) versus 2331 (SD 478 Dynes.$s^{-1}cm^{-5}$); p = 0.004 at 14 weeks' gestation and 2510 Dynes.$s^{-1}cm^{-5}m^2$ (SD 239 Dynes.$s^{-1}cm^{-5}m^2$) versus 2195 Dynes.$s^{-1}cm^{-5}$ (SD 328 Dynes.$s^{-1}cm^{-5}$); p = 0.001 at 24 weeks' gestation. The TPR and TPRI were both higher at 30 weeks' gestation, however statistical significance was not reached. Women who developed pre-eclampsia clearly did not demonstrate the same degree of change in their vascular tone compared to high-risk women with a normal pregnancy outcome.

The resultant haemodynamic profile of a low CO / high TPR state was evident at all time points, contradicting the hyperdynamic theory of a high CO / low TPR state prior to the clinical onset of disease seen in previous studies (39-43, 50, 496). This profile had previously been shown in a mid-gestational (20 - 23 weeks' gestation) case-controlled study (36) and one late third trimester study (35 - 37 weeks' gestation) (53), however our results, most importantly, show this longitudinally and that this is evident from as early as 14 weeks' gestation.

One of the most salient findings for women who developed gestational hypertension was the markedly elevated heart rate compared to women with a normal pregnancy outcome, reaching significance between 14 and 24 weeks' gestation; 85 bpm (SD 8 bpm) versus 73 bpm (SD 9 bpm); p = 0.001 and 93 bpm (SD 16 bpm) versus 78 bpm (SD 9 bpm); p = 0.014. Furthermore, stroke volume and stroke volume index were all significantly lower at all time points compared to high-risk women with a normal pregnancy outcome; stroke volume (67.4ml [SD 4.7 ml] versus 74.6 ml [SD 12.9ml]; p = 0.004, at 14 weeks' gestation and 66.2 ml [SD 8.0 ml] versus 72.4 ml {SD 12.6 ml); p = 0.024 at 30 weeks' gestation and stroke volume index [36.9 ml/m^2 (SD 1.7 ml/m^2) versus 43.3 ml/m^2 (SD 6.7 ml/m^2); p <0. 001, at 14 weeks' gestations and 34.7 ml/m^2 (SD 3.4 ml/m^2) versus 40.2 ml/m^2 (6.3 ml/m^2); p < 0.001, at 30 weeks' gestation. This resulted in slightly higher cardiac output and cardiac index values compared to high-risk women with a normal outcome, however statistical significance was not reached. Although the MAP was also significantly elevated in women who developed gestational hypertension at each time point, statistically higher TPR values were not reached. The indexed equivalent TPRI did, however, reach significance compared to the high-risk women with a normal outcome.

The SV/SVI, MAP and TPR/TPRI findings were in keeping with a previous study at 35-37 weeks' gestation, however the group did not show the heart rate elevation that we did (53). Based on the cardiac output and heart rate results, women destined to develop gestational hypertension could potentially be differentiated from those who develop pre-eclampsia.

The primary aim of Study 5 (Chapter 8), was to assess whether any measures of maternal cardiovascular function had potential as markers for the prediction of late-onset pre-eclampsia, in women already stratified as high-risk through first

trimester screening and at what gestation these markers could be most effective. In terms of assessing whether cardiovascular parameters would be useful for the prediction of an adverse pregnancy outcome in this group of women, there were no strong markers. When the cardiovascular parameters were assessed for specific adverse outcomes, a number of markers performed well.

For the prediction of late-onset pre-eclampsia, total peripheral resistance, cardiac output and the equivalent indexed measures were very good markers with receiver operating curve AUC ranging from 0.80 to 0.83 for cardiac output and cardiac index and 0.84 to 0.86 for total peripheral resistance and total peripheral resistance index respectively. These markers were equally as effective at the early gestations alone compared to all time points. In regard to gestational hypertension, stroke volume index and heart rate were very good predictors, with receiver operating curve AUCs = 0.86 and 0.87 at the early gestation points and all time points respectively for both markers. Mean arterial pressure was an exceptionally good marker for gestational hypertension in the first half of pregnancy with an AUC = 0.94, which is distinct from pre-eclampsia with an AUC = 0.72.

There is certainly potential for cardiovascular markers to be used for the prediction of hypertensive disorders, despite none of the cardiac variables working well for the prediction of a SGA infant. What is promising is that pre-eclampsia and gestational hypertension do not have all of the same markers in common; therefore, these diseases can potentially be differentiated, and this can occur in the first half of pregnancy.

9.2 Strengths and limitations

There were a number of strengths to this research, including the longitudinal design of the study and very good attendance from the women involved. The echocardiograms were also performed by a single operator (myself) using the same machine for every scan. This eliminated inter-operator issues associated with measurements and variation between different ultrasound equipment. Other studies report a single person analysing the measurements; however, this does not correct for inter-operator error secondary to multiple echocardiographers.

Differences in measurements tend to arise at the point of acquisition and less so at the level of analysis.

Echocardiograms are labour intensive with a high-level of technical skill and expertise required, especially in comparison to other methods of acquiring cardiovascular data such as automated Doppler devices. Furthermore, pre-eclampsia is relatively rare, complicating 3-5% of pregnancies (1, 2, 61, 78, 538), thereby hindering our ability to achieve a large sample size of adverse outcomes. Despite these factors, the combination of the longitudinal study design, single operator and echocardiogram methodology counterbalanced these limitations. Overall, these important strengths contributed to the high quality of data collected.

A further limitation of this work was that women were not identified for inclusion into the study until they had completed first trimester screening. This resulted in the first echocardiogram being performed at the earliest time point of 14 weeks' gestation. Although pre-conception cardiovascular data would have provided useful baseline information, anticipating when women will become pregnant is difficult. The natural average monthly fecundity is approximately 20% (539) with the cumulative pregnancy rate at 40 - 90 % after 12 months (540-542). It was simply not feasible to recruit women preconception or prior to first trimester screening.

With respect to data collection beyond 30 weeks' gestation, cardiovascular information in the late third trimester or post-partum would have been a valuable addition to my research, however the major aim of the project was to investigate these parameters prior to the manifestation of symptoms and signs of pre-eclampsia. Consequently, as our intent was to identify additional screening tools, the study was designed so that the last scan was performed at 30 weeks' gestation. There is also controversy regarding the optimum time for post-partum follow up, with some suggesting 6 - 12 months to enable sufficient time for the cardiovascular system to return to normal post pregnancy (51, 351, 394, 460). As post-partum changes where not the major focus of this research, these examinations were not included in the study design. The study design included echocardiograms at four time points as we felt any more scans would lead to poor recruitment and higher drop-out rates.

Another limitation to our study was the method of indexation applied to our data. We reported raw and indexed data in our study, using the widely accepted Du Boise body surface area formula. This paper, written in 1916, only included a small series of men (n = 9) who were obviously not pregnant (470). Furthermore, body shape changes in pregnancy and the validity of using BSA may become less appropriate compared to the use of BSA in the non-pregnant population. Normalising cardiovascular measures to compensate for body size is recommended by leading international cardiac institutions, however there are no guidelines with regard to indexation in pregnancy. We included BSA indexed measures as this is the most widely used method and would allow a direct comparison with other studies. Alternative methods of indexation using height exponents and fat free mass have been explored in the general population, with the later method demonstrating this approach is more accurate. Our study was not designed to assess the different forms of indexation in pregnancy, although consideration of this complexity in regard to our results was discussed.

9.3 Future directions

Future work investigating the potential inclusion of cardiovascular markers in pre-eclampsia screening, specifically cardiac output or total peripheral resistance, would require confirmation with larger prospective studies for validation. To facilitate increasing the number of participants, the use of cardiac output monitoring using an automated Doppler device such as the USCOM or a thoracic bioreactance device like the NICOM (Non-invasive Cardiac Output Monitor) may be a reasonable way forward. Automated Doppler devices were available to assess cardiac output prior to this study starting, however, the equipment had not been well validated (381, 387, 543).

The USCOM device uses continuous wave Doppler analysis of the aortic blood flow and is operator dependent, requiring some training. A significant problem with this device is that the aortic outflow diameter is derived from patient height and not a direct measurement. Additionally, the continuous Doppler measurement is not necessarily at the level of the aortic inflow with both of these issues a potential source of significant error (383, 544). The NICOM device is

operator independent, however a recent study of both devices showed only fair agreement with transthoracic echocardiography in the third trimester and poor agreement in the first and second trimesters. Furthermore, the mean percentage difference between these devices and echocardiography were reported between 30 % and 70 %, which is undesirable (383). These devices need to demonstrate improved reliability and validation to reach transthoracic echocardiography Doppler standards, with the development of device specific reference ranges a possible solution to counteract the inherent bias of this equipment (545).

The scarcity of obstetric and cardiac ultrasound skills has certainly inhibited maternal echocardiograms becoming a routine process. An alternative solution to using automated devices would be to upskill sonographers to perform a limited echocardiogram involving a 2D measurement of the LVOT and PW Doppler through the LVOT to calculate stroke volume and heart rate. This would require more training than the USCOM device, in addition to the procurement of an appropriate transducer and software, however the limited echocardiogram could be performed at the same time as the routine obstetric ultrasound scans.

A recent consensus from the International Working Group on Maternal haemodynamics has recommended transthoracic Doppler echocardiography as one of the most accurate techniques for measuring cardiac output. The group also identified cardiovascular magnetic resonance imaging (CMR) as an alternative emerging technique that rivals echocardiography. CMR calculation of stroke volume does not have issues relating to geometric assumptions that are associated with echocardiography, thereby demonstrating accurate and reproducible cardiac output results (509, 546). However, the downside of CMR includes limited availability, high cost and specific expertise required to obtain high quality imaging and interpretation, which does not support this method becoming common practice in the foreseeable future.

Indexation of cardiovascular parameters certainly requires further investigation to determine what is the most appropriate method to apply during pregnancy. There have been significant advances in assessing body composition using magnetic resonance imaging, air displacement plethysmography, deuterium dilution hydrometry and bioelectrical impedance analysis, either or all of which may prove

more accurate than body surface area calculations based on a very small non-pregnant population (547, 548).

Finally, while this thesis was in the final stages of writing, the National Institute of Clinical Excellence updated their Hypertension in Pregnancy Guideline in July 2019 and recommended no change to the method of pre-eclampsia screening risk assessment, citing inadequate sensitivity and specificity to alternative screening methods. The inclusion of cardiovascular markers could potentially improve the efficacy of first trimester screening algorithms and increase acceptance of this important tool.

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Appendices

Appendix A. Pre-eclampsia secondary cardiovascular variables

Outcome	Normal Mean (SD)	PE Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
LVM				0.950*		0.955*
- 14 weeks	125.0 (25.0)	122.8 (33.5)	-1.91 (-24.61, 20.80)	0.869	4.11 (-18.36, 26.58)	0.720
- 20 weeks	126.4 (25.1)	128.4 (33.9)	0.13 (-22.85, 23.11)	0.991	6.06 (-16.54, 28.67)	0.599
- 24 weeks	128.2 (23.7)	129.8 (34.0)	-0.32 (-23.27, 22.63)	0.978	5.69 (-16.94, 28.32)	0.622
- 30 weeks	130.8 (25.3)	132.8 (29.5)	0.10 (-20.24, 20.45)	0.992	6.03 (-13.92, 25.98)	0.554
LVMI				0.906*		0.914*
- 14 weeks	72.4 (12.3)	71.8 (15.8)	-0.45 (-11.22, 10.32)	0.934	1.83 (-8.87, 12.54)	0.737
- 20 weeks	72.5 (11.9)	73.9 (15.5)	0.77 (-9.76, 11.29)	0.887	3.00 (-7.38, 13.37)	0.571
- 24 weeks	72.3 (11.1)	73.7 (16.0)	0.62 (-10.18, 11.42)	0.911	2.89 (-7.85, 13.64)	0.598
- 30 weeks	72.4 (12.3)	74.3 (12.1)	1.14 (-7.40, 9.68)	0.793	3.38 (-5.08, 11.83)	0.434
VTI				0.927*		0.926*
- 14 weeks	24.09 (3.19)	22.17 (3.08)	-1.85 (-4.01, 0.31)	0.094	-1.94 (-4.13, 0.24)	0.081
- 20 weeks	24.21 (3.38)	22.63 (3.09)	-1.65 (-3.85, 0.55)	0.141	-1.74 (-3.98, 0.50)	0.127
- 24 weeks	23.87 (3.01)	22.50 (2.53)	-1.32 (-3.16, 0.51)	0.157	-1.42 (-3.28, 0.45)	0.136
- 30 weeks	22.94 (3.32)	21.62 (2.69)	-1.37 (-3.33, 0.60)	0.172	-1.46 (-3.47, 0.56)	0.156
LVOT				0.045*		0.046*
- 14 weeks	1.99 (0.13)	1.91 (0.21)	-0.08 (-0.22, 0.06)	0.249	-0.05 (-0.19, 0.09)	0.469
- 20 weeks	1.99 (0.14)	1.91 (0.20)	-0.09 (-0.23, 0.05)	0.195	-0.06 (-0.19, 0.08)	0.388
- 24 weeks	1.99 (0.13)	1.95 (0.20)	-0.05 (-0.19, 0.08)	0.438	-0.02 (-0.15, 0.11)	0.746
- 30 weeks	2.00 (0.12)	1.96 (0.20)	-0.05 (-0.19, 0.08)	0.438	-0.02 (-0.15, 0.11)	0.740
EF Simpson				0.036*		0.035*
- 14 weeks	67.38 (3.67)	65.24 (2.65)	-2.36 (-4.37, -0.34)	0.022	-2.67 (-4.72, -0.62)	**0.011**
- 20 weeks	68.07 (3.06)	66.21 (3.84)	-1.67 (-4.33, 0.98)	0.217	-1.99 (-4.55, 0.58)	0.129
- 24 weeks	65.59 (3.62)	65.31 (3.10)	-0.43 (-2.69, 1.82)	0.705	-0.74 (-3.03, 1.54)	0.524
- 30 weeks	66.29 (3.48)	66.43 (3.70)	0.23 (-2.36, 2.82)	0.861	-0.07 (-2.65, 2.51)	0.960

Outcome	Normal Mean (SD)	PE Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
EF M-mode				0.042*		0.041*
- 14 weeks	66.60 (3.63)	65.88 (3.31)	-0.81 (-3.16, 1.55)	0.501	-1.10 (-3.31, 1.11)	0.330
- 20 weeks	67.54 (4.60)	66.25 (2.60)	-1.24 (-3.32, 0.83)	0.241	-1.52 (-3.41, 0.37)	0.115
- 24 weeks	67.07 (3.81)	65.53 (3.23)	-1.63 (-3.96, 0.70)	0.172	-1.90 (-4.13, 0.33)	0.094
- 30 weeks	65.79 (4.19)	67.13 (3.19)	1.37 (-0.98, 3.73)	0.253	1.12 (-1.34, 3.58)	0.372
FS M-mode				0.011*		0.010*
- 14 weeks	36.96 (2.96)	36.19 (2.27)	-0.85 (-2.51, 0.82)	0.318	-0.88 (-2.43, 0.67)	0.264
- 20 weeks	38.07 (3.36)	36.58 (2.03)	-1.49 (-3.07, 0.09)	0.065	-1.53 (-2.99, -0.06)	**0.041**
- 24 weeks	37.23 (3.00)	36.04 (2.30)	-1.28 (-2.98, 0.41)	0.138	-1.31 (-2.94, 0.32)	0.115
- 30 weeks	36.28 (3.05)	37.31 (2.57)	1.03 (-0.84, 2.89)	0.281	1.00 (-0.95, 2.96)	0.314
s Sep				0.046*		0.044*
- 14 weeks	10.03 (1.59)	9.44 (1.32)	-0.57 (-1.52, 0.38)	0.240	-0.62 (-1.60, 0.36)	0.215
- 20 weeks	10.05 (1.34)	9.38 (1.28)	-0.69 (-1.60, 0.22)	0.138	-0.73 (-1.72, 0.26)	0.151
- 24 weeks	10.00 (1.25)	9.17 (1.74)	-0.86 (-2.04, 0.32)	0.154	-0.91 (-2.09, 0.28)	0.134
- 30 weeks	9.64 (1.28)	8.39 (1.32)	-1.25 (-2.18, -0.33)	0.008	-1.30 (-2.22, -0.38)	**0.006**
s LVFW				0.928*		0.926*
- 14 weeks	11.98 (2.21)	10.06 (0.71)	-1.95 (-2.67, -1.23)	<0.001	-2.01 (-2.72, -1.30)	**<0.001**
- 20 weeks	11.97 (2.18)	10.27 (1.25)	-1.73 (-2.72, -0.74)	0.001	-1.79 (-2.92, -0.66)	**0.002**
- 24 weeks	11.96 (2.36)	10.36 (1.97)	-1.62 (-3.04, -0.20)	0.026	-1.68 (-3.14, -0.23)	**0.023**
- 30 weeks	11.43 (2.25)	9.62 (1.86)	-1.90 (-3.26, -0.53)	0.006	-1.96 (-3.37, -0.56)	**0.006**
s RVFW				0.458*		0.461*
- 14 weeks	15.49 (1.95)	14.83 (3.08)	-0.64 (-2.71, 1.42)	0.542	-0.59 (-2.66, 1.48)	0.577
- 20 weeks	16.24 (2.16)	14.67 (1.88)	-1.54 (-2.89, -0.19)	0.025	-1.48 (-2.85, -0.11)	**0.034**
- 24 weeks	15.56 (1.77)	13.89 (1.19)	-1.73 (-2.63, -0.83)	<0.001	-1.68 (-2.59, -0.77)	**<0.001**
- 30 weeks	15.67 (1.73)	14.81 (2.58)	-0.91 (-2.65, 0.83)	0.306	-0.86 (-2.64, 0.91)	0.341

Outcome	Normal Mean (SD)	PE Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
MV E				0.371*		0.373*
- 14 weeks	85.86 (13.90)	82.32 (7.71)	-3.53 (-9.64, 2.57)	0.257	-3.76 (-10.19, 2.66)	0.251
- 20 weeks	87.84 (15.24)	80.07 (12.18)	-8.06 (-16.91, 0.78)	0.074	-8.28 (-17.44, 0.87)	0.076
- 24 weeks	82.60 (14.76)	79.20 (11.17)	-3.38 (-11.57, 4.81)	0.419	-3.61 (-11.91, 4.70)	0.395
- 30 weeks	76.75 (12.23)	75.34 (6.48)	-1.84 (-7.08, 3.41)	0.492	-2.06 (-7.55, 3.44)	0.464
MV A				0.005*		0.005*
- 14 weeks	49.98 (9.56)	52.93 (9.60)	2.89 (-3.81, 9.59)	0.398	3.39 (-3.52, 10.30)	0.336
- 20 weeks	50.20 (7.80)	49.20 (10.59)	-1.69 (-8.93, 5.54)	0.646	-1.24 (-8.32, 5.84)	0.731
- 24 weeks	51.18 (8.30)	52.93 (11.24)	1.47 (-6.17, 9.12)	0.706	1.97 (-5.52, 9.46)	0.606
- 30 weeks	52.43 (8.62)	49.35 (8.88)	-3.62 (-9.86, 2.62)	0.255	-3.14 (-9.22, 2.94)	0.312
MV E/A				0.063*		0.063*
- 14 weeks	1.79 (0.40)	1.61 (0.35)	-0.17 (-0.43, 0.08)	0.176	-0.20 (-0.46, 0.06)	0.136
- 20 weeks	1.80 (0.44)	1.68 (0.32)	-0.10 (-0.34, 0.14)	0.394	-0.13 (-0.37, 0.11)	0.292
- 24 weeks	1.66 (0.40)	1.54 (0.33)	-0.10 (-0.34, 0.14)	0.403	-0.13 (-0.36, 0.11)	0.290
- 30 weeks	1.49 (0.27)	1.56 (0.22)	0.08 (-0.08, 0.24)	0.341	0.05 (-0.11, 0.21)	0.520
IVRT				0.028*		0.030*
- 14 weeks	92.23 (12.23)	92.75 (16.66)	0.42 (-10.88, 11.71)	0.943	-0.02 (-10.50, 10.46)	0.997
- 20 weeks	90.69 (13.62)	98.94 (9.36)	8.44 (1.35, 15.52)	0.020	7.96 (0.71, 15.21)	**0.031**
- 24 weeks	94.46 (11.85)	95.19 (13.21)	0.64 (-8.51, 9.80)	0.890	0.26 (-8.65, 9.16)	0.955
- 30 weeks	97.84 (11.05)	99.25 (15.69)	2.12 (-8.56, 12.79)	0.698	1.74 (-7.32, 10.80)	0.706
DT				0.478*		0.481*
- 14 weeks	151.55 (26.46)	141.88 (18.79)	-9.69 (-23.62, 4.25)	0.173	-10.32 (-24.92, 4.28)	0.166
- 20 weeks	149.89 (15.89)	138.94 (17.95)	-11.00 (-23.42, 1.41)	0.082	-11.54 (-23.77, 0.69)	0.064
- 24 weeks	151.78 (19.17)	151.00 (24.18)	-1.35 (-17.89, 15.19)	0.873	-2.00 (-18.29, 14.30)	0.810
- 30 weeks	150.05 (19.24)	152.88 (21.84)	2.66 (-12.49, 17.82)	0.731	2.02 (-12.53, 16.57)	0.785

Outcome	Normal Mean (SD)	PE Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
A Dur				0.323*		0.322*
- 14 weeks	120.73 (19.38)	117.00 (17.97)	-3.60 (-16.30, 9.09)	0.578	-3.49 (-16.12, 9.13)	0.588
- 20 weeks	116.92 (14.17)	118.88 (16.12)	2.04 (-9.12, 13.20)	0.720	2.13 (-9.17, 13.44)	0.712
- 24 weeks	118.90 (17.02)	121.69 (9.11)	2.28 (-5.10, 9.66)	0.545	2.39 (-5.14, 9.92)	0.533
- 30 weeks	117.68 (16.79)	124.31 (7.95)	7.39 (0.50, 14.28)	0.035	7.50 (0.42, 14.58)	**0.038**
e Sep				0.743*		0.733*
- 14 weeks	14.86 (2.41)	13.44 (2.56)	-1.42 (-3.19, 0.36)	0.119	-1.45 (-3.24, 0.34)	0.113
- 20 weeks	14.70 (2.67)	13.18 (1.86)	-1.48 (-2.88, -0.08)	0.038	-1.51 (-2.91, -0.10)	**0.035**
- 24 weeks	14.06 (2.33)	12.89 (2.92)	-1.15 (-3.16, 0.86)	0.261	-1.19 (-3.06, 0.68)	0.213
- 30 weeks	13.12 (2.76)	11.12 (2.49)	-2.03 (-3.82, -0.25)	0.025	-2.08 (-3.87, -0.28)	**0.023**
a Sep				0.010*		0.010*
- 14 weeks	8.06 (1.62)	8.69 (1.27)	0.66 (-0.27, 1.58)	0.163	0.66 (-0.22, 1.54)	0.142
- 20 weeks	8.29 (1.54)	7.95 (0.96)	-0.36 (-1.11, 0.39)	0.344	-0.36 (-1.16, 0.44)	0.378
- 24 weeks	8.63 (1.35)	9.24 (1.36)	0.62 (-0.34, 1.57)	0.205	0.62 (-0.23, 1.48)	0.152
- 30 weeks	9.23 (1.82)	8.83 (1.50)	-0.40 (-1.49, 0.70)	0.476	-0.39 (-1.49, 0.71)	0.491
e/a Sep				0.284*		0.279*
- 14 weeks	1.91 (0.49)	1.58 (0.44)	-0.33 (-0.64, -0.02)	0.038	-0.34 (-0.64, -0.04)	**0.027**
- 20 weeks	1.84 (0.49)	1.68 (0.32)	-0.14 (-0.38, 0.10)	0.253	-0.15 (-0.39, 0.10)	0.240
- 24 weeks	1.67 (0.41)	1.43 (0.40)	-0.24 (-0.51, 0.04)	0.099	-0.24 (-0.49, -0.00)	**0.049**
- 30 weeks	1.49 (0.43)	1.29 (0.35)	-0.19 (-0.45, 0.06)	0.137	-0.20 (-0.46, 0.05)	0.121
E/e Sep				0.256*		0.245*
- 14 weeks	5.89 (1.17)	6.26 (0.91)	0.36 (-0.30, 1.03)	0.284	0.34 (-0.33, 1.02)	0.314
- 20 weeks	6.08 (1.16)	6.12 (0.91)	0.01 (-0.65, 0.68)	0.971	-0.01 (-0.68, 0.66)	0.981
- 24 weeks	5.98 (1.11)	6.35 (1.31)	0.36 (-0.54, 1.26)	0.433	0.35 (-0.46, 1.15)	0.401
- 30 weeks	6.09 (1.47)	7.09 (1.64)	0.99 (-0.15, 2.13)	0.089	0.98 (-0.16, 2.13)	0.093

Outcome	Normal Mean (SD)	PE Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
e LVFW				0.570*		0.587*
- 14 weeks	18.86 (3.29)	16.91 (3.50)	-1.97 (-4.40, 0.45)	0.111	-2.23 (-4.54, 0.08)	0.059
- 20 weeks	18.56 (3.49)	16.00 (2.41)	-2.47 (-4.27, -0.67)	0.007	-2.72 (-4.57, -0.87)	**0.004**
- 24 weeks	17.64 (3.48)	15.72 (2.96)	-1.90 (-4.03, 0.22)	0.079	-2.16 (-4.23, -0.09)	**0.041**
- 30 weeks	17.02 (2.88)	15.04 (3.32)	-1.83 (-4.13, 0.46)	0.118	-2.09 (-4.28, 0.10)	0.062
a LVFW				0.564*		0.574*
- 14 weeks	8.46 (1.67)	8.34 (1.07)	-0.12 (-0.94, 0.69)	0.765	-0.15 (-0.93, 0.63)	0.705
- 20 weeks	8.43 (1.44)	8.05 (0.84)	-0.41 (-1.08, 0.26)	0.231	-0.44 (-1.09, 0.22)	0.191
- 24 weeks	8.90 (1.76)	8.77 (1.27)	-0.15 (-1.09, 0.80)	0.763	-0.17 (-1.11, 0.78)	0.727
- 30 weeks	9.10 (1.80)	8.26 (1.66)	-0.77 (-1.95, 0.42)	0.204	-0.79 (-1.93, 0.36)	0.178
e/a LVFW				0.344*		0.350*
- 14 weeks	2.31 (0.59)	2.08 (0.63)	-0.23 (-0.66, 0.21)	0.305	-0.25 (-0.65, 0.15)	0.220
- 20 weeks	2.27 (0.61)	2.01 (0.39)	-0.24 (-0.54, 0.05)	0.107	-0.26 (-0.55, 0.02)	0.072
- 24 weeks	2.05 (0.54)	1.85 (0.55)	-0.19 (-0.57, 0.19)	0.333	-0.21 (-0.59, 0.16)	0.265
- 30 weeks	1.95 (0.54)	1.89 (0.62)	-0.07 (-0.49, 0.36)	0.763	-0.09 (-0.48, 0.30)	0.647
E/e LVFW				0.757*		0.749*
- 14 weeks	4.65 (0.94)	5.03 (1.06)	0.38 (-0.35, 1.11)	0.309	0.45 (-0.26, 1.16)	0.215
- 20 weeks	4.81 (0.80)	5.09 (1.07)	0.25 (-0.48, 0.98)	0.504	0.32 (-0.42, 1.05)	0.396
- 24 weeks	4.83 (1.13)	5.19 (1.26)	0.37 (-0.51, 1.24)	0.412	0.44 (-0.42, 1.29)	0.315
- 30 weeks	4.62 (0.97)	5.21 (1.15)	0.54 (-0.26, 1.33)	0.185	0.61 (-0.16, 1.38)	0.122
e RVFW				0.449*		0.437*
- 14 weeks	17.66 (3.10)	16.69 (4.96)	-0.97 (-4.30, 2.36)	0.569	-0.79 (-3.91, 2.33)	0.621
- 20 weeks	18.02 (3.03)	16.91 (4.70)	-1.06 (-4.23, 2.10)	0.511	-0.88 (-3.75, 1.99)	0.548
- 24 weeks	17.08 (2.91)	17.10 (4.24)	-0.12 (-3.00, 2.75)	0.933	0.05 (-2.59, 2.69)	0.970
- 30 weeks	17.82 (3.76)	15.94 (4.40)	-2.01 (-5.06, 1.03)	0.195	-1.86 (-4.92, 1.20)	0.234

Outcome	Normal Mean (SD)	PE Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
a RVFW				0.019*		0.021*
- 14 weeks	12.55 (2.83)	15.07 (3.20)	2.56 (0.36, 4.77)	0.023	2.49 (0.35, 4.64)	**0.023**
- 20 weeks	12.73 (3.20)	14.27 (2.15)	1.46 (-0.17, 3.10)	0.079	1.39 (-0.29, 3.07)	0.104
- 24 weeks	13.71 (3.07)	13.48 (1.23)	-0.24 (-1.36, 0.88)	0.676	-0.29 (-1.45, 0.86)	0.621
- 30 weeks	14.48 (3.38)	14.52 (3.19)	-0.01 (-2.28, 2.26)	0.994	-0.04 (-2.23, 2.15)	0.973
e/a RVFW				0.003*		0.004*
- 14 weeks	1.47 (0.41)	1.18 (0.48)	-0.30 (-0.63, 0.03)	0.073	-0.27 (-0.57, 0.03)	0.081
- 20 weeks	1.50 (0.42)	1.21 (0.39)	-0.27 (-0.54, 0.01)	0.056	-0.24 (-0.48, 0.00)	0.053
- 24 weeks	1.31 (0.35)	1.28 (0.36)	-0.03 (-0.28, 0.22)	0.821	0.00 (-0.22, 0.22)	>0.999
- 30 weeks	1.30 (0.38)	1.16 (0.44)	-0.14 (-0.44, 0.17)	0.380	-0.11 (-0.42, 0.20)	0.485

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). a: a wave velocity, A dur: A wave duration, DT: deceleration time, e: e wave velocity, EF: ejection fraction, FS: fractional shortening, H-R: high-risk, IVRT: isovolumetric relaxation time, LVFW: left ventricular free wall, LVOT: left ventricular outflow tract, L-R: low-risk, MV: mitral valve, PE: pre-eclampsia, RV: right ventricle, s: s wave velocity, Sep: septal**,** VTI: velocity time integral.

Appendix B Gestational hypertension secondary cardiovascular variables

Outcome	Normal Mean (SD)	GH Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
LVM				0.678*		0.654*
- 14 weeks	125.0 (25.0)	131.5 (26.3)	6.81 (-11.47, 25.09)	0.465	4.62 (-18.48, 27.72)	0.695
- 20 weeks	126.4 (25.1)	122.0 (10.5)	5.26 (-17.41, 27.94)	0.649	2.58 (-25.85, 31.02)	0.859
- 24 weeks	128.2 (23.7)	138.7 (39.3)	8.30 (-18.06, 34.65)	0.537	6.12 (-25.23, 37.47)	0.702
- 30 weeks	130.8 (25.3)	133.2 (49.1)	0.69 (-32.01, 33.39)	0.967	-1.56 (-38.46, 35.35)	0.934
LVMI				0.673*		0.642*
- 14 weeks	72.4 (12.3)	71.8 (11.4)	-0.52 (-8.58, 7.53)	0.899	-0.97 (-10.31, 8.37)	0.838
- 20 weeks	72.5 (11.9)	66.7 (3.2)	-2.08 (-9.90, 5.74)	0.602	-2.76 (-12.98, 7.47)	0.597
- 24 weeks	72.3 (11.1)	72.9 (14.6)	-0.17 (-10.10, 9.77)	0.973	-0.61 (-12.12, 10.89)	0.917
- 30 weeks	72.4 (12.3)	68.9 (19.9)	-4.20 (-17.57, 9.16)	0.538	-4.68 (-19.20, 9.84)	0.528
VTI				0.154*		0.152*
- 14 weeks	24.09 (3.19)	22.91 (2.02)	-1.11 (-2.65, 0.43)	0.159	-0.95 (-2.61, 0.71)	0.263
- 20 weeks	24.21 (3.38)	22.01 (1.57)	-2.22 (-3.61, -0.83)	0.002	-2.05 (-3.63, -0.46)	**0.011**
- 24 weeks	23.87 (3.01)	21.59 (1.17)	-2.24 (-3.34, -1.14)	<0.001	-2.07 (-3.32, -0.83)	**0.001**
- 30 weeks	22.94 (3.32)	22.32 (1.87)	-0.67 (-2.17, 0.83)	0.383	-0.50 (-2.08, 1.07)	0.533
LVOT				0.194*		0.186*
- 14 weeks	1.99 (0.13)	1.94 (0.11)	-0.05 (-0.13, 0.03)	0.220	-0.08 (-0.18, 0.02)	0.129
- 20 weeks	1.99 (0.14)	1.94 (0.07)	-0.05 (-0.11, 0.02)	0.143	-0.08 (-0.15, -0.00)	**0.044**
- 24 weeks	1.99 (0.13)	1.98 (0.05)	-0.02 (-0.06, 0.03)	0.418	-0.05 (-0.11, 0.01)	0.111
- 30 weeks	2.00 (0.12)	1.94 (0.08)	-0.07 (-0.13, -0.01)	0.028	-0.10 (-0.17, -0.02)	**0.010**
EF Simpson				0.014*		0.013*
- 14 weeks	67.38 (3.67)	65.43 (2.49)	-1.91 (-3.89, 0.06)	0.058	-1.65 (-3.56, 0.25)	0.089
- 20 weeks	68.07 (3.06)	64.73 (2.55)	-3.19 (-5.44, -0.95)	0.005	-2.90 (-5.37, -0.43)	**0.021**
- 24 weeks	65.59 (3.62)	66.14 (2.12)	0.30 (-1.51, 2.10)	0.748	0.55 (-1.20, 2.31)	0.538
- 30 weeks	66.29 (3.48)	63.96 (3.36)	-2.25 (-4.75, 0.26)	0.079	-1.96 (-4.49, 0.57)	0.128

Outcome	Normal Mean (SD)	GH Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
EF M-mode				0.085*		0.087*
- 14 weeks	66.60 (3.63)	70.08 (5.30)	3.39 (-0.19, 6.97)	0.063	3.97 (0.56, 7.39)	**0.022**
- 20 weeks	67.54 (4.60)	67.27 (3.63)	0.14 (-2.68, 2.97)	0.921	0.78 (-2.00, 3.57)	0.582
- 24 weeks	67.07 (3.81)	67.25 (2.51)	0.10 (-1.81, 2.02)	0.916	0.70 (-1.06, 2.46)	0.434
- 30 weeks	65.79 (4.19)	63.73 (4.62)	-2.02 (-5.24, 1.19)	0.217	-1.40 (-4.75, 1.95)	0.413
FS M-mode				0.187*		0.190*
- 14 weeks	36.96 (2.96)	39.65 (4.87)	2.61 (-0.65, 5.88)	0.117	3.04 (-0.01, 6.09)	0.051
- 20 weeks	38.07 (3.36)	37.33 (2.95)	-0.34 (-2.66, 1.98)	0.776	0.10 (-2.23, 2.42)	0.935
- 24 weeks	37.23 (3.00)	37.18 (2.12)	-0.14 (-1.74, 1.45)	0.863	0.30 (-1.12, 1.72)	0.681
- 30 weeks	36.28 (3.05)	38.19 (6.42)	1.90 (-2.36, 6.17)	0.382	2.35 (-1.64, 6.34)	0.249
s Sep				0.064*		0.064*
- 14 weeks	10.03 (1.59)	10.92 (1.43)	0.91 (-0.11, 1.93)	0.079	0.78 (-0.35, 1.91)	0.175
- 20 weeks	10.05 (1.34)	10.28 (0.44)	0.09 (-0.45, 0.62)	0.755	-0.05 (-0.61, 0.52)	0.876
- 24 weeks	10.00 (1.25)	10.02 (1.91)	-0.00 (-1.30, 1.29)	0.995	-0.14 (-1.49, 1.21)	0.842
- 30 weeks	9.64 (1.28)	10.43 (1.75)	0.79 (-0.40, 1.98)	0.193	0.65 (-0.49, 1.79)	0.262
s LVFW				0.011*		0.011*
- 14 weeks	11.98 (2.21)	11.63 (2.18)	-0.38 (-1.90, 1.15)	0.630	-0.66 (-2.24, 0.92)	0.413
- 20 weeks	11.97 (2.18)	10.63 (1.67)	-1.60 (-2.87, -0.33)	0.014	-1.89 (-3.26, -0.52)	**0.007**
- 24 weeks	11.96 (2.36)	11.53 (2.39)	-0.45 (-2.12, 1.22)	0.598	-0.74 (-2.40, 0.92)	0.385
- 30 weeks	11.43 (2.25)	10.47 (2.57)	-1.04 (-2.83, 0.75)	0.254	-1.33 (-3.04, 0.37)	0.126
s RVFW				0.076*		0.072*
- 14 weeks	15.49 (1.95)	16.34 (1.45)	0.87 (-0.20, 1.93)	0.112	0.57 (-0.38, 1.52)	0.239
- 20 weeks	16.24 (2.16)	15.72 (1.14)	-0.52 (-1.45, 0.41)	0.272	-0.83 (-1.59, -0.06)	**0.035**
- 24 weeks	15.56 (1.77)	16.25 (3.00)	0.62 (-1.39, 2.64)	0.543	0.33 (-1.59, 2.24)	0.738
- 30 weeks	15.67 (1.73)	15.40 (2.26)	-0.32 (-1.87, 1.22)	0.681	-0.63 (-2.01, 0.74)	0.368

Outcome	Normal Mean (SD)	GH Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
MV E				0.753*		0.758*
- 14 weeks	85.86 (13.90)	89.99 (13.12)	4.13 (-5.11, 13.36)	0.381	4.75 (-4.51, 14.00)	0.315
- 20 weeks	87.84 (15.24)	86.60 (13.53)	-1.40 (-11.26, 8.46)	0.781	-0.74 (-10.47, 8.99)	0.882
- 24 weeks	82.60 (14.76)	83.92 (8.15)	1.34 (-5.16, 7.84)	0.686	1.97 (-4.94, 8.88)	0.576
- 30 weeks	76.75 (12.23)	79.49 (13.58)	2.32 (-7.08, 11.71)	0.629	2.97 (-6.87, 12.80)	0.555
MV A				0.290*		0.291*
- 14 weeks	49.98 (9.56)	61.66 (13.24)	11.63 (2.66, 20.59)	0.011	11.94 (3.42, 20.45)	**0.006**
- 20 weeks	50.20 (7.80)	66.94 (16.75)	17.41 (6.28, 28.55)	0.002	17.67 (7.04, 28.30)	**0.001**
- 24 weeks	51.18 (8.30)	71.95 (22.28)	20.49 (5.78, 35.20)	0.006	20.80 (6.60, 34.99)	**0.004**
- 30 weeks	52.43 (8.62)	68.20 (16.83)	15.22 (4.00, 26.45)	0.008	15.52 (5.38, 25.66)	**0.003**
MV E/A				0.284*		0.289*
- 14 weeks	1.79 (0.40)	1.50 (0.27)	-0.29 (-0.49, -0.08)	0.006	-0.28 (-0.48, -0.08)	**0.006**
- 20 weeks	1.80 (0.44)	1.37 (0.41)	-0.44 (-0.73, -0.14)	0.004	-0.43 (-0.71, -0.14)	**0.003**
- 24 weeks	1.66 (0.40)	1.25 (0.31)	-0.40 (-0.62, -0.17)	0.001	-0.39 (-0.62, -0.15)	**0.001**
- 30 weeks	1.49 (0.27)	1.21 (0.26)	-0.27 (-0.46, -0.09)	0.004	-0.26 (-0.47, -0.06)	**0.011**
IVRT				0.868*		0.867*
- 14 weeks	92.23 (12.23)	91.94 (14.56)	-0.40 (-10.38, 9.59)	0.938	1.61 (-7.98, 11.20)	0.742
- 20 weeks	90.69 (13.62)	90.79 (13.93)	0.93 (-8.92, 10.78)	0.853	2.98 (-6.19, 12.14)	0.525
- 24 weeks	94.46 (11.85)	97.31 (15.92)	2.77 (-8.07, 13.61)	0.616	4.83 (-5.00, 14.66)	0.336
- 30 weeks	97.84 (11.05)	96.36 (15.82)	-0.72 (-11.89, 10.45)	0.900	1.34 (-10.28, 12.96)	0.821
DT				0.208*		0.205*
- 14 weeks	151.55 (26.46)	144.31 (20.19)	-7.25 (-22.00, 7.50)	0.335	-7.57 (-23.68, 8.54)	0.357
- 20 weeks	149.89 (15.89)	137.86 (20.73)	-10.71 (-25.28, 3.87)	0.150	-10.99 (-26.49, 4.51)	0.165
- 24 weeks	151.78 (19.17)	133.38 (26.56)	-18.94 (-36.97, -0.91)	0.039	-19.27 (-37.88, -0.65)	**0.043**
- 30 weeks	150.05 (19.24)	135.44 (36.36)	-14.76 (-39.05, 9.53)	0.234	-15.08 (-40.56, 10.40)	0.246

Outcome	Normal Mean (SD)	GH Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
A Dur				0.887*		0.888*
- 14 weeks	120.73 (19.38)	117.50 (14.25)	-3.10 (-13.59, 7.39)	0.562	-2.12 (-12.84, 8.60)	0.698
- 20 weeks	116.92 (14.17)	114.43 (10.93)	-1.84 (-9.70, 6.01)	0.645	-0.86 (-8.66, 6.95)	0.830
- 24 weeks	118.90 (17.02)	113.81 (17.73)	-5.61 (-17.98, 6.76)	0.374	-4.61 (-16.62, 7.40)	0.452
- 30 weeks	117.68 (16.79)	114.94 (13.40)	-1.97 (-11.82, 7.88)	0.695	-0.96 (-11.52, 9.59)	0.858
e Sep				0.003*		0.003*
- 14 weeks	14.86 (2.41)	15.68 (3.20)	0.83 (-1.35, 3.00)	0.457	0.50 (-1.84, 2.83)	0.677
- 20 weeks	14.70 (2.67)	14.89 (1.69)	-0.22 (-1.77, 1.32)	0.779	-0.56 (-2.12, 1.00)	0.485
- 24 weeks	14.06 (2.33)	13.35 (3.13)	-0.69 (-2.83, 1.44)	0.525	-1.03 (-3.17, 1.11)	0.345
- 30 weeks	13.12 (2.76)	14.71 (3.10)	1.55 (-0.60, 3.71)	0.158	1.21 (-0.78, 3.19)	0.233
a Sep				0.191*		0.195*
- 14 weeks	8.06 (1.62)	9.15 (2.14)	1.11 (-0.34, 2.57)	0.135	1.22 (-0.17, 2.61)	0.084
- 20 weeks	8.29 (1.54)	8.81 (0.83)	0.51 (-0.17, 1.18)	0.143	0.61 (-0.13, 1.36)	0.107
- 24 weeks	8.63 (1.35)	10.05 (2.70)	1.43 (-0.37, 3.23)	0.120	1.54 (-0.26, 3.34)	0.093
- 30 weeks	9.23 (1.82)	9.41 (1.08)	0.19 (-0.67, 1.05)	0.668	0.31 (-0.63, 1.24)	0.522
e/a Sep				0.021*		0.022*
- 14 weeks	1.91 (0.49)	1.74 (0.27)	-0.18 (-0.39, 0.04)	0.105	-0.24 (-0.46, -0.01)	**0.038**
- 20 weeks	1.84 (0.49)	1.70 (0.17)	-0.18 (-0.37, 0.02)	0.071	-0.24 (-0.44, -0.03)	**0.024**
- 24 weeks	1.67 (0.41)	1.40 (0.46)	-0.26 (-0.58, 0.05)	0.103	-0.32 (-0.65, 0.01)	0.054
- 30 weeks	1.49 (0.43)	1.56 (0.22)	0.07 (-0.11, 0.25)	0.462	0.01 (-0.17, 0.18)	0.932
E/e Sep				0.358*		0.359*
- 14 weeks	5.89 (1.17)	5.95 (1.44)	0.05 (-0.93, 1.04)	0.918	0.27 (-0.75, 1.29)	0.606
- 20 weeks	6.08 (1.16)	5.85 (0.96)	-0.03 (-0.85, 0.80)	0.953	0.20 (-0.61, 1.01)	0.629
- 24 weeks	5.98 (1.11)	6.73 (2.25)	0.74 (-0.76, 2.24)	0.334	0.96 (-0.51, 2.44)	0.201
- 30 weeks	6.09 (1.47)	5.66 (1.56)	-0.44 (-1.53, 0.66)	0.435	-0.20 (-1.17, 0.76)	0.678

Outcome	Normal Mean (SD)	GH Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
e LVFW				0.345*		0.355*
- 14 weeks	18.86 (3.29)	17.45 (2.80)	-1.43 (-3.44, 0.57)	0.161	-1.78 (-4.08, 0.52)	0.130
- 20 weeks	18.56 (3.49)	16.76 (3.04)	-2.02 (-4.28, 0.24)	0.080	-2.35 (-4.20, -0.50)	**0.013**
- 24 weeks	17.64 (3.48)	15.74 (2.04)	-1.88 (-3.48, -0.29)	0.021	-2.23 (-3.64, -0.83)	**0.002**
- 30 weeks	17.02 (2.88)	15.93 (3.05)	-0.95 (-3.08, 1.17)	0.380	-1.31 (-3.02, 0.41)	0.135
a LVFW				0.270*		0.274*
- 14 weeks	8.46 (1.67)	9.15 (1.90)	0.68 (-0.63, 1.99)	0.307	0.77 (-0.49, 2.02)	0.230
- 20 weeks	8.43 (1.44)	7.93 (0.86)	-0.61 (-1.35, 0.13)	0.104	-0.53 (-1.42, 0.37)	0.249
- 24 weeks	8.90 (1.76)	8.41 (1.65)	-0.51 (-1.68, 0.66)	0.396	-0.42 (-1.56, 0.72)	0.470
- 30 weeks	9.10 (1.80)	8.57 (1.04)	-0.46 (-1.29, 0.38)	0.282	-0.37 (-1.22, 0.48)	0.396
e/a LVFW				0.233*		0.232*
- 14 weeks	2.31 (0.59)	1.94 (0.34)	-0.36 (-0.63, -0.10)	0.007	-0.42 (-0.63, -0.22)	**<0.001**
- 20 weeks	2.27 (0.61)	2.11 (0.30)	-0.16 (-0.40, 0.08)	0.201	-0.22 (-0.43, -0.01)	**0.043**
- 24 weeks	2.05 (0.54)	1.95 (0.52)	-0.09 (-0.46, 0.28)	0.629	-0.15 (-0.43, 0.13)	0.281
- 30 weeks	1.95 (0.54)	1.88 (0.43)	-0.08 (-0.39, 0.24)	0.636	-0.14 (-0.37, 0.09)	0.236
E/e LVFW				0.982*		0.977*
- 14 weeks	4.65 (0.94)	5.28 (1.16)	0.63 (-0.16, 1.42)	0.118	0.73 (-0.13, 1.59)	0.095
- 20 weeks	4.81 (0.80)	5.29 (1.21)	0.55 (-0.27, 1.37)	0.187	0.65 (-0.16, 1.45)	0.115
- 24 weeks	4.83 (1.13)	5.43 (1.01)	0.61 (-0.11, 1.33)	0.099	0.71 (0.03, 1.38)	**0.040**
- 30 weeks	4.62 (0.97)	5.28 (1.83)	0.61 (-0.61, 1.83)	0.325	0.72 (-0.38, 1.81)	0.200
e RVFW				0.077*		0.070*
- 14 weeks	17.66 (3.10)	19.88 (3.27)	2.23 (-0.04, 4.50)	0.054	1.46 (-0.54, 3.46)	0.152
- 20 weeks	18.02 (3.03)	19.08 (4.78)	0.50 (-2.95, 3.95)	0.776	-0.29 (-3.54, 2.96)	0.862
- 24 weeks	17.08 (2.91)	17.43 (5.81)	0.22 (-3.65, 4.09)	0.913	-0.56 (-4.22, 3.10)	0.764
- 30 weeks	17.82 (3.76)	17.34 (5.42)	-0.61 (-4.29, 3.07)	0.746	-1.41 (-4.68, 1.86)	0.397

Outcome	Normal Mean (SD)	GH Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
a RVFW				<0.001*		<0.001*
- 14 weeks	12.55 (2.83)	13.91 (2.56)	1.40 (-0.41, 3.22)	0.130	1.95 (0.33, 3.58)	**0.019**
- 20 weeks	12.73 (3.20)	12.95 (2.62)	0.49 (-1.51, 2.49)	0.631	1.05 (-0.93, 3.03)	0.298
- 24 weeks	13.71 (3.07)	17.34 (5.10)	3.62 (0.20, 7.04)	0.038	4.19 (0.71, 7.67)	**0.018**
- 30 weeks	14.48 (3.38)	13.71 (4.10)	-0.82 (-3.65, 2.01)	0.570	-0.23 (-3.14, 2.68)	0.876
e/a RVFW				0.125*		0.130*
- 14 weeks	1.47 (0.41)	1.50 (0.52)	0.02 (-0.33, 0.38)	0.893	-0.10 (-0.40, 0.20)	0.512
- 20 weeks	1.50 (0.42)	1.55 (0.57)	-0.00 (-0.42, 0.41)	0.989	-0.13 (-0.51, 0.25)	0.503
- 24 weeks	1.31 (0.35)	1.11 (0.52)	-0.20 (-0.55, 0.15)	0.265	-0.33 (-0.68, 0.02)	0.065
- 30 weeks	1.30 (0.38)	1.37 (0.52)	0.08 (-0.28, 0.43)	0.671	-0.05 (-0.38, 0.27)	0.743

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). a: a wave velocity, A dur: A wave duration, DT: deceleration time, e: e wave velocity, EF: ejection fraction, FS: fractional shortening, GH: gestational hypertension, H-R: high-risk, IVRT: isovolumetric relaxation time, LVFW: left ventricular free wall, LVOT: left ventricular outflow tract, L-R: low-risk, MV: mitral valve, RV: right ventricle, s: s wave velocity, Sep: septal**,** VTI: velocity time integral.

Appendix C Small for gestational age secondary cardiovascular variables

Outcome	Normal Mean (SD)	SGA Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
LVM				0.378*		0.379*
- 14 weeks	125.0 (25.0)	104.7 (17.9)	-19.64 (-29.45, -9.82)	<0.001	-17.77 (-26.69, -8.86)	**<0.001**
- 20 weeks	126.4 (25.1)	107.7 (18.9)	-22.15 (-32.89, -11.41)	<0.001	-20.34 (-30.52, -10.17)	**<0.001**
- 24 weeks	128.2 (23.7)	111.7 (16.4)	-19.93 (-29.65, -10.22)	<0.001	-18.03 (-26.69, -9.36)	**<0.001**
- 30 weeks	130.8 (25.3)	119.8 (21.2)	-15.49 (-27.23, -3.74)	0.010	-13.68 (-24.34, -3.02)	**0.012**
LVMI				0.248*		0.251*
- 14 weeks	72.4 (12.3)	64.7 (8.6)	-7.37 (-12.15, -2.59)	0.003	-6.48 (-11.07, -1.89)	**0.006**
- 20 weeks	72.5 (11.9)	65.5 (10.6)	-8.47 (-14.18, -2.75)	0.004	-7.63 (-13.28, -1.98)	**0.008**
- 24 weeks	72.3 (11.1)	66.9 (8.3)	-7.00 (-11.84, -2.16)	0.005	-6.11 (-10.68, -1.54)	**0.009**
- 30 weeks	72.4 (12.3)	70.0 (11.1)	-4.13 (-10.13, 1.86)	0.176	-3.31 (-8.99, 2.37)	0.253
VTI				0.283*		0.283*
- 14 weeks	24.09 (3.19)	22.82 (3.30)	-1.35 (-3.00, 0.31)	0.111	-1.39 (-3.10, 0.31)	0.110
- 20 weeks	24.21 (3.38)	23.23 (3.85)	-1.30 (-3.24, 0.63)	0.186	-1.34 (-3.29, 0.61)	0.178
- 24 weeks	23.87 (3.01)	21.96 (3.87)	-2.07 (-3.96, -0.17)	0.033	-2.11 (-4.04, -0.17)	**0.033**
- 30 weeks	22.94 (3.32)	22.38 (2.96)	-0.78 (-2.37, 0.82)	0.340	-0.81 (-2.45, 0.82)	0.329
LVOT				0.511*		0.510*
- 14 weeks	1.99 (0.13)	1.85 (0.16)	-0.14 (-0.21, -0.06)	<0.001	-0.13 (-0.20, -0.06)	**0.001**
- 20 weeks	1.99 (0.14)	1.89 (0.14)	-0.12 (-0.20, -0.05)	0.001	-0.11 (-0.18, -0.04)	**0.001**
- 24 weeks	1.99 (0.13)	1.89 (0.12)	-0.13 (-0.20, -0.06)	<0.001	-0.12 (-0.18, -0.05)	**<0.001**
- 30 weeks	2.00 (0.12)	1.88 (0.14)	-0.15 (-0.22, -0.07)	<0.001	-0.14 (-0.21, -0.07)	**<0.001**
EF Simpson				0.750*		0.748*
- 14 weeks	67.38 (3.67)	66.74 (3.51)	-0.69 (-2.51, 1.13)	0.457	-0.77 (-2.65, 1.10)	0.420
- 20 weeks	68.07 (3.06)	67.85 (3.47)	0.02 (-1.76, 1.80)	0.982	-0.06 (-1.88, 1.76)	0.948
- 24 weeks	65.59 (3.62)	65.86 (2.21)	0.11 (-1.27, 1.48)	0.879	0.04 (-1.29, 1.37)	0.952
- 30 weeks	66.29 (3.48)	65.58 (3.21)	-0.48 (-2.23, 1.28)	0.594	-0.55 (-2.36, 1.27)	0.554

Outcome	Normal Mean (SD)	SGA Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
EF M-mode				0.126*		0.126*
- 14 weeks	66.60 (3.63)	67.04 (2.83)	0.36 (-1.19, 1.90)	0.648	0.35 (-1.24, 1.95)	0.666
- 20 weeks	67.54 (4.60)	65.70 (8.51)	-1.77 (-5.71, 2.16)	0.378	-1.77 (-5.75, 2.22)	0.385
- 24 weeks	67.07 (3.81)	64.90 (4.19)	-2.21 (-4.30, -0.12)	0.038	-2.21 (-4.33, -0.10)	**0.041**
- 30 weeks	65.79 (4.19)	65.34 (3.80)	-0.52 (-2.56, 1.52)	0.615	-0.52 (-2.63, 1.59)	0.628
FS M-mode				0.175*		0.175*
- 14 weeks	36.96 (2.96)	37.04 (2.20)	-0.01 (-1.23, 1.21)	0.987	0.04 (-1.19, 1.28)	0.946
- 20 weeks	38.07 (3.36)	37.54 (3.44)	-0.51 (-2.25, 1.24)	0.570	-0.46 (-2.20, 1.29)	0.606
- 24 weeks	37.23 (3.00)	35.41 (3.38)	-1.89 (-3.57, -0.21)	0.028	-1.84 (-3.55, -0.12)	**0.036**
- 30 weeks	36.28 (3.05)	35.81 (3.01)	-0.60 (-2.19, 0.99)	0.462	-0.54 (-2.17, 1.08)	0.512
s Sep				0.854*		0.841*
- 14 weeks	10.03 (1.59)	9.36 (1.43)	-0.68 (-1.42, 0.07)	0.074	-0.74 (-1.47, -0.02)	**0.045**
- 20 weeks	10.05 (1.34)	9.60 (1.61)	-0.47 (-1.26, 0.32)	0.245	-0.52 (-1.33, 0.29)	0.206
- 24 weeks	10.00 (1.25)	9.56 (1.38)	-0.46 (-1.15, 0.23)	0.191	-0.52 (-1.23, 0.19)	0.153
- 30 weeks	9.64 (1.28)	8.92 (1.19)	-0.72 (-1.34, -0.09)	0.024	-0.79 (-1.42, -0.15)	**0.015**
s LVFW				0.576*		0.563*
- 14 weeks	11.98 (2.21)	12.23 (2.54)	0.14 (-1.10, 1.38)	0.826	0.00 (-1.19, 1.19)	0.997
- 20 weeks	11.97 (2.18)	12.57 (2.45)	0.51 (-0.70, 1.72)	0.409	0.39 (-0.81, 1.59)	0.524
- 24 weeks	11.96 (2.36)	11.82 (2.12)	-0.21 (-1.32, 0.90)	0.706	-0.34 (-1.39, 0.71)	0.522
- 30 weeks	11.43 (2.25)	11.35 (2.33)	-0.22 (-1.41, 0.98)	0.719	-0.35 (-1.46, 0.76)	0.537
s RVFW				0.079*		0.075*
- 14 weeks	15.49 (1.95)	15.11 (1.66)	-0.28 (-1.16, 0.60)	0.537	-0.34 (-1.23, 0.55)	0.448
- 20 weeks	16.24 (2.16)	16.02 (2.18)	-0.23 (-1.34, 0.88)	0.690	-0.29 (-1.34, 0.77)	0.594
- 24 weeks	15.56 (1.77)	15.73 (1.99)	0.06 (-0.92, 1.04)	0.897	0.00 (-0.95, 0.95)	0.996
- 30 weeks	15.67 (1.73)	14.79 (2.05)	-0.97 (-1.97, 0.04)	0.059	**-1.04 (-2.05, -0.03)**	**0.043**

Outcome	Normal Mean (SD)	SGA Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
MV E				0.169*		0.175*
- 14 weeks	85.86 (13.90)	88.17 (16.61)	2.41 (-5.50, 10.31)	0.551	1.54 (-5.50, 8.58)	0.669
- 20 weeks	87.84 (15.24)	86.73 (18.01)	-1.40 (-10.04, 7.24)	0.750	-2.18 (-10.03, 5.67)	0.586
- 24 weeks	82.60 (14.76)	80.68 (16.00)	-1.89 (-9.71, 5.93)	0.636	-2.72 (-9.91, 4.47)	0.459
- 30 weeks	76.75 (12.23)	80.35 (12.69)	3.17 (-3.11, 9.46)	0.323	2.35 (-3.77, 8.46)	0.452
MV A				0.677*		0.688*
- 14 weeks	49.98 (9.56)	48.40 (13.47)	-0.95 (-7.33, 5.43)	0.770	-0.66 (-6.72, 5.41)	0.832
- 20 weeks	50.20 (7.80)	51.88 (13.22)	1.10 (-4.99, 7.20)	0.723	1.34 (-4.49, 7.17)	0.653
- 24 weeks	51.18 (8.30)	50.62 (16.49)	-0.70 (-8.16, 6.77)	0.855	-0.43 (-7.69, 6.83)	0.907
- 30 weeks	52.43 (8.62)	54.85 (13.03)	1.99 (-4.08, 8.07)	0.520	2.22 (-3.54, 7.98)	0.450
MV E/A				0.436*		0.449*
- 14 weeks	1.79 (0.40)	2.00 (0.81)	0.20 (-0.17, 0.57)	0.285	0.17 (-0.17, 0.51)	0.324
- 20 weeks	1.80 (0.44)	1.76 (0.49)	-0.04 (-0.28, 0.19)	0.727	-0.07 (-0.28, 0.15)	0.537
- 24 weeks	1.66 (0.40)	1.74 (0.59)	0.08 (-0.19, 0.35)	0.575	0.05 (-0.21, 0.31)	0.700
- 30 weeks	1.49 (0.27)	1.53 (0.36)	0.03 (-0.13, 0.20)	0.696	0.01 (-0.15, 0.16)	0.922
IVRT				0.708*		0.708*
- 14 weeks	92.23 (12.23)	89.50 (14.71)	-2.42 (-9.54, 4.70)	0.505	-1.55 (-8.27, 5.16)	0.650
- 20 weeks	90.69 (13.62)	90.76 (19.84)	0.12 (-9.26, 9.50)	0.980	0.88 (-8.07, 9.83)	0.847
- 24 weeks	94.46 (11.85)	95.18 (10.43)	0.51 (-4.98, 6.00)	0.857	1.37 (-3.88, 6.62)	0.609
- 30 weeks	97.84 (11.05)	99.66 (13.31)	2.39 (-4.16, 8.93)	0.475	3.26 (-3.31, 9.82)	0.331
DT				0.768*		0.771*
- 14 weeks	151.55 (26.46)	147.24 (19.56)	-4.15 (-14.94, 6.63)	0.450	-4.48 (-15.64, 6.67)	0.431
- 20 weeks	149.89 (15.89)	144.55 (25.48)	-5.00 (-16.91, 6.90)	0.410	-5.28 (-17.38, 6.82)	0.393
- 24 weeks	151.78 (19.17)	142.63 (18.02)	-9.27 (-18.62, 0.07)	0.052	-9.58 (-19.29, 0.12)	0.053
- 30 weeks	150.05 (19.24)	145.18 (21.75)	-4.63 (-15.49, 6.23)	0.403	-4.96 (-16.19, 6.27)	0.387

Outcome	Normal Mean (SD)	SGA Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
A Dur				0.705*		0.700*
- 14 weeks	120.73 (19.38)	115.61 (10.30)	-4.34 (-11.06, 2.37)	0.205	-3.86 (-10.43, 2.71)	0.250
- 20 weeks	116.92 (14.17)	109.92 (14.02)	-7.19 (-14.36, -0.02)	0.049	-6.75 (-13.50, 0.00)	0.050
- 24 weeks	118.90 (17.02)	111.97 (11.28)	-7.69 (-14.31, -1.06)	0.023	-7.20 (-13.82, -0.57)	0.033
- 30 weeks	117.68 (16.79)	111.87 (14.73)	-5.35 (-13.26, 2.56)	0.185	-4.84 (-12.78, 3.11)	0.233
e Sep				0.645*		0.662*
- 14 weeks	14.86 (2.41)	14.90 (3.47)	-0.07 (-1.69, 1.56)	0.936	-0.25 (-1.75, 1.25)	0.741
- 20 weeks	14.70 (2.67)	13.99 (3.13)	-0.66 (-2.17, 0.86)	0.395	-0.82 (-2.26, 0.61)	0.260
- 24 weeks	14.06 (2.33)	13.60 (2.71)	-0.42 (-1.74, 0.90)	0.532	-0.60 (-1.89, 0.69)	0.364
- 30 weeks	13.12 (2.76)	12.35 (2.47)	-0.79 (-2.08, 0.50)	0.229	-0.97 (-2.25, 0.31)	0.137
a Sep				0.271*		0.278*
- 14 weeks	8.06 (1.62)	7.66 (1.08)	-0.36 (-0.98, 0.26)	0.251	-0.27 (-0.90, 0.37)	0.409
- 20 weeks	8.29 (1.54)	8.40 (1.99)	0.04 (-0.92, 1.01)	0.929	0.13 (-0.79, 1.05)	0.787
- 24 weeks	8.63 (1.35)	8.18 (1.28)	-0.48 (-1.15, 0.18)	0.154	-0.39 (-1.00, 0.22)	0.209
- 30 weeks	9.23 (1.82)	8.27 (1.37)	-1.00 (-1.78, -0.22)	0.012	-0.91 (-1.65, -0.16)	**0.017**
e/a Sep				0.276*		0.289*
- 14 weeks	1.91 (0.49)	2.00 (0.63)	0.07 (-0.23, 0.37)	0.642	0.03 (-0.25, 0.31)	0.828
- 20 weeks	1.84 (0.49)	1.74 (0.52)	-0.06 (-0.32, 0.20)	0.639	-0.10 (-0.33, 0.14)	0.411
- 24 weeks	1.67 (0.41)	1.72 (0.53)	0.08 (-0.17, 0.33)	0.536	0.04 (-0.20, 0.28)	0.739
- 30 weeks	1.49 (0.43)	1.53 (0.38)	0.07 (-0.14, 0.27)	0.517	0.03 (-0.16, 0.22)	0.777
E/e Sep				0.613*		0.612*
- 14 weeks	5.89 (1.17)	6.15 (1.62)	0.34 (-0.43, 1.11)	0.387	0.36 (-0.40, 1.12)	0.355
- 20 weeks	6.08 (1.16)	6.45 (1.83)	0.33 (-0.52, 1.17)	0.451	0.34 (-0.51, 1.19)	0.430
- 24 weeks	5.98 (1.11)	6.07 (1.33)	0.07 (-0.58, 0.71)	0.840	0.08 (-0.56, 0.73)	0.795
- 30 weeks	6.09 (1.47)	6.75 (1.72)	0.64 (-0.20, 1.49)	0.137	0.66 (-0.19, 1.52)	0.129

Outcome	Normal Mean (SD)	SGA Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
e LVFW				0.393*		0.389*
- 14 weeks	18.86 (3.29)	17.96 (3.87)	-1.15 (-3.06, 0.77)	0.239	-1.41 (-3.30, 0.49)	0.145
- 20 weeks	18.56 (3.49)	18.30 (3.46)	-0.28 (-2.01, 1.46)	0.754	-0.51 (-2.26, 1.23)	0.567
- 24 weeks	17.64 (3.48)	17.67 (2.57)	-0.05 (-1.47, 1.36)	0.940	-0.30 (-1.72, 1.12)	0.678
- 30 weeks	17.02 (2.88)	17.28 (2.26)	0.30 (-0.94, 1.54)	0.638	0.05 (-1.13, 1.23)	0.932
a LVFW				0.502*		0.510*
- 14 weeks	8.46 (1.67)	8.21 (1.93)	-0.25 (-1.19, 0.69)	0.605	-0.18 (-1.12, 0.77)	0.714
- 20 weeks	8.43 (1.44)	9.20 (3.34)	0.70 (-0.82, 2.22)	0.366	0.76 (-0.76, 2.28)	0.327
- 24 weeks	8.90 (1.76)	8.48 (1.94)	-0.49 (-1.45, 0.48)	0.324	-0.42 (-1.37, 0.54)	0.391
- 30 weeks	9.10 (1.80)	8.93 (1.56)	-0.15 (-0.99, 0.69)	0.723	-0.08 (-0.92, 0.76)	0.847
e/a LVFW				0.199*		0.208*
- 14 weeks	2.31 (0.59)	2.34 (0.77)	-0.00 (-0.37, 0.37)	0.990	-0.05 (-0.41, 0.31)	0.791
- 20 weeks	2.27 (0.61)	2.11 (0.53)	-0.14 (-0.41, 0.14)	0.339	-0.18 (-0.45, 0.09)	0.194
- 24 weeks	2.05 (0.54)	2.17 (0.52)	0.15 (-0.12, 0.41)	0.272	0.10 (-0.15, 0.35)	0.421
- 30 weeks	1.95 (0.54)	2.00 (0.45)	0.05 (-0.19, 0.29)	0.664	0.01 (-0.23, 0.24)	0.947
E/e LVFW				0.128*		0.126*
- 14 weeks	4.65 (0.94)	5.15 (1.61)	0.58 (-0.17, 1.34)	0.132	0.59 (-0.16, 1.34)	0.124
- 20 weeks	4.81 (0.80)	4.90 (1.41)	0.09 (-0.56, 0.73)	0.794	0.09 (-0.57, 0.75)	0.787
- 24 weeks	4.83 (1.13)	4.61 (0.90)	-0.20 (-0.68, 0.28)	0.421	-0.19 (-0.68, 0.30)	0.444
- 30 weeks	4.62 (0.97)	4.72 (0.91)	0.07 (-0.39, 0.54)	0.765	0.07 (-0.40, 0.55)	0.757
e RVFW				0.205*		0.197*
- 14 weeks	17.66 (3.10)	17.08 (3.96)	-0.54 (-2.42, 1.34)	0.573	-0.65 (-2.57, 1.27)	0.507
- 20 weeks	18.02 (3.03)	18.24 (3.00)	0.25 (-1.26, 1.76)	0.747	0.15 (-1.42, 1.72)	0.850
- 24 weeks	17.08 (2.91)	17.23 (3.77)	-0.00 (-1.80, 1.80)	0.999	-0.11 (-1.99, 1.77)	0.912
- 30 weeks	17.82 (3.76)	16.54 (3.47)	-1.43 (-3.25, 0.40)	0.125	-1.54 (-3.48, 0.41)	0.121

Outcome	Normal Mean (SD)	SGA Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
a RVFW				0.124*		0.130*
- 14 weeks	12.55 (2.83)	12.18 (2.78)	-0.44 (-1.86, 0.97)	0.541	-0.21 (-1.63, 1.20)	0.767
- 20 weeks	12.73 (3.20)	13.49 (3.26)	0.61 (-1.05, 2.27)	0.472	0.81 (-0.81, 2.43)	0.329
- 24 weeks	13.71 (3.07)	13.24 (2.93)	-0.55 (-2.05, 0.95)	0.475	-0.33 (-1.74, 1.08)	0.647
- 30 weeks	14.48 (3.38)	13.29 (3.16)	-1.31 (-2.96, 0.35)	0.122	-1.08 (-2.70, 0.54)	0.192
e/a RVFW				0.378*		0.387*
- 14 weeks	1.47 (0.41)	1.50 (0.58)	0.04 (-0.23, 0.31)	0.775	0.01 (-0.26, 0.28)	0.943
- 20 weeks	1.50 (0.42)	1.42 (0.37)	-0.06 (-0.25, 0.14)	0.568	-0.08 (-0.28, 0.12)	0.413
- 24 weeks	1.31 (0.35)	1.40 (0.51)	0.09 (-0.15, 0.33)	0.461	0.06 (-0.18, 0.30)	0.619
- 30 weeks	1.30 (0.38)	1.28 (0.28)	-0.01 (-0.16, 0.15)	0.934	-0.04 (-0.21, 0.13)	0.670

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). a: a wave velocity, A dur: A wave duration, DT: deceleration time, e: e wave velocity, EF: ejection fraction, FS: fractional shortening, H-R: high-risk, IVRT: isovolumetric relaxation time, LVFW: left ventricular free wall, LVOT: left ventricular outflow tract, L-R: low-risk, MV: mitral valve, RV: right ventricle, s: s wave velocity, Sep: septal, SGA: small for gestational age, VTI: velocity time integral.

Appendix D Preterm birth secondary cardiovascular variables

Outcome	Normal Mean (SD)	PTL Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
LVM				0.191*		0.234*
- 14 weeks	125.0 (25.0)	124.9 (12.4)	0.17 (-11.43, 11.76)	0.978	-2.87 (-13.17, 7.44)	0.585
- 20 weeks	126.4 (25.1)	120.7 (26.0)	-6.28 (-29.19, 16.63)	0.591	-10.00 (-38.33, 18.33)	0.489
- 24 weeks	128.2 (23.7)	135.4 (7.5)	6.63 (-1.33, 14.60)	0.103	3.01 (-6.12, 12.15)	0.518
- 30 weeks	130.8 (25.3)	148.2 (13.4)	16.84 (3.56, 30.12)	0.013	13.11 (-2.46, 28.69)	0.099
LVMI				0.180*		0.214*
- 14 weeks	72.4 (12.3)	67.9 (5.9)	-4.37 (-9.95, 1.21)	0.125	-5.52 (-11.32, 0.27)	0.062
- 20 weeks	72.5 (11.9)	64.2 (14.1)	-8.01 (-20.32, 4.30)	0.202	-9.51 (-24.19, 5.17)	0.204
- 24 weeks	72.3 (11.1)	70.7 (3.9)	-1.48 (-5.76, 2.81)	0.500	-2.92 (-8.27, 2.43)	0.284
- 30 weeks	72.4 (12.3)	76.1 (3.4)	3.93 (-1.05, 8.92)	0.122	2.44 (-4.32, 9.20)	0.479
VTI				0.733*		0.701*
- 14 weeks	24.09 (3.19)	21.27 (1.77)	-2.75 (-4.36, -1.14)	0.001	-2.70 (-4.27, -1.12)	**0.001**
- 20 weeks	24.21 (3.38)	22.47 (2.56)	-2.06 (-4.38, 0.26)	0.082	-1.98 (-4.29, 0.33)	0.093
- 24 weeks	23.87 (3.01)	22.12 (5.23)	-1.94 (-6.41, 2.52)	0.394	-1.86 (-6.27, 2.54)	0.407
- 30 weeks	22.94 (3.32)	21.21 (3.67)	-2.02 (-5.19, 1.16)	0.213	-1.93 (-5.03, 1.16)	0.221
LVOT				0.246*		0.397*
- 14 weeks	1.99 (0.13)	2.04 (0.11)	0.06 (-0.04, 0.15)	0.238	0.04 (-0.04, 0.11)	0.314
- 20 weeks	1.99 (0.14)	2.04 (0.12)	0.06 (-0.04, 0.15)	0.228	0.04 (-0.04, 0.12)	0.343
- 24 weeks	1.99 (0.13)	2.06 (0.15)	0.07 (-0.05, 0.18)	0.272	0.05 (-0.05, 0.14)	0.325
- 30 weeks	2.00 (0.12)	2.08 (0.12)	0.08 (-0.01, 0.17)	0.078	0.06 (-0.01, 0.14)	0.111
EF Simpson				0.575*		0.572*
- 14 weeks	67.38 (3.67)	66.73 (3.40)	-0.61 (-3.92, 2.70)	0.717	-0.55 (-3.92, 2.82)	0.750
- 20 weeks	68.07 (3.06)	66.02 (5.00)	-1.87 (-6.62, 2.87)	0.439	-1.79 (-6.76, 3.17)	0.479
- 24 weeks	65.59 (3.62)	65.68 (2.58)	-0.06 (-2.66, 2.54)	0.964	0.02 (-2.85, 2.89)	0.990
- 30 weeks	66.29 (3.48)	67.19 (0.87)	0.99 (-0.26, 2.23)	0.120	1.07 (-0.36, 2.51)	0.142

Outcome	Normal Mean (SD)	PTL Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
EF M-mode				0.838*		0.833*
- 14 weeks	66.60 (3.63)	64.15 (4.07)	-2.54 (-5.89, 0.80)	0.136	-2.42 (-5.83, 0.98)	0.162
- 20 weeks	67.54 (4.60)	64.79 (5.78)	-3.18 (-8.09, 1.73)	0.205	-2.99 (-7.85, 1.87)	0.227
- 24 weeks	67.07 (3.81)	64.88 (3.26)	-2.76 (-5.67, 0.15)	0.063	-2.58 (-5.33, 0.18)	0.067
- 30 weeks	65.79 (4.19)	64.07 (2.85)	-2.16 (-4.81, 0.49)	0.110	-1.96 (-4.56, 0.63)	0.138
FS M-mode				0.719*		0.712*
- 14 weeks	36.96 (2.96)	35.06 (3.05)	-1.97 (-4.50, 0.55)	0.125	-1.98 (-4.54, 0.58)	0.130
- 20 weeks	38.07 (3.36)	35.55 (4.34)	-2.89 (-6.55, 0.78)	0.123	-2.90 (-6.57, 0.78)	0.122
- 24 weeks	37.23 (3.00)	35.56 (2.48)	-2.13 (-4.36, 0.09)	0.060	-2.14 (-4.40, 0.12)	0.063
- 30 weeks	36.28 (3.05)	34.95 (2.06)	-1.70 (-3.62, 0.22)	0.082	-1.70 (-3.62, 0.21)	0.082
s Sep				0.425*		0.415*
- 14 weeks	10.03 (1.59)	10.61 (1.86)	0.60 (-0.92, 2.12)	0.439	0.60 (-0.93, 2.14)	0.442
- 20 weeks	10.05 (1.34)	11.94 (3.03)	1.76 (-0.74, 4.25)	0.168	1.77 (-0.72, 4.27)	0.163
- 24 weeks	10.00 (1.25)	11.19 (2.04)	1.06 (-0.61, 2.73)	0.215	1.07 (-0.58, 2.72)	0.205
- 30 weeks	9.64 (1.28)	10.14 (1.17)	0.40 (-0.60, 1.39)	0.435	0.40 (-0.54, 1.33)	0.403
s LVFW				0.340*		0.334*
- 14 weeks	11.98 (2.21)	12.44 (1.20)	0.43 (-0.67, 1.52)	0.444	0.46 (-0.76, 1.68)	0.461
- 20 weeks	11.97 (2.18)	12.97 (1.93)	0.95 (-0.74, 2.63)	0.272	1.00 (-0.83, 2.82)	0.285
- 24 weeks	11.96 (2.36)	13.07 (0.62)	1.07 (0.27, 1.87)	0.009	1.11 (0.23, 1.99)	**0.014**
- 30 weeks	11.43 (2.25)	12.93 (2.24)	1.39 (-0.55, 3.34)	0.160	1.43 (-0.63, 3.49)	0.173
s RVFW				0.271*		0.294*
- 14 weeks	15.49 (1.95)	14.63 (1.08)	-0.85 (-1.83, 0.14)	0.091	-0.87 (-1.88, 0.13)	0.089
- 20 weeks	16.24 (2.16)	16.16 (2.52)	-0.07 (-2.34, 2.19)	0.950	-0.11 (-2.31, 2.10)	0.925
- 24 weeks	15.56 (1.77)	15.91 (1.82)	0.27 (-1.32, 1.85)	0.742	0.23 (-1.34, 1.80)	0.774
- 30 weeks	15.67 (1.73)	15.38 (1.03)	-0.37 (-1.38, 0.65)	0.479	-0.41 (-1.38, 0.56)	0.406

Outcome	Normal Mean (SD)	PTL Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
MV E				0.104*		0.111*
- 14 weeks	85.86 (13.90)	82.28 (11.36)	-3.58 (-13.20, 6.04)	0.466	-3.32 (-13.34, 6.70)	0.516
- 20 weeks	87.84 (15.24)	81.82 (6.93)	-8.58 (-16.88, -0.28)	0.043	-8.20 (-16.12, -0.27)	**0.043**
- 24 weeks	82.60 (14.76)	92.00 (29.75)	7.15 (-18.48, 32.78)	0.584	7.51 (-18.04, 33.06)	0.564
- 30 weeks	76.75 (12.23)	87.11 (23.36)	7.67 (-12.78, 28.11)	0.462	8.04 (-11.87, 27.96)	0.429
MV A				0.066*		0.070*
- 14 weeks	49.98 (9.56)	53.62 (9.24)	3.58 (-4.10, 11.26)	0.361	3.01 (-3.36, 9.38)	0.355
- 20 weeks	50.20 (7.80)	60.08 (21.64)	8.26 (-9.58, 26.10)	0.364	7.45 (-8.39, 23.29)	0.357
- 24 weeks	51.18 (8.30)	60.69 (21.19)	8.31 (-9.31, 25.93)	0.355	7.55 (-8.46, 23.55)	0.355
- 30 weeks	52.43 (8.62)	63.74 (16.27)	9.83 (-3.54, 23.21)	0.150	9.05 (-2.80, 20.90)	0.135
MV E/A				0.007*		0.007*
- 14 weeks	1.79 (0.40)	1.57 (0.29)	-0.22 (-0.47, 0.03)	0.080	-0.20 (-0.42, 0.03)	0.089
- 20 weeks	1.80 (0.44)	1.53 (0.65)	-0.28 (-0.82, 0.26)	0.310	-0.25 (-0.72, 0.22)	0.304
- 24 weeks	1.66 (0.40)	1.66 (0.82)	-0.00 (-0.70, 0.70)	0.995	0.03 (-0.63, 0.68)	0.931
- 30 weeks	1.49 (0.27)	1.46 (0.55)	-0.05 (-0.50, 0.41)	0.840	-0.01 (-0.40, 0.37)	0.938
IVRT				0.736*		0.725*
- 14 weeks	92.23 (12.23)	90.75 (6.28)	0.01 (-5.79, 5.81)	0.998	-0.15 (-5.62, 5.31)	0.956
- 20 weeks	90.69 (13.62)	88.25 (9.19)	-1.91 (-10.29, 6.46)	0.654	-2.26 (-9.75, 5.23)	0.554
- 24 weeks	94.46 (11.85)	90.25 (17.33)	-3.94 (-18.77, 10.88)	0.602	-4.20 (-18.60, 10.20)	0.568
- 30 weeks	97.84 (11.05)	98.00 (15.83)	1.19 (-12.30, 14.68)	0.863	0.93 (-12.30, 14.15)	0.891
DT				0.956*		0.958*
- 14 weeks	151.55 (26.46)	148.00 (39.19)	-3.38 (-35.98, 29.23)	0.839	-2.97 (-35.99, 30.06)	0.860
- 20 weeks	149.89 (15.89)	135.12 (29.97)	-11.68 (-37.53, 14.16)	0.376	-10.65 (-35.55, 14.26)	0.402
- 24 weeks	151.78 (19.17)	145.88 (29.10)	-3.34 (-26.95, 20.27)	0.781	-2.42 (-25.70, 20.86)	0.838
- 30 weeks	150.05 (19.24)	140.38 (13.25)	-6.70 (-20.04, 6.63)	0.325	-5.77 (-17.01, 5.47)	0.314

Outcome	Normal Mean (SD)	PTL Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
A Dur				0.507*		0.491*
- 14 weeks	120.73 (19.38)	122.10 (17.13)	1.50 (-12.87, 15.88)	0.838	1.11 (-12.42, 14.64)	0.872
- 20 weeks	116.92 (14.17)	106.50 (23.48)	-9.74 (-29.58, 10.10)	0.336	-10.35 (-30.03, 9.33)	0.303
- 24 weeks	118.90 (17.02)	117.00 (27.65)	-1.84 (-24.66, 20.98)	0.874	-2.39 (-24.87, 20.09)	0.835
- 30 weeks	117.68 (16.79)	110.50 (25.24)	-5.80 (-26.44, 14.84)	0.582	-6.39 (-26.35, 13.58)	0.531
e Sep				0.598*		0.592*
- 14 weeks	14.86 (2.41)	16.24 (2.12)	1.39 (-0.39, 3.16)	0.127	1.43 (-0.34, 3.20)	0.113
- 20 weeks	14.70 (2.67)	15.23 (4.24)	0.61 (-2.88, 4.09)	0.734	0.68 (-2.65, 4.00)	0.690
- 24 weeks	14.06 (2.33)	14.78 (3.28)	0.78 (-1.91, 3.46)	0.570	0.84 (-1.68, 3.36)	0.515
- 30 weeks	13.12 (2.76)	12.94 (2.93)	-0.18 (-2.68, 2.32)	0.887	-0.13 (-2.38, 2.13)	0.913
a Sep				0.023*		0.022*
- 14 weeks	8.06 (1.62)	8.81 (1.99)	0.78 (-0.84, 2.40)	0.347	0.71 (-0.65, 2.08)	0.306
- 20 weeks	8.29 (1.54)	9.67 (2.40)	1.25 (-0.67, 3.16)	0.201	1.16 (-0.50, 2.81)	0.170
- 24 weeks	8.63 (1.35)	10.93 (2.63)	2.20 (0.10, 4.30)	0.040	2.12 (0.26, 3.97)	**0.025**
- 30 weeks	9.23 (1.82)	11.51 (2.89)	2.17 (-0.19, 4.54)	0.072	2.09 (-0.05, 4.24)	0.056
e/a Sep				0.002*		0.002*
- 14 weeks	1.91 (0.49)	1.90 (0.37)	-0.01 (-0.33, 0.30)	0.931	0.00 (-0.24, 0.25)	0.979
- 20 weeks	1.84 (0.49)	1.65 (0.53)	-0.15 (-0.57, 0.28)	0.503	-0.12 (-0.48, 0.24)	0.503
- 24 weeks	1.67 (0.41)	1.42 (0.43)	-0.22 (-0.56, 0.12)	0.204	-0.20 (-0.48, 0.08)	0.164
- 30 weeks	1.49 (0.43)	1.20 (0.43)	-0.26 (-0.60, 0.08)	0.137	-0.24 (-0.51, 0.04)	0.087
E/e Sep				0.003*		0.002*
- 14 weeks	5.89 (1.17)	5.10 (0.68)	-0.80 (-1.41, -0.18)	0.011	-0.79 (-1.42, -0.16)	**0.014**
- 20 weeks	6.08 (1.16)	5.65 (1.33)	-0.57 (-1.75, 0.61)	0.343	-0.56 (-1.69, 0.56)	0.324
- 24 weeks	5.98 (1.11)	6.52 (2.74)	0.43 (-1.91, 2.77)	0.721	0.44 (-1.89, 2.77)	0.713
- 30 weeks	6.09 (1.47)	6.81 (1.29)	0.61 (-0.56, 1.77)	0.308	0.62 (-0.51, 1.76)	0.282

Outcome	Normal Mean (SD)	PTL Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
e LVFW				0.535*		0.530*
- 14 weeks	18.86 (3.29)	17.08 (2.56)	-1.81 (-3.99, 0.37)	0.104	-1.60 (-3.23, 0.04)	0.056
- 20 weeks	18.56 (3.49)	16.80 (2.00)	-1.31 (-3.08, 0.46)	0.146	-1.05 (-2.20, 0.09)	0.072
- 24 weeks	17.64 (3.48)	16.19 (1.54)	-1.07 (-2.54, 0.41)	0.156	-0.82 (-1.88, 0.25)	0.132
- 30 weeks	17.02 (2.88)	15.87 (1.27)	-0.64 (-1.93, 0.64)	0.326	-0.40 (-1.44, 0.65)	0.459
a LVFW				<0.001*		<0.001*
- 14 weeks	8.46 (1.67)	8.17 (1.17)	-0.30 (-1.31, 0.71)	0.563	-0.31 (-1.29, 0.68)	0.545
- 20 weeks	8.43 (1.44)	9.40 (1.14)	0.84 (-0.16, 1.83)	0.099	0.82 (-0.16, 1.81)	0.100
- 24 weeks	8.90 (1.76)	10.65 (0.92)	1.63 (0.68, 2.58)	0.001	1.62 (0.60, 2.65)	**0.002**
- 30 weeks	9.10 (1.80)	10.27 (1.01)	1.13 (0.09, 2.17)	0.033	1.13 (0.03, 2.22)	**0.043**
e/a LVFW				0.053*		0.056*
- 14 weeks	2.31 (0.59)	2.15 (0.54)	-0.16 (-0.61, 0.29)	0.494	-0.13 (-0.49, 0.23)	0.478
- 20 weeks	2.27 (0.61)	1.82 (0.42)	-0.34 (-0.71, 0.03)	0.074	-0.31 (-0.60, -0.01)	**0.041**
- 24 weeks	2.05 (0.54)	1.52 (0.12)	-0.43 (-0.65, -0.20)	<0.001	-0.40 (-0.64, -0.16)	**0.001**
- 30 weeks	1.95 (0.54)	1.55 (0.17)	-0.31 (-0.56, -0.06)	0.014	-0.28 (-0.57, 0.00)	0.052
E/e LVFW				0.148*		0.081*
- 14 weeks	4.65 (0.94)	4.92 (1.00)	0.27 (-0.56, 1.10)	0.523	0.22 (-0.49, 0.94)	0.540
- 20 weeks	4.81 (0.80)	4.90 (0.39)	-0.12 (-0.61, 0.37)	0.641	-0.19 (-0.65, 0.28)	0.434
- 24 weeks	4.83 (1.13)	5.70 (1.75)	0.69 (-0.85, 2.23)	0.380	0.63 (-0.98, 2.24)	0.445
- 30 weeks	4.62 (0.97)	5.44 (1.09)	0.59 (-0.46, 1.65)	0.270	0.53 (-0.69, 1.75)	0.394
e RVFW				0.570*		0.576*
- 14 weeks	17.66 (3.10)	17.14 (4.60)	-0.51 (-4.22, 3.20)	0.787	-0.53 (-4.13, 3.06)	0.771
- 20 weeks	18.02 (3.03)	17.81 (3.05)	0.49 (-2.24, 3.23)	0.724	0.45 (-2.20, 3.10)	0.738
- 24 weeks	17.08 (2.91)	16.24 (3.70)	-0.30 (-3.68, 3.09)	0.864	-0.35 (-3.85, 3.15)	0.845
- 30 weeks	17.82 (3.76)	16.17 (3.59)	-1.11 (-4.42, 2.21)	0.513	-1.18 (-4.38, 2.02)	0.470

Outcome	Normal Mean (SD)	PTL Mean (SD)	Unadjusted Difference in Means (95% C.I)	Unadjusted p value	Adjusted Difference in Means (95% C.I)	Adjusted p value
a RVFW				0.137*		0.128*
- 14 weeks	12.55 (2.83)	12.39 (3.96)	-0.11 (-3.32, 3.10)	0.946	-0.20 (-2.93, 2.52)	0.885
- 20 weeks	12.73 (3.20)	14.78 (5.00)	1.50 (-2.59, 5.59)	0.473	1.40 (-2.16, 4.95)	0.441
- 24 weeks	13.71 (3.07)	16.46 (6.97)	2.28 (-3.47, 8.02)	0.438	2.20 (-3.14, 7.53)	0.420
- 30 weeks	14.48 (3.38)	16.10 (3.37)	1.10 (-1.80, 4.00)	0.458	1.04 (-1.53, 3.61)	0.428
e/a RVFW				0.688*		0.654*
- 14 weeks	1.47 (0.41)	1.54 (0.71)	0.06 (-0.51, 0.63)	0.831	0.06 (-0.48, 0.61)	0.822
- 20 weeks	1.50 (0.42)	1.29 (0.40)	-0.04 (-0.45, 0.37)	0.863	-0.05 (-0.41, 0.32)	0.803
- 24 weeks	1.31 (0.35)	1.12 (0.55)	-0.04 (-0.56, 0.48)	0.885	-0.05 (-0.55, 0.45)	0.844
- 30 weeks	1.30 (0.38)	1.05 (0.32)	-0.10 (-0.47, 0.27)	0.608	-0.11 (-0.44, 0.21)	0.501

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). a: a wave velocity, A dur: A wave duration, DT: deceleration time, e: e wave velocity, EF: ejection fraction, FS: fractional shortening, H-R: high-risk, IVRT: isovolumetric relaxation time, LVFW: left ventricular free wall, LVOT: left ventricular outflow tract, L-R: low-risk, MV: mitral valve, PTL: preterm birth, RV: right ventricle, s: s wave velocity, Sep: septal, VTI: velocity time integral.

Appendix E Pre-eclampsia secondary cardiovascular outcomes with gestation

Outcome (Time)	Normal: Mean (SD)	Normal: Unadj. Diff vs T1 (95% C.I)	Norm: unadj. p value	Normal: Adj. Diff vs T1 (95% C.I)	Norm: Adj. p value	PE: Mean (SD)	PE: Unadj. Diff vs T1(95% C.I)	PE: Unadj. p value	PE: Adj. Diff vs T1(95% C.I)	PE: p value
LVM - 14wks	125.0 (25.0)		.		.	122.8 (33.5)		0.950*		0.955*
- 20wks	126.4 (25.1)	3.6 (-0.1, 7.2)	0.058	3.6 (-0.1, 7.3)	0.053	128.4 (33.9)	5.6 (-4.9, 16.0)	0.295	5.6 (-4.9, 16.0)	0.295
- 24wks	128.2 (23.7)	5.4 (1.3, 9.5)	0.009	5.4 (1.3, 9.5)	0.009	129.8 (34.0)	7.0 (0.5, 13.5)	0.035	7.0 (0.5, 13.5)	0.035
- 30wks	130.8 (25.3)	7.8 (3.1, 12.9)	0.001	8.1 (3.2, 13.0)	**0.001**	132.8 (29.5)	10.0 (4.9, 15.1)	0.000	10.0 (4.9, 15.1)	**0.000**
LVMI - 14wks	72.4 (12.3)		.		.	71.8 (15.8)		0.906*		0.914*
- 20wks	72.5 (11.9)	0.9 (-1.2, 3.0)	0.403	0.9 (-1.1, 3.0)	0.376	73.9 (15.5)	2.1 (-3.3, 7.5)	0.443	2.1 (-3.3, 7.5)	0.443
- 24wks	72.3 (11.1)	0.8 (-1.4, 3.0)	0.487	0.8 (-1.4, 3.0)	0.482	73.7 (16.0)	1.9 (-1.8, 5.5)	0.317	1.9 (-1.8, 5.5)	0.317
- 30wks	72.4 (12.3)	0.8 (-1.8, 3.5)	0.542	0.9 (-1.8, 3.6)	0.518	74.3 (12.1)	2.4 (-1.3, 6.2)	0.204	2.4 (-1.3, 6.2)	0.204
VTI - 14wks	24.09 (3.19)		.		.	22.17 (3.08)		0.927*		0.926*
- 20wks	24.21 (3.38)	0.27 (-0.42, 0.95)	0.445	0.26 (-0.42, 0.94)	0.452	22.63 (3.09)	0.46 (-0.97, 1.90)	0.527	0.46 (-0.97, 1.90)	0.527
- 24wks	23.87 (3.01)	-0.20 (-1.08, 0.69)	0.665	-0.20 (-1.08, 0.69)	0.661	22.50 (2.53)	0.33 (-1.02, 1.68)	0.633	0.33 (-1.02, 1.68)	0.633
- 30wks	22.94 (3.32)	-1.03 (-1.82, -0.24)	0.011	-1.04 (-1.82, -0.25)	0.010	21.62 (2.69)	-0.55 (-2.65, 1.56)	0.609	-0.55 (-2.65, 1.56)	0.609
LVOT - 14wks	1.99 (0.13)		.		.	1.91 (0.21)		0.045*		0.046*
- 20wks	1.99 (0.14)	0.01 (-0.01, 0.03)	0.326	0.01 (-0.01, 0.03)	0.304	1.91 (0.20)	0.00 (-0.06, 0.06)	0.989	0.00 (-0.06, 0.06)	0.989
- 24wks	1.99 (0.13)	0.01 (-0.00, 0.03)	0.091	0.01 (-0.00, 0.03)	**0.088**	1.95 (0.20)	0.04 (0.02, 0.07)	0.002	0.04 (0.02, 0.07)	**0.002**
- 30wks	2.00 (0.12)	0.02 (0.00, 0.04)	0.015	0.02 (0.01, 0.04)	**0.013**	1.96 (0.20)	0.05 (0.02, 0.09)	0.002	0.05 (0.02, 0.09)	**0.002**
EF Simp - 14wks	67.38 (3.67)		.		.	65.24 (2.65)		0.036*		0.035*
- 20wks	68.07 (3.06)	0.54 (-0.57, 1.66)	0.340	0.53 (-0.59, 1.65)	0.354	66.21 (3.84)	1.23 (-0.62, 3.08)	0.193	1.21 (-0.65, 3.07)	0.201
- 24wks	65.59 (3.62)	-1.59 (-2.66, -0.53)	0.003	-1.61 (-2.68, -0.55)	0.003	65.31 (3.10)	0.33 (-1.03, 1.68)	0.637	0.31 (-1.04, 1.66)	0.653
- 30wks	66.29 (3.48)	-1.14 (-2.27, -0.02)	0.045	-1.18 (-2.30, -0.05)	0.041	66.43 (3.70)	1.44 (-0.32, 3.21)	0.109	1.43 (-0.35, 3.20)	0.115
EF M-mode - 14wks	66.60 (3.63)		.		.	65.88 (3.31)		0.042*		0.041*
- 20wks	67.54 (4.60)	0.80 (-0.36, 1.96)	0.175	0.79 (-0.37, 1.95)	0.181	66.25 (2.60)	0.37 (-1.39, 2.12)	0.682	0.37 (-1.39, 2.12)	0.682
- 24wks	67.07 (3.81)	0.46 (-0.71, 1.64)	0.439	0.45 (-0.72, 1.62)	0.451	65.53 (3.23)	-0.36 (-1.53, 0.82)	0.552	-0.36 (-1.53, 0.82)	0.552
- 30wks	65.79 (4.19)	-0.93 (-2.03, 0.16)	0.094	-0.97 (-2.06, 0.12)	0.080	67.13 (3.19)	1.25 (-1.28, 3.78)	0.334	1.25 (-1.28, 3.78)	0.334

Outcome (Time)	Normal: Mean (SD)	Normal: Unadj. Diff vs T1 (95% C.I)	Norm: unadj. p value	Normal: Adj. Diff vs T1 (95% C.I)	Norm: Adj. p value	PE: Mean (SD)	PE: Unadj. Diff vs T1 (95% C.I)	PE: Unadj. p value	PE: Adj. Diff vs T1 (95% C.I)	PE: p value
FS M-mode - 14wks	36.96 (2.96)		.		.	36.19 (2.27)		0.011*		0.010*
- 20wks	38.07 (3.36)	1.03 (0.23, 1.84)	0.012	1.04 (0.23, 1.84)	**0.011**	36.58 (2.03)	0.39 (-0.98, 1.76)	0.577	0.39 (-0.98, 1.76)	0.577
- 24wks	37.23 (3.00)	0.29 (-0.65, 1.23)	0.549	0.28 (-0.66, 1.22)	0.556	36.04 (2.30)	-0.15 (-1.06, 0.77)	0.751	-0.15 (-1.06, 0.77)	0.751
- 30wks	36.28 (3.05)	-0.75 (-1.57, 0.07)	0.072	-0.76 (-1.57, 0.05)	0.064	37.31 (2.57)	1.12 (-0.82, 3.07)	0.258	1.12 (-0.82, 3.07)	0.258
SEP_s - 14wks	10.03 (1.59)		.		.	9.44 (1.32)		0.046*		0.044*
- 20wks	10.05 (1.34)	0.06 (-0.38, 0.50)	0.782	0.05 (-0.39, 0.49)	0.815	9.38 (1.28)	-0.06 (-0.71, 0.59)	0.860	-0.06 (-0.71, 0.59)	0.860
- 24wks	10.00 (1.25)	0.01 (-0.41, 0.44)	0.950	0.01 (-0.41, 0.44)	0.949	9.17 (1.74)	-0.28 (-1.27, 0.72)	0.586	-0.28 (-1.27, 0.72)	0.586
- 30wks	9.64 (1.28)	-0.37 (-0.76, 0.01)	0.059	-0.37 (-0.75, 0.02)	0.060	8.39 (1.32)	-1.05 (-1.33, -0.78)	0.000	-1.05 (-1.33, -0.78)	**0.000**
LVFW_s - 14wks	11.98 (2.21)		.		.	10.06 (0.71)		0.928*		0.926*
- 20wks	11.97 (2.18)	-0.01 (-0.47, 0.46)	0.977	-0.01 (-0.48, 0.45)	0.955	10.27 (1.25)	0.21 (-0.58, 1.00)	0.602	0.21 (-0.58, 1.00)	0.602
- 24wks	11.96 (2.36)	-0.03 (-0.49, 0.43)	0.898	-0.03 (-0.49, 0.43)	0.900	10.36 (1.97)	0.30 (-0.77, 1.37)	0.584	0.30 (-0.77, 1.37)	0.584
- 30wks	11.43 (2.25)	-0.49 (-1.11, 0.12)	0.115	-0.49 (-1.11, 0.12)	0.118	9.62 (1.86)	-0.44 (-1.56, 0.68)	0.438	-0.44 (-1.56, 0.68)	0.438
RV_s - 14wks	15.49 (1.95)		.		.	14.83 (3.08)		0.458*		0.461*
- 20wks	16.24 (2.16)	0.73 (0.22, 1.25)	0.005	0.73 (0.22, 1.24)	0.005	14.67 (1.88)	-0.16 (-1.22, 0.90)	0.765	-0.16 (-1.22, 0.90)	0.765
- 24wks	15.56 (1.77)	0.15 (-0.32, 0.62)	0.531	0.15 (-0.32, 0.62)	0.522	13.89 (1.19)	-0.94 (-2.51, 0.63)	0.242	-0.94 (-2.51, 0.63)	0.242
- 30wks	15.67 (1.73)	0.25 (-0.25, 0.75)	0.330	0.26 (-0.24, 0.76)	0.315	14.81 (2.58)	-0.02 (-1.27, 1.23)	0.976	-0.02 (-1.27, 1.23)	0.976
MV_E - 14wks	85.86 (13.90)		.		.	82.32 (7.71)		0.371*		0.373*
- 20wks	87.84 (15.24)	2.27 (-1.04, 5.59)	0.179	2.26 (-1.04, 5.57)	0.180	80.07 (12.18)	-2.26 (-8.69, 4.18)	0.492	-2.26 (-8.69, 4.18)	0.492
- 24wks	82.60 (14.76)	-3.28 (-6.36, -0.20)	0.037	-3.28 (-6.37, -0.19)	0.037	79.20 (11.17)	-3.12 (-8.93, 2.68)	0.292	-3.12 (-8.93, 2.68)	0.292
- 30wks	76.75 (12.23)	-8.68 (-11.74, -5.62)	0.000	-8.69 (-11.76, -5.62)	**0.000**	75.34 (6.48)	-6.98 (-11.95, -2.01)	0.006	-6.98 (-11.95, -2.01)	**0.006**
MV_A - 14wks	49.98 (9.56)		.		.	52.93 (9.60)		0.005*		0.005*
- 20wks	50.20 (7.80)	0.86 (-1.33, 3.04)	0.442	0.90 (-1.27, 3.08)	0.416	49.20 (10.59)	-3.73 (-8.79, 1.33)	0.149	-3.73 (-8.79, 1.33)	0.149
- 24wks	51.18 (8.30)	1.42 (-0.78, 3.61)	0.205	1.42 (-0.77, 3.62)	0.204	52.93 (11.24)	0.00 (-5.00, 5.01)	0.999	0.00 (-5.00, 5.01)	0.999
- 30wks	52.43 (8.62)	2.94 (0.67, 5.20)	0.011	2.96 (0.69, 5.22)	0.010	49.35 (8.88)	-3.57 (-7.66, 0.52)	0.087	-3.57 (-7.66, 0.52)	0.087

Outcome (Time)	Normal: Mean (SD)	Normal: Unadj. Diff vs T1 (95% C.I)	Norm: unadj. p value	Normal: Adj. Diff vs T1 (95% C.I)	Norm: Adj. p value	PE: Mean (SD)	PE: Unadj. Diff vs T1 (95% C.I)	PE: Unadj. p value	PE: Adj. Diff vs T1 (95% C.I)	PE: p value
MV_EA - 14wks	1.79 (0.40)		.		.	1.61 (0.35)		0.063*		0.063*
- 20wks	1.80 (0.44)	0.00 (-0.09, 0.09)	0.990	-0.00 (-0.09, 0.09)	0.986	1.68 (0.32)	0.07 (-0.11, 0.25)	0.440	0.07 (-0.11, 0.25)	0.440
- 24wks	1.66 (0.40)	-0.14 (-0.22, -0.06)	0.001	-0.14 (-0.22, -0.06)	0.001	1.54 (0.33)	-0.07 (-0.21, 0.07)	0.348	-0.07 (-0.21, 0.07)	0.348
- 30wks	1.49 (0.27)	-0.30 (-0.38, -0.23)	0.000	-0.30 (-0.38, -0.23)	0.000	1.56 (0.22)	-0.05 (-0.22, 0.12)	0.557	-0.05 (-0.22, 0.12)	0.557
IVRT - 14wks	92.23 (12.23)		.		.	92.75 (16.66)		0.028*		0.030*
- 20wks	90.69 (13.62)	-1.83 (-5.53, 1.87)	0.332	-1.79 (-5.49, 1.91)	0.342	98.94 (9.36)	6.19 (-0.93, 13.30)	0.088	6.19 (-0.93, 13.30)	0.088
- 24wks	94.46 (11.85)	2.21 (-1.29, 5.70)	0.215	2.16 (-1.33, 5.65)	0.225	95.19 (13.21)	2.44 (-4.64, 9.52)	0.500	2.44 (-4.64, 9.52)	0.500
- 30wks	97.84 (11.05)	4.80 (1.33, 8.27)	0.007	4.74 (1.27, 8.20)	**0.007**	99.25 (15.69)	6.50 (-3.23, 16.23)	0.191	6.50 (-3.23, 16.23)	0.191
DT - 14wks	151.55 (26.46)		.		.	141.88 (18.79)		0.478*		0.481*
- 20wks	149.89 (15.89)	-1.62 (-7.48, 4.23)	0.587	-1.72 (-7.61, 4.17)	0.567	138.94 (17.95)	-2.94 (-12.07, 6.20)	0.528	-2.94 (-12.07, 6.20)	0.528
- 24wks	151.78 (19.17)	0.79 (-4.76, 6.34)	0.780	0.80 (-4.72, 6.31)	0.777	151.00 (24.18)	9.12 (-2.73, 20.98)	0.131	9.12 (-2.73, 20.98)	0.131
- 30wks	150.05 (19.24)	-1.35 (-8.36, 5.66)	0.706	-1.35 (-8.34, 5.65)	0.706	152.88 (21.84)	11.00 (-6.44, 28.44)	0.216	11.00 (-6.44, 28.44)	0.216
A_DUR - 14wks	120.73 (19.38)		.		.	117.00 (17.97)		0.323*		0.322*
- 20wks	116.92 (14.17)	-3.77 (-7.88, 0.35)	0.073	-3.75 (-7.85, 0.34)	0.072	118.88 (16.12)	1.88 (-5.91, 9.66)	0.637	1.88 (-5.91, 9.66)	0.637
- 24wks	118.90 (17.02)	-1.20 (-5.62, 3.23)	0.596	-1.20 (-5.61, 3.21)	0.594	121.69 (9.11)	4.69 (-4.95, 14.33)	0.341	4.69 (-4.95, 14.33)	0.341
- 30wks	117.68 (16.79)	-3.68 (-8.75, 1.38)	0.154	-3.68 (-8.73, 1.37)	0.153	124.31 (7.95)	7.31 (-3.75, 18.37)	0.195	7.31 (-3.75, 18.37)	0.195
SEP_e - 14wks	14.86 (2.41)		.		.	13.44 (2.56)		0.743*		0.733*
- 20wks	14.70 (2.67)	-0.19 (-0.81, 0.43)	0.545	-0.20 (-0.82, 0.42)	0.529	13.18 (1.86)	-0.26 (-1.37, 0.85)	0.650	-0.26 (-1.37, 0.85)	0.650
- 24wks	14.06 (2.33)	-0.82 (-1.45, -0.18)	0.012	-0.81 (-1.45, -0.18)	**0.012**	12.89 (2.92)	-0.55 (-1.48, 0.38)	0.245	-0.55 (-1.48, 0.38)	0.245
- 30wks	13.12 (2.76)	-1.70 (-2.34, -1.05)	0.000	-1.69 (-2.33, -1.05)	**0.000**	11.12 (2.49)	-2.32 (-3.56, -1.07)	0.000	-2.32 (-3.56, -1.07)	**0.000**
SEP_a - 14wks	8.06 (1.62)		.		.	8.69 (1.27)		0.010*		0.010*
- 20wks	8.29 (1.54)	0.28 (-0.09, 0.64)	0.136	0.28 (-0.08, 0.65)	0.132	7.95 (0.96)	-0.74 (-1.47, -0.01)	0.048	-0.74 (-1.47, -0.01)	**0.048**
- 24wks	8.63 (1.35)	0.59 (0.19, 0.98)	0.004	0.58 (0.18, 0.98)	**0.004**	9.24 (1.36)	0.55 (-0.33, 1.42)	0.220	0.55 (-0.33, 1.42)	0.220
- 30wks	9.23 (1.82)	1.19 (0.69, 1.69)	0.000	1.18 (0.68, 1.68)	**0.000**	8.83 (1.50)	0.14 (-0.45, 0.72)	0.650	0.14 (-0.45, 0.72)	0.650

Outcome (Time)	Normal: Mean (SD)	Normal: Unadj. Diff vs T1 (95% C.I)	Norm: unadj. p value	Normal: Adj. Diff vs T1 (95% C.I)	Norm: Adj. p value	PE: Mean (SD)	PE: Unadj. Diff vs T1 (95% C.I)	PE: Unadj. p value	PE: Adj. Diff vs T1 (95% C.I)	PE: p value
SEP_ea - 14wks	1.91 (0.49)		.		.	1.58 (0.44)		0.284*		0.279*
- 20wks	1.84 (0.49)	-0.09 (-0.19, 0.01)	0.071	-0.09 (-0.20, 0.01)	0.067	1.68 (0.32)	0.10 (-0.07, 0.26)	0.258	0.10 (-0.07, 0.26)	0.258
- 24wks	1.67 (0.41)	-0.25 (-0.35, -0.14)	0.000	-0.25 (-0.35, -0.14)	**0.000**	1.43 (0.40)	-0.15 (-0.32, 0.02)	0.076	-0.15 (-0.32, 0.02)	0.076
- 30wks	1.49 (0.43)	-0.43 (-0.55, -0.31)	0.000	-0.43 (-0.55, -0.30)	**0.000**	1.29 (0.35)	-0.29 (-0.50, -0.08)	0.006	-0.29 (-0.50, -0.08)	**0.006**
SEP_Ee - 14wks	5.89 (1.17)		.		.	6.26 (0.91)		0.256*		0.245*
- 20wks	6.08 (1.16)	0.22 (-0.08, 0.51)	0.149	0.22 (-0.07, 0.51)	0.143	6.12 (0.91)	-0.13 (-0.81, 0.54)	0.696	-0.13 (-0.81, 0.54)	0.696
- 24wks	5.98 (1.11)	0.10 (-0.19, 0.38)	0.503	0.09 (-0.19, 0.38)	0.519	6.35 (1.31)	0.10 (-0.51, 0.70)	0.757	0.10 (-0.51, 0.70)	0.757
- 30wks	6.09 (1.47)	0.20 (-0.21, 0.60)	0.336	0.19 (-0.21, 0.59)	0.351	7.09 (1.64)	0.83 (-0.03, 1.68)	0.058	0.83 (-0.03, 1.68)	0.058
LVFW_e - 14wks	18.86 (3.29)		.		.	16.91 (3.50)		0.570*		0.587*
- 20wks	18.56 (3.49)	-0.41 (-1.03, 0.21)	0.196	-0.42 (-1.04, 0.20)	0.181	16.00 (2.41)	-0.91 (-2.18, 0.36)	0.162	-0.91 (-2.18, 0.36)	0.162
- 24wks	17.64 (3.48)	-1.26 (-1.97, -0.56)	0.000	-1.26 (-1.97, -0.56)	**0.000**	15.72 (2.96)	-1.20 (-1.98, -0.41)	0.003	-1.20 (-1.98, -0.41)	**0.003**
- 30wks	17.02 (2.88)	-2.01 (-2.75, -1.26)	0.000	-2.01 (-2.75, -1.26)	**0.000**	15.04 (3.32)	-1.87 (-3.54, -0.19)	0.029	-1.87 (-3.54, -0.19)	**0.029**
LVFW_a - 14wks	8.46 (1.67)		.		.	8.34 (1.07)		0.564*		0.574*
- 20wks	8.43 (1.44)	-0.01 (-0.46, 0.45)	0.976	-0.00 (-0.46, 0.45)	0.984	8.05 (0.84)	-0.29 (-1.11, 0.52)	0.482	-0.29 (-1.11, 0.52)	0.482
- 24wks	8.90 (1.76)	0.45 (-0.02, 0.92)	0.058	0.45 (-0.02, 0.91)	0.060	8.77 (1.27)	0.43 (-0.20, 1.06)	0.184	0.43 (-0.20, 1.06)	0.184
- 30wks	9.10 (1.80)	0.56 (0.02, 1.11)	0.044	0.55 (0.01, 1.10)	**0.047**	8.26 (1.66)	-0.08 (-0.81, 0.64)	0.823	-0.08 (-0.81, 0.64)	0.823
LVFW_ea - 14wks	2.31 (0.59)		.		.	2.08 (0.63)		0.344*		0.350*
- 20wks	2.27 (0.61)	-0.05 (-0.18, 0.07)	0.391	-0.06 (-0.18, 0.07)	0.375	2.01 (0.39)	-0.07 (-0.28, 0.14)	0.511	-0.07 (-0.28, 0.14)	0.511
- 24wks	2.05 (0.54)	-0.27 (-0.39, -0.15)	0.000	-0.27 (-0.39, -0.15)	**0.000**	1.85 (0.55)	-0.23 (-0.39, -0.08)	0.003	-0.23 (-0.39, -0.08)	**0.003**
- 30wks	1.95 (0.54)	-0.35 (-0.50, -0.20)	0.000	-0.35 (-0.50, -0.20)	**0.000**	1.89 (0.62)	-0.19 (-0.30, -0.08)	0.001	-0.19 (-0.30, -0.08)	**0.001**
LVFW_Ee - 14wks	4.65 (0.94)		.		.	5.03 (1.06)		0.757*		0.749*
- 20wks	4.81 (0.80)	0.19 (0.01, 0.37)	0.043	0.19 (0.01, 0.38)	**0.036**	5.09 (1.07)	0.06 (-0.42, 0.54)	0.803	0.06 (-0.42, 0.54)	0.803
- 24wks	4.83 (1.13)	0.18 (-0.06, 0.43)	0.148	0.18 (-0.06, 0.43)	0.149	5.19 (1.26)	0.17 (-0.15, 0.49)	0.301	0.17 (-0.15, 0.49)	0.301
- 30wks	4.62 (0.97)	0.02 (-0.22, 0.26)	0.870	0.02 (-0.22, 0.26)	0.864	5.21 (1.15)	0.18 (-0.29, 0.65)	0.448	0.18 (-0.29, 0.65)	0.448

Outcome (Time)	Normal: Mean (SD)	Normal: Unadj. Diff vs T1 (95% C.I)	Norm: unadj. p value	Normal: Adj. Diff vs T1 (95% C.I)	Norm: Adj. p value	PE: Mean (SD)	PE: Unadj. Diff vs T1 (95% C.I)	PE: Unadj. p value	PE: Adj. Diff vs T1 (95% C.I)	PE: p value
RV_e - 14wks	17.66 (3.10)		.		.	16.69 (4.96)		0.449*		0.437*
- 20wks	18.02 (3.03)	0.32 (-0.41, 1.05)	0.387	0.32 (-0.41, 1.05)	0.388	16.91 (4.70)	0.23 (-1.06, 1.52)	0.729	0.23 (-1.06, 1.52)	0.729
- 24wks	17.08 (2.91)	-0.43 (-1.24, 0.37)	0.290	-0.43 (-1.23, 0.38)	0.300	17.10 (4.24)	0.41 (-1.68, 2.50)	0.700	0.41 (-1.68, 2.50)	0.700
- 30wks	17.82 (3.76)	0.30 (-0.67, 1.27)	0.544	0.33 (-0.64, 1.29)	0.508	15.94 (4.40)	-0.75 (-2.55, 1.05)	0.417	-0.75 (-2.55, 1.05)	0.417
RV_a - 14wks	12.55 (2.83)		.		.	15.07 (3.20)		0.019*		0.021*
- 20wks	12.73 (3.20)	0.31 (-0.45, 1.07)	0.429	0.31 (-0.46, 1.08)	0.429	14.27 (2.15)	-0.79 (-2.41, 0.82)	0.336	-0.79 (-2.41, 0.82)	0.336
- 24wks	13.71 (3.07)	1.21 (0.51, 1.91)	0.001	1.20 (0.49, 1.90)	**0.001**	13.48 (1.23)	-1.59 (-3.42, 0.24)	0.089	-1.59 (-3.42, 0.24)	0.089
- 30wks	14.48 (3.38)	2.02 (1.13, 2.91)	0.000	1.99 (1.09, 2.88)	**0.000**	14.52 (3.19)	-0.55 (-2.87, 1.78)	0.644	-0.55 (-2.87, 1.78)	0.644
RV_ea - 14wks	1.47 (0.41)		.		.	1.18 (0.48)		0.003*		0.004*
- 20wks	1.50 (0.42)	0.00 (-0.07, 0.08)	0.927	0.00 (-0.07, 0.08)	0.909	1.21 (0.39)	0.03 (-0.15, 0.22)	0.718	0.03 (-0.15, 0.22)	0.718
- 24wks	1.31 (0.35)	-0.17 (-0.25, -0.08)	0.000	-0.16 (-0.25, -0.08)	**0.000**	1.28 (0.36)	0.10 (-0.07, 0.28)	0.245	0.10 (-0.07, 0.28)	0.245
- 30wks	1.30 (0.38)	-0.18 (-0.29, -0.07)	0.001	-0.18 (-0.28, -0.07)	**0.001**	1.16 (0.44)	-0.02 (-0.26, 0.23)	0.885	-0.02 (-0.26, 0.23)	0.885

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). a: a wave velocity, A dur: A wave duration, DT: deceleration time, e: e wave velocity, EF: ejection fraction, FS: fractional shortening, H-R: high-risk, IVRT: isovolumetric relaxation time, LVFW: left ventricular free wall, LVOT: left ventricular outflow tract, L-R: low-risk, MV: mitral valve, PE: pre-eclampsia, RV: right ventricle, s: s wave velocity, Sep: septal, Simp: Simpson's biplane method, VTI: velocity time integral.

Appendix F Gestational hypertension secondary cardiovascular outcomes with gestation

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	GH Mean (SD)	GH Unadj. Diff vs T1 (95% C.I)	GH Unadj p value	GH Adj Diff vs T1 (95% C.I)	GH Adj p value
LVM - 14wks	125.0 (25.0)		.		.	131.5 (26.3)		0.678*		0.654*
- 20wks	126.4 (25.1)	3.6 (-0.1, 7.2)	0.058	3.6 (-0.1, 7.3)	0.053	122.0 (10.5)	1.9 (-11.4, 15.2)	0.783	1.5 (-11.8, 14.7)	0.828
- 24wks	128.2 (23.7)	5.4 (1.3, 9.5)	0.009	5.4 (1.3, 9.5)	**0.009**	138.3 (39.3)	6.8 (-6.8, 20.3)	0.330	6.8 (-6.8, 20.3)	0.330
- 30wks	130.8 (25.3)	7.8 (3.1, 12.9)	0.001	8.1 (3.2, 13.0)	**0.001**	133.2 (49.1)	1.7 (-22.8, 26.2)	0.890	1.7 (-22.8, 26.2)	0.890
LVMI - 14wks	72.4 (12.3)		.		.	71.8 (11.4)		0.673*		0.642*
- 20wks	72.5 (11.9)	0.9 (-1.2, 3.0)	0.403	0.9 (-1.1, 3.0)	0.376	66.7 (3.2)	-0.7 (-7.9, 6.4)	0.843	-0.9 (-8.0, 6.2)	0.804
- 24wks	72.3 (11.1)	0.8 (-1.4, 3.0)	0.487	0.8 (-1.4, 3.0)	0.482	72.9 (14.6)	1.1 (-6.0, 8.2)	0.763	1.1 (-6.0, 8.2)	0.763
- 30wks	72.4 (12.3)	0.8 (-1.8, 3.5)	0.542	0.9 (-1.8, 3.6)	0.518	68.9 (19.9)	-2.9 (-15.9, 10.1)	0.662	-2.9 (-15.9, 10.1)	0.662
VTI - 14wks	24.09 (3.19)		.		.	22.91 (2.02)		0.154*		0.152*
- 20wks	24.21 (3.38)	0.26 (-0.42, 0.95)	0.450	0.26 (-0.42, 0.94)	0.452	22.01 (1.57)	-0.85 (-2.64, 0.94)	0.354	-0.84 (-2.63, 0.95)	0.359
- 24wks	23.87 (3.01)	-0.20 (-1.08, 0.69)	0.665	-0.20 (-1.08, 0.69)	**0.660**	21.59 (1.17)	-1.33 (-2.48, -0.17)	0.025	-1.33 (-2.48, -0.17)	**0.025**
- 30wks	22.94 (3.32)	-1.03 (-1.82, -0.24)	0.011	-1.04 (-1.83, -0.25)	**0.010**	22.32 (1.87)	-0.59 (-1.77, 0.59)	0.325	-0.59 (-1.77, 0.59)	0.325
LVOT - 14wks	1.99 (0.13)		.		.	1.94 (0.11)		0.194*		0.186*
- 20wks	1.99 (0.14)	0.01 (-0.01, 0.03)	0.337	0.01 (-0.01, 0.03)	0.313	1.94 (0.07)	0.01 (-0.04, 0.06)	0.686	0.01 (-0.04, 0.06)	0.704
- 24wks	1.99 (0.13)	0.01 (-0.00, 0.03)	0.097	0.01 (-0.00, 0.03)	0.094	1.98 (0.05)	0.04 (-0.02, 0.11)	0.180	0.04 (-0.02, 0.11)	0.180
- 30wks	2.00 (0.12)	0.02 (0.00, 0.04)	0.016	0.02 (0.00, 0.04)	**0.013**	1.94 (0.08)	0.00 (-0.04, 0.05)	0.879	0.00 (-0.04, 0.05)	0.879
EF Simp - 14wks	67.38 (3.67)		.		.	65.43 (2.49)		0.014*		0.013*
- 20wks	68.07 (3.06)	0.56 (-0.56, 1.68)	0.325	0.55 (-0.57, 1.67)	0.339	64.73 (2.55)	-0.72 (-3.92, 2.49)	0.661	-0.70 (-3.97, 2.57)	0.676
- 24wks	65.59 (3.62)	-1.62 (-2.68, -0.55)	0.003	-1.63 (-2.70, -0.56)	**0.003**	66.14 (2.12)	0.59 (-1.21, 2.40)	0.520	0.58 (-1.25, 2.40)	0.537
- 30wks	66.29 (3.48)	-1.14 (-2.26, -0.01)	0.048	-1.16 (-2.29, -0.03)	**0.044**	63.96 (3.36)	-1.47 (-4.80, 1.86)	0.387	-1.47 (-4.80, 1.86)	0.387
EF M-mode - 14wks	66.60 (3.63)		.		.	70.08 (5.30)		0.085*		0.087*
- 20wks	67.54 (4.60)	0.81 (-0.35, 1.97)	0.170	0.80 (-0.36, 1.96)	0.176	67.27 (3.63)	-2.43 (-6.38, 1.51)	0.227	-2.39 (-6.32, 1.54)	0.233
- 24wks	67.07 (3.81)	0.46 (-0.71, 1.63)	0.439	0.45 (-0.72, 1.61)	**0.453**	67.25 (2.51)	-2.83 (-5.37, -0.29)	0.029	-2.83 (-5.37, -0.29)	**0.029**
- 30wks	65.79 (4.19)	-0.93 (-2.02, 0.17)	0.098	-0.97 (-2.06, 0.12)	**0.082**	63.73 (4.62)	-6.34 (-11.41, -1.28)	0.014	-6.34 (-11.41, -1.28)	**0.014**

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	GH Mean (SD)	GH Unadj. Diff vs T1 (95% C.I)	GH Unadj p value	GH Adj Diff vs T1 (95% C.I)	GH Adj p value
FS M-mode - 14wks	36.96 (2.96)		.		.	39.65 (4.87)		0.187*		0.190*
- 20wks	38.07 (3.36)	1.03 (0.23, 1.84)	0.012	1.04 (0.24, 1.85)	0.011	37.33 (2.95)	-1.92 (-5.53, 1.69)	0.298	-1.90 (-5.51, 1.71)	0.302
- 24wks	37.23 (3.00)	0.29 (-0.65, 1.23)	0.549	0.28 (-0.66, 1.22)	0.562	37.18 (2.12)	-2.47 (-4.74, -0.19)	0.034	-2.47 (-4.74, -0.19)	**0.034**
- 30wks	36.28 (3.05)	-0.75 (-1.57, 0.07)	0.072	-0.77 (-1.58, 0.04)	0.061	38.19 (6.42)	-1.46 (-3.97, 1.05)	0.253	-1.46 (-3.97, 1.05)	0.253
SEP_s - 14wks	10.03 (1.59)		.		.	10.92 (1.43)		0.064*		0.064*
- 20wks	10.05 (1.34)	0.06 (-0.38, 0.50)	0.799	0.05 (-0.39, 0.49)	0.818	10.28 (0.44)	-0.77 (-1.58, 0.04)	0.061	-0.77 (-1.57, 0.02)	0.055
- 24wks	10.00 (1.25)	0.01 (-0.41, 0.43)	0.967	0.01 (-0.41, 0.43)	0.958	10.02 (1.91)	-0.91 (-2.19, 0.37)	0.165	-0.91 (-2.19, 0.37)	0.165
- 30wks	9.64 (1.28)	-0.37 (-0.76, 0.01)	0.058	-0.36 (-0.75, 0.02)	0.064	10.43 (1.75)	-0.50 (-1.97, 0.98)	0.510	-0.50 (-1.97, 0.98)	0.510
LVFW_s - 14wks	11.98 (2.21)		.		.	11.63 (2.18)		0.011*		0.011*
- 20wks	11.97 (2.18)	-0.01 (-0.47, 0.46)	0.977	-0.01 (-0.48, 0.45)	0.965	10.63 (1.67)	-1.23 (-2.07, -0.39)	0.004	-1.24 (-2.08, -0.40)	**0.004**
- 24wks	11.96 (2.36)	-0.03 (-0.49, 0.43)	0.898	-0.03 (-0.49, 0.43)	0.911	11.53 (2.39)	-0.10 (-1.62, 1.42)	0.894	-0.10 (-1.62, 1.42)	0.894
- 30wks	11.43 (2.25)	-0.49 (-1.11, 0.12)	0.115	-0.48 (-1.10, 0.13)	0.124	10.47 (2.57)	-1.16 (-3.22, 0.90)	0.270	-1.16 (-3.22, 0.90)	0.270
RV_s - 14wks	15.49 (1.95)		.		.	16.34 (1.45)		0.076*		0.072*
- 20wks	16.24 (2.16)	0.73 (0.22, 1.25)	0.005	0.73 (0.22, 1.24)	0.005	15.72 (1.14)	-0.65 (-1.88, 0.58)	0.299	-0.67 (-1.89, 0.56)	0.286
- 24wks	15.56 (1.77)	0.15 (-0.32, 0.62)	0.542	0.15 (-0.32, 0.62)	0.530	16.25 (3.00)	-0.09 (-1.93, 1.74)	0.919	-0.09 (-1.93, 1.74)	0.919
- 30wks	15.67 (1.73)	0.24 (-0.25, 0.74)	0.336	0.26 (-0.24, 0.76)	0.312	15.40 (2.26)	-0.94 (-2.24, 0.35)	0.152	-0.94 (-2.24, 0.35)	0.152
MV_E - 14wks	85.86 (13.90)		.		.	89.99 (13.12)		0.753*		0.758*
- 20wks	87.84 (15.24)	2.27 (-1.04, 5.59)	0.179	2.25 (-1.05, 5.56)	0.182	86.60 (13.53)	-3.26 (-12.71, 6.20)	0.500	-3.23 (-12.69, 6.23)	0.503
- 24wks	82.60 (14.76)	-3.28 (-6.36, -0.20)	0.037	-3.29 (-6.38, -0.20)	0.037	83.92 (8.15)	-6.07 (-14.17, 2.04)	0.143	-6.07 (-14.17, 2.04)	0.143
- 30wks	76.75 (12.23)	-8.68 (-11.74, -5.63)	0.000	-8.71 (-11.79, -5.64)	0.000	79.49 (13.58)	-10.49 (-20.40, -0.59)	0.038	-10.49 (-20.40, -0.59)	0.038
MV_A - 14wks	49.98 (9.56)		.		.	61.66 (13.24)		0.290*		0.291*
- 20wks	50.20 (7.80)	0.86 (-1.32, 3.04)	0.439	0.91 (-1.27, 3.08)	0.414	66.94 (16.75)	6.65 (0.42, 12.88)	0.036	6.64 (0.43, 12.85)	**0.036**
- 24wks	51.18 (8.30)	1.42 (-0.77, 3.62)	0.204	1.42 (-0.77, 3.62)	0.204	71.95 (22.28)	10.28 (0.05, 20.52)	0.049	10.28 (0.05, 20.52)	**0.049**
- 30wks	52.43 (8.62)	2.94 (0.68, 5.21)	0.011	2.96 (0.69, 5.22)	0.010	68.20 (16.83)	6.54 (-3.13, 16.21)	0.185	6.54 (-3.13, 16.21)	0.185

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% CI)	Normal Unadj p value	Normal Adj Diff vs T1 (95% CI)	Normal Adj p value	GH Mean (SD)	GH Unadj. Diff vs T1 (95% CI)	GH Unadj p value	GH Adj Diff vs T1 (95% CI)	GH Adj p value
MV_EA - 14wks	1.79 (0.40)		.		.	1.50 (0.27)		0.284*		0.289*
- 20wks	1.80 (0.44)	0.00 (-0.09, 0.09)	0.985	-0.00 (-0.09, 0.09)	0.990	1.37 (0.41)	-0.15 (-0.31, 0.01)	0.062	-0.15 (-0.31, 0.01)	0.063
- 24wks	1.66 (0.40)	-0.14 (-0.22, -0.06)	0.001	-0.14 (-0.22, -0.06)	**0.001**	1.25 (0.31)	-0.25 (-0.40, -0.11)	0.001	-0.25 (-0.40, -0.11)	**0.001**
- 30wks	1.49 (0.27)	-0.30 (-0.38, -0.23)	0.000	-0.30 (-0.38, -0.23)	**0.000**	1.21 (0.26)	-0.29 (-0.55, -0.03)	0.027	-0.29 (-0.55, -0.03)	**0.027**
IVRT - 14wks	92.23 (12.23)		.		.	91.94 (14.56)		0.868*		0.867*
- 20wks	90.69 (13.62)	-1.83 (-5.53, 1.87)	0.333	-1.77 (-5.47, 1.93)	0.348	90.79 (13.93)	-0.50 (-7.30, 6.30)	0.886	-0.41 (-7.18, 6.36)	0.905
- 24wks	94.46 (11.85)	2.21 (-1.28, 5.70)	0.215	2.16 (-1.33, 5.65)	0.225	97.31 (15.92)	5.38 (-2.74, 13.49)	0.194	5.38 (-2.74, 13.49)	0.194
- 30wks	97.84 (11.05)	4.81 (1.34, 8.28)	0.007	4.76 (1.29, 8.22)	**0.007**	96.36 (15.82)	4.49 (-8.81, 17.80)	0.508	4.48 (-8.85, 17.82)	0.510
DT - 14wks	151.55 (26.46)		.		.	144.31 (20.19)		0.208*		0.205*
- 20wks	149.89 (15.89)	-1.63 (-7.48, 4.22)	0.585	-1.67 (-7.56, 4.23)	0.579	137.86 (20.73)	-5.09 (-20.97, 10.80)	0.530	-5.09 (-20.94, 10.77)	0.529
- 24wks	151.78 (19.17)	0.75 (-4.80, 6.31)	0.790	0.76 (-4.76, 6.28)	0.787	133.38 (26.56)	-10.94 (-27.48, 5.60)	0.195	-10.94 (-27.48, 5.60)	0.195
- 30wks	150.05 (19.24)	-1.37 (-8.37, 5.64)	0.703	-1.36 (-8.38, 5.65)	0.703	135.44 (36.36)	-8.88 (-28.81, 11.06)	0.383	-8.88 (-28.81, 11.06)	0.383
A_DUR - 14wks	120.73 (19.38)		.		.	117.50 (14.25)		0.887*		0.888*
- 20wks	116.92 (14.17)	-3.76 (-7.88, 0.35)	0.073	-3.74 (-7.84, 0.36)	0.074	114.43 (10.93)	-2.51 (-7.97, 2.95)	0.368	-2.47 (-7.96, 3.02)	0.377
- 24wks	118.90 (17.02)	-1.18 (-5.60, 3.25)	0.603	-1.20 (-5.62, 3.22)	0.594	113.81 (17.73)	-3.69 (-12.05, 4.67)	0.387	-3.69 (-12.05, 4.67)	0.387
- 30wks	117.68 (16.79)	-3.69 (-8.76, 1.37)	0.153	-3.72 (-8.77, 1.33)	0.149	114.94 (13.40)	-2.56 (-11.08, 5.96)	0.556	-2.56 (-11.08, 5.96)	0.556
SEP_e - 14wks	14.86 (2.41)		.		.	15.68 (3.20)		0.003*		0.003*
- 20wks	14.70 (2.67)	-0.19 (-0.81, 0.43)	0.551	-0.19 (-0.81, 0.43)	0.542	14.89 (1.69)	-1.24 (-3.30, 0.82)	0.240	-1.24 (-3.30, 0.81)	0.235
- 24wks	14.06 (2.33)	-0.82 (-1.45, -0.18)	0.012	-0.81 (-1.44, -0.17)	**0.012**	13.35 (3.13)	-2.34 (-4.19, -0.48)	0.013	**-2.34 (-4.19, -0.48)**	**0.013**
- 30wks	13.12 (2.76)	-1.70 (-2.35, -1.05)	0.000	-1.68 (-2.33, -1.04)	**0.000**	14.71 (3.10)	-0.97 (-3.63, 1.68)	0.473	-0.97 (-3.63, 1.68)	0.473
SEP_a - 14wks	8.06 (1.62)		.		.	9.15 (2.14)		0.191*		0.195*
- 20wks	8.29 (1.54)	0.27 (-0.09, 0.64)	0.143	0.28 (-0.09, 0.65)	0.135	8.81 (0.83)	-0.33 (-1.88, 1.22)	0.673	-0.33 (-1.88, 1.22)	0.677
- 24wks	8.63 (1.35)	0.59 (0.19, 0.98)	0.004	0.58 (0.18, 0.98)	**0.004**	10.05 (2.70)	0.90 (-1.67, 3.47)	0.492	0.90 (-1.67, 3.47)	0.492
- 30wks	9.23 (1.82)	1.19 (0.69, 1.69)	0.000	1.18 (0.68, 1.68)	**0.000**	9.41 (1.08)	0.26 (-1.51, 2.04)	0.772	0.26 (-1.51, 2.04)	0.772

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% CI)	Norm Unadj p value	Norm Adj Diff vs T1 (95% CI)	Norm Adj p value	GH Mean (SD)	GH Unadj. Diff vs T1 (95% CI)	GH Unadj p value	GH Adj Diff vs T1 (95% CI)	GH Adj p value
SEP_ea - 14wks	1.91 (0.49)		.		.	1.74 (0.27)		0.021*		0.022*
- 20wks	1.84 (0.49)	-0.09 (-0.19, 0.01)	0.072	-0.09 (-0.19, 0.01)	0.069	1.70 (0.17)	-0.10 (-0.30, 0.10)	0.346	-0.10 (-0.30, 0.10)	0.341
- 24wks	1.67 (0.41)	-0.25 (-0.35, -0.14)	0.000	-0.25 (-0.35, -0.14)	**0.000**	1.40 (0.46)	-0.33 (-0.61, -0.06)	0.019	-0.33 (-0.61, -0.06)	**0.019**
- 30wks	1.49 (0.43)	-0.43 (-0.55, -0.31)	0.000	-0.43 (-0.55, -0.30)	**0.000**	1.56 (0.22)	-0.18 (-0.38, 0.01)	0.068	-0.18 (-0.38, 0.01)	0.068
SEP_Ee - 14wks	5.89 (1.17)		.		.	5.95 (1.44)		0.358*		0.359*
- 20wks	6.08 (1.16)	0.22 (-0.08, 0.51)	0.152	0.21 (-0.08, 0.51)	0.156	5.85 (0.96)	0.14 (-0.66, 0.94)	0.732	0.15 (-0.65, 0.94)	0.720
- 24wks	5.98 (1.11)	0.10 (-0.19, 0.38)	0.508	0.09 (-0.20, 0.38)	0.537	6.73 (2.25)	0.78 (-0.44, 2.01)	0.209	0.78 (-0.44, 2.01)	0.209
- 30wks	6.09 (1.47)	0.20 (-0.21, 0.60)	0.338	0.18 (-0.22, 0.58)	0.372	5.66 (1.56)	-0.29 (-1.67, 1.09)	0.682	-0.29 (-1.67, 1.09)	0.682
LVFW_e - 14wks	18.86 (3.29)		.		.	17.45 (2.80)		0.345*		0.355*
- 20wks	18.56 (3.49)	-0.41 (-1.02, 0.21)	0.200	-0.42 (-1.03, 0.20)	0.186	16.76 (3.04)	-1.00 (-3.51, 1.52)	0.438	-0.99 (-3.50, 1.52)	0.439
- 24wks	17.64 (3.48)	-1.26 (-1.97, -0.56)	0.000	-1.26 (-1.96, -0.55)	**0.000**	15.74 (2.04)	-1.71 (-3.79, 0.36)	0.105	-1.71 (-3.79, 0.36)	0.105
- 30wks	17.02 (2.88)	-2.00 (-2.75, -1.26)	0.000	-1.99 (-2.74, -1.25)	**0.000**	15.93 (3.05)	-1.53 (-3.95, 0.90)	0.218	-1.53 (-3.95, 0.90)	0.218
LVFW_a - 14wks	8.46 (1.67)		.		.	9.15 (1.90)		0.270*		0.274*
- 20wks	8.43 (1.44)	-0.01 (-0.46, 0.44)	0.975	-0.00 (-0.45, 0.45)	0.994	7.93 (0.86)	-1.30 (-2.67, 0.07)	0.063	-1.30 (-2.68, 0.08)	0.066
- 24wks	8.90 (1.76)	0.45 (-0.02, 0.92)	0.058	0.45 (-0.02, 0.91)	0.060	8.41 (1.65)	-0.74 (-2.07, 0.59)	0.274	-0.74 (-2.07, 0.59)	0.274
- 30wks	9.10 (1.80)	0.56 (0.02, 1.11)	0.043	0.56 (0.02, 1.11)	**0.044**	8.57 (1.04)	-0.57 (-1.84, 0.69)	0.373	-0.57 (-1.84, 0.69)	0.373
LVFW_ea - 14wks	2.31 (0.59)		.		.	1.94 (0.34)		0.233*		0.232*
- 20wks	2.27 (0.61)	-0.05 (-0.18, 0.07)	0.394	-0.06 (-0.18, 0.07)	0.375	2.11 (0.30)	0.15 (-0.03, 0.34)	0.109	0.15 (-0.04, 0.34)	0.111
- 24wks	2.05 (0.54)	-0.27 (-0.39, -0.15)	0.000	-0.27 (-0.39, -0.15)	**0.000**	1.95 (0.52)	0.00 (-0.29, 0.30)	0.986	0.00 (-0.29, 0.30)	0.986
- 30wks	1.95 (0.54)	-0.35 (-0.50, -0.20)	0.000	-0.35 (-0.50, -0.20)	**0.000**	1.88 (0.43)	-0.06 (-0.31, 0.18)	0.612	-0.06 (-0.31, 0.18)	0.612
LVFW_Ee - 14wks	4.65 (0.94)		.		.	5.28 (1.16)		0.982*		0.977*
- 20wks	4.81 (0.80)	0.19 (0.00, 0.37)	0.046	0.19 (0.01, 0.37)	**0.039**	5.29 (1.21)	0.11 (-0.52, 0.73)	0.736	0.11 (-0.52, 0.73)	0.736
- 24wks	4.83 (1.13)	0.18 (-0.07, 0.42)	0.152	0.18 (-0.07, 0.42)	0.158	5.43 (1.01)	0.16 (-0.74, 1.05)	0.733	0.16 (-0.74, 1.05)	0.733
- 30wks	4.62 (0.97)	0.02 (-0.23, 0.26)	0.888	0.01 (-0.23, 0.26)	0.917	5.28 (1.83)	-0.00 (-1.23, 1.22)	0.998	-0.00 (-1.23, 1.22)	0.998
RV_e - 14wks	17.66 (3.10)		.		.	19.88 (3.27)		0.077*		0.070*
- 20wks	18.02 (3.03)	0.32 (-0.40, 1.05)	0.383	0.32 (-0.40, 1.05)	0.381	19.08 (4.78)	-1.40 (-4.30, 1.50)	0.342	-1.43 (-4.31, 1.46)	0.333
- 24wks	17.08 (2.91)	-0.44 (-1.25, 0.36)	0.281	-0.43 (-1.24, 0.37)	0.294	17.43 (5.81)	-2.45 (-4.97, 0.06)	0.055	-2.45 (-4.97, 0.06)	0.055
- 30wks	17.82 (3.76)	0.29 (-0.68, 1.26)	0.555	0.33 (-0.64, 1.30)	0.505	17.34 (5.42)	-2.55 (-4.65, -0.44)	0.018	-2.55 (-4.65, -0.44)	0.018

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Norm Unadj p value	Norm Adj Diff vs T1 (95% C.I)	Norm Adj p value	GH Mean (SD)	GH Unadj. Diff vs T1 (95% C.I)	GH Unadj p value	GH Adj Diff vs T1 (95% C.I)	GH Adj p value
RV_a - 14wks	12.55 (2.83)		.		.	13.91 (2.56)		0.000*		0.000*
- 20wks	12.73 (3.20)	0.31 (-0.45, 1.07)	0.428	0.31 (-0.46, 1.08)	0.424	12.95 (2.62)	-0.60 (-2.87, 1.67)	0.603	-0.59 (-2.86, 1.68)	0.609
- 24wks	13.71 (3.07)	1.21 (0.51, 1.91)	0.001	1.20 (0.49, 1.90)	**0.001**	17.34 (5.10)	3.43 (-0.25, 7.11)	0.068	3.43 (-0.25, 7.11)	0.068
- 30wks	14.48 (3.38)	2.02 (1.13, 2.91)	0.000	1.99 (1.10, 2.88)	**0.000**	13.71 (4.10)	-0.20 (-3.14, 2.75)	0.896	-0.20 (-3.14, 2.75)	0.896
RV_ea - 14wks	1.47 (0.41)		.		.	1.50 (0.52)		0.125*		0.130*
- 20wks	1.50 (0.42)	0.00 (-0.07, 0.08)	0.913	0.01 (-0.07, 0.08)	0.895	1.55 (0.57)	-0.02 (-0.49, 0.44)	0.922	-0.02 (-0.49, 0.44)	0.916
- 24wks	1.31 (0.35)	-0.17 (-0.25, -0.08)	0.000	-0.16 (-0.25, -0.08)	**0.000**	1.11 (0.52)	-0.39 (-0.66, -0.12)	0.004	-0.39 (-0.66, -0.12)	**0.004**
- 30wks	1.30 (0.38)	-0.18 (-0.29, -0.07)	0.001	-0.18 (-0.28, -0.07)	**0.001**	1.37 (0.52)	-0.13 (-0.44, 0.18)	0.418	-0.13 (-0.44, 0.18)	0.418

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). a: a wave velocity, A dur: A wave duration, DT: deceleration time, e: e wave velocity, EF: ejection fraction, FS: fractional shortening, GH: gestational hypertension, H-R: high-risk, IVRT: isovolumetric relaxation time, LVFW: left ventricular free wall, LVOT: left ventricular outflow tract, L-R: low-risk, MV: mitral valve, RV: right ventricle, s: s wave velocity, Sep: septal, Simp: Simpson's biplane method, T1: first trimester, VTI: velocity time integral.

Appendix G SGA secondary cardiovascular outcomes with gestation

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	SGA Mean (SD)	SGA Unadj. Diff vs T1 (95% C.I)	SGA Unadj p value	SGA Adj Diff vs T1 (95% C.I)	SGA Adj p value
LVM - 14wks	125.0 (25.0)		.		.	104.70 (17.91)		0.378*		0.379*
- 20wks	126.4 (25.1)	3.6 (-0.1, 7.2)	0.058	3.6 (-0.1, 7.3)	0.053	107.67 (18.90)	0.96 (-5.29, 7.21)	0.763	0.99 (-5.26, 7.24)	0.757
- 24wks	128.2 (23.7)	5.4 (1.3, 9.5)	0.009	5.4 (1.3, 9.5)	**0.009**	111.73 (16.36)	5.02 (0.32, 9.73)	0.036	5.05 (0.37, 9.73)	**0.034**
- 30wks	130.8 (25.3)	7.8 (3.1, 12.9)	0.001	8.1 (3.2, 13.0)	**0.001**	119.83 (21.19)	12.06 (6.13, 18.00)	0.000	12.07 (6.14, 18.01)	**0.000**
LVMI - 14wks	72.4 (12.3)		.		.	64.71 (8.62)		0.248*		0.251*
- 20wks	72.5 (11.9)	0.9 (-1.2, 3.0)	0.403	0.9 (-1.1, 3.0)	0.376	65.53 (10.58)	-0.24 (-4.07, 3.59)	0.902	-0.24 (-4.07, 3.58)	0.902
- 24wks	72.3 (11.1)	0.8 (-1.4, 3.0)	0.487	0.8 (-1.4, 3.0)	0.482	66.90 (8.34)	1.13 (-1.74, 3.99)	0.440	1.13 (-1.73, 3.98)	0.439
- 30wks	72.4 (12.3)	0.8 (-1.8, 3.5)	0.542	0.9 (-1.8, 3.6)	0.518	70.01 (11.12)	4.03 (0.34, 7.72)	0.032	4.00 (0.32, 7.68)	**0.033**
VTI - 14wks	24.09 (3.19)		.		.	22.82 (3.30)		0.283*		0.283*
- 20wks	24.21 (3.38)	0.27 (-0.42, 0.95)	0.444	0.26 (-0.42, 0.94)	0.451	23.23 (3.85)	0.31 (-1.30, 1.92)	0.706	0.31 (-1.30, 1.92)	0.702
- 24wks	23.87 (3.01)	-0.20 (-1.08, 0.69)	0.665	-0.20 (-1.08, 0.69)	0.662	21.96 (3.87)	-0.91 (-2.27, 0.44)	0.185	-0.91 (-2.27, 0.44)	0.187
- 30wks	22.94 (3.32)	-1.03 (-1.82, -0.24)	0.011	-1.03 (-1.82, -0.25)	**0.010**	22.38 (2.96)	-0.46 (-1.88, 0.96)	0.527	-0.46 (-1.88, 0.97)	0.532
LVOT - 14wks	1.99 (0.13)		.		.	1.85 (0.16)		0.511*		0.510*
- 20wks	1.99 (0.14)	0.01 (-0.01, 0.03)	0.335	0.01 (-0.01, 0.03)	0.310	1.89 (0.14)	0.02 (-0.00, 0.05)	0.093	0.02 (-0.00, 0.05)	0.090
- 24wks	1.99 (0.13)	0.01 (-0.00, 0.03)	0.095	0.01 (-0.00, 0.03)	0.094	1.89 (0.12)	0.02 (-0.01, 0.06)	0.150	0.02 (-0.01, 0.06)	0.147
- 30wks	2.00 (0.12)	0.02 (0.00, 0.04)	0.015	0.02 (0.00, 0.04)	**0.014**	1.88 (0.14)	0.01 (-0.03, 0.05)	0.534	0.01 (-0.03, 0.05)	0.528
EF Simp - 14wks	67.38 (3.67)		.		.	66.74 (3.51)		0.750*		0.748*
- 20wks	68.07 (3.06)	0.55 (-0.56, 1.67)	0.331	0.54 (-0.58, 1.66)	0.345	67.85 (3.47)	1.26 (-0.22, 2.75)	0.094	1.25 (-0.24, 2.74)	0.100
- 24wks	65.59 (3.62)	-1.61 (-2.67, -0.54)	0.003	-1.62 (-2.68, -0.55)	**0.003**	65.86 (2.21)	-0.81 (-2.32, 0.71)	0.297	-0.80 (-2.33, 0.72)	0.301
- 30wks	66.29 (3.48)	-1.14 (-2.26, -0.02)	0.047	-1.16 (-2.29, -0.03)	**0.045**	65.58 (3.21)	-0.93 (-2.63, 0.77)	0.286	-0.93 (-2.64, 0.77)	0.284
EF M-mode - 14wks	66.60 (3.63)		.		.	67.04 (2.83)		0.126*		0.126*
- 20wks	67.54 (4.60)	0.82 (-0.34, 1.98)	0.166	0.81 (-0.35, 1.97)	0.173	65.70 (8.51)	-1.31 (-5.29, 2.67)	0.518	-1.31 (-5.29, 2.66)	0.517
- 24wks	67.07 (3.81)	0.46 (-0.71, 1.63)	0.439	0.45 (-0.71, 1.62)	0.445	64.90 (4.19)	-2.11 (-3.97, -0.25)	0.026	-2.11 (-3.97, -0.25)	**0.026**
- 30wks	65.79 (4.19)	-0.92 (-2.02, 0.18)	0.101	-0.94 (-2.04, 0.15)	0.092	65.34 (3.80)	-1.80 (-3.91, 0.31)	0.094	-1.82 (-3.94, 0.30)	0.093

Outcome - Time	Norm Mean (SD)	Norm Unadj. Diff vs T1 (95% C.I)	Norm Unadj p value	Norm Adj Diff vs T1 (95% C.I)	Norm Adj p value	SGA Mean (SD)	SGA Unadj. Diff vs T1 (95% C.I)	SGA Unadj p value	SGA Adj Diff vs T1 (95% C.I)	SGA Adj p value
FS M-mode - 14wks	36.96 (2.96)		.		.	37.04 (2.20)		0.175*		0.175*
- 20wks	38.07 (3.36)	1.03 (0.23, 1.84)	0.012	1.03 (0.23, 1.84)	**0.012**	37.54 (3.44)	0.54 (-1.16, 2.24)	0.535	0.53 (-1.17, 2.24)	0.540
- 24wks	37.23 (3.00)	0.29 (-0.66, 1.23)	0.552	0.28 (-0.66, 1.22)	0.556	35.41 (3.38)	-1.59 (-3.07, -0.11)	0.035	-1.60 (-3.08, -0.11)	**0.035**
- 30wks	36.28 (3.05)	-0.75 (-1.57, 0.07)	0.072	-0.76 (-1.57, 0.05)	0.067	35.81 (3.01)	-1.34 (-2.97, 0.29)	0.108	-1.35 (-2.98, 0.29)	0.108
SEP_s - 14wks	10.03 (1.59)		.		.	9.36 (1.43)		0.854*		0.841*
- 20wks	10.05 (1.34)	0.06 (-0.38, 0.50)	0.788	0.05 (-0.39, 0.50)	0.807	9.60 (1.61)	0.27 (-0.50, 1.04)	0.494	0.28 (-0.49, 1.05)	0.482
- 24wks	10.00 (1.25)	0.01 (-0.41, 0.43)	0.956	0.01 (-0.41, 0.44)	0.949	9.56 (1.38)	0.23 (-0.59, 1.05)	0.583	0.24 (-0.58, 1.06)	0.571
- 30wks	9.64 (1.28)	-0.37 (-0.76, 0.01)	0.058	-0.36 (-0.75, 0.02)	0.064	8.92 (1.19)	-0.41 (-1.18, 0.35)	0.289	-0.41 (-1.17, 0.35)	0.295
LVFW_s - 14wks	11.98 (2.21)		.		.	12.23 (2.54)		0.576*		0.563*
- 20wks	11.97 (2.18)	-0.01 (-0.47, 0.46)	0.977	-0.02 (-0.48, 0.45)	0.948	12.57 (2.45)	0.36 (-0.82, 1.54)	0.547	0.37 (-0.81, 1.55)	0.537
- 24wks	11.96 (2.36)	-0.03 (-0.49, 0.43)	0.898	-0.03 (-0.49, 0.43)	0.903	11.82 (2.12)	-0.38 (-1.58, 0.81)	0.531	-0.37 (-1.57, 0.82)	0.541
- 30wks	11.43 (2.25)	-0.49 (-1.11, 0.12)	0.114	-0.49 (-1.11, 0.13)	0.118	11.35 (2.33)	-0.85 (-2.01, 0.31)	0.150	-0.84 (-2.00, 0.32)	0.154
RV_s - 14wks	15.49 (1.95)		.		.	15.11 (1.66)		0.079*		0.075*
- 20wks	16.24 (2.16)	0.73 (0.22, 1.24)	0.005	0.74 (0.23, 1.25)	**0.005**	16.02 (2.18)	0.79 (-0.27, 1.84)	0.145	0.79 (-0.26, 1.85)	0.139
- 24wks	15.56 (1.77)	0.15 (-0.32, 0.62)	0.538	0.15 (-0.32, 0.62)	0.526	15.73 (1.99)	0.49 (-0.24, 1.23)	0.191	0.50 (-0.24, 1.24)	0.185
- 30wks	15.67 (1.73)	0.25 (-0.25, 0.74)	0.333	0.26 (-0.24, 0.76)	0.309	14.79 (2.05)	-0.45 (-1.30, 0.41)	0.306	-0.44 (-1.29, 0.42)	0.316
MV_E - 14wks	85.86 (13.90)		.		.	88.17 (16.61)		0.169*		0.175*
- 20wks	87.84 (15.24)	2.28 (-1.03, 5.59)	0.177	2.24 (-1.07, 5.54)	0.184	86.73 (18.01)	-1.53 (-5.88, 2.82)	0.491	-1.48 (-5.84, 2.88)	0.505
- 24wks	82.60 (14.76)	-3.28 (-6.36, -0.20)	0.037	-3.27 (-6.34, -0.19)	**0.037**	80.68 (16.00)	-7.57 (-13.28, -1.86)	0.009	-7.53 (-13.23, -1.82)	**0.010**
- 30wks	76.75 (12.23)	-8.67 (-11.73, -5.61)	0.000	-8.67 (-11.74, -5.59)	**0.000**	80.35 (12.69)	-7.90 (-14.63, -1.18)	0.021	-7.86 (-14.59, -1.13)	**0.022**
MV_A - 14wks	49.98 (9.56)		.		.	48.40 (13.47)		0.677*		0.688*
- 20wks	50.20 (7.80)	0.90 (-1.27, 3.07)	0.416	0.95 (-1.22, 3.13)	0.390	51.88 (13.22)	2.96 (-2.25, 8.16)	0.266	2.95 (-2.25, 8.14)	0.267
- 24wks	51.18 (8.30)	1.45 (-0.74, 3.64)	0.196	1.47 (-0.73, 3.66)	0.190	50.62 (16.49)	1.70 (-3.70, 7.09)	0.537	1.69 (-3.71, 7.09)	0.540
- 30wks	52.43 (8.62)	2.98 (0.72, 5.24)	0.010	3.04 (0.79, 5.30)	**0.008**	54.85 (13.03)	5.93 (0.94, 10.91)	0.020	5.92 (0.93, 10.90)	**0.020**

Outcome - Time	Norm Mean (SD)	Norm Unadj. Diff vs T1 (95% C.I)	Norm Unadj p value	Norm Adj Diff vs T1 (95% C.I)	Norm Adj p value	SGA Mean (SD)	SGA Unadj. Diff vs T1 (95% C.I)	SGA Unadj p value	SGA Adj Diff vs T1 (95% C.I)	SGA Adj p value
MV_EA - 14wks	1.79 (0.40)		.		.	2.00 (0.81)		0.436*		0.449*
- 20wks	1.80 (0.44)	0.00 (-0.09, 0.09)	0.986	-0.00 (-0.09, 0.09)	0.973	1.76 (0.49)	-0.24 (-0.53, 0.05)	0.101	-0.24 (-0.53, 0.05)	0.103
- 24wks	1.66 (0.40)	-0.14 (-0.22, -0.06)	0.001	-0.14 (-0.22, -0.06)	**0.001**	1.74 (0.59)	-0.26 (-0.52, -0.00)	0.047	-0.26 (-0.52, -0.00)	**0.049**
- 30wks	1.49 (0.27)	-0.30 (-0.38, -0.23)	0.000	-0.31 (-0.38, -0.23)	**0.000**	1.53 (0.36)	-0.47 (-0.77, -0.17)	0.002	-0.47 (-0.76, -0.17)	**0.002**
IVRT - 14wks	92.23 (12.23)		.		.	89.50 (14.71)		0.708*		0.708*
- 20wks	90.69 (13.62)	-1.83 (-5.53, 1.87)	0.332	-1.78 (-5.47, 1.92)	0.347	90.76 (19.84)	0.71 (-6.78, 8.21)	0.852	0.66 (-6.81, 8.13)	0.863
- 24wks	94.46 (11.85)	2.21 (-1.28, 5.70)	0.215	2.16 (-1.33, 5.64)	0.225	95.18 (10.43)	5.14 (-1.14, 11.41)	0.109	5.08 (-1.19, 11.35)	0.112
- 30wks	97.84 (11.05)	4.80 (1.34, 8.27)	0.007	4.74 (1.29, 8.20)	**0.007**	99.66 (13.31)	9.61 (2.38, 16.84)	0.009	9.56 (2.34, 16.77)	**0.009**
DT - 14wks	151.55 (26.46)		.		.	147.24 (19.56)		0.768*		0.771*
- 20wks	149.89 (15.89)	-1.64 (-7.48, 4.20)	0.582	-1.66 (-7.54, 4.22)	0.581	144.55 (25.48)	-2.49 (-13.27, 8.29)	0.651	-2.45 (-13.23, 8.33)	0.656
- 24wks	151.78 (19.17)	0.71 (-4.84, 6.25)	0.802	0.72 (-4.80, 6.25)	0.797	142.63 (18.02)	-4.41 (-14.70, 5.88)	0.401	-4.37 (-14.65, 5.90)	0.404
- 30wks	150.05 (19.24)	-1.38 (-8.38, 5.61)	0.698	-1.35 (-8.35, 5.65)	0.705	145.18 (21.75)	-1.86 (-13.35, 9.63)	0.752	-1.82 (-13.29, 9.65)	0.756
A_DUR - 14wks	120.73 (19.38)		.		.	115.61 (10.30)		0.705*		0.700*
- 20wks	116.92 (14.17)	-3.77 (-7.88, 0.34)	0.072	-3.76 (-7.86, 0.33)	0.071	109.92 (14.02)	-6.62 (-11.27, -1.97)	0.005	-6.65 (-11.29, -2.02)	**0.005**
- 24wks	118.90 (17.02)	-1.22 (-5.64, 3.20)	0.587	-1.26 (-5.68, 3.15)	0.575	111.97 (11.28)	-4.57 (-10.66, 1.53)	0.142	-4.60 (-10.70, 1.49)	0.139
- 30wks	117.68 (16.79)	-3.66 (-8.72, 1.39)	0.156	-3.73 (-8.77, 1.31)	0.147	111.87 (14.73)	-4.67 (-12.39, 3.04)	0.235	-4.71 (-12.41, 3.00)	0.231
SEP_e - 14wks	14.86 (2.41)		.		.	14.90 (3.47)		0.645*		0.662*
- 20wks	14.70 (2.67)	-0.19 (-0.81, 0.42)	0.538	-0.21 (-0.82, 0.41)	0.511	13.99 (3.13)	-0.79 (-1.77, 0.20)	0.117	-0.78 (-1.76, 0.20)	0.121
- 24wks	14.06 (2.33)	-0.82 (-1.45, -0.18)	0.011	-0.82 (-1.45, -0.19)	**0.011**	13.60 (2.71)	-1.17 (-2.30, -0.04)	0.042	-1.16 (-2.29, -0.04)	**0.043**
- 30wks	13.12 (2.76)	-1.70 (-2.34, -1.05)	0.000	-1.70 (-2.34, -1.06)	**0.000**	12.35 (2.47)	-2.42 (-3.57, -1.27)	0.000	-2.41 (-3.56, -1.27)	**0.000**
SEP_a - 14wks	8.06 (1.62)		.		.	7.66 (1.08)		0.271*		0.278*
- 20wks	8.29 (1.54)	0.28 (-0.09, 0.64)	0.139	0.29 (-0.08, 0.65)	0.127	8.40 (1.99)	0.68 (-0.19, 1.55)	0.124	0.68 (-0.19, 1.54)	0.124
- 24wks	8.63 (1.35)	0.59 (0.19, 0.98)	0.004	0.59 (0.19, 0.98)	**0.004**	8.18 (1.28)	0.47 (-0.10, 1.03)	0.109	0.46 (-0.10, 1.03)	0.109
- 30wks	9.23 (1.82)	1.19 (0.69, 1.69)	0.000	1.19 (0.69, 1.69)	**0.000**	8.27 (1.37)	0.55 (-0.22, 1.33)	0.163	0.55 (-0.22, 1.32)	0.165

Outcome - Time	Normal Mean (SD)	Norm Unadj. Diff vs T1 (95% C.I)	Norm Unadj p value	Norm Adj Diff vs T1 (95% C.I)	Norm Adj p value	SGA Mean (SD)	SGA Unadj. Diff vs T1 (95% C.I)	SGA Unadj p value	SGA Adj Diff vs T1 (95% C.I)	SGA Adj p value
SEP_ea - 14wks	1.91 (0.49)		.		.	2.00 (0.63)		0.276*		0.289*
- 20wks	1.84 (0.49)	-0.09 (-0.20, 0.01)	0.068	-0.10 (-0.20, 0.00)	0.062	1.74 (0.52)	-0.23 (-0.38, -0.07)	0.004	-0.23 (-0.38, -0.07)	**0.004**
- 24wks	1.67 (0.41)	-0.25 (-0.35, -0.15)	0.000	-0.25 (-0.35, -0.14)	**0.000**	1.72 (0.53)	-0.24 (-0.40, -0.09)	0.002	-0.24 (-0.39, -0.09)	**0.002**
- 30wks	1.49 (0.43)	-0.43 (-0.55, -0.31)	0.000	-0.43 (-0.55, -0.31)	**0.000**	1.53 (0.38)	-0.43 (-0.63, -0.23)	0.000	-0.43 (-0.63, -0.23)	**0.000**
SEP_Ee - 14wks	5.89 (1.17)		.		.	6.15 (1.62)		0.613*		0.612*
- 20wks	6.08 (1.16)	0.22 (-0.07, 0.51)	0.139	0.22 (-0.07, 0.52)	0.130	6.45 (1.83)	0.21 (-0.24, 0.66)	0.359	0.21 (-0.24, 0.65)	0.361
- 24wks	5.98 (1.11)	0.10 (-0.18, 0.38)	0.489	0.10 (-0.18, 0.38)	0.484	6.07 (1.33)	-0.17 (-0.66, 0.31)	0.483	-0.17 (-0.66, 0.31)	0.479
- 30wks	6.09 (1.47)	0.20 (-0.20, 0.61)	0.329	0.20 (-0.20, 0.60)	0.320	6.75 (1.72)	0.51 (-0.19, 1.20)	0.155	0.50 (-0.19, 1.20)	0.155
LVFW_e - 14wks	18.86 (3.29)		.		.	17.96 (3.87)		0.393*		0.389*
- 20wks	18.56 (3.49)	-0.40 (-1.02, 0.21)	0.200	-0.42 (-1.03, 0.20)	0.183	18.30 (3.46)	0.47 (-0.97, 1.90)	0.523	0.48 (-0.96, 1.91)	0.513
- 24wks	17.64 (3.48)	-1.26 (-1.97, -0.56)	0.000	-1.26 (-1.96, -0.56)	**0.000**	17.67 (2.57)	-0.17 (-1.57, 1.24)	0.816	-0.15 (-1.56, 1.25)	0.829
- 30wks	17.02 (2.88)	-2.00 (-2.75, -1.26)	0.000	-2.00 (-2.75, -1.26)	**0.000**	17.28 (2.26)	-0.56 (-2.04, 0.92)	0.460	-0.55 (-2.03, 0.93)	0.470
LVFW_a - 14wks	8.46 (1.67)		.		.	8.21 (1.93)		0.502*		0.510*
- 20wks	8.43 (1.44)	-0.01 (-0.46, 0.44)	0.972	-0.00 (-0.45, 0.45)	0.998	9.20 (3.34)	0.94 (-0.67, 2.55)	0.251	0.94 (-0.67, 2.54)	0.254
- 24wks	8.90 (1.76)	0.45 (-0.02, 0.91)	0.059	0.45 (-0.02, 0.91)	0.060	8.48 (1.94)	0.21 (-0.74, 1.16)	0.662	0.21 (-0.74, 1.15)	0.668
- 30wks	9.10 (1.80)	0.57 (0.02, 1.12)	0.041	0.57 (0.02, 1.11)	**0.041**	8.93 (1.56)	0.67 (-0.18, 1.51)	0.121	0.66 (-0.18, 1.50)	0.122
LVFW_ea - 14wks	2.31 (0.59)		.		.	2.34 (0.77)		0.199*		0.208*
- 20wks	2.27 (0.61)	-0.05 (-0.18, 0.07)	0.399	-0.06 (-0.18, 0.07)	0.373	2.11 (0.53)	-0.19 (-0.51, 0.14)	0.258	-0.19 (-0.51, 0.14)	0.259
- 24wks	2.05 (0.54)	-0.27 (-0.39, -0.15)	0.000	-0.27 (-0.39, -0.15)	**0.000**	2.17 (0.52)	-0.12 (-0.39, 0.15)	0.390	-0.12 (-0.39, 0.15)	0.392
- 30wks	1.95 (0.54)	-0.35 (-0.50, -0.20)	0.000	-0.35 (-0.50, -0.20)	**0.000**	2.00 (0.45)	-0.30 (-0.60, 0.01)	0.057	-0.29 (-0.60, 0.01)	0.057
LVFW_Ee - 14wks	4.65 (0.94)		.		.	5.15 (1.61)		0.128*		0.126*
- 20wks	4.81 (0.80)	0.19 (0.00, 0.37)	0.046	0.19 (0.01, 0.37)	**0.041**	4.90 (1.41)	-0.31 (-0.94, 0.33)	0.343	-0.31 (-0.94, 0.33)	0.342
- 24wks	4.83 (1.13)	0.18 (-0.07, 0.42)	0.152	0.18 (-0.06, 0.43)	0.149	4.61 (0.90)	-0.60 (-1.19, -0.01)	0.047	-0.60 (-1.19, -0.01)	0.047
- 30wks	4.62 (0.97)	0.02 (-0.23, 0.26)	0.893	0.02 (-0.22, 0.26)	0.863	4.72 (0.91)	-0.49 (-1.06, 0.08)	0.091	-0.49 (-1.06, 0.08)	0.090
RV_e - 14wks	17.66 (3.10)		.		.	17.08 (3.96)		0.205*		0.197*
- 20wks	18.02 (3.03)	0.32 (-0.40, 1.05)	0.384	0.32 (-0.41, 1.05)	0.389	18.24 (3.00)	1.11 (-0.25, 2.48)	0.110	1.12 (-0.24, 2.48)	0.107
- 24wks	17.08 (2.91)	-0.44 (-1.24, 0.36)	0.282	-0.44 (-1.24, 0.37)	0.287	17.23 (3.77)	0.10 (-1.36, 1.56)	0.894	0.11 (-1.35, 1.57)	0.886
- 30wks	17.82 (3.76)	0.29 (-0.67, 1.26)	0.552	0.30 (-0.66, 1.27)	0.538	16.54 (3.47)	-0.59 (-2.44, 1.25)	0.528	-0.59 (-2.43, 1.26)	0.534

Outcome - Time	Normal Mean (SD)	Norm Unadj. Diff vs T1 (95% C.I)	Norm Unadj p value	Norm Adj Diff vs T1 (95% C.I)	Norm Adj p value	SGA Mean (SD)	SGA Unadj. Diff vs T1 (95% C.I)	SGA Unadj p value	SGA Adj Diff vs T1 (95% C.I)	SGA Adj p value
RV_a - 14wks	12.55 (2.83)		.		.	12.18 (2.78)		0.124*		0.130*
- 20wks	12.73 (3.20)	0.31 (-0.45, 1.07)	0.428	0.32 (-0.45, 1.09)	0.413	13.49 (3.26)	1.36 (-0.20, 2.92)	0.088	1.34 (-0.22, 2.90)	0.092
- 24wks	13.71 (3.07)	1.21 (0.51, 1.91)	0.001	1.20 (0.50, 1.91)	**0.001**	13.24 (2.93)	1.11 (0.00, 2.21)	0.049	1.09 (-0.01, 2.18)	0.052
- 30wks	14.48 (3.38)	2.02 (1.14, 2.91)	0.000	2.01 (1.12, 2.89)	**0.000**	13.29 (3.16)	1.16 (-0.27, 2.59)	0.113	1.14 (-0.29, 2.57)	0.118
RV_ea - 14wks	1.47 (0.41)		.		.	1.50 (0.58)		0.378*		0.387*
- 20wks	1.50 (0.42)	0.00 (-0.07, 0.08)	0.905	0.00 (-0.07, 0.08)	0.917	1.42 (0.37)	-0.09 (-0.31, 0.13)	0.414	-0.09 (-0.31, 0.13)	0.424
- 24wks	1.31 (0.35)	-0.17 (-0.25, -0.08)	0.000	-0.16 (-0.25, -0.08)	**0.000**	1.40 (0.51)	-0.12 (-0.29, 0.06)	0.205	-0.11 (-0.29, 0.06)	0.212
- 30wks	1.30 (0.38)	-0.18 (-0.29, -0.07)	0.001	-0.18 (-0.29, -0.07)	**0.001**	1.28 (0.28)	-0.23 (-0.47, 0.01)	0.062	-0.23 (-0.47, 0.01)	0.064

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). a: a wave velocity, A dur: A wave duration, DT: deceleration time, e: e wave velocity, EF: ejection fraction, FS: fractional shortening, H-R: high-risk, IVRT: isovolumetric relaxation time, LVFW: left ventricular free wall, LVOT: left ventricular outflow tract, L-R: low-risk, MV: mitral valve, RV: right ventricle, s: s wave velocity, Sep: septal, SGA: small for gestational age, Simp: Simpson's biplane method, T1: first trimester, VTI: velocity time integral

Appendix H Preterm birth secondary cardiovascular outcomes with gestation

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	PTL Mean (SD)	PTL Unadj. Diff vs T1 (95% C.I)	PTL Unadj p value	PTL Adj Diff vs T1 (95% C.I)	PTL Adj p value
LVM - 14wks	125.0 (25.0)		.		.	124.9 (12.4)		0.191*		0.234*
- 20wks	126.4 (25.1)	3.6 (-0.1, 7.2)	0.065	3.6 (-0.1, 7.3)	0.060	120.7 (26.0)	-3.0 (-25.7, 19.8)	0.797	-3.6 (-26.8, 19.6)	0.762
- 24wks	128.2 (23.7)	5.4 (1.3, 9.5)	0.010	5.4 (1.3, 9.5)	**0.011**	135.4 (7.5)	11.8 (5.6, 18.0)	0.000	11.2 (4.7, 17.7)	**0.001**
- 30wks	130.8 (25.3)	7.8 (3.1, 12.9)	0.002	8.1 (3.2, 13.0)	**0.001**	148.2 (13.4)	24.6 (9.5, 39.7)	0.001	24.0 (8.6, 39.3)	**0.002**
LVMI - 14wks	72.4 (12.3)		.		.	67.9 (5.9)		0.180*		0.214*
- 20wks	72.5 (11.9)	0.9 (-1.2, 3.0)	0.422	0.9 (-1.1, 3.0)	0.394	64.2 (14.1)	-2.8 (-14.4, 8.8)	0.639	-3.1 (-14.9, 8.8)	0.611
- 24wks	72.3 (11.1)	0.8 (-1.4, 3.0)	0.508	0.8 (-1.4, 3.0)	0.507	70.7 (3.9)	3.7 (0.5, 6.8)	0.024	3.4 (-1.0, 6.8)	0.054
- 30wks	72.4 (12.3)	0.8 (-1.8, 3.5)	0.561	0.9 (-1.8, 3.6)	0.538	76.1 (3.4)	9.1 (1.8, 16.4)	0.015	8.8 (1.3, 16.3)	**0.021**
VTI - 14wks	24.09 (3.19)		.		.	21.27 (1.77)		0.733*		0.701*
- 20wks	24.21 (3.38)	0.27 (-0.42, 0.95)	0.449	0.26 (-0.42, 0.94)	0.456	22.47 (2.56)	0.96 (-0.93, 2.85)	0.321	0.98 (-0.92, 2.87)	0.313
- 24wks	23.87 (3.01)	-0.20 (-1.08, 0.69)	0.665	-0.20 (-1.08, 0.68)	0.659	22.12 (5.23)	0.61 (-3.21, 4.44)	0.753	0.63 (-3.19, 4.45)	0.746
- 30wks	22.94 (3.32)	-1.03 (-1.82, -0.24)	0.011	-1.04 (-1.83, -0.26)	**0.009**	21.21 (3.67)	-0.30 (-2.63, 2.04)	0.804	-0.28 (-2.61, 2.06)	0.816
LVOT - 14wks	1.99 (0.13)		.		.	2.04 (0.11)		0.246*		0.397*
- 20wks	1.99 (0.14)	0.01 (-0.01, 0.03)	0.331	0.01 (-0.01, 0.03)	0.306	2.04 (0.12)	0.01 (-0.03, 0.05)	0.612	0.01 (-0.04, 0.05)	0.701
- 24wks	1.99 (0.13)	0.01 (-0.00, 0.03)	0.094	0.01 (-0.00, 0.03)	0.092	2.06 (0.15)	0.03 (-0.01, 0.06)	0.139	0.02 (-0.01, 0.06)	0.186
- 30wks	2.00 (0.12)	0.02 (0.00, 0.04)	0.015	0.02 (0.01, 0.04)	**0.013**	2.08 (0.12)	0.05 (0.03, 0.07)	0.000	0.05 (0.03, 0.07)	**0.000**
EF Simp - 14wks	67.38 (3.67)		.		.	66.73 (3.40)		0.575*		0.572*
- 20wks	68.07 (3.06)	0.55 (-0.57, 1.67)	0.334	0.54 (-0.59, 1.66)	0.349	66.02 (5.00)	-0.71 (-2.79, 1.37)	0.504	-0.71 (-2.79, 1.37)	0.504
- 24wks	65.59 (3.62)	-1.60 (-2.67, -0.54)	0.003	-1.62 (-2.69, -0.55)	**0.003**	65.68 (2.58)	-1.05 (-2.67, 0.57)	0.205	-1.05 (-2.67, 0.57)	0.205
- 30wks	66.29 (3.48)	-1.14 (-2.26, -0.02)	0.047	-1.17 (-2.30, -0.03)	**0.043**	67.19 (0.87)	0.46 (-1.97, 2.88)	0.712	0.46 (-1.97, 2.88)	0.712
EF M-mode - 14wks	66.60 (3.63)		.		.	64.15 (4.07)		0.838*		0.833*
- 20wks	67.54 (4.60)	0.80 (-0.36, 1.96)	0.176	0.79 (-0.37, 1.95)	0.183	64.79 (5.78)	0.17 (-2.43, 2.77)	0.899	0.22 (-2.40, 2.84)	0.870
- 24wks	67.07 (3.81)	0.46 (-0.71, 1.64)	0.439	0.45 (-0.72, 1.62)	0.449	64.88 (3.26)	0.25 (-2.09, 2.58)	0.835	0.30 (-2.06, 2.66)	0.804
- 30wks	65.79 (4.19)	-0.94 (-2.03, 0.16)	0.094	-0.96 (-2.05, 0.12)	0.083	64.07 (2.85)	-0.55 (-2.85, 1.74)	0.636	-0.50 (-2.84, 1.83)	0.673

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	PTL Mean (SD)	PTL Unadj. Diff vs T1 (95% C.I)	PTL Unadj p value	PTL Adj Diff vs T1 (95% C.I)	PTL Adj p value
FS M-mode - 14wks	36.96 (2.96)		.		.	35.06 (3.05)		0.719*		0.712*
- 20wks	38.07 (3.36)	1.03 (0.23, 1.84)	0.012	**1.03 (0.23, 1.84)**	**0.012**	35.55 (4.34)	0.12 (-1.72, 1.95)	0.898	0.11 (-1.70, 1.93)	0.902
- 24wks	37.23 (3.00)	0.29 (-0.65, 1.23)	0.548	0.29 (-0.65, 1.23)	0.552	35.56 (2.48)	0.13 (-1.73, 1.99)	0.892	0.12 (-1.73, 1.98)	0.896
- 30wks	36.28 (3.05)	-0.75 (-1.57, 0.07)	0.071	-0.76 (-1.57, 0.05)	0.066	34.95 (2.06)	-0.48 (-2.25, 1.30)	0.597	-0.48 (-2.25, 1.28)	0.591
SEP_s - 14wks	10.03 (1.59)		.		.	10.61 (1.86)		0.425*		0.415*
- 20wks	10.05 (1.34)	0.06 (-0.38, 0.50)	0.776	0.06 (-0.38, 0.50)	0.789	11.94 (3.03)	1.22 (-0.10, 2.55)	0.071	1.23 (-0.09, 2.55)	0.068
- 24wks	10.00 (1.25)	0.02 (-0.41, 0.44)	0.943	0.02 (-0.40, 0.44)	0.934	11.19 (2.04)	0.47 (-0.43, 1.38)	0.305	0.48 (-0.41, 1.38)	0.291
- 30wks	9.64 (1.28)	-0.37 (-0.76, 0.01)	0.059	-0.36 (-0.75, 0.02)	0.066	10.14 (1.17)	-0.57 (-1.76, 0.61)	0.343	-0.57 (-1.74, 0.61)	0.346
LVFW_s - 14wks	11.98 (2.21)		.		.	12.44 (1.20)		0.340*		0.334*
- 20wks	11.97 (2.18)	-0.01 (-0.47, 0.46)	0.977	-0.01 (-0.48, 0.45)	0.962	12.97 (1.93)	0.51 (-0.96, 1.99)	0.497	0.52 (-0.96, 2.01)	0.489
- 24wks	11.96 (2.36)	-0.03 (-0.49, 0.43)	0.898	-0.03 (-0.49, 0.43)	0.906	13.07 (0.62)	0.61 (-0.52, 1.74)	0.291	0.62 (-0.51, 1.75)	0.280
- 30wks	11.43 (2.25)	-0.49 (-1.11, 0.12)	0.115	-0.49 (-1.10, 0.13)	0.121	12.93 (2.24)	0.47 (-1.08, 2.03)	0.551	0.49 (-1.07, 2.04)	0.541
RV_s - 14wks	15.49 (1.95)		.		.	14.63 (1.08)		0.271*		0.294*
- 20wks	16.24 (2.16)	0.73 (0.22, 1.25)	0.005	0.73 (0.22, 1.25)	**0.005**	16.16 (2.52)	1.51 (-1.11, 4.13)	0.259	1.50 (-1.11, 4.12)	0.260
- 24wks	15.56 (1.77)	0.15 (-0.32, 0.62)	0.541	0.15 (-0.32, 0.62)	0.529	15.91 (1.82)	1.26 (-0.18, 2.70)	0.086	1.26 (-0.18, 2.69)	0.087
- 30wks	15.67 (1.73)	0.24 (-0.25, 0.74)	0.335	0.26 (-0.24, 0.76)	0.313	15.38 (1.03)	0.73 (-0.66, 2.12)	0.303	0.72 (-0.66, 2.10)	0.304
MV_E - 14wks	85.86 (13.90)		.		.	82.28 (11.36)		0.104*		0.111*
- 20wks	87.84 (15.24)	2.27 (-1.05, 5.58)	0.180	2.24 (-1.06, 5.55)	0.184	81.82 (6.93)	-2.73 (-12.97, 7.51)	0.601	-2.64 (-12.86, 7.59)	0.613
- 24wks	82.60 (14.76)	-3.28 (-6.36, -0.20)	0.037	-3.29 (-6.37, -0.20)	**0.037**	92.00 (29.75)	7.45 (-15.89, 30.79)	0.531	7.55 (-15.82, 30.91)	0.527
- 30wks	76.75 (12.23)	-8.69 (-11.74, -5.63)	0.000	-8.71 (-11.79, -5.64)	**0.000**	87.11 (23.36)	2.56 (-17.42, 22.53)	0.802	2.65 (-17.29, 22.60)	0.794
MV_A - 14wks	49.98 (9.56)		.		.	53.62 (9.24)		0.066*		0.070*
- 20wks	50.20 (7.80)	0.88 (-1.30, 3.06)	0.429	0.94 (-1.24, 3.11)	0.398	60.08 (21.64)	5.56 (-6.67, 17.78)	0.373	5.38 (-6.60, 17.36)	0.379
- 24wks	51.18 (8.30)	1.43 (-0.76, 3.63)	0.201	1.44 (-0.76, 3.64)	0.199	60.69 (21.19)	6.16 (-7.39, 19.71)	0.373	5.98 (-7.37, 19.33)	0.380
- 30wks	52.43 (8.62)	2.96 (0.70, 5.23)	0.010	2.99 (0.73, 5.26)	**0.010**	63.74 (16.27)	9.21 (0.87, 17.55)	0.030	9.03 (0.89, 17.17)	**0.030**

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	PTL Mean (SD)	PTL Unadj. Diff vs T1 (95% C.I)	PTL Unadj p value	PTL Adj Diff vs T1 (95% C.I)	PTL Adj p value
MV_EA - 14wks	1.79 (0.40)		.		.	1.57 (0.29)		0.007*		0.007*
- 20wks	1.80 (0.44)	0.00 (-0.09, 0.09)	0.985	-0.00 (-0.09, 0.09)	0.983	1.53 (0.65)	-0.06 (-0.45, 0.33)	0.770	-0.05 (-0.44, 0.33)	0.793
- 24wks	1.66 (0.40)	-0.14 (-0.22, -0.06)	0.001	-0.14 (-0.22, -0.06)	**0.001**	1.66 (0.82)	0.08 (-0.59, 0.75)	0.819	0.08 (-0.58, 0.75)	0.803
- 30wks	1.49 (0.27)	-0.30 (-0.38, -0.23)	0.000	-0.30 (-0.38, -0.23)	**0.000**	1.46 (0.55)	-0.13 (-0.47, 0.21)	0.455	-0.12 (-0.46, 0.21)	0.472
IVRT - 14wks	92.23 (12.23)		.		.	90.75 (6.28)		0.736*		0.725*
- 20wks	90.69 (13.62)	-1.82 (-5.53, 1.88)	0.335	-1.76 (-5.46, 1.94)	0.351	88.25 (9.19)	-3.74 (-9.26, 1.78)	0.184	-3.87 (-9.39, 1.66)	0.170
- 24wks	94.46 (11.85)	2.21 (-1.28, 5.70)	0.215	2.18 (-1.32, 5.67)	0.222	90.25 (17.33)	-1.74 (-13.25, 9.77)	0.767	-1.87 (-13.43, 9.70)	0.752
- 30wks	97.84 (11.05)	4.83 (1.36, 8.30)	0.006	4.80 (1.33, 8.27)	**0.007**	98.00 (15.83)	6.01 (-3.32, 15.34)	0.207	5.88 (-3.50, 15.27)	0.219
DT - 14wks	151.55 (26.46)		.		.	148.00 (39.19)		0.956*		0.958*
- 20wks	149.89 (15.89)	-1.62 (-7.48, 4.23)	0.587	-1.73 (-7.62, 4.16)	0.564	135.12 (29.97)	-9.93 (-45.68, 25.82)	0.586	-9.41 (-44.86, 26.03)	0.603
- 24wks	151.78 (19.17)	0.79 (-4.76, 6.34)	0.780	0.79 (-4.72, 6.31)	0.778	145.88 (29.10)	0.82 (-19.38, 21.02)	0.936	1.34 (-18.01, 20.69)	0.892
- 30wks	150.05 (19.24)	-1.35 (-8.37, 5.66)	0.706	-1.36 (-8.36, 5.63)	0.703	140.38 (13.25)	-4.68 (-37.04, 27.69)	0.777	-4.16 (-35.86, 27.53)	0.797
A_DUR - 14wks	120.73 (19.38)		.		.	122.10 (17.13)		0.507*		0.491*
- 20wks	116.92 (14.17)	-3.76 (-7.88, 0.36)	0.073	-3.71 (-7.81, 0.39)	0.076	106.50 (23.48)	-15.00 (-34.51, 4.51)	0.132	-15.17 (-34.77, 4.43)	0.129
- 24wks	118.90 (17.02)	-1.16 (-5.59, 3.27)	0.608	-1.17 (-5.59, 3.26)	0.605	117.00 (27.65)	-4.50 (-19.44, 10.44)	0.555	-4.67 (-19.74, 10.40)	0.544
- 30wks	117.68 (16.79)	-3.70 (-8.77, 1.37)	0.153	-3.67 (-8.73, 1.39)	0.155	110.50 (25.24)	-11.00 (-21.18, -0.83)	0.034	-11.17 (-21.43, -0.91)	**0.033**
SEP_e - 14wks	14.86 (2.41)		.		.	16.24 (2.12)		0.598*		0.592*
- 20wks	14.70 (2.67)	-0.19 (-0.81, 0.43)	0.545	-0.20 (-0.82, 0.42)	0.531	15.23 (4.24)	-0.97 (-3.06, 1.12)	0.363	-0.95 (-3.02, 1.11)	0.365
- 24wks	14.06 (2.33)	-0.82 (-1.45, -0.18)	0.012	-0.81 (-1.45, -0.18)	**0.012**	14.78 (3.28)	-1.42 (-3.00, 0.15)	0.077	-1.41 (-2.95, 0.14)	0.075
- 30wks	13.12 (2.76)	-1.70 (-2.34, -1.05)	0.000	-1.69 (-2.33, -1.05)	**0.000**	12.94 (2.93)	-3.26 (-5.50, -1.03)	0.004	-3.25 (-5.45, -1.04)	**0.004**
SEP_a - 14wks	8.06 (1.62)		.		.	8.81 (1.99)		0.023*		0.022*
- 20wks	8.29 (1.54)	0.28 (-0.08, 0.64)	0.131	0.29 (-0.08, 0.65)	0.123	9.67 (2.40)	0.75 (0.12, 1.38)	0.020	0.73 (0.11, 1.35)	**0.020**
- 24wks	8.63 (1.35)	0.59 (0.19, 0.98)	0.004	0.59 (0.19, 0.99)	**0.004**	10.93 (2.63)	2.01 (1.08, 2.94)	0.000	1.99 (1.08, 2.90)	**0.000**
- 30wks	9.23 (1.82)	1.19 (0.69, 1.69)	0.000	1.19 (0.68, 1.69)	**0.000**	11.51 (2.89)	2.58 (1.20, 3.97)	0.000	2.57 (1.20, 3.93)	**0.000**

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	PTL Mean (SD)	PTL Unadj. Diff vs T1 (95% C.I)	PTL Unadj p value	PTL Adj Diff vs T1 (95% C.I)	PTL Adj p value
SEP_ea - 14wks	1.91 (0.49)		.		.	1.90 (0.37)		0.002*		0.002*
- 20wks	1.84 (0.49)	-0.09 (-0.20, 0.01)	0.070	-0.10 (-0.20, 0.01)	**0.066**	1.65 (0.53)	-0.23 (-0.37, -0.08)	0.002	-0.22 (-0.36, -0.08)	**0.002**
- 24wks	1.67 (0.41)	-0.25 (-0.35, -0.14)	0.000	-0.25 (-0.35, -0.14)	**0.000**	1.42 (0.43)	-0.46 (-0.55, -0.36)	0.000	-0.45 (-0.55, -0.36)	**0.000**
- 30wks	1.49 (0.43)	-0.43 (-0.55, -0.31)	0.000	-0.43 (-0.55, -0.31)	**0.000**	1.20 (0.43)	-0.67 (-0.73, -0.62)	0.000	-0.67 (-0.72, -0.62)	**0.000**
SEP_Ee - 14wks	5.89 (1.17)		.		.	5.10 (0.68)		0.003*		0.002*
- 20wks	6.08 (1.16)	0.22 (-0.08, 0.51)	0.151	0.22 (-0.08, 0.51)	0.148	5.65 (1.33)	0.44 (-0.60, 1.48)	0.404	0.45 (-0.58, 1.47)	0.396
- 24wks	5.98 (1.11)	0.10 (-0.19, 0.38)	0.505	0.09 (-0.19, 0.38)	0.523	6.52 (2.74)	1.32 (-0.74, 3.39)	0.210	1.32 (-0.74, 3.39)	0.209
- 30wks	6.09 (1.47)	0.20 (-0.21, 0.60)	0.337	0.19 (-0.21, 0.59)	0.356	6.81 (1.29)	1.60 (0.70, 2.50)	0.001	1.60 (0.71, 2.50)	**0.000**
LVFW_e - 14wks	18.86 (3.29)		.		.	17.08 (2.56)		0.535*		0.530*
- 20wks	18.56 (3.49)	-0.41 (-1.03, 0.21)	0.196	-0.42 (-1.04, 0.20)	0.181	16.80 (2.00)	0.09 (-0.76, 0.94)	0.841	0.12 (-0.71, 0.96)	0.773
- 24wks	17.64 (3.48)	-1.26 (-1.97, -0.56)	0.000	-1.26 (-1.97, -0.56)	**0.000**	16.19 (1.54)	-0.52 (-1.51, 0.47)	0.302	-0.49 (-1.49, 0.52)	0.343
- 30wks	17.02 (2.88)	-2.01 (-2.75, -1.26)	0.000	-2.01 (-2.75, -1.26)	**0.000**	15.87 (1.27)	-0.84 (-2.24, 0.56)	0.238	-0.81 (-2.22, 0.61)	0.264
LVFW_a - 14wks	8.46 (1.67)		.		.	8.17 (1.17)		0.000*		0.000*
- 20wks	8.43 (1.44)	-0.01 (-0.46, 0.45)	0.976	-0.00 (-0.46, 0.45)	0.984	9.40 (1.14)	1.13 (0.78, 1.47)	0.000	1.12 (0.78, 1.47)	**0.000**
- 24wks	8.90 (1.76)	0.45 (-0.02, 0.92)	0.058	0.45 (-0.02, 0.91)	0.060	10.65 (0.92)	2.38 (0.99, 3.77)	0.001	2.37 (0.98, 3.77)	**0.001**
- 30wks	9.10 (1.80)	0.56 (0.02, 1.11)	0.044	0.55 (0.01, 1.10)	**0.046**	10.27 (1.01)	1.99 (0.51, 3.48)	0.008	1.99 (0.50, 3.48)	**0.009**
LVFW_ea - 14wks	2.31 (0.59)		.		.	2.15 (0.54)		0.053*		0.056*
- 20wks	2.27 (0.61)	-0.05 (-0.18, 0.07)	0.395	-0.06 (-0.18, 0.07)	0.375	1.82 (0.42)	-0.24 (-0.37, -0.10)	0.001	-0.23 (-0.37, -0.10)	**0.001**
- 24wks	2.05 (0.54)	-0.27 (-0.39, -0.15)	0.000	-0.27 (-0.39, -0.15)	**0.000**	1.52 (0.12)	-0.54 (-0.92, -0.16)	0.006	-0.53 (-0.92, -0.15)	**0.007**
- 30wks	1.95 (0.54)	-0.35 (-0.50, -0.20)	0.000	-0.35 (-0.50, -0.20)	**0.000**	1.55 (0.17)	-0.51 (-0.90, -0.11)	0.012	-0.50 (-0.90, -0.10)	**0.014**
LVFW_Ee - 14wks	4.65 (0.94)		.		.	4.92 (1.00)		0.148*		0.081*
- 20wks	4.81 (0.80)	0.19 (0.00, 0.37)	0.048	0.19 (0.01, 0.37)	**0.040**	4.90 (0.39)	-0.20 (-0.83, 0.43)	0.533	-0.22 (-0.84, 0.41)	0.495
- 24wks	4.83 (1.13)	0.18 (-0.07, 0.42)	0.154	0.18 (-0.07, 0.43)	0.155	5.70 (1.75)	0.60 (-0.89, 2.09)	0.429	0.58 (-0.91, 2.08)	0.445
- 30wks	4.62 (0.97)	0.02 (-0.23, 0.26)	0.903	0.02 (-0.23, 0.26)	0.898	5.44 (1.09)	0.34 (-1.07, 1.75)	0.637	0.32 (-1.10, 1.75)	0.657
RV_e - 14wks	17.66 (3.10)		.		.	17.14 (4.60)		0.570*		0.576*
- 20wks	18.02 (3.03)	0.33 (-0.40, 1.05)	0.381	0.32 (-0.40, 1.05)	0.383	17.81 (3.05)	1.33 (-0.64, 3.31)	0.186	1.31 (-0.70, 3.32)	0.202
- 24wks	17.08 (2.91)	-0.45 (-1.25, 0.36)	0.275	-0.44 (-1.24, 0.37)	0.286	16.24 (3.70)	-0.23 (-4.07, 3.60)	0.906	-0.25 (-4.13, 3.63)	0.898
- 30wks	17.82 (3.76)	0.29 (-0.68, 1.25)	0.562	0.32 (-0.65, 1.29)	0.519	16.17 (3.59)	-0.31 (-3.59, 2.97)	0.854	-0.33 (-3.63, 2.97)	0.845

Outcome - Time	Normal Mean (SD)	Normal Unadj. Diff vs T1 (95% C.I)	Normal Unadj p value	Normal Adj Diff vs T1 (95% C.I)	Normal Adj p value	PTL Mean (SD)	PTL Unadj. Diff vs T1 (95% C.I)	PTL Unadj p value	PTL Adj Diff vs T1 (95% C.I)	PTL Adj p value
RV_a - 14wks	12.55 (2.83)		.		.	12.39 (3.96)		0.137*		0.128*
- 20wks	12.73 (3.20)	0.32 (-0.45, 1.08)	0.417	0.32 (-0.44, 1.09)	0.408	14.78 (5.00)	1.92 (0.52, 3.33)	0.007	1.92 (0.56, 3.29)	**0.006**
- 24wks	13.71 (3.07)	1.21 (0.51, 1.92)	0.001	1.20 (0.50, 1.91)	**0.001**	16.46 (6.97)	3.60 (0.12, 7.08)	0.043	3.60 (0.14, 7.06)	**0.041**
- 30wks	14.48 (3.38)	2.03 (1.14, 2.92)	0.000	2.00 (1.10, 2.89)	**0.000**	16.10 (3.37)	3.24 (0.89, 5.59)	0.007	3.24 (0.87, 5.60)	**0.007**
RV_ea - 14wks	1.47 (0.41)		.		.	1.54 (0.71)		0.688*		0.654*
- 20wks	1.50 (0.42)	0.00 (-0.07, 0.08)	0.915	0.00 (-0.07, 0.08)	0.909	1.29 (0.40)	-0.09 (-0.28, 0.09)	0.323	-0.10 (-0.31, 0.10)	0.315
- 24wks	1.31 (0.35)	-0.17 (-0.25, -0.08)	0.000	-0.16 (-0.25, -0.08)	**0.000**	1.12 (0.55)	-0.27 (-0.63, 0.10)	0.157	-0.28 (-0.66, 0.10)	0.153
- 30wks	1.30 (0.38)	-0.18 (-0.29, -0.07)	0.001	-0.18 (-0.28, -0.07)	**0.001**	1.05 (0.32)	-0.34 (-0.61, -0.07)	0.012	-0.35 (-0.63, -0.07)	**0.013**

All data values are expressed as mean, differences in means and 95% Confidence interval (C.I). P values marked with an asterisk are for test of time-by-group interaction (i.e. whether the difference in means between groups varies over time). a: a wave velocity, A dur: A wave duration, DT: deceleration time, e: e wave velocity, EF: ejection fraction, FS: fractional shortening, H-R: high-risk, IVRT: isovolumetric relaxation time, LVFW: left ventricular free wall, LVOT: left ventricular outflow tract, L-R: low-risk, MV: mitral valve, PTL: preterm birth, RV: right ventricle, s: s wave velocity, Sep: septal, Simp: Simpson's biplane method, T1: first trimester, VTI: velocity time integral.