Pelvic Floor Repair: Novel Surgical Methods, Regenerative Medicine, and Women's Perspectives of Scar-Less Surgery

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Dedication

This PhD is dedicated to my parents, **Ahmad** and **Mehrangiz**, who suffered in separation and silence for me to become a woman of substance, my husband **John** who is my anchor, and my daughter **Nadia** who is my most important achievement and my hope in life.

And, finally, to my brother, **Hossain**, who doubted my ability but shared his scholarship with me at a time of war and economic uncertainty, saying “we will either survive or die together”.

Abstract

Pelvic floor disorders (PFDs), such as prolapse and urinary incontinence, affects approximately 60% of women in their lifetime. I have been trained in advanced minimally invasive surgery for these conditions. Despite advanced surgical methods, the failure rates remained high. Moreover, recently the United States Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA) have removed synthetic mesh and biological material for vaginal repair from the market due to global mesh class-action. Consequently, gynaecologists have been left with conservative management or surgery with native tissue repair which has high failure rates, requiring repeat surgery in over 20% of cases. The current conservative management options such as physiotherapy and topical oestrogen rely on patient compliance. In addition, medication used for conditions such as urge urinary incontinence, Lichen sclerosis and genitourinary syndrome of menopause may have adverse effects or be contraindicated, leaving the patients with compromised quality of life.

The overarching theme of my work has been to introduce an innovative first-line conservative management which does not rely on patient compliance. This includes pelvic-floor physiotherapy,fractional CO2 (FxCO2) vaginal laser, Platelet Rich Plasma (PRP), and oestrogen cream. This approach will minimise the need for PFD surgery which is a burden economically on the patient and the national healthcare system. Surgery is also associated with possible complications that may negatively affect quality of life. When surgery is necessary, I seek to maximise surgical outcomes with pre-operative management followed by use of innovative autologous PRP graft intraoperatively. This approach has shown, through our initial cohort study, to reduce failure ratesand possible complications. Consolidating my research in PhD-by-prior-published-work will provide a coherent narrative about improving quality of life for women with PFDs through first- line innovative methods and advanced minimally invasive surgery utilising autologous PRP graftif surgery is required.

Key words

Pelvic floor disorders, single incision laparoscopy, platelet rich plasma, fractional CO2 laser, autologous graft, women health, quality of life.

Declaration

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

I declare that this thesis is composed of my original work and contains no previously published or work by another person except where due reference has been made in the text. I have stated the contribution of other co-authored publications that I have included inthis thesis. This thesis does not contain any content that has been submitted to qualify forthe award of degree or diploma in any other university or tertiary institution. No professional editing was used in the production of any of the included published works or in preparation of this thesis.

Name & date signature:

Fariba Behnia-WillisonJuly 1st 2021

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Table of Contents

Table of Contents

List of Tables

List of Figures

List of Abbreviations

AAS	Activity Assessment Scale
ASAS	American Society of Anesthesiologist Score
ePAQ-PF	Electronic Personal Assessment Questionnaire-Pelvic Floor
FDA	Food And Drug Administration
FI	Faecal Incontinence
GSM	Genitourinary Syndrome of Menopause
ICD-9	International Classification of Disease Diagnosis Code 618x
LS	Lichen Sclerosus
MIS	Minimally Invasive Surgery
MS-CCAD	Market Scan Commercial Claims and Encounters Data
PFD	Pelvic Floor Disorder
PFDI	Pelvic Floor Distress Inventory
PFDQ	Pelvic Floor Dysfunction Questionnaire
PFIQ	Pelvic Floor Impact Questionnaire
POP	Pelvic Organ Prolapse
POPDI	Pelvic Organ Prolapse Distress Inventory
POP-Q	International Continence Society Pelvic Organ Prolapse Quantification
PRP	Platelet Rich Plasma
SILS	Single Incision Laparoscopic Surgery
SSQ-8	Surgical Satisfaction Questionnaire-8
SUI	Stress Urinary Incontinence
TGA	Therapeutic Goods Administration
UDI	Urinary Distress Inventory
WHO	World Health Organization

Introduction

Background

This doctoral thesis presents and reflects upon a researcher's peer-reviewed research on minimally invasive surgery and regenerative treatments before and after surgery, in the field of gynaecology. This chapter reveals the arc of a researcher's personal and professional background, which is conveyed through 'My Story', a first-person narrative of the author's life, highlighting the influential experiences that illuminate themotivation for and direction of the research presented. From this foundation, this chapter also demonstrates the current knowledge gaps in women's health research andprovides a clear statement of the aims and objectives of this thesis, alongside the original contribution to knowledge confirmed through this research.

Chapter 1 offers a critical review of the literature, which identifies key knowledge gapsin the research and so establishes the foundation for substantiating the significance of the research presented herein. Chapters 2 to 11 present 12 peer-reviewed journal articles [1-12], that document the progression and contribution of the author's research over aneight-year period and portray its positive impact on women's health and a transformation of knowledge in this field. A detailed explanation of the conclusions drawn from this research as well as recommendations for future work in the applicationof regenerative treatments in gynaecology are presented in Conclusions. This thesis asserts as its original contribution to knowledge that innovative regenerative procedures improve the outcomes of minimally invasive pelvic floor surgery or mitigate the need for surgery.

I have owned and run a gynaecological practice since 2009 and have been fully committed to research throughout my professional career. It is unusual for a private practitioner to conduct research in their private rooms as it is costly to the business, however this demonstrates the passion I have for research and improving the lives of women. The inspiration for this research has been women and their health needs, especially when standard practices cannot provide the best possible outcomes or women are requesting alternative methods. To establish

improved practices that can deal more effectively with pelvic floor disorders (PFDs), innovation needs to be blended with research to determine what really happens for women. This thesis provides the outcomes of first-generation innovation in regenerative non-surgical and surgical procedures that deal with PFDs.

As a PhD-by-prior-published-work Chapters 2-11 of this thesis comprise publications that were in the public domain before I enrolled in the degree. A PhD-by-prior-published-work requires the presentation of the research, how it clusters and how it summons an original contribution to knowledge. This is a distinctive mode of doctorate. It develops through a lifetime of research. Therefore, to frame and contextualize this research requires an understanding of the researcher, here conveyed in my story 'The Revolutions.'

My Story 'The Revolutions'

"I learned that every mortal would taste death, but only some will taste life."
Rumi[1]

All research emerges from a context. All research is summoned by a researcher. This doctoral thesis is no exception. When I was ten years old, the Iranian Revolution and war between Iraq and Iran erupted. Alongside the widespread catastrophic suffering tothe people of both nations that these events caused, the destinies of children born to parents who worked for the monarchy under the leadership of the Shah, including mine,were irrevocably changed forever. Overnight, my life was thrown into turmoil as my father went from a revered member of the Shah government to an enemy of the state, and consequently was up for execution.

The day when one of the elders of my family came to our house telling my mother thatthe body of her husband would be brought to the city following his execution, and to get her children ready with their mourning clothes for his funeral is forever imprinted upon my memory. My father was the sole income earner for our family of six childrenand we relied solely on his

[1] MLA (7th ed.), Jalāl, al-Dīn R, and Coleman Barks. The Essential Rumi., 1997. Print.

ability to provide financially for our family, as my mother had never had a salaried position. My mother, startled by the news, started to talk loudlyto God. At the time, I was sitting on my bed listening intently. I could not ascertain whether she was praying to or accusing God for putting her in this situation. I rememberher saying, *"What do you expect me to do with six children, especially four girls withouta father?"* At that time, it was commonplace that girls without a father could be subjected to predation and abuse due to the absence of a paternal figure to protect and provide for them. I pulled my blanket over my ears and cried quietly because I did notwant to lose my father nor be forced into a life of uncertainty. Never in my life have I

ever felt such fear or vulnerability, but most of all, I hated how dependent my mother was on my father, and how helpless she was in that moment. As a ten-year-old girl, I made a vow that I would find the means to be an independent woman.

In the morning, I heard my father's voice, and with great excitement and amazement Irushed to embrace him. Instead of being gathered safely into his arms and wrapped in the loving embrace, which I so craved, my father was in a frenzy. He rushed around barking orders and collecting valuables that we would need to flee as a family. We wereinstructed to bring a small bag of possessions of no more than 2kg. It transpired that my dad had arranged for the evening garbage truck to smuggle us out of town. Around 6 pm, when the garbage bins were being collected, we scrambled into the garbage truckas quietly as we could, fleeing the place we used to call home ever felt such fear or vulnerability, but most of all, I hated how dependent my mother was on my father, and how helpless she was in that moment. As a ten-year-old girl, I made a vow that I would find the means to be an independent woman.

Years later, I found out that the person ordered to execute my father saved his life. He recognised my father as the person whose charity looked after many orphans, includinghim and his wife. He did not believe my father deserved to be executed and saw it as adishonourable

act and an oversight of the government to kill a good man who was simply affiliated with the previous government. He gave my father his own bicycle andtold him to flee as fast as he could. When I reflect on these events, I can see why charityand caring for others became such an integral part of my life and career. Now that I aman older woman, I wonder if my ten-year-old self would be satisfied with what I have achieved.

The research presented in this doctorate captures just one trajectory of my career and life. To grasp the research is to understand the researcher. Hence, before documenting the research conducted, its impact and original contribution to knowledge, it is important that the framework for these publications is presented.

After fleeing the city that I called home, and seeking refuge in a new city, I encounteredmany obstacles. Even though time passed and individuals in the government realised my father did not deserve execution, they still marked him as 'not pro-revolutionary government'. This meant that we could not possess any land, businesses, and we werelimited in our career options. Despite achieving top marks in the university entrance exam, I was not permitted to study medicine in Iran.

I ended up studying nursing and started to date a surgeon, who became the love of mylife. Tragically, he was killed in a bombing while performing surgery on a soldier. Theother doctors I was working with told my father that I should migrate to another countryto restore my life emotionally and to fulfill my goal to study medicine. I applied to Bonn Medical School in Germany and the university accepted my application. To secure my place I needed to provide the university with two essential documents: the original copy of my high-school transcripts and a German translation. Unfortunately, the government held the original transcripts and banned them from being released to me by the translator. However, the day I went to collect my translation of the transcript,I was informed that the translator had died. Due to the chaos of this unexpected death,a staff member mistakenly gave me the original documents along with

the translation. I took this as an opportunity to immediately leave Iran and study medicine in Germany, in a language I did not know.

Following a year of grueling and relentless hard work, I managed to learn German and completed the Studien College certificate as a prerequisite of medical school. Despite German being my second language, I earned the honour of being Dux of the Studien College. From this experience I learned to value opportunity, education, and tenacity.

Growing up in the Middle East, I was surrounded by the belief that women's health was a taboo subject. When I was a child, my mother and other female relatives used totake my siblings and I to the bathroom to cover up their urinary issues, pretending thatwe were the ones needing to use the bathroom. My mother did not even speak to my father about her health problems. In Germany, to my surprise, I also realised that women did not speak about sex or women's health issues, even to their general practitioner (GP).

After eight years of living in Germany, I married an Australian and migrated to Perth. My husband was a member of an Open Brethren church, which included in its philosophy that *'women are sinners who have to be submissive to their husbands at anycost'*. Divorce was frowned upon, other sexualities were not respected or tolerated, and women were only permitted to work from home. I presented as somewhat of achallenge, since I was a doctor, an intelligent and independent woman, and a forward thinker, who did a lot of charity work and took care of other people. To say it simply, Idid not fit the traditional Brethren church's mould. Within this system, I discovered very quickly that there was a significant degree of discomfort for women to discuss andaddress their health issues, and to my surprise I soon learned that this discomfort was experienced by women from all over Australia. Everyone was happy to talk about pregnancy, throw baby showers and chat about the fertility movement, which is perhaps because men are involved in that part of a woman's life. The ramifications and impactof birth on intimacy and the pelvic floor, however, were issues seen as taboo, and it became apparent

that women's health issues were a global problem.

Each woman and man are born from the vagina or 10 cm above it, and yet we are all hesitant to talk about ***vaginas***. Why is this so? ***A vagina is just another organ!*** I promised myself to be someone who would become the ***'Voice for Vaginas'*** and so, with all my power, knowledge and skills, I endeavoured to help women globally.

In Perth, I conceived a child and was immediately drawn to the warmth and professionalism of my obstetrician Dr Paul Cohen. I respected and appreciated his mannerism and subsequently started my training in obstetrics and gynaecology. I had abelief that women would open to a female health care provider more comfortably in themale-dominated gynaecological field of the 1990s. I equipped myself with cutting-edgeand advanced surgical techniques, did my Masters of Minimally Invasive Surgery withthe College of Surgeons, and started to perform Single Incision Laparoscopy, to reducecomplications and provide better surgical outcomes. I became interested in advanced laparovaginal pelvic floor repair (PFR) with synthetic mesh augmentation and minimally invasive surgery for PFR and was skilled enough to combat many pelvic floor disorders.

One day, I was challenged by a 30-year-old patient who rushed into my office crying, stressed, and threatening to kill herself. She stated that she had been diagnosed with breast cancer at the age of 27, had undergone removal of her ovaries and both breasts, and had been abandoned by her husband because he could not toleratethe situation. Fortunately, she met a new partner who was supportive and remained byher side during her chemotherapy journey. As a result of the side-effects of the chemotherapy however, she could not have intercourse with her partner due to severe vaginal atrophy, which could not be treated with traditional hormone therapy due to its contraindication with breast cancer. My patient was told by numerous doctors that she should be happy that she was alive and had received good care in Australia. Her legitimate question was however, *"What is the meaning of life if there is no quality of life?"* She could

not be a mother, a wife, and now not even a lover. I understood her point and felt powerless and speechless when I realised that as an accomplished gynaecologist, I had nothing to offer her. I felt that I was not trained and somewhat oblivious to certain disorders, such as severe atrophic vaginitis, which is an area of women's health that cannot be surgically treated. I reassured her that I could help her, just to buy time and come up with some solution.

That same day, I had an invitation to a "PRP Vampire face lift", where PRP stood for Platelet-Rich-Plasma. Afterwards, I felt as if a lightbulb had gone off when I saw a photo of a face, where half of the face was treated with injected PRP. The picture showed a significant difference in the rejuvenation of the skin, and I immediately thought *"this is what she needs in her vagina; something autologous and regenerative".* Even though I knew I was risking my registration and reputation, I askedher to come to my office, where I injected her vagina with PRP. Two months later shewas sexually active, and to my astonishment and delight, when she returned, she requested that I inject her face instead! I knew that I may be on to something and sent out a letter asking GPs to refer patients to me with similar conditions. Out of the initial100 patients, 55 were either GPs or their wives, who presented for the treatment. I treated atrophic vagina and lichen sclerosis patients who were resistant to conservativemanagement. They all had pain and I treated them with needles and PRP, until I came across the CO_2 laser, which causes microtrauma in a painless way such that the area being treated is receptive for PRP to be used afterwards. Although we were treating atrophic vaginitis and lichen sclerosis patients, some also reported an improvement in their urinary incontinence and prolapse symptoms, and they started to cancel their urodynamic investigations and pelvic floor surgeries.

This preliminary, yet fundamental work encouraged me to further investigate the role of PRP and CO_2 laser and expand my study of them to include urinary incontinence (UI), prolapse, urinary tract infection (UIT), atrophic vagina, lichen sclerosis (LS), abnormal scar tissue and mesh complications. I also explored the use of these modalitieswith atypical gynaecology, such

as female genital mutilation (FGM), gender reassignment surgery and severely affected labia fusion due to hypoestrogenism.

To my surprise, I started to feel that my medical colleagues were undermining my workand in fact causing me difficulties by involving the Medical Board (AHPRA; Australian Health Practitioner Regulation Agency), even though I was conducting scientificresearch that moved through the peer review process and onto publication. On one hand, the unit gained credit for my publications, and on the other hand I was not supported for my innovative work on sexual dysfunction, which was downplayed as 'primarily aesthetic'. The downplaying of sexual function demonstrates one way in which women's health and wellbeing is decentred, marginalised or even denied.

The battle to change these perceptions is ongoing despite my published work and thatI have presented nationally and internationally at events held by the American Association of Gynaecologic Laparoscopy (AAGL), European Uro-gynaecology Association (EUGA) International Uro-gynaecology Association (IUGA) and Austrasia Gynaecologic Endoscopic Society (AGES). As yet, I have not presented mywork in my own department, but change in attitudes is possible, as demonstrated by a medical colleague who had previously been skeptical about the therapeutic benefits of administering PRP in the regeneration of tissue. That colleague now has more positiveand open view on PRP procedures following personal experience with successful repairof tendonitis.

I also care for many mesh patients who experience a very good outcome with laparoscopic mesh for pelvic organ prolapse repair, especially if the uterus has not beenremoved. I have witnessed severe complications of patients who had received vaginal mesh, which caused devastating effects, leaving them with a disability and severely affected quality of life. These poor outcomes resulted in a global Mesh Class Action, with many mesh products withdrawn from the market in many countries. Inquiries into this class action revealed that the companies

were awareof these complications but falsified or did not publish the results, simply to gain accessto the market. This lesson demonstrated that any new technology and device must be assessed according to the regulatory bodies without any bias before it becomes mainstream and accepted treatment.

I knew that orthopaedics had advancements in regenerative medicine much earlier thanother specialities, hence my participation in the musculoskeletal and orthopaedic fields. At one conference, I came across tissue engineering for cartilage repair, and I immediately began thinking that this was the way to augment tissue for vaginal repairs.Similarly, I also learnt about the RegenLab company's jelly-like membrane, based on PRP for tendon repair [13, 14]. I started to develop and perfect a biological graft basedon PRP that had the potential to replace mesh in an autologous fashion, after first ensuring that all ethical protocols and research integrity structures were in place. My finished formula is the culminating result of countless hours spent perfecting the ratio of the portions of blood, hyaluronic acid (HA), fat, and stem cells. To date, we have tested the graft on 100 women with a follow-up of two years. The results are very promising, and the data shows a significant statistical positive outcome. I feel I am finally about to leave behind a legacy, that adds to the body of scientific knowledge and helps women globally.

Today, as I write this introduction to my doctoral thesis, I realise that the meaning of lifeis not in merely overcoming barriers and difficulties but in having a purpose. Wealth fame, and recognition are meaningless without the fulfillment of your life's calling. I am no longer the shattered child in 1979, the teenager who lost her first love in a war, the young lady who migrated to Germany alone with very little money and much sorrow, the wife who was cursed by the church for her independence, nor am I the downtrodden, traditional gynaecologist I could have become. While all these events have shaped me, they do not define, imprison nor limit me. I often wonder if thewounds for each of these women, the ones that were once me,

have healed, and do theyapprove of the woman I have become? May my past wounds inspire me to serve womenthrough healing, so that we may be among those who taste life.

These experiences in 'The Revolutions' formed the very foundation of this thesis. The latter part of this introduction serves to demonstrate the current knowledge gaps in women's health research and provides a clear statement of the aims and objectives of this thesis, alongside the original contribution to knowledge confirmed through this research.

A PhD-by-prior-published-work requires contextual statements, to show how the research has been deployed throughout the field. The 11 articles and one book chapter presented in this doctorate are being used by other researchers investigating PFDs andinfluencing practitioners, especially those articles on regenerative procedures. For example, the 2017 [6] article on the use of fractional CO_2 laser ($FxCO_2$) on genitourinary syndrome of menopause (GSM) is currently escalating in citations (67 in Google Scholar), with 4 (2017), 14 (2018), 15 (2019), 23 (2020). The 2016 [7] article on platelet-rich-plasma (PRP) therapy has 30 cites (Google Scholar) and the $FxCO_2$ laser article published in 2019 [5] already has 9 citations (according to Google Scholar).

I was invited to submit the book chapter by Professor Pedro Escobar of the renowned Clevland Clinic and, as the only Austrlian author, the invitation provides a sense of the esteem held for my work with international experts in the field.

Influence of this doctoral research on the practice of improving women's PFDs has beenshown at three levels. The first is the outcomes of my own patients after the research has demonstrated a procedure's safety and potential efficacy. So far, the author has treated more than 5000 cases with no complication and 85% efficacy. This includes prospective and current patients attending research-based information sessions, so thatthey can make informed decisions about their own health, as well as consent to proceedures. The second level is the research-led

teaching, training, and workshops I have delivered to clinicians in Australia and overseas, examples include:

Teaching, Training, and workshops:

- I have collaborated with Dr Ian Holten MBBS, FRACS, FFRCS (Plast) Lon., a plastic surgeon, in Victoria, Australia. I establisheda regenerative medicine centre in his office in VIC 2015-2016. I trained Dr Holten andhis staff in vaginal laser treatment and monitored and reported the outcome of their cohort of patients. I have learned fat grafting, stem cell harvesting from Dr Holten andhave been using fat grafting in the management of women with severe scarring, such as female genital mutilation (FGM) victims, male-to-female gender-affirmation surgery, and severe scarring due to lichen sclerosus or hypoestrogenism. Our cooperation resulted in the successful publication of the role of platelet-rich plasma (PRP) in vulval lichen sclerosus. This is a landmark paper on the alternative management of lichen sclerosus, which is used in this thesis.
- I have been invited to general practitioner (GP) educational sessions, with attendance of 40-100 in Adelaide and 500-1000 GPs at national conferences. I have been involvedwith this educational activity since 2015. I presented the role of regenerative medicinein pelvic floor disorders and explained the science behind these modalities, the importance of patient selection, feasibility, safety, and outcome. I also run yearly GP educational sessions for Adelaide based GPs on surgical and non-surgical management of prolapseand incontinence, sexual dysfunction, and management of obesity.
- Australasian Gynaecological Endoscopic and Surgery runs cadaver workshop for 50 gynaecologists and fellows in gynaecological training. I was invited to be the national faculty member alongside with Dr Howard Salvay our international faculty from USAto teach and demonstrate advanced laparoscopy and Single Incision Laparoscopic Surgery (SILS) at the inaugural workshop in Australia in 2015.
- The European Uro-gynaecological Association hosted a sponsored symposium where I

presented on the role of regenerative medicine in gynaecology where 100 attendees of gynaecologists and fellows participated in 2018.

- The American Association of Gynecological Laparoscopists invited me to be a member of their faculty and run workshops on regenerative medicine and teaching to their members on the advanced cutting-edge alternative methods in the treatment of pelvic floor disorders where 200 attendees of gynaecologists and fellows participated in 2019.
- I presented my methods of regenerative medicine and FGM reversal with fat grafting at Desert Flower Centre in Berlin, Germany where 6 specialist attendees were present in 2019.
- I am a faculty member of annual Flinders Endogynaecology Department Suturing workshop since 2004, I have regularly presented my innovative work in regenerative medicine and SILS from 2016-2019. The workshops typically have 20 fellow gynaecologists attending.
- I was a faculty member for annual animal workshop at Centre for Advanced Reproductive Endoscopy in Sydney where I demonstrated advanced laparoscopic skillsincluding SILS and presented my regenerative work in gynaecology to 10 fellow gynaecologists per workshop, 2016-2019. I also establish the regenerative treatment atthis centre.
- I was running national dry Lab workshop and live surgery in Single Incision Laparoscopic Surgery for gynaecologists. The workshop was supported by Applied Medical where up to 30 fellows and gynaecologists were trained from 2014- 2018. Each year I have run four workshops.
- I was the trainer and consultant for vaginal laser workshops sponsored by the company High Tech Medical where 2-6 GPs or specialists attended the workshop from 2014-2018.
- I was the trainer and consultant for PRP workshops for the BioBridge Foundation from 2018-2020. The attendees were from 20 GPs and specialists
- I have demonstrated fat grafting for Gynaecologists undergoing training on FGM from 2016 until now. These workshops involve specialized one-on-one training.
- I was invited to present my research and my innovative methods of regenerative medicine in

pelvic floor disorders to Perioperative Nurses Association in Adelaide 2021.

- The Women's Health and Research Institute of Australia (WHRIA) has provided in principle agreement to establish Desert Flower Sydney for victims of female genital mutilation (FGM), I willprovide training to four gynaecologists in 2021 in Adelaide.

Invited speaking:

The impact of my research is especially evident noting the numerous invitations from various organisations and foundations to run workshops and present asa keynote speaker, examples are presented in Table1.

Table 1. List of workshops invited speaker and presenter have been conducted by myself.

Organisation	Year	Topic	Role	Attnedees
Australasian Gynaecological Endoscopic and Surgery	2016, 2019, 2020	Laparoscopic Surgery	Invited Speaker	200 gynaecologists
American Association of Gynecologic Laparoscopists	2019	Advances in Laparoscopic Surgery	Invited Speaker	200 fellows and gynaecologists
European Urogynaecological Association	2018	Laparoscopic Surgery in Gynaecological application	Invited Speaker	100 GPs and specialists
The Cleveland Clinic, USA	2011	First Single Incision Laparoscopic Hysteropexy	Clinical Presenter and Invited Speaker	60 pioneering surgens in the filed
Pelvic Pain Foundation	2021 Via Zoom	Pelvic Floor Management	Invited Speaker	150 GPs and specialists
Desert Flower Centre Germany	2018	FGM and the Modern Treatments	Invited Speaker	10 specialists

Clemont-Ferrand France	2018	Beyond Gynaecologic Surgery	Invited Speaker	200 gynaecologists
Adelaide University Medical Society	2021	Modern Trend in Gynaecology	Invited Speaker	Teaching 150 medical students
Flinders University Surgical Society	2018, 2021	FGM and the Modern Treatments	Invited Speaker	Teaching to 150 medical students

My 2007 publication – included as publication 12 in this thesis on laparoscopic paravaginal repair of anterior compartment prolapse has received a number of citations (40 so far documented in Google Scholar), which has made substantial use of the author'stableinformation and approaches, demonstrating this research is having a high level of influence on gynaecological practice. For example, the robotic-assisted laparoscopic surgery for hysterectomy and pelvic organ prolapse repair employed by Paraiso et al. (2014) [15], demonstrated the safety and efficacy of this approach for hysterectomy and pelvic organ prolapse repair. Rardin et al. (2011) [16], Maher et al. (2013) [17] and Bakir et al. (2020) [18] have also investigated and reported on the successful use of minimally invasive surgery to repair different types and stages pelvicfloor organ prolapse.

Other research works by me regarding single incision laparoscopic surgery (SILS), such as the 2012 paper [10] and 2013 paper [9] have received significant attention and have been cited 43 times in total (according to Google Scholar). Songet et al. (2013) [19], Takase-Sanchez and Hale (2013) [20], Cerruto et al. (2015) [21], Chenet al. (2015) [22] and Yang et al. (2015) [23] all reported feasibility and safety, cosmesis and patient satisfaction of SILS. Figurelli et al. (2014) [24] conducted a long-term study (>3 years), and compared SILS with multiple port laparoscopic surgery in 134 patientswho underwent both procedures. The study by Strickland et al. (2010) [11] stated, "by contrast, no significant difference was observed between the two methods of access in all the parameters studied in the group of diagnostic laparoscopies … our experience demonstrates that SILS is feasible and safe for gynaecological procedures … this

approach may result in a smooth postoperative course and shorter hospital stay and can thus be promoted to a day care procedure". Regarding the natural orifice translumenalendoscopic surgery (NOTES) method, the publication has been – according to Google Scholar - cited 77 times.

My early publications on the utilisation of PRP therapy and $FxCO_2$ laser for PFDs, have earned several citing articles, which make substantial use of my information, findings, and approaches. This has led to a significant influence on the attempt to make regenerative medicine a non-surgical, non-invasive, and non-hormonal approach, suitable for clinical procedures. For example, Paraiso et al. (2020) [25] conducted the first randomised control trial (RCT) comparing $FxCO_2$ laser with hormone therapy, while Filippini et al. (2020) [26] confirmed the efficacy of $FxCO_2$ laser treatment in postmenopausal women with GSM. The same outcomes regarding feasibility, safety and efficacy were stated in [27, 28] for breast cancer survivor womenwith GSM symptoms to improve vaginal atrophy.

My 2019 [5] publication regarding the use of $FxCO_2$ laser to treat stress urinary incontinence (SUI) has also been further investigated by other researchers [29-32]. Cañadas et al. (2021) [29] for instance, conducted a prospective multi-centre study on patients with confirmed urodynamic SUI graded as mild or moderate. The study stated"vaginal CO_2 laser was found to be effective for mild-to-moderate SUI over a follow- up period of 1 year, according to a variety of objective and subjective parameters. Thewide range of parameters enables optimal patient consultation and subsequent treatment". In parallel with the benefits mentioned in the literature, longer follow-up with larger cohort and RCTs are necessary to better understand the possible short- andlong-term effects. As with all medical treatments and devices, sufficient high-quality evidence is required, to confirm that the decision to use laser-based devices for vaginaltreatments is a safe and effective approach [30-32].

My 2016 [7] publication on the use of PRP for vulvovaginal autoimmune conditions like lichen sclerosus has been cited 31 times (according to Google Scholar).Numerous research works have also been conducted based on the reported outcomes ofthis publication, which have also provided support evidence for the efficacy and feasibility of PRP for the treatment of several gynaecological conditions [33-38]. For example, the concluding remarks stated in a study by Dawood and Salem (2018) [33] were "PRP is an innovative therapeutic modality, as it is affordable, simple, easily performed, and effective...the risks of PRP therapy as infection, bleeding, and nerve damage, appear to be minimal". While this study and many others on PRP therapy conclude that large RCTs are required to confirm its efficacy and safety in gynaecology, many researchers are opportunistic about the therapeutic potential of PRP and are in support of the need to provide more academic training in this area of gynaecology [38,39].

In terms of using combined PRP therapy in combination with $FxCO_2$ laser to treat gynaecological conditions, the outcomes of the author's 2021 [1] publication in using this combinational treatment for urge urinary incontinence has been supported by several other independent studies [29, 38, 39]. While the outcomes are promising, the conclusions remain the same, such that more detailed exploration of these regenerativetherapies is needed to establish the evidence required to prove they are safe and effective to merit their approval as clinical practice.

The PhD by Prior Publication requires the presentation of the research, how it clusters and how it summons an original contribution to knowledge. This is a distinctive mode of doctorate. It develops through a lifetime of research. Therefore, to frame and contextualize this research requires an understanding of the researcher.

Background and Motivation

Pelvic floor disorders such as prolapse, and UI affect approximately 60% of women intheir lifetime [43]. I have been trained in advanced minimally invasive surgery for these conditions.

Despite advanced surgical methods, the failure rates remained high. Moreover, recently the United States Food and Drug Administration (FDA) and the Therapeutic Goods Administration (TGA) removed synthetic mesh and biological material for vaginal repair from the market due to the global Mesh Class Action [40, 44]. Consequently, gynaecologists have been left with conservative management or surgery with native tissue repair, which has a high failure rate, requiring repeat surgery in over 20% of cases. The current conservative management options such as physiotherapy and topical oestrogen rely on patient compliance. In addition, medicationused for conditions such as urge urinary incontinence (UUI), LS, and genitourinary syndrome of menopause (GMS) may have side effects or be contraindicated, leaving patients with reduced quality of life [45, 46].

I have been deeply involved in gynaecological research since 2005. My research can be broadly categorised into advanced laparovaginal surgery and non-surgical management of gynaecological disorders. In advanced laparovaginal surgery research,I have published articles in medical journals on vaginal surgery such as site-specific vaginal repair, innovative biological augmentation of level two pelvic organ prolapse with autologous graft, vaginal natural orifice transluminal endoscopic surgery (vNOTES) [2], and presented newer concepts in vaginal procedures in reconstructive surgery, and in advanced laparoscopy. Since 2013, I have researched and published studies that have investigated the safety, efficacy, feasibility, and outcome of regenerative, non-surgical and non-hormonal treatments for PFDs, and other debilitating gynaecological conditions (such as LS, GSM, FGM), focusing on clinical outcomes and patient outcomes, including changes in quality of life and personal wellbeing. The outcomes of these studies have been promising, suggesting that regenerative medicines such as platelet-rich-plasmid (PRP) therapy, and/or the use of the fractional CO_2 ($FxCO_2$) laser could play an important role as new first-line treatment solutions in gynaecology, that have little/no reliance on patient compliance and are not contraindicated with any existing medications. With there being ample small-scale studies to provide the preliminary evidence

needed to justify their potentialuse in the clinic, to make this a reality, the next stage of investigation is to conduct large, randomised controlled trials.

The research presented in this doctoral thesis confirms my original contribution.Further, I continue to publish on multiple prospective studies utilising $FxCO_2$ laser andPRP for prolapse, recurrent UTI, mesh complication, coital incontinence, abnormal scarring secondary to FGM and transgender surgery. I am also evaluating the role of abiological autologous PRP graft in prolapse repair augmentation. Currently, I have over100 cases, with up to 2 years of follow-up data.

Thesis Objectives

The overarching imperative of my studies has been to introduce new innovative first-line (conservative) management solutions, which do not rely on patient compliance such as PRP therapy and $FxCO_2$ laser. This approach will minimise the need for PFD surgery and other major procedures, that have risk profiles, high failure rates, long recovery times, and an economic liability for the patient and the Australian health caresystem.

When surgery is required and necessary, I seek to maximise the outcomes of these procedures by usingpre-operative regenerative treatment followed by use of an innovative biological autologous PRP graft intra-operatively, and finally post-operative regenerative booster treatment to reduce scaring and healing time. From the initial cohort study conducted by my colleagues and I, we were able to demonstrate that this approach can reduce surgery failure rates and possible complications.

The consolidation and chronological order of my published research in this thesis has allowed me to prepare a coherent narrative about how to improve the quality of life for women - suffering fromPFDs, LS, GSM and FGM - using new/innovative non-invasive, non-surgical, regenerative therapies that if proven safe and effective (both short- and long-term) could act as

new revolutionary first-line treatment solutions that reduce/eliminate the need for surgical intervention.

Thesis Outline

This doctoral thesis provides a coherent picture of my research to investigate the safety,efficacy, and feasibility for the use of various regenerative medicines to treat a wide range of gynaecological conditions that are major contributors to morbidity and reducedquality of life. The regenerative medicines that are the focus of this thesis are PRP therapy and the $FxCO_2$ laser, with studies undertaken to assess the clinical and patient outcomes for these therapies in treating PFDs, LS, GSM, as well as abnormal scarringsecondary to FGM and male-to-female gender affirmation surgery.

Eleven chapters have been presented, to provide a logical explanation of my systemic and scientific progression of work, to meet the defined aims of my research. **Chapter 1** provides a comprehensive critical and updated literature review and addresses the knowledge gaps as well as the significance of my research in more detail. The review provides a comprehensive explanation of PFDs including urge urinary incontinence (UUI), stress urinary incontinence (SUI), and pelvic organ prolapse (POP). The reviewalso focuses on GSM, LS, and FGM, which are other 'begin' yet debilitating gynaecological issues that are significantly overlooked by the Australian health care system. These conditions need to be given greater priority as they have a high prevalence in Australia and are major contributors to morbidity and reduced quality of life.

An explanation of the advanced laparoscopic surgery techniques used to treat PFDs andthe evolution of these techniques into evermore minimally invasive procedures has been provided. Lastly, the potential role and mechanism of different regenerative medicines in gynaecology have been discussed, which includes the challenges/limitations associated with

current treatments and how regenerative medicines like PRP and $FxCO_2$ laser may be able to overcome some of these shortcomings.

Chapters 2 to 11 present a collection of twelve manuscripts that have been published inpeer-reviewed journals (see Section 1.4). These publications present the findings of mywork in applying PRP therapy and/or $FxCO_2$ laser in gynaecology, highlighting their potential use as first-line treatments solutions. The evidence established from these studies (and others) is sufficient to merit approval to investigate these therapies furtherby conducting randomised controlled trials.

The advancement of the laparoscopic techniques in gynaecological conditions and the innovative approaches are further discussed in **Chapters 2 to 6**. These chapters start with laparoscopic paravaginal repair of anterior compartment prolapses followed by graft-reinforced anterior colporrhaphy for central defects. The manuscripts presented in this chapter, illustrate the feasibility and safety of the latest minimally surgical techniques, largely because they not only achieve clinical outcomes, but also significantly improve cosmesis and reduced analgesic needs post-operation. The evolution and success of these advanced surgical techniques has been demonstrated with use of single incision laparoscopic surgery (SILS) in mesh sacrohysteropexy in various publications. Lastly, two manuscripts have been presented that discuss the development of the most advance surgical technique, termed transvaginal natural translumenal endoscopic surgery (vNOTES), which has essentially enabled surgeons and gynaecologists to revisit the vaginal orifice to treat many pelvic and abdominal pathologies in a ‘scarless’ manner.

The manuscript in **Chapter 7** investigates the potential role of regenerative PRP therapy in treatment of LS. Twenty-eight patients with confirmed LS during a two-yeartime were treated with PRP, and it was concluded that almost all women in this study showed improvement in LS symptoms. The manuscripts presented in **Chapters 8 and9** investigate the safety, efficacy,

and feasibility of $FxCO_2$ laser in treatment for GSM and SUI. The improved clinical and patient outcomes reported in these studies providestrong evidence that this regenerative medicine has promising potential to serve a non-surgical, non-hormonal, low risk treatment option for women with GSM and SUI.

In **Chapters 10 and 11**, two manuscripts have been presented that investigate the safetyand efficacy of combined transvaginal $FxCO_2$ laser and PRP treatment for SUI and UUI. The positive outcomes of these innovative studies suggest that this combination of regenerative therapy has the potential to as novel treatment option for SUI and UUIand provides a solid foundation for further investigation for their combined use to treat other gynaecological conditions.

The **Conclusions** provides a comprehensive summary of the main outcomes of this extensive study into PRP therapy and $FxCO_2$ laser and their use in gynaecology. A discussion regarding the future direction for this work is provided, including recommendations for further research and feasibility studies, and highlights the importance of progressing to randomised controlled trials to establish the safety, efficacy, and feasibility profiles required to seek approval to use these therapies as standard clinical practice.

Publications Presented in this Thesis

Chapter 2

1. Laparoscopic paravaginal repair of anterior compartment prolapses.

F Behnia-Willison, EI Seman, JR Cook, RT O'Shea, MJNC Keirse.Journal of Minimally Invasive Gynecology 2007;14 (4), 475-480.

Chapter 3

2. Success rates and outcomes of laparoscopic mesh sacrohysteropexy.

S Daniels, D Robson, M Palacz, S Howell, T Nguyen, **F Behnia-Willison.** Australian and New Zealand Journal of Obstetrics and Gynaecology 2020; 60 (2),244-249.

Chapter 4

3. Single incision laparoscopic surgery (SILS) in gynaecology: feasibility andoperative outcomes.

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Australian and New Zealand Journal of Obstetrics and Gynaecology 2012; 52 (4),366-370.

Chapter 5

4. A laparoendoscopic single-site surgery approach to mesh sacrohysteropexy.

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5. Techniques for Single-Port Urogynecology and Pelvic Reconstructive Surgery(Book Chapter).

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Chapter 6

6. Transvaginal natural orifice translumenal endoscopic surgery (NOTES): a survey of women's views on a new technique.

AD Strickland, MGA Norwood, **F Behnia-Willison**, SA Olakkengil, PJ Hewett.Surgical Endoscopy 2010; 24 (10), 2424-2431.

7. Middle Eastern women's attitudes and expectations towards vaginal natural orifice transluminal endoscopic surgery (vNOTES): a survey-based observational study. **F Behnia-Willison**, T Nguyen, A Rezaeimotlagh, J Baekelandt, PJ Hewett. Surgical Endoscopy, 2021; 1-8 doi: 10.1007/s00464-020-08193-0.

Chapter 7

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Chapter 8

9. Safety and long-term efficacy of fractional CO2 laser treatment in women sufferingfrom genitourinary syndrome of menopause.

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Chapter 9

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Chapter 10

11. Promising impact of platelet rich plasma and carbon dioxide laser for stress urinary incontinence.

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Chapter 11

12. Feasibility, safety, and efficacy of fractional micro-ablative CO2 vaginal (FxCO2)laser treatment and platelet-rich plasma (PRP) in women with urge urinary incontinence.

F Behnia-Willison, TTT Nguyen, S Krneta, C McPhail., S Bahadori, N Willison, P Aryan, A Lam, M Fidela R Paraiso.

Open Access Journal of Gynecology 2021;6: 1 DOI: 10.23880/oajg-16000213

Primary Theme of My Research

The primary theme of my research has been to minimise the necessity for surgery by providing new/innovative first-line, non-invasive treatments for patients (utilisingregenerative medicine). The objective of the non-invasive regenerative medicines is toachieve clinical outcomes, also improve quality of life, personal wellbeing, and toreduce recovery time, side effects/complications, and the economic burden to thepatient and to any health care system simultaneously. Furthermore, when surgery isinevitable, I seek to maximise the outcomes of these procedures via utilisation of pre-and post-operative regenerative treatments to expedite healing, and thus reduce failurerates and possible complications.

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Chapter 1: Literature Review on Pelvic Floor Repair, Novel SurgicalMethods, Regenerative Medicine, and Women's Perspectives of Scarless Surgery

1.1 Introduction

I am a Senior Consultant Gynaecologist at the Flinders Medical Centre and the Southern Adelaide Local Health Network. I hold the position of Senior Lecturer with the College of Medicine and Public Health at Flinders University and I conduct regularworkshops to teach Single Incision Laparoscopy to specialists and senior gynaecologytrainees. I own and operate FBW Gynaecology Plus Pty Ltd in Adelaide, South Australia, which is a practice with a large patient base that provides me with the opportunity to research innovative surgical and non-surgical procedures that benefit women's health.

My medical training has benefitted from international expertise. I completed my MBBSin Ruhr Universitat, Bochum, Germany in 1995. I then undertook Obstetrics and Gynaecology training in Sydney, Australia, and completed my fellowship in Vaginal Reconstructive Single Incision Laparoscopic Surgery (SILS) for the treatment ofbenign gynaecology conditions such as endometriosis, pelvic floor disorders such as prolapse and urinary incontinence. I completed a Master degree in Minimally InvasiveSurgery at the University of Adelaide with the College of Surgeons, which extendedmy gynaecological expertise into Minimally Invasive Surgery. In 2016, I attended advanced gynaecological plastic and reconstructive workshops in USA to treat womenwith abnormal vulvovaginal conditions such as Female Genital Mutilation (FGM) or childbirth trauma.

Throughout my career. I have been constantly searching for new solutions to improve gynaecological outcomes for women. After my extensive training in advanced laparoscopy and vaginal repair, I was the first to perform SILS for gynaecological conditions in Australia and (to the best of my knowledge) performed the first single-

port mesh hysteropexy in the world. In 2013, I conducted the first Australian pilot studyfor MonaLisa Touch^{TM} laser treatment and gynaecological Platelet-Rich-Plasma (PRP)therapy. These treatments have been embraced by numerous Australian gynaecologists who are currently researching the safety and efficacy of each modality. In 2019, I received competitive research grant funding to conduct a randomised control trial of PRP therapy versus normal saline from the Australasian Gynaecological Society of Surgery.

I am currently developing a biological autologous PRP graft for augmentation of vaginal native tissue repair. The need for this product was instigated by the US Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration(TGA) when medical device registration of synthetic vaginal mesh was withdrawn fromthe market [1]. The decision to withdraw these products was due to the high prevalenceof serious adverse complications such as chronic pain, mesh erosion, infection, bleeding, and urinary problems.

Patients' complaints and class actions exposed manufacturers like Johnson & Johnsonwho had falsified their study results and failed to report adverse outcomes to the appropriate regulatory bodies. Currently, gynaecologists are limited in their ability to perform vaginal repair and have had to revert to methods that may be considered outdated and associated with higher failure rates. The fear surrounding the use of vaginal mesh has also negatively affected the use of abdominal mesh, which until now,was considered the 'gold standard' approach for apical vaginal prolapse. The negativemindset towards mesh has also resulted in a significant reduction in the use of syntheticsling surgery, which has been the preferred approach for treating stress incontinence, largely because it is less invasive than laparoscopic colposuspension.

The approach I have adopted to women's wellbeing goes beyond treatment. My focus is to achieve the best possible clinical outcome for each patient, such that there is a significant improvement in quality of life, self-confidence, self-esteem, and empowerment. My holistic and innovative approach to gynaecology is based on the motto, *'I don't treat the problem; I*

treat the person'. This underlying principle is whatdrives and motivates me to achieve the best surgical and aesthetically acceptable outcome possible. My approach to treatment is to always explore the most minimally invasive approach first, from both a hormonal and surgical angle. Ultimately, I strive to establish the 'best' minimally invasive approach to treatment for each and every patient that enters my clinic, making sure that the treatment plan developed is the 'best'in regard to minimal invasiveness, clinical outcome and personal wellbeing.

To demonstrate my dedication to women's health and wellbeing, in 2018, I establishedDesert Flower South Australia (DFSA); a non-for-profit charity that raises awareness and offers medical care to girls and women who are victims of Female GenitalMutilation (FGM). The WHO estimates FGM affects +200 million women and girls worldwide, and in a 2019 report by the Australian Institute of Health and Welfare [2], it was estimated 200,000 girls and women born elsewhere but living in Australia in 2020 had undergone FGM during their lifetime. DFSA offers girls and women medicaladvice and care, surgical treatments, as well as social, psychological, and educational support. Furthermore, information is provided about evidence-based, non-surgicaltreatments and minimally invasive reconstructive surgeries that can be used to restore normal form and function of the external genitalia and vagina.

Through social media, and by presenting at seminars, workshops, conferences, and symposiums, I strive to educate and bring awareness to the world about the many 'socially taboo' issues surrounding women's health. In my efforts to bring these issuesto light, I hope to empower women to voice their concerns, seek help, and to never suffer in silence. I am a devout activist for the intersectional female movement and forthe life of my career (and thereafter) I will always strive to work towards improving women's health and wellbeing.

1.2 Pelvic Floor Disorders

Pelvic Flow Disorders (PFD), such as prolapse, and urinary incontinence are common

conditions among women globally [3]. Many women, however, are reluctant to seek medical or surgical intervention due to possible associated complications, social embarrassment, financial burden, and possible failure rate [3, 4]. Millions of women worldwide are impacted by pelvic floor dysfunction, but personal embarrassment and social taboos prevent open discussion on the topic [5, 6]. The conditions associated with PFDs such as urinary incontinence (UI) [7], faecal incontinence (FI) [8], and pelvic organ prolapse (POP) [9, 10] can have a profound adverse effect on women's social, sexual, psychological, and financial well-being, resulting in social isolation, lossof income, and reduced quality of life. About 40% of women are affected by POP [11],1 in 3 to 4 women will experience UI [12] and 1 in 10 will experience FI [8].

POP is defined as the abnormal descent or herniation of the pelvic organs from their normal position, resulting in an abnormal sensation or function [13, 14]. It is a commoncondition with an incidence of 40-60%, with 12-19% of women requiring surgical correction [18, 41-43]. Main risk factors for POP are parity, vaginal delivery, age, and obesity [3, 46, 47]. Surgery is preferential for younger women with more severe symptoms related to quality of life, bowel, and sexual function [48].

UI is defined as the involuntary loss of urine [12], with the most common forms beingstress urinary incontinence (SUI) and urge urinary incontinence (UUI). SUI is the unintentional loss of urine, because of physical movement or activities that put pressure(stress) on the bladder such as coughing, laughing, sneezing, heavy lifting, jumping andrunning [14, 35, 36]. SUI is the consequence of a weakened or damaged urethral sphincter and/or the pelvic floor muscles, such that they cannot dependably hold urine[15]. SUI is often seen in women after pregnancy and childbirth [37, 38]. UUI is the involuntary loss of urine followed a sense of urgency due to the development of a hypersensitive detrusor muscle [15]. Patients often report triggers of

UUI by events such as running water, handwashing, orgasm, changes in posture or position, and evenchanges in temperature. In Australia, the reported prevalence of UUI is up to 45%, butit is suspected this statistic is significantly underestimated [34].

The gold standard for PFD diagnosis is to perform a urodynamic study, where the pressure within the bladder is recorded according to the woman's sensation of needingto void. For SUI, the pressure within the bladder is recorded when a leak occurs when performing the Valsalva manoeuvre (a breathing technique that involves forced expiration against a closed glottis). A helpful tool in diagnosis is getting the patient to keep a bladder diary. For UUI and SUI it is also important to rule out a urinary tract infection and assess the woman for urethral hypermobility or intrinsic sphincter deficiency, respectively.

1.2.1 Contemporary Treatments for PFDs

Treatments for PFDs are classified as either first-, second-, third- and last-line treatments, with each presenting their own set of advantages and disadvantages [3, 16].Treatment efficacy and success is measured by a patient's report on the reduction of PFD symptoms and subsequent urodynamic studies. The clinical success of available treatments is highly variable and largely dependent on patient compliance, opinion, andawareness/understanding of the condition [17].

First-line treatments are non-pharmacologics and lifestyle modifications such as reducing caffeine intake, taking supplemental magnesium, using a magnetic chair, pelvic floor exercises and bladder retraining, avoiding lifting, constipation, high-impactactivities and to use vaginal pessaries devices (for POP). Hormone replacement therapy(HRT) is also explored if these approaches are unsuccessful in relieving symptoms. Theuse of HRT in women who currently have (or have a history) of hormone-sensitive cancer will need to be treated with more caution as evidence suggests use of HRT is contraindicated in this cohort [17]. Vaginal pessary devices (used for POP and SI) alsohave their own risks such as voiding and faecal dysfunction,

laceration to the vaginal wall, abnormal discharge, bleeding, and in rare cases visceral perforation. In the instance that the device limits a patient's sexual activities, instruction and training mustbe provided so the patient can safely remove and reinsert the device [18].

In severe cases of UUI, where first-line measures fail to relieve symptoms, anticholinergic drugs are prescribed. Although anticholinergics have been shown to improve symptoms, they create a widespread blockade of cholinergic activity that oftenresults (even at low doses) in an array of side effects such as headache, impaired memory, reduced cognitive function, behavioural disturbances, anxiety, insomnia, constipation, flushing and arrhythmias [19]. Furthermore, caution must be taken whenusing some of these medications (e.g., atropine and imipramine) as evidence suggests glaucoma, hyperthyroidism, and tachyarrhythmia are conditions negatively impacted by anticholinergics [19].

Third-line treatments for UUI include percutaneous tibial nerve stimulation (PTNS), and botulinum toxin A. PTNS is a minimally invasive form of neuromodulation that aims to alter/modulate nerve activity, by using a device to produce mild electrical pulsesthat delivers mild electrical impulses to the tibial nerves to indirectly stimulate the sacral nerve plexus, which helps the bladder regulate its function [20, 21]. While this treatment can be quite effective, is well tolerated and has minimal side effects, there isthe need for maintenance therapy and the 'ideal' long-term treatment frequency has yetto be established and largely depends on the individual's response to treatment.

Intravesical botulism toxin A ('Botox') offers clinically significant improvements in adults with UUI by inhibiting calcium-mediated release of acetylcholine vesicles at thepre-synaptic neuromuscular junction in peripheral nerve endings, resulting in temporary chemo denervation and muscle relaxation for up to 6 months [22, 23]. WhileBotox is well tolerated, with minimal risk of systemic side effects, the main disadvantage is that it is a temporary solution. Injections delivered directly into the detrusor muscle need to be repeated to prevent the return of UUI

symptoms.

Last-line treatments for UUI include sacral neuromodulation (SNM) and major surgeries. SNM is another mode of neuromodulation delivered by implantation of the electrical stimulation InterStim® device. InterStim® is effectively a bladder'pacemaker', which acts on the sacral nerves to modify abnormal reflexes in the sacral
and pelvic nerves [24, 25]. However, device replacement is required when the battery runs out, and a high surgical revision of 33% exists due to complications [24]. Major surgeries include detrusor myomectomy, augmentation cystoplasty, urinary diversion, and continent urinary diversion, which are an absolute last-line approach to treat the most severe cases of IUU [24].

Unfortunately, for SUI and POP, when first-line treatments fail, surgical intervention is the next best option. For many years, laparoscopic Burch colposuspension (LBC) was performed for the management of SUI, but during the last decade, it has been replaced by the mid-urethral sling as the standard surgery. Despite LBC having a long-term success rate of 85%, which is equal to that of the mid-urethral sling, it lost popularity largely because it has a longer operating time and in-patient stay [26].

Sling surgery however, has recently become an area of concern, especially following the TGA's concerns surrounding the use of synthetic mesh. As a result of the serious complications that may occur (e.g., severe chronic pain, groin pain, mesh erosion, and bladder perforation) the TGA removed several transvaginal mesh products from the Australian Register of Therapeutic Goods (ARTG). In particular, all transvaginal meshproducts, whose sole use is for the treatment of POP via transvaginal implantation, wereremoved from the ARTG in 2017 [1]. Native tissue repair (NTR) is now the common practice to treat POP, but unfortunately it is associated with a high rate of recurrence (30-50%), and often requires the use of other surgical techniques and grafts to improveoutcomes [5, 27, 28]. For SUI, many

gynaecologists have had to revert to LBC, but having lost its popularity over the last decade, many have either lost the skill, or have not received adequate training to safety perform this surgery. Surgical skills however, can now be easily improved/obtained with the establishment of simulation and interactive learning centres [29, 30]. Patient education to improve compliance can alsosignificantly improve the clinical outcomes of conservative (first-line) treatments [31, 32].

1.2.2 Advanced Laparoscopic Surgery in PFDs

Laparoscopic 'keyhole' surgery, also known as minimally-invasive surgery (MIS), has revolutionised the field of surgery [33]. Every day, hundreds of women in Australia undergo laparoscopic surgery for the treatment of gynaecologic problems [34]. Until recently, this involved open abdominal surgery for the treatment of common conditionssuch as prolapse, incontinence, fibroids, removal of the uterus (hysterectomy) and endometriosis. Modern technology allows surgeons to conduct laparoscopic surgery tothe same standards as open surgery, all thanks to the development of microelectronic techniques. Laparoscopic surgeries have gradually replaced traditional open surgeries due to lesser post-operative morbidity, shorter hospitalisation, faster convalescence, and better cosmetic outcome [33, 34].

1.2.3 Single Incision Laparoscopic Surgery

Single Incision Laparoscopic Surgery (SILS) is a specialised type of MIS, performed by making a single incision at the umbilicus [33-35]. SILS may have superior benefits when compared with conventional laparoscopic surgery by minimising blood loss andpost-operative pain, having a shorter recovery time, improved cosmesis as well as decreasing the potential complications associated with the use of multiple accessory ports [33-35]. SILS is the forerunner of Single Port Robotic Surgery, which is anticipatedto replace all conventional laparoscopies over the next decade.

In 2012, my colleagues and I published a case series analysis of 84 women scheduled to undergo SILS for endometriosis, division of adhesions, hysterectomy, mesh sacrohysteropexy and ovarian cystectomy [34, 35]. This study demonstrated SILS is a feasible and safe technique and can be performed for different gynaecological problems. Patient satisfaction was high (averaged at 8 out of 10) because of the elimination of visible scaring and improved cosmesis, acceptable operative time, and reduced analgesic requirements post-operatively (less pain and complications).In these detailed systematic reviews in colorectal surgeries, Jin et al. (2015) [33] investigated the efficacy of single incision laparoscopic appendectomy and concluded that SILS holds the promise of improving postoperative recovery and cosmetic result with equal efficacy and safety, whereas it is associated with higher surgical difficulty with longer surgical time when compared conventional laparoscopy. Zhao et al. (2015) [35] concluded that SILS is more convenient and has better efficacy than conventional laparoscopy and could provide a promising surgical approach for right colon diseases.

Recently, laparoscopy and endoscopy have been allied together to deliver the most advanced minimally invasive surgery surgical technique called Natural Orifice Translumenal Endoscopic Surgery (NOTES), which offers the possibility of surgery without visible scars [36]. The idea of incisionless surgery is of significant interest to surgeons and others interested in this field of investigation. In gynaecology, NOTES is performed through the vagina (vNOTES). Transvaginal entry offers potential benefits because it gains access to the peritoneal cavity without the need to open an abdominal viscus, hence it reduces complications associated with abdominal incisions (e.g.,bleeding, herination, infection). The development of vNOTES has essentially enabled surgeons and gynaecologists to revisit the vaginal orifice to treat many pelvic and abdominal pathologies in a ‘scarless’ manner [36, 37].

Much of the discussion pertaining to vNOTES however, focuses on technical and training issues, with little attention (to date) paid to the opinions of women. A study byStrickland et al.

[33] sought the perceptions of 300 female health care workers and patients in relation to their views on vNOTES. In all groups and across all ages, significant skepticism was documented for peritoneal access using the transvaginal route. Furthermore, while vNOTES offers women a scarless operation with the possibility of less pain than that experienced with standard laparoscopic surgery or SILS, the effect of vNOTES on sexual function was expressed as a particular concern by younger women. In Australia, women remain to be convinced about the potential advantages of the emerging vNOTES technology [36, 37].

There are several recent small-scale studies that have been reported for the use of vNOTES to treat POP with positive results. A study by Liu et al. [38] described the surgical techniques and short-term outcomes for 26 cases of vNOTES sacrocolpopexyfor the treatment of stages II to IV POP. Statistically significant improvements in bothphysical prolapse and quality of life at one month after surgery were observed and there were no complications of mesh exposure, pain, hematoma, infection, or new urinary incontinence. The study concluded, that vNOTES is a feasible approach for sacrocolpopexy, with promising short-term efficacy and safety data. The same conclusion was made in a later study by Lu et al. [39], who conducted a retrospective study for 35 patients with severe POP (≥stage III), where during 1-13 months of follow-up, no severe complication or recurrence were observed. Both studies concluded that larger studies across multiple sites and surgeons should evaluate the long-term efficacyand safety profile of vNOTES sacrocolpopexy.

1.3 Benign Gynaecological Conditions with High Morbidity and Reduced Quality of Life

1.3.1 Genitourinary Syndrome of Menopause (GSM)

Lif expectancy for women has increased significantly during the past century andmany women will now spend more than one-third of their lives in menopause [40] Many of these postmenopausal women, who expect to maintain good health and a highquality of life into their postmenopausal years, consider sexual health and relationshipsatisfaction to be of paramount importance [41-43]. The sexual health of postmenopausal women can be undermined by the progressive ageing of the body, as well as by Genitourinary Syndrome of Menopause (GSM) [44]. GSM, previously known as atrophic vaginitis, is a multifaceted oestrogen-dependent condition that oftenoccurs as a manifestation of menopause [45]. The fall in oestrogen resulting from menopause causes the vaginal epithelium to become thin and pale, lose vascularity and collagen fibres, leading to decreased engorgement, lubrication, and reduced elasticity [46, 47]. Vaginal smears of patients suffering from GSM demonstrate a unique morphology, whereby

superficial cells are scant and there is an increase in intermediate and parabasal cells in hypoestrogenemic conditions, which along with decreased glycogen-rich cells, promotes increased vaginal pH ≥5 [48]. These conditions increasethe risk of developing symptoms such as dryness, burning, itching, irritation, abnormaldischarge, recurrent thrush and superficial dyspareunia, which are likely to cause an altered response to sexual stimuli [49]. The discomfort associated with sexual intercourse (dyspareunia) often leads to a vicious cycle of decreased desire, arousal, orgasm, and frequency of coitus, resulting in loss of self-confidence and depression throughout the pre- and post-menopausal stages [50]. It is estimated that about 8-22% of pre-menopausal women and 40-57% of post- menopausal women experience symptoms resulting from GSM [51-53], however, only 1 in 5 women experiencing these symptoms will consult a physician on issues related to GSM [42, 53]. Current therapies for GSM include hormonal therapy with oestrogenalone (ET) or with oestrogen-progestin (EPT). Whilst these therapies may be effective in increasing vaginal lubrication and reducing dyspareunia, they have not been shown to consistently increase sexual desire or activity [46, 54].

1.3.2 Lichen Sclerosis

Lichen Sclerosis (LS) is a chronic autoimmune inflammatory dermatosis characterisedby a lymphocytic response that has a predilection for the genital skin in both sexes andan association with several other autoimmune diseases [55, 56]. Women are 6 to 10 times more likely to be affected than men. LS may involve complications of erosion, vaginal atrophy, and scarring as a result of inflammation and altered fibroblast function,leading to fibrosis of the upper dermis [57]. There can also be purpura, hyperpigmentation, fissures, and edema. LS mainly affects the anogenital area of the skin, in more than a 5:1 ratio when compared with extragenital skin [55, 58]. LS affectsaround 1 in 80 women, where ~4% of women with LS will go on to develop vulvar cancer [59]. LS can happen at any age but is most common in middle-aged and elderly women.

The aetiology of LS is uncertain although there is evidence for linkages between autoimmune mechanisms and the pathogenesis of this condition. LS is a scarring process and may cause loss of the labia minora, sealing of the clitoral hood, and buryingof the clitoris. In women, vulvar LS can present with progressive pruritus, dyspareunia,dysuria, or genital bleeding [55, 60]. These symptoms may also occur in post- menopausal women due to the lack of estrogen in the vaginal area. LS has a considerable impact on affected patients physically, emotionally, and psychologically,affecting their quality of life through pain and embarrassment and having a significantimpact on their sexual lives, and intimate relationships. In cases where patients areresistant to therapy, the quality of life can be severely impacted, hence other alternative treatments need to be studied and considered [57, 60].

1.4 Emerging Challenges in Western Medicine

To add to the complexities associated with treatment, numerous gynaecological conditions have only recently become prominent in Western medicine. Globalisation has led to the prominence of gender equality and reproductive rights within the global community. As a result, women in Australia are more frequently approaching pelvic floor surgeons with atypical gynaecological conditions, such as FGM complications and male-to-female gender affirmation scars/complications [61, 62]. Gynaecologists are also faced with the challenge to find alternative treatment modalities for women that are, or consider themselves to be, very well informed. Women are increasingly better informed, educated, and connected through social media and wish to be a part ofthe doctor-patient decision making [63, 64]. With greater awareness and education, women worldwide are increasingly seeking non-surgical and non-hormonal treatmentsfor these disorders [6]. Research into non-surgical and non-hormonal treatments, however, has been limited and more research is required to develop new knowledge, processes, and clinical practice that can assist women with PFDs and other gynaecological conditions such as LS and GSM [6, 8, 65]. There is now a well- established

trend into investigating the new use of various regenerative medicines as minimally invasive treatments to achieve safe and effective tissue healing and regeneration, with minimal downtime and complications [66, 67].

1.5 Regenerative Medicine in PFDs, LS, and GSM

Following the problems associated with surgical and conservative management ofPFDs, and the emerging issues for Western medicine, this section provides an overview of research published by my fellow researchers and I [41, 55, 68, 69]. Taken together, the findings from these studies seek to overcome some of the problems described aboveand are the centrepiece of this thesis. This section presents non-hormonal and/or non- surgical treatments that minimise patient compliance requirements and include, Fractional CO2 Laser (FxCO2), Platelet-Rich-Plasma (PRP), or a combination of both. Each treatment is the subject of one or more of the included publications and have generated positive clinical outcomes, such that when used independently or in concert,the potential they have to improve women's health could be revolutionary and liberating.

1.5.1 Fractional CO2 Laser Therapy

Laser is an acronym for Light Amplification by Stimulated Emission of Radiation. Laser treatments are used for many therapeutic purposes in multiple disciplines, suchas dermatology [70], plastic and reconstructive surgery [71], ophthalmology, and more recently, gynaecology [69, 72-74]. The $FxCO_2$ laser requires adequate water- content of the tissue for the ablative and thermal effect to take place. As illustrated inFigure 1, the $FxCO_2$ laser has a biphasic action. First, it superficially causes microablative trauma to the tissue and secondly, generates heat into the deeper layer of the tissue to promote the production of heat shock proteins 70 and 47. The transferof heat to cells is likely responsible for the denaturation of collagen (i.e., it loses its three-dimensional structure and activity) [68]. Since the laser reaction is exothermic, the heat generated then dissipates into adjacent cells and causes the 'residual thermaleffect', which is thought to stimulate collagen production [75]. In essence, themicrotrauma and heat

shock proteins regenerate tissue through a cascade of biological responses, including the activation of fibrocytes to fibroblasts, formation of new collagen elastic fibres, activation of endothelial growth factor (GF), activation of GF-β, and new extracellular matrix [76, 77]. The effects of $FxCO_2$ laser can last for a period of six months, before repeat treatment is needed. Since 1990, scientists have been working to reduce the adverse effects $FxCO_2$ laser therapy through methods based on Rox Anderson's selective photothermolysis theory and the development of new scanners and laser devices that deliver short pulses with high energies [78].

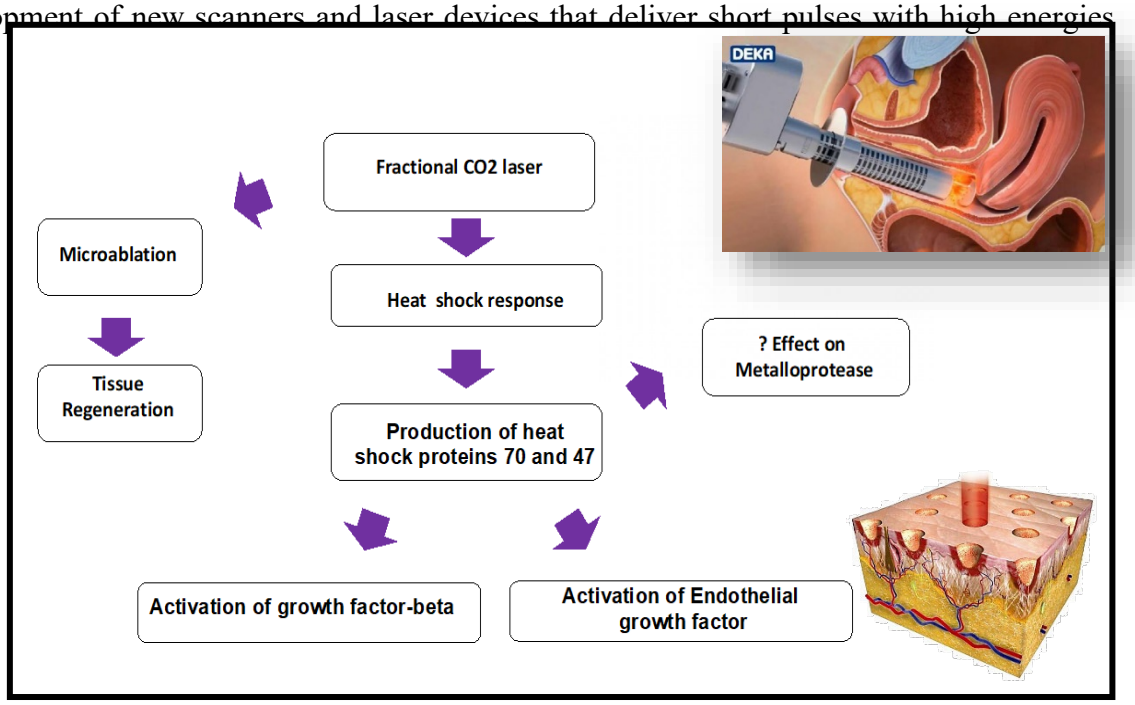

Figure 1. The schematic effects of $FxCO_2$ laser on the tissue [68].

1.5.2 Molecular Mechanism of the FxCO2 Laser

Wound healing is a complex biological process. Blood coagulation, inflammation, new tissue formation, and tissue regeneration are involved. These processes require the participation of several cell types such as keratinocytes, fibroblasts, endothelial cells, and immune cells [79]. Cell migration, proliferation, differentiation, and deposition of extracellular matrix are activated during wound healing. In particular, the proliferation and migration of fibroblasts play an important role in the formation of granulation tissue and lead to wound closure.

During fibroblast migration and proliferation, several intracellular and intercellular pathways are activated and coordinated [80]. Recent studies focusing on oral fibroblasts in dentistry have reported that the use of $FxCO_2$ laser can heal wounds. Studies have shown that a pulsed CO_2 laser increases the secretion of fibroblast GF in normal and colloidal skin fibroblasts *in vitro*, therebyenhancing cell replication and the increased ability of collagen organisation against fibrosis [81, 82]. Previous experiments have demonstrated $FxCO_2$ laser can induce proliferation of fibrochondrocytes and fibroblasts. During wound healing via $FxCO_2$ laser, proliferated fibroblasts migrate to the wound area, compose the new extracellular matrix, and conduce wound healing. Dermal fibroblast activation, proliferation, and migration during $FxCO_2$ laser treatment also occurs [82]. CO_2 laserincreases fibroblast proliferation and appears to stimulate secretion of basic fibroblastGF and TGF-β1. Due to the function of these GFs, the use of pulsed CO_2 laser may support normal wound healing. These findings may explain the beneficial effects of CO_2 laser resurfacing at the cellular level and support the use of pulsed CO_2 laser in the management of colloidal scar tissue [71]. Other studies have shown that use of theCO_2 laser increases cell proliferation and secretion of angiogenic molecules byactivating the cellular redox pathway and transient increase in mitochondrial reactiveoxygen species [40, 83].

1.5.3 FxCO2 Laser Therapy for Vaginal Regeneration and Rejuvenation

$FxCO_2$ laser can stimulate proliferation of the mucosal cells, collagen production and neovascularisation in the vulvo-vaginal walls and urinary tract structures. Each laser treatment stimulates the tissue regeneration process, which takes numerous weeks.

Significant improvements can be seen even after the first treatment, such that the vaginal mucosa becomes more nourished and hydrated, and the epithelium becomes thicker, more toned, and elastic [84, 85]. The correct vaginal pH becomes reestablished, which helps maintain its natural protective barrier, as well as the dominance of *Lactobacillus* spp., and

reduces the risk of infection. Enhanced vaginaltissues at the urethral opening may reduce problems with incontinence and improve sexual function [44, 86]. $FxCO_2$ laser vaginal regeneration and revitalisation in itself however, cannot guarantee a heightened sexual response, since desire, arousal and orgasm are complex, highly personal responses [50].

The role of $FxCO_2$ laser in uro-gynaecology has largely focused on treating GSM, which works on the basis of microablation of 20-30% of the surface area [71]. In 2014,the FDA approved $FxCO_2$ laser for incision, excision, ablation, vaporisation, and coagulation of body soft tissues (not specifically the vagina) in various medicalspecialties [40, 47, 87]. Despite all these capabilities, the role of $FxCO_2$ laser in gynaecology needs to be researched further in multiple clinics to establish the safety, efficacy, and possible adverse side effects [88]. $FxCO_2$ laser has been used in the treatment of GSM, particularly to address vaginal dryness, pruritis and dyspareunia [89]. The results are promising, with improved vaginal health index due to thickened epithelium, neovascularisation, and neocollagenisation. Histological findings confirm increased collagen, elastin and epithelial cell layers after $FxCO_2$ laser therapy [88, 90]. Clinical applications of $FxCO_2$ lasers in gynecological diseases have so far, proven to be safe and effective, and aim to extend beyond GSM [68, 91].

1.5.4 Platelet-Rich-Plasma Therapy

Platelet-Rich-Plasma (PRP) therapy is another non-invasive, non-hormonal method fortissue repair, healing, and regeneration**.** There are several ways of preparing PRP, the most common method consists of a two-step process, where a patient's blood is drawnand initially centrifuged to separate red blood cells, which is followed by a second centrifugation step to concentrate the PRP [83, 92]. The PRP is the component of bloodthat is thought to promote tissue healing and regeneration as it contains important GFs,cytokines, chemokines, proteins, nutrients, minerals, and monocytes, all of which are known to play an important biological role in the process of wound healing [66, 93, 94].

The theory behind PRP, is that when it is applied to damaged tissue, it not only hydratesand nourishes the tissue with important minerals and vitamins, but following platelet activation, the release of various bioactive molecules contributes to cell migration, proliferation, differentiation, angiogenesis, removal of tissue debris, and regeneration of new healthy tissue [95]. The application of PRP has minimal risk and negligible sideeffects due to its autologous nature (i.e., immunological complications are mitigated asPRP is prepared from the patient's own blood) [96, 97].

PRP has been widely used in orthopaedics, dentistry, dermatology, and cosmetic surgery fields to facilitate tissue repair and regeneration, wound haemostasis, wound sealing, reduced scarring, augmentation of bone grafts, and treatment of tendonitis [94, 98, 99]. Increased epithelialisation has been demonstrated in both acute traumatic wounds and chronic diabetic wounds when treated with PRP [100]. PRP with or without microneedling has also been described as a new and promising modality for the treatment of atrophic acne scars [97, 101].

While the centrifugation method is the standard process for PRP preparation, new methods are being explored. For example, a study by Behnia-Willison et al. [64] investigated a new regenerative approach based on injection of PRP to treat 28 womenwith a histologic diagnosis of LS and were unresponsive to topical steroid therapy. Theresults were promising, such that a significant reduction in symptoms, atrophy and degree of sclerosis were observed.

1.5.5 Molecular Mechanism of Platelet-Rich-Plasma

In addition to supraphysiological platelet counts, PRP contains water, minerals, coagulation factors, GFs, chemokines, cytokines, and other plasma proteins. As illustrated in Figure 2, and outlined in Table 1, upon platelet activation, the release of numerous bioactive molecules is thought to facilitate wound homeostasis and healing,and tissue regeneration [102].

On a molecular level, the GFs stimulate healing by attracting stem cells in the new formed

fibrin matrix, which triggers tissue repair and regeneration. The GFs also suppress the cytokine response, which limits inflammation. The recruitment of macrophages promotes tissue healing through phagocytosis of old cells, which are replaced with a population of new cells, that give rise to new and healthy epithelial tissue. PRP also contains a small quantity of leucocytes, which have an antimicrobial role in the tissue regenerative process [103]. Another mechanism of action of PRP is through its effect on fibroblast cells. Studies have shown PRP increases the proliferation, migration and colony formation of tissue fibroblast cells and thus can potentially repair scars [102].

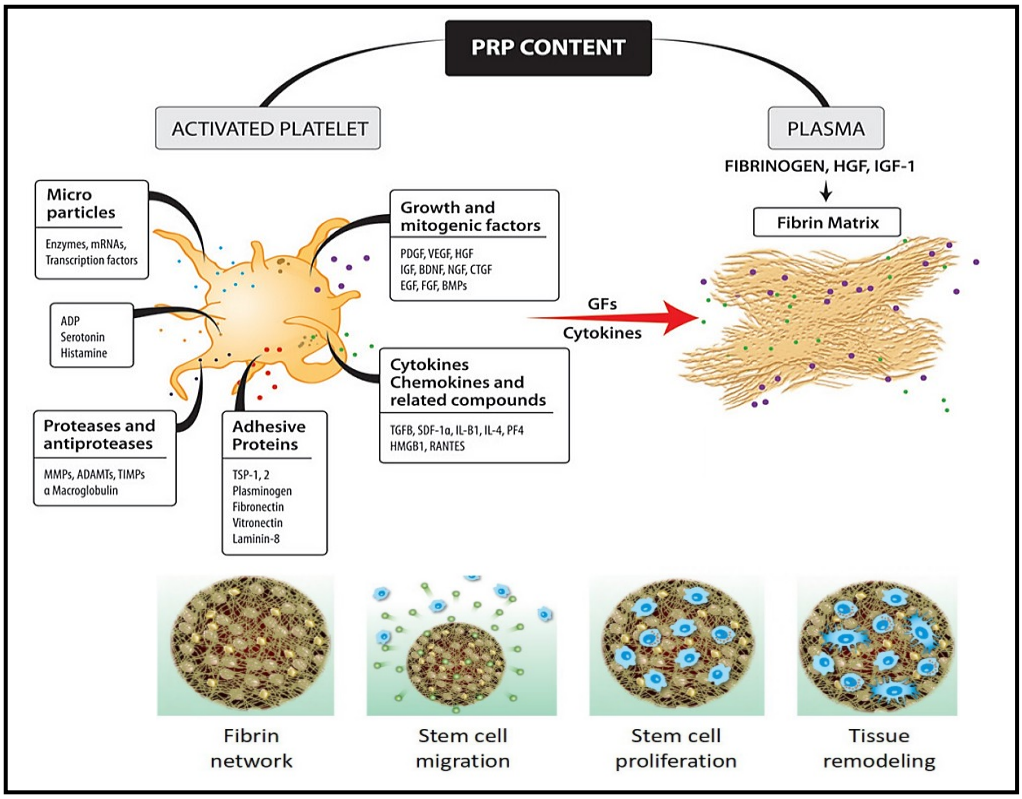

Figure 2. A schematic of the important bioactive molecules and mediatorsreleased from activated PRP for tissue repair and regeneration [104].

In recent years, PRP has been the focus of many different research projects, each generating their own set of promising results. Given that the protocols for PRP preparation often vary widely between these studies, and are not well documented, it makes it very difficult to compare results across different studies.

Table 1. The types of GFs present in PRP and their role in the processof tissue repair and regeneration [105].

Growth factor	**Function**
Platelet-derived GF	Enhances collagen synthesis, bone cell proliferation fibroblast chemotaxis and proliferative activity, and macrophage activation.
Transforming GF-β	Enhances synthesis of type I collagen, promotes angiogenesis, stimulates chemotaxisof immune cells, inhibits osteoclast formation and bone resorption.
Vascular endothelial GF	Stimulates angiogenesis, migration andmitosis of endothelial cells, increases permeability of the vessels, stimulates chemotaxis of macrophages and neutrophils.
Epidermal GF	Stimulates cellular proliferation, differentiation of epithelial cells, promotescytokine secretion by mesenchymal and epithelial cells.
Hepatocyte GF	Angiogenesis stimulator
Fibroblast GF	Promotes proliferation of mesenchymal cells, chondrocytes and osteoblasts, stimulates the growth and differentiation of chondrocytes and osteoblasts.
Insulin-like GF-1	Promotes cell growth, differentiation, recruitment in bone, blood vessel, skin andother tissues, stimulates collagen synthesis together with Platelet-derived GF.

To establish a simple method for organising and comparing the results in the literature, the PAW classification system was developed. PAW isbased on three main components: (1) the *absolute number* of platelets, (2) the mode of *plateletactivation*, and (3) the presence or absence of *white blood cells.* By analysing these three components, publications on PRP can be accurately compared [105, 106].

1.5.6 Applications of PRP Therapy

Recently, PRP therapy has been used to treat skin conditions, chronic wounds, scars, burns, and alopecia areata [102, 107]. In regard to soft tissue defects, since PRP contains antibacterial and anti-inflammatory compounds, it also plays an important role in diminishing edema, ecchymosis, and infection [99, 108]. The repair and restorative effects of PRP on bones, tendons, cartilage, muscles, and skin has led to its use in orthopedic and plastic surgery [109] [110, 111]. PRP has also been investigated as a means to treat osteoarthritis [111, 112].

1.5.7 PRP Therapy for Vaginal Regeneration and Rejuvenation

Conventional vaginal reconstructive surgery has been performed over many decades. PRP therapy has the potential to serve as a non-surgical method and/or as an adjuvant treatmentfor pre-, intra-, and post-operative management for PFDs [113-115]. As previously described, the PRP is extracted, separated, and concentrated from the patient's blood, and then injected directly into the repair site. The injected platelets are activated, and the bioactive molecules released stimulate the tissue repair and regeneration process (see Figure 2). Various studies have demonstrated that this method can improve sexual dysfunction by reducing vaginal dryness, atrophy, and laxity [116-118].

Figure 3. Photograph of different stages of preparing PRP from blood.

Figure 4. The different applications of PRP from tissue regeneration to use in surgery as an autologous PRP graft (Curtesy of RegenLab).

1.5.8 FxCO2 Laser in Combination with PRP Therapy

Together, $FxCO_2$ laser and PRP have synergistic properties that can expedite tissue repair, fibroblast proliferation, and increase collagen production [68, 119]. The combination of

$FxCO_2$ laser and PRP is superior to individual treatments due to antibacterial and anti-inflammatory properties of PRP, as shown for treatment of wrinkles, scars and hyperpigmentation [120]. The use of $FxCO_2$ laser with PRP has also achieved effective repigmentation, while $FxCO_2$ laser alone, has shown poor improvement. Recently, the application of combining of $FxCO_2$ laser with PRP showed promising effect in reducing the symptoms of GSM and SUI [68, 90]. Table 2 provides a summary of just some (of the many) studies that have been conducted to test the safety and efficacy of $FxCO_2$ laser, PRP therapy, or both for the treatment of various gynecological issues.

Table2. A summary of some of the small-scale studies conducted to investigate the safetyand efficacy $FxCO_2$ laser, PRP therapy, or both for the treatment of various gynecological issues.

[1]APFQ: Australian Pelvic Floor Questionnaire

[2]VAS: Visual Analogue Scale

[3]PFDI: Pelvic Floor Distress Inventory Questionnaire

[4]ICIQ-UI SF: International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form

[5]VHI: Vaginal Health Index

[6]OAB-q: Overactive Bladder Questionnaire

[7]FSFI: Female Sexual Function Index

[8]ICIQ-FLUTS: International Consultation on Incontinence Questionnaires- Female Urinary Tract Symptoms

[9]PGI-I: Patient Global Impression of Improvement Index

[10]KHQ: King's Health Questionnaire

$FxCO_2$ Laser Studies					
Study	Therapy	Indication	Study details	Assessment	Main findings

Behnia-Willison,2019 [69]	MonaLisa Touch®	SUI	Prospective observation (n=58), 12–24-month follow-up.	APFQ[1]	80% and 75% of patientsreported improvement inSUI symptoms at 3-6 month and 12–24-month follow-up, respectively.

Najafian,2018 [121]	IDS $FxCO_2$	SUI	Clinical trial (n=55),6-month follow-up.	SUI severity, VAS[2]	Reduction of SUI severity score from 8.56±0.62 at baseline to7.87±0.93 at 6-month follow-up ($p<0.0001$).
Menachem, 2016 [122]	Alma FemiLift	SUI	Retrospective multicentre evaluation (n=133), 3–12-month follow-up.	PFDI[3], VAS, VVA symptom questionnaire	80.6% reported not usingsanitary pads following treatment, compared to 47.8% prior to treatment.Over 97% of patients reported no or mild urgency compared to the initial results of 7.9% and 5.3%, respectively.

Franic, 2020 [91]	Alma FemiLift	SUI	Prospectivetwo-centre study (n=85), 6-month follow-up	ICIQ-UI SF[4], coughtest, VAS	Mean ICIQ-UI SF score reduced from 12.0 (baseline), 7.0 (post-first treatment), and 3.5 (post-second treatment) (P < 0.001). ICIQ-UI SF score was 5 at 6-month follow-up. SUI symptoms improved with53.5% of women experiencing moderate to
					severe SUI symptoms at6-month follow-up compared to 73% at baseline.
Perino, 2016 [85]	MonaLisa Touch ®	Overactive bladder	Prospective observation(n=30), 1 month follow-up	VHI[5], VAS, micturition diary, OAB-q^6	Improvements at T1 (1 month) were seen in VVA symptoms, VHI score, micturition diary, urge episodes, and OAB-q (p<0.0001)

Behnia - Williso n,2017 [41]	MonaL isa Touch ®	GSM	Prospecti ve observatio n(n=102), 12–24-month follow-up	APFQ, GSM symptoms	84% of patients reported significant improvementsin GSM symptoms. Secondary outcomes showed statistically significant improvement (p>0.003).
Sokol, 2016 [123]	MonaL isa Touch ®	GSM	Prospecti ve observatio n (n=30), 12-month follow-up	VAS, VHI, FSFI[7],12-item Short Form questionn aires	Significant improvements seen in VAS for all symptoms aswell as in VHI and FSFI (p<.001). 92% ‘satisfied’or ‘very satisfied’ with treatment outcomes.

Isaza, 2018 [124]	MonaLisa Touch ®	GSM	Prospective observation(n=161), 36-month follow-up	1-hour pad weight test, ICIQ-UI SF	Significant improvement in ICIQ-UI SF scores and1-hr sanitary pad weight test at 12 months (both p<0.001), 24 months (both p<0.001), and 36 months (both p<0.001). Improvements remained statistically significant at 36-month follow-up.
Athanasiou, 2018 [52]	MonaLisa Touch ®	GSM	Retrospective observation(n=94), 12-month follow-up	VAS, ICIQ-UI SF, ICIQ-FLUTS[8], Urogenital Distress Inventory-6,FSFI	Significant improvement in symptom severity at 1-month post-final treat. Dyspareunia and dryness decreased from 9 and 8 atbaseline to 0 for both symptoms (P<0.001) FSFI and frequency of sexual intercourse increased from 10.8 and 1 at baseline to 27.8 and 4 (P<0.001). These benefits remained unchanged at 12-month follow-up.

Paraiso, 2019 [53]	MonaLisa Touch® vs. vaginal E2 cream	GSM	RCT (n=69), 6-month follow-up	VAS, PGI-I[9]	As per PGI-I, 85.8% of laser participants rated their improvement as 'better or much better' and 78.5% reported being either 'satisfied orvery satisfied' comparedto 70% and 73.3% in the oestrogen group.
Pitsouni, 2016 [40]	MonaLisa Touch®	GSM	Prospective observation (n=53), 3-month follow-up	VHI, FSFI, ICIQ-FLUTS, ICIQ-UI SF, Urogenital Distress Inventory-6,KHQ[10]	VMV, VHIS, and FSFI increased significantly. Significant improvementseen in symptoms of dyspareunia, dryness, burning, itching, dysuria,frequency, UUI, SUI, and scores on the ICIQ- FLUTS, ICIQ-UI SF, UDI-6 and KHQ at 3-month follow-up.
Cruz, 2018 [46]	MonaLisa Touch® vs.	VVA	CT (n=45), 5-month follow-up	VHI, VAS, FSFI	Significant improvementseen in VHI in all study groups. Improvements indryness, dyspareunia, and burning seen in

					laser
	vaginal E2 cream				+ oestriol and laser only($p<0.009$). Laser + oestriol had significant improvement in FSFI score ($p<0.004$).
Salvatore , 2013 [89]	MonaLisa Touch ®	VVA, vaginal laxity, UI	Prospective observation(n=38), 1 month follow-up	VAS	Reduction in mean VAS values for dysuria (1.3 to 0.4), urinary urgency (2.6 to 0.8), UI (1.6 to 0.7), and SUI (3.1 to 1.3) at baseline and after 3 sessions, respectively. Histology showed growth of new collagen and elastic fibres.
Salvatore , 2015 [86]	MonaLisa Touch ®	VVA	Prospective observation (n=50), 3-month follow-up	FSFI, 12-item Short Form questionnaires	VVA symptoms - vaginaldryness, vaginal burning,vaginal itching, dyspareunia, dysuria- improved at 12-week follow-up $p < .001$). VHIS increased from 13.1 ± 2.5 (baseline) to. 23.1 ± 1.9 (12-week

					follow-up) ($p < .001$).

					Significant improvementin quality of life ($p<.001$).
PRP Therapy					
Behnia-Willison,2016 [55]	PRP injection	LS	Prospective observation (n=28), 12–24-month follow-up	Verbal interview on symptom severity, colposcopy	On colposcopy at 12 months, lesions not seen in 8, lesions smaller in 17, and lesions unchanged in 3 women. 15 women experienced no associated symptoms and 13 had intermittent symptoms including itch, pain, and dyspareunia.
$FxCO_2$ Laser and PRP Therapy					
Behnia-Willison,2020 [68]	MonaLisa Touch®	SUI	Prospective observation (n=62), 12-24 month follow up	APFQ	66% women reported improved SUI symptomsat 3–6-month follow-up ($p<0.001$). Of the 37 women reached for 12-month follow-up, 62% reported maintained improvements in SUI symptoms.

Gaspar, 2011 [125]	MonaLisa Touch ®	VVA	Case control (n=92), 3-month follow up	Sexual health, histology	Decreased discomfort during sex and improvement in vaginalmucous histology.

1.5.9 A Biological Autologous PRP Graft for PFDs

Use of polypropylene transvaginal mesh is no longer accepted in the global market due to unfavourable publicity related to complications of increased reoperation rates, mesh erosion, and dyspareunia [126-128]. The latest trend has shifted towards abdominal or laparoscopic mesh sacrocolpopexy, and innovative approaches to mesh erosion management [129, 130]. Other surgical techniques using biological autologous grafts or absorbable mesh to augment POP have been trialled, with systematic reviews based on low quality evidence demonstrating minimal advantages regarding rates on awareness of prolapse or reoperation, in comparison with native tissue repair (NTR) [18, 131-133].

As summarised in Table 2, low-to-moderate quality evidence suggests higher recurrence rates for anterior prolapse after NTR than with biological grafts [134]. Recent RCTs comparing various surgical approaches, robotic-assisted techniques, mesh, or sutures conclude insignificant difference regarding effectiveness or incidence of recurrence, requiring or currently undergoing further investigation [135-142]. Pre-operative ultrasonography has been assessed showing minimal influence on planned surgery [143, 144]. New paravaginal repair techniques with and without biological graft show promising results [145-147].

As an alternative to current techniques (e.g., NTR), I have considered the use of a novel biological autologous graft prepared with PRP, to augment POP surgery (see Figure 5). This type of graft will act as a biological support, while also delivering PRP to facilitate the repair

and regeneration of damaged tissue/organs. I hypothesise that when a biological membrane, created from PRP and calcium gluconate is attached to the endopelvic fascia, the release of bioactive molecules from the activated platelets, will accelerate the process of tissue healing and regeneration of the endopelvic fascia. To date, the use of this kind of graft in gynaecological surgery is entirely novel and has not been previously described in the literature.

Table 3. A summary of the studies conducted to investigate the safety and efficacy different types of grafts used in the field of gynaecology to treat various PFDs.

[1]POP-Q: International Continence Society Pelvic Organ Prolapse Quantification

[2]PFDQ: Pelvic Floor Dysfunction Questionnaire

[3]MS-CCAE: Market Scan Commercial Claims and Encounters Data (for baseline demographics)
[4]ICD-9: International Classification of Disease Diagnosis Code 618x. [5]ePAQ-PF: Electronic Personal Assessment Questionnaire-Pelvic Floor[6]ASA: American Society of Anaesthesiologist score
[7]SSQ-8: Surgical Satisfaction Questionnaire-8 [8]PFDI: Pelvic Floor Distress Inventory Questionnaire[9]UDI: Urinary Distress Inventory
[10]CRADI: Colorectal-Anal Distress Inventory

[1]POPDI: Pelvic Organ Prolapse Distress Inventory

[12]PGI-I: Patients Global Impression of Improvement

[13]PFIQ: Pelvic Floor Impact Questionnaire

[14]AAS: Activity Assessment Scale
[15]IUA/ICS International Urogynecological Association/ International Continence SocietyJoint Classification System

Epidemiology Studies				
Study	Study Objective	Study details	Assessment	Main findings
Hendrix, 2002 [65]	Cross sectional analysis to describe prevalence of POP across different ethnicities	n=27, 342 No follow-up	Baseline questionnaire for demographics and patient characteristics, POP-Q[1].	For women with a uterus,the rate of uterine prolapse was 14.2%, cystocele 34.4%, and rectocele 18.6%. AfricanAmerican women have lowest risk of prolapse. Hispanic women have highest risk.
Ellerkmann, 2001 [148]	Cross sectional analysis to compare symptoms related to pelvic floor dysfunction with location and severity of prolapse.	n=237 2yr follow-up	PFDQ[2], empty supine stress test, postvoid urine measurement, urethral mobility, POP-Q.	Women with POP experience symptoms that do not necessarilycorrelate with compartment specific defects. Increasing severity of POP is weakly-to-moderately associated with specific
				symptoms. Voiding dysfunction was associated with increasing severity of

				anterior and apical POP.
Wu, 2014 [149]	Cross sectional analysis to estimatelifetime risk of SUI, POP, or both using population-based data.	n=101 77,480 3yr follow-up	MS-CCAE[3], ICD-9[4]	Estimated lifetime risk ofsurgery for SUI or POP in women is 20% by age of 80 years. Separately, 13.6% for SUI and 12.6% for POP.
Elenskaia,2013 [4]	Prospective cohortstudy to evaluate changes of pelvic organ support, symptoms, and quality of life afterchildbirth.	n=182 5yr follow-up	POP-Q, ePAQ-PF[5].	Prolapse symptoms worsened at 14 weeks ($p<0.001$), and 1 year ($p=0.006$) after vaginal delivery but not at 5 years. No changes in prolapse symptoms occurred after caesarean. Significant increase in faecal incontinence was observed in both deliverygroups 5 years after delivery.

Kapoor, 2009 [150]	Prospective, single-centre study to establish whether symptom severity influences women's choice of pessaries or surgery.	n=680 5yr follow-up	Sheffield Prolapse Symptoms Questionnaire.	251 women chose surgery whereas 429 chose pessaries. Womenchoosing surgery were younger with higher bother scores for abdominal pain (p = 0.04), need for vaginal digitation (p = 0.02), andincomplete bowel emptying (p = 0.01. Women choosing surgerywere more likely to be sexually active (p < 0.0001) with more perceived issues with sexual function.
Surgical Techniques				
Unger, 2017 [27]	Retrospective comparative, cohort, single tertiary centre analysis to estimaterates of recurrent POP, 6 years after	n=1381 6yr follow-up	Health care system-wide electronic medical recordfor preoperative and	Estimate recurrence ratesfor uterosacral ligament colpopexy, laparoscopic,and robotic sacral colpopexy may be as high as 40-60% 6 years after surgery. Median

	different surgical techniques.		postoperativ edata, POP-Q.	(range) months for failure were as follows: uterosacral 17.1 (7.6-41); laparoscopic 10.1 (4.7-25.1); robotic 9.7 (1.6-17.2). By year 6, the recurrence rates were 43%, 49%, and 57% respectively.
Tibi, 2019 [28]	Retrospective, cohort, multicentre analysis to compare complications associated with different POP repair methods in elderly women.	n=680 5yr follow-up	ASA[6] score, transvaginal ultrasound, urodynamics ,SSQ-8[7], Clavien-Dindo surgical complication grading scale	By 30 days post-operatively, complicationrates were lower in the sacrocolpopexy group compared to native tissuerepair, and vaginal mesh repair in women aged 70-80 years (p=0.039).
Chang, 2021 [151]	Matched case control study, singetertiary centre, withcross sectional survey to identify risk factors for prolapse recurrence	n=153 7yr follow-up	POP-Q, PelvicFloor Distress Inventory Short Form-20 questionnair e.	153 cases were matchedwith 487 controls. Patients with a preoperative genital hiatus of 4cm (p=0.01) orgreater and need for concurrent anterior

	after sacrocolpopexy.			colporrhaphy at the timeof their initial surgery had a higher chance of prolapse recurrence (p=0.03). Women who underwent concurrent posterior colporrhaphy (p=0.02) and were of a younger age (p=0.01) had lower risk of recurrence.
Jelovsek, 2018 [152]	RCT to determineeffect of uterosacral ligament suspension vs. sacrospinous ligament fixation +/- perioperative behavioural therapy for POP onsurgical outcomes and prolapse symptoms (E-OPITMAL	n=285 5yr follow-up	POP-Q, PFDI[8],UDI[9], CRADI[10], POPDI[11], PGI-I[12]	Estimated probability of surgical failure was 61.5% with uterosacral ligament suspension vs 70.3% with sacrospinousligament fixation with insignificant difference. Nonsignificant differencebetween usual care (48.5%) vs perioperative behavioural therapy

	Trial).			and pelvic floor muscle training (48%).
Paraiso, 2011 [139]	Randomised controlled, blinded,single-centre trial to compare conventional laparoscopic and robotic-assisted laparoscopic sacrocolpopexy forvaginal apex prolapse.	n=78 1yr follow-up	POP-Q, PFDI-20, PFIQ-7[13], PISQ, EQ-5D,AAS[14]	The robotic group (n=40)had significantly longer total operative time (+67-minute difference, p<0.001), higher pain post-operatively (median20 days compared with 11 days, p<0.005) and incurred a greater cost (mean difference $1,936,p=0.008, in comparison with laparoscopic group (n=38).

Lone, 2014 [143]	Prospective cohortstudy to determineif pre-operative pelvic floor ultrasonography contributes to clinical findings and management.	n=158 1yr follow-up	POP-Q, PFUS consisting of 2D-transperineal ultrasound andhigh frequency 2D/3D endovaginal ultrasound.	105 women with POP and/or incontinence, 53 asymptomatic women ascontrols. 26 women had an additional ultrasound diagnoses and 46 womenby 1 year. PFUS helped identify additional conditions to that diagnosed clinically but did not change surgical management at baseline
				or management at follow-up.

Rodriguez,2005 [144]	Clinical trial to describe a new transvaginal paravaginal technique with concomitant suburethral sling for high-grade cystocele.	n=98 1-4yr follow-up	POP-Q, dynamic pelvicMRI, urodynamics voiding dysfunction and incontinence symptom questionnaire,UDI-6, globalquality of life questionnaire,postvoid residual.	Postoperative POP-Q scores showed 85% of patients with stage 0-1 and 2% with stage 3. 70% of patients with previous SUI were asymptomatic post-operatively. Quality of life improved significantly from 4.7 to1 ($p<0.005$). This paravaginal repair was concluded to be safe andsimple with excellent anatomic results and minimal complications.
Tawfeek, 2005 [145]	Retrospective observational studyto evaluate outcome of bilateral paravaginal repair using White's	n=47 29mth follow-up	POP-Q, urodynamics voiding dysfunction questionnaire,verbal assessment	Overall subjective satisfaction rate was 88.5%. Urinary and prolapse symptoms generally improved, dyspareunia was rare, but

	technique for anterior vaginal wall prolapse.		(sexual and bowel function), Likert scale (subjective satisfaction).	no significant change inbowel symptoms.
Biological Graft Studies				
Khong, 2011 [153]	Case series for use of Surgisis (xenograft) mesh for the treatment ofpolypropylene mesh erosion into the vagina.	n=9 6mth follow-up	POP-Q.	Five women were curedat follow-up (median 6 months, range 2-32 months), whereas three still had mesh erosion and one patient requiredrepeat surgery. Surgisis is a potentially useful treatment for large vaginal mesh defects of 1-4cm.
Winkelman, 2021 [133]	Respective cohortstudy to compare composite outcomes after posterior colporrhaphy	n=67 73mth follow-up	POP-Q, PFDI-20, 5-point Likert scale concerning satisfaction and recommenda	Objective failure was similar for biologic graft(37%) and native tissue (42%) groups (p=0.72). Subjective failure was more likely in biologic graft group (60%) than

	with and without		tion	
	biologic graft augmentation.		on of surgical procedure, PGI-I, Decision Regret Scale, PFIQ-7.	native tissue group (33%). Overall, 84% reported symptomatic improvement. Reoperation rate was 15%.

Simsiman,2006 [146]	Prospective cohortstudy to determine efficacy of vaginal paravaginal repair using porcine dermal graft augmentation to correct advanced anterior vaginal prolapse.	n=111 2yr follow-up	POP-Q, standardised questionnaire.	80% of patients were available for follow-up. Overall cure rate was 78%. All patients had concomitant surgery. Anterior anatomic failurerate was 23%. 16.7% of women had vagina mucosal erosion associated with the graft which resolved with wound debridement and topical oestrogen except one case requiring a colpectomy. The study concluded that this technique was safe and effective.

Novi, 2009 [147]	Retrospective repeated measurescohort study to compare vaginal paravaginal repairof anterior wall prolapse using porcine vs human dermal graft.	n=72 25mth follow-up	POP-Q.	72 women underwent porcine tissue implants, and 45 women underwent cadaveric dermal implants. Relativerisk for objective failure for the porcine dermal group was 0.45 compared with the cadaveric dermal group, hence the risk of recurrence was lower using porcine implants.
Synthetic Graft Studies				
Ferrando , 2021 [137]	Prospective, randomised trial tocompare prolapse recurrence and theincidence of mesh exposure between Restorelle® Y mesh and dual flatmesh.	n=62 2yr follow-up	PFDI-20, POP-Q.	No mesh exposures for all women. PFDI-20 scores improved significantly for all women with no significant differences inmean improvement and recurrence rates betweenthe groups. 9.1% reported subjective vaginal bulge symptoms.

				20.5% had objective recurrence, with 22.2% undergoing reoperation.
Nager, 2019 [135]	Randomised, controlled, superiority, multicentre, trial tocompare vaginal mesh hysteropexy vs. vaginal hysterectomy with uterosacral ligament suspension for POPrecurrence.	n=183 3yr follow-up	POP-Q, PFDI,PGI-I, Incontinence Severity Index,PFIQ-7, Functional Activity Scale, POP/Incontinence Sexual Function Questionnaire,IUGA-Revised (PISQ-IR), body image scale.	99 women underwent vaginal mesh hysteropexy, and 90 underwent vaginal hysterectomy with uterosacral ligament suspension. Vaginal mesh hysteropexy compared with vaginal hysterectomy with uterosacral ligament suspension did not resultin a significantly lower rate of the composite prolapse outcome after follow-up.

Matthews,2020 [136]	Randomised controlled, single-blind, multicentre,trial for permanentvs. absorbable suture for vaginal	n=204 1yr follow-up	IUA/ICS[15], POP-Q, PFDI-20, PFIQ-7, PISQ-IR, Clavien-Dindo surgical	102 women had permanent sutures and 102 had delayed absorbable sutures. Rateof permanent suture exposure was 5.1%
	mesh fixation during total hysterectomy and sacrocolpopexy (PACT Trial).		complication grading scale.	compared to 7.0% for delayed absorbable (risk ratio 0.73, 95% CI 0.24-2.22). The majority were asymptomatic. Composite success ratewas 93% for permanent compared with 95% for absorbable but not significantly different (p=0.43). Suture type did not affect mesh or permanent suture exposure rates.

Glazener, 2020 [140]	Randomised controlled, multicentre, trial for mesh inlay, mesh kit or nativetissue repair for women having repeat anterior/posterior prolapse surgery	n=154 2yr follow-up	POP Symptom Score, VAS, EQ-5D-3L, PGI-I, ICIQ, POP-Q. IUGA/ICS	No statistical difference between mesh inlay, mesh kit, and native tissue repair with POP- SS at 1 year. Serious adverse events were similar across groups ranging 7-13%. Cumulative mesh exposure rates over 2 years was 13% in mesh
	(PROSPECT Trial).			inlay arm of which 4 women needed reoperation, and 9% in mesh kit arm with 2 women requiring reoperation. Insufficient evidence for mesh inlay or mesh kits for repeat prolapse surgery.

Menefee, 2020 [142]	Three-arm randomised, controlled, trial to compare 3 differentapical suspension repairs for vault prolapse (ASPIRe Trial).	n=360 5yr follow-up	PFDI-20, POP-Q, patient-reported outcome questionnaires.	Randomisation and surgical treatment of women is complete. Thestudy is in the follow upphase to provide level I evidence on risks and benefits of mesh vs native tissue apical repairs.
Davidson, 2020 [154]	Retrospective cohort study with cross sectional survey to compare outcomes after laparoscopic uterosacral	n=97	POP-Q.	42 patients underwent MSH and 55 underwent USLH. One in five patients experienced recurrence with less than10% requiring repeat surgery. No significant
	ligament hysteropexy (USLH) and mesh sacrohysteropexy (MSH) for POP recurrence.			difference between MSH and USLH in recurrence rate.
PRP Graft Studies				

Parizzi, 2017 [155]	*In vivo*, whole animal study to analyse effect of PRP-gel coating ofpolypropylene mesh (PPM) on inflammation, collagen, and smooth muscle in rabbit vagina.	n=45 90day follow-up	Histological analysis.	15 rabbits in the PRP- mesh group, 15 rabbits inthe sham group, 15 rabbits in mesh-only group. The PRP group had a lower inflammatory infiltrate count at 30 days (p=0.0175). Deposition of collagen III increased with use of PRP at 90 days (p=0.022).
Cardoso, 2019, [156]	*In vivo*, whole animal study to investigate use of PRP on tooth extraction sites in	n=30 42day follow-up	Clinical, microtomographic, microscopic, immunohistoc hemical	Compared to control group, the PRP-treatedgroup showed significantly increasedbone formation,
	rats treated with bisphosphates.		evaluations of bisphosphonate-related osteonecrosis of jaw samples.	vascularisation, andVEGF expression.

Medel, 2015 [157]	*In vitro* study on human vaginal tissue to investigate healing potential ofPRP on human vaginal fibroblast attachment to absorbable and permanent vaginal implants.	n=14	Immunocyto chemistry analyses.	10 samples from postmenopausal women, and 4 samples from asymptomatic control subjects during vaginal hysterectomy or repair were collected. POP HVFs were similar to control HVFs in attachment to different implants and proliferation rate after 6 days. However, attachment of POP HVFsto both meshes (Vicryl and Restorelle) was significantly increased after coating with PRP ($p<0.001$) for 2 hours
				suggesting potential reduction in mesh-related complications in vivo.

Baretto, 2019 [158]	Randomised, double-blind, controlled, clinicaltrial to determine effectiveness of PRP vs. subacromial corticosteroid injections for rotator cuff impingement syndrome	n=51 6mth follow-up	Disabilities of the Arm, Shoulder and hand, University of California Los Angeles shoulder ratingscale, Constant-Murley shoulder outcome score.	25 patients in corticoid group, 26 patients in PRP group. No significant difference of outcome measures for both groupsat 1, 3, and 6 months of treatment ($p<0.05$). Both groups showed significant improvement in DASH and UCLA scores compared to baseline but CMS at 6 months with steroids was lower than baseline.

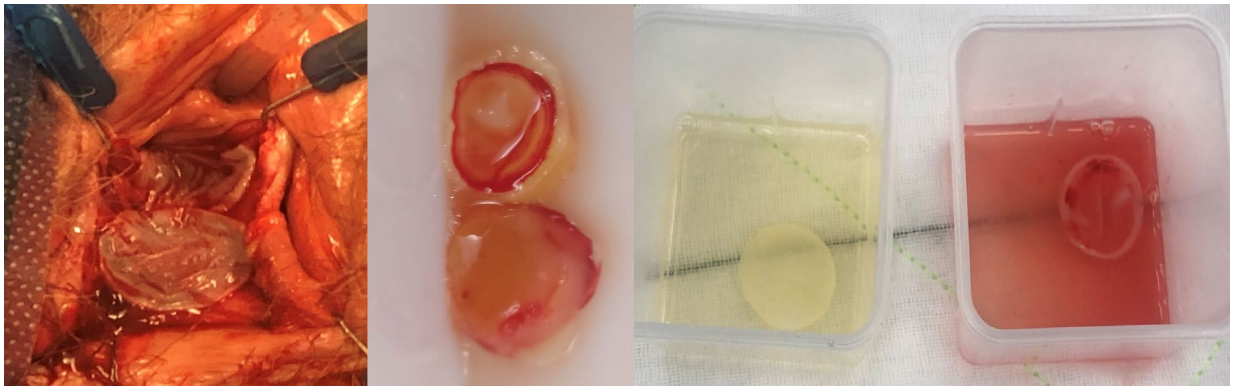

Figure 5. Photographs of NTR of vagina with biological autologous graft augmentation (Courtesy of FBW Gynecology Plus).

1.6 Summary and Themes of the Current Research

Since 2013, I have undertaken a significant amount of research to determine the safety,efficacy, and feasibility of non-surgical, and non-hormonal treatments for PFDs, LS, and GSM,

focusing not only on clinical outcomes, but also patient outcomes such as improved quality of life and personal wellbeing. The results of my researched have been published in several peer-review medical and research journals that provide insight and new knowledge on the following:

- A variety of surgical approaches that trend towards MIS [27-29, 31]. These studiesconfirm there is a need for regenerative medicine, and in some instances could potentially replace surgical approaches.
- The use of PRP therapy has demonstrated promising potential to significantly improve symptoms of LS in women, who were resistance to conventional steroid treatments. During follow-up, these women reported improvement in dyspareunia, recurrent urinary tract infections (UTIs), UUI, and POP [20].
- Studies of SUI treatment with $FxCO_2$ laser, have provided evidence that it can resolve SUI, via microtrauma and thermal effect regeneration of collagen and neovascularisation [8, 35, 50, 73].
- Studies investigating the combined use of $FxCO_2$ and PRP have provided evidencethat the microtrauma and thermal effect of the laser, as well as the result of PRP increasing stem cell stimulation, migration, and proliferation, was a painlessapplication that reduced healing time by 40-50%. The combination $FxCO_2$ and PRP therapy, allows rehydration of severe atrophic tissue, synthesis of collagen and neo-vascularisation, which resolved atrophy, SUI and UUI with statistically significant results [35, 166].
- Currently, I have papers in preparation for publication that describe prospective studies utilising $FxCO_2$ and PRP therapy for prolapse, recurrent UITs, meshcomplications, coital incontinence, and abnormal scarring secondary to FGM and male-to-female gender affirmation surgery.
- I am also evaluating the role of a biological autologous PRP graft in prolapse repair augmentation. To date, I have over 100 cases, with up to 2 years of follow-up data.

The overarching theme of my research has been to minimise the need for surgery by providing new/innovative first-line, non-invasive treatments for patients. The objectiveof these non-invasive regenerative medicines is to achieve clinical outcomes, while alsoimprove quality of life, personal wellbeing, and to reduce recovery time, side effects/complications, and the economic burden to the patient and to the Australian health care system. Furthermore, when surgery is required, I seek to maximise the outcomes of these procedures via use of pre- and post-operative regenerative treatments, such like the use of an autologous PRP graft to facilitate healing, and thus reduce failure rates and complications.

The consolidation of my research in this thesis has allowed me to prepare a coherent narrative about how to improve the quality of life for women - suffering from PFDs andother highly debilitating conditions such as GSM and LS - using new/innovative non- invasive, non-surgical, regenerative therapies that if proven safe and effective (both short- and long-term) could act as new revolutionary first-line treatment solutions that reduce/eliminate the need for surgical intervention.

As previously discussed, the success of current first-line treatments used ingynaecology are highly dependent on patient compliance. Furthermore, current MIS procedures are not appealing to many women, with only 15% deciding to have MIS when diagnosed with a PFD [154]. This results in a significant number of women having a reduced quality of life, as they are left to suffer the negative impacts of PFD symptoms. For the women that do undergo surgery, as many as 40% will require correctional surgery, due to the low success rate of PFD procedures, in particular, for POP [159].

From my own experience as a gynaecologist, and from my analysis of the literature, there is a clear need to develop new and improved first-line treatments that have less adverse side effects (i.e., HRT), and are less reliant on patient compliance. From the countless small-scale studies

conducted to investigate regenerative therapies such as $FxCO_2$ laser and PRP, there is a strong trend to suggest that their application can eitherdelay or mitigate the need to proceed with surgery, and/or increase the success rate of surgeries that are deemed necessary.

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Chapter 2: Laparoscopic Paravaginal Repair of Anterior Compartment Prolapse

2.1 Introductory comments

For thousands of years, it was common belief among medical practitioners that sickness was merely the result of ‘bad blood’. Influential physicians like Hippocrates and Galen establishedthe principle that the human body is filled with four humors: black bile, yellow bile, phlegm, and blood. When these humors were in equilibrium, health prevailed, but when they fell out ofbalance or were weakened in some way, disease ensued. The purpose of practicing good personal hygiene was to keep the humors balanced, and the goal of medical treatment was to correct humoral imbalances. Sick/diseased individuals were often diagnosed to have an‘overabundance of blood’, which in effect disrupted the balance of the four humors [1].

The consequence of following this philosophy paints a rather dark history for medicine, as it led to the development of surgical techniques and equipment that appear (and often are) brutalby modern standards. While doctors (then and now), are expected to operate according to the adage: *Primum non nocere* (Latin phrase meaning, ‘*first, do no harm’*), history shows this hasoften been easier said than done. For example, trepanation is humanity’s oldest form of surgery,which is the practice of boring holes in the skull as a means of curing illness. Historical collections at the Claude Moore Health Sciences Library (University of Virginia) hold an impressive set of the best surviving examples of surgical tools used in first century AD. One such tool is the fearsome looking vaginal dilator/speculum, where ancient texts have reported its use to diagnose and treat vaginal and uterine disorders. The discovery of this instrument (buried in 79 AD under the ashes at Pompeii’s House of the Surgeon) highlights the early beginnings of obstetrics and gynaecology [2]. On a positive note, history does show that surgical intervention was generally used as a last-line of treatment. Physicians would initially focus their efforts in treating illness by using less invasive, non-surgical first-line treatments such as poultices (i.e., herbal/plant-based pastes with supposed healing properties), bloodletting (with a lancet or leeches) and cupping. These remedies, however, were largely

ineffective and unfortunately many individuals endured enormous suffering due to the illness/disease itself, and/or from the consequences (pain and infection) of surgical intervention.

Fast forward to the 21st century, the field of medicine has advanced exorbitantly withremarkable breakthroughs made across all areas of medicine. Humanity has established a richknowledge base that provides a relatively thorough understanding of the human body and the nature of countless disease processes (e.g., infections, cancers, genetic disorders, etc.). With animmense collection of highly effective and safe drugs/therapeutics, as well as new surgical techniques, anaesthetics, antibiotics, high-powered imaging technologies, precision purpose- built medical equipment and a continuous commitment to knowledge discovery, skills trainingand education, humanity has never been better equipped to treat illness and disease. These advancements, however, do not make the medical field complete. There remain countless knowledge gaps, such that our understanding of the human body remains incomplete and there lies many diseases/conditions that lack effective treatments, techniques and tools for detectionand cure.

Given the remarkable evolution of surgical techniques and technology, its modern use has largely shifted to become a first-line approach to treatment. It appears the ancient adage of '*first, do no harm'* has shifted to '*beneficence*'. The concern here is that these great surgical advancements now cover up the ancient realisation that best practise for restoring health is to first explore other less invasive strategies. This has become increasingly apparent in gynaecology, where surgical treatments for some types of pelvic organ prolapse and urinary incontinence are associated with a high failure rate of 30-40% and require repeat intervention in up to 50% of cases [3]. Each day, hundreds of women in Australia undergo surgery for treatment of gynaecological problems. Until recently, this involved invasive open abdominal surgery (laparotomy) for the treatment of common conditions such as prolapse, incontinence, fibroids, removal of uterus (hysterectomy) and endometriosis.

2.2 The New Age of Laparoscopic Surgery

Over the past 150 years, substantial improvements in the art and science of surgery have beenmade, with credit to the development of antiseptic techniques, anaesthetic agents, antibiotics, surgical nutrition, and organ transplantation [3]. For some time however, the basic tools and techniques remained basically unchanged, such that the core task of surgery was to 'cut and suture' the body using hand instruments and direct visualisation of and contact with the organor tissue [3]. During the last decade of the 20th century, advancements in high-resolution videoimaging, scoping technology, and microscopic instrumentation has resulted in a paradigm shiftin the performance of surgery, where many procedures in many surgical specialties have beenconverted from invasive open surgeries to less invasive 'keyhole' procedures.

Keyhole surgery, is a minimally invasive surgery method used to access the interior of the bodythrough a small incision, removing the need for open surgery. Since this practice involves smaller incisions or in some cases, no incision at all, it offers the benefits of reduced pain, haemorrhaging and recovery [4, 5]. Laparoscopic surgery is a type of keyhole surgery used toaccess the abdomen and female pelvic organs. It involves the use of a laparoscope, which is a fibre-optic instrument that allows viewing of the affected area by snaking the cable from a small incision made in the abdomen.

Laparoscopy in humans was first performed by Jacobeus in 1911. During 1991-1997, the literature features numerous studies reporting on the use of this technique in gynaecology [6- 8]. For example, Vancaillie et al. [5] reported on laparoscopic bladder neck suspension, Schaub et al. [9] on laparoscopic sacral colpopexy, and Romano et al. [10] on laparoscopic colposuspension for the surgical management of vaginal vault prolapse. Rich et al. [11] did the laparoscopic repair of paravaginal defects and Smith et al. [12] described a suturing techniquefor enterocoele repair and mesh sacrocolpopexy for posterior and apical prolapse.

As a result of the clinical success of laparoscopic surgery, it has now become the accepted gold standard for many operations previously performed via laparotomy (open abdominal surgery). Innovators expanded its use as a diagnostic tool to a surgical treatment solution to carryout operative

procedures such as resection, suturing, excision, and complete organ removal. The commonly noted advantages of this minimally invasive surgical technique is a rapid recovery time, a shorter hospital stay, reduced pain, and improved cosmesis [4]. To demonstrate the safety and efficacy of laparoscopy in gynaecology, Behnia-Willison et al. [13] assessed the clinical outcomes (in terms of perioperative morbidity and repair durability) of laparoscopic paravaginal repair of anterior vaginal prolapse for 200 women aged 31-89. The results of the laparoscopic intervention alone were promising as it achieved restoration of the lateral sulci in98.6% of patients, including those with combined defects. The objective success rate after laparoscopic repair - defined as a POPQ score of >2 at all times during follow up - was 76.4%.It was concluded that the cure rate could be increased by 10% with follow-up graft-reinforcedanterior colporrhaphy to correct residual central defects. It is important to note that the study was limited by the difficulties associated with the assessment of the results of prolapse surgeryand paravaginal repair. This was largely due to patients suffering from multiple attachment defects, complications from previous surgeries and/or incontinence, the high recurrence rate ofthis condition, and the challenge of maintaining long-term follow-up. Hence, while the results are encouraging, further investigation is required.

Carey et al. (2006) [14], compare short-term, and long-term outcomes for laparoscopic Burch colposuspension (LBC) and open Burch colposuspension (OBC) for the treatment of urinary stress incontinence in a randomised surgical trial with single blinding. Results showed no significant differences in objective and subjective measures of cure and patient satisfaction at short term and long term follow up. Laparoscopic colposuspension was associated with less intraoperative blood loss, less post-operative pain, and quicker return to normal activities. This paper reassured the gynaecologist that this procedure can be performed laparoscopically as the cure rate was the same in both arms. Garry et al. (2006) [15], also compared the complication rates of laparoscopic hysterectomy and abdominal hysterectomy in the eVAluate study. Which showed a higher rate of major complications than abdominal hysterectomy but was associated with less pain, shorter hospital-stay, and better quality of life than abdominal hysterectomy. Currently with surgical

workshop (dry lab, animal lab and cadaver labs), awareness of anatomy and improved visibility and advanced laparoscopic instruments theses complication have reduced significantly.

2.3 Aim

To assess the result and outcome of laparoscopic paravaginal repair for anterior vaginal prolapse in terms of perioperative morbidity, repair durability and success rate in 212 women undergoing laparoscopic paravaginal repair based on Longitudinal study of a consecutive seriesof women assessed with the pelvic organ prolapse quantification (POPQ) system before and after laparoscopic paravaginal repair of anterior vaginal prolapse.

2.4 Summary

Laparoscopic paravaginal repair followed by graft-reinforced anterior colporrhaphy for central defects, when necessary, is associated with a low morbidity rate and achieves an anatomic curerate greater than 80%.

2.5 Publication in this chapter

Laparoscopic paravaginal repair of anterior compartment prolapses. **F Behnia-Willison**, EI Seman, JR Cook, RT O'Shea, MJNC Keirse.Journal of Minimally Invasive Gynecology 2007;14 (4), 475-480.

2.6 Author contribution

I was responsible (20%) for the research design and (70%) for clinical data collection and analysis and (40%) writing and editing of the manuscript. Prof O'Shea and Dr Seman were responsible (40% each) for the research design and (10% each) for the data analysis Dr Keirsewas responsible (70%) of writing and editing for the manuscript.

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Laparoscopic paravaginal repair of anterior compartment prolapse

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KEYWORDS:
Cystocele;
POPQ;
Prolapse;
Colporrhaphy

Abstract

STUDY OBJECTIVE: To assess the results of laparovaginal repair of anterior vaginal prolapse in terms of perioperative morbidity and repair durability.

DESIGN: Longitudinal study of a consecutive series of women assessed with the pelvic organ prolapse quantification (POPQ) system before and after laparoscopic paravaginal repair of anterior vaginal prolapse (Canadian Task Force classification II-2).

SETTING: University hospital in South Australia.

PATIENTS: Two hundred twelve women undergoing laparoscopic paravaginal repair for anterior compartment prolapse, with average follow-up of 14.2 months and 10 (4.7%) lost to follow-up.

INTERVENTIONS: All women underwent bilateral laparoscopic paravaginal repair that was combined with uterosacral hysteropexy or colpopexy in women with concomitant level I defects (n = 42) and supralevator repair in those with posterior fascia defects (n = 47). Recurrences were treated with graft-reinforced anterior colporrhaphy (n = 18).

MEASUREMENTS AND MAIN RESULTS: Nine women (4.2%) had major complications, and there were 61 minor complications. The POPQ assessment on follow-up (mean 14.2 months) gave a prolapse cure of the laparoscopic repair of 76% (95% CI 70.7%– 82.1%). Eighteen of 23 women with a residual central defect subsequently had a graft-reinforced anterior colporrhaphy, after a mean interval of 14 months, which increased the cure rate to 84% (95% CI 79.6%–89.3%).

CONCLUSION: Laparoscopic paravaginal repair followed by graft-reinforced anterior colporrhaphy for central defects, when necessary, is associated with a low morbidity rate and achieves an anatomic cure rate greater than 80%.

A satisfactory cure rate for anterior vaginal prolapse has eluded gynecologists for a very long time.[1,2] The traditional surgical technique, anterior colporrhaphy, which has changed little since the early 20th century, is still widely used despite few published data on its durability and widely varying failure rates ranging up to 70%.[1,3] It is based on the concept that cystoceles are usually caused by generalized relaxation or weakening of the anterior endopelvic fascia and that this can be corrected by plication.[1,2]

An alternative approach was proposed by George R. White in 1909, whose autopsy dissections indicated that anterior vaginal prolapse was caused by detachment of the

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pubocervical fascia laterally from the arcus tendineus fasciae pelvis (ATFP).[4] That cystoceles could be reduced by repairing these defects was largely ignored until 1976, when Richardson et al[5] described lateral, transverse (superior), and midline defects in the pubocervical fascia as responsiblefor anterior wall prolapse. Lateral defects have since been found in two thirds of women with anterior vaginal pro- lapse,[6,7] although there is some discrepancy between pre- operative and intraoperative diagnoses.[7–9]

Paravaginal repair, first reported as a vaginal procedure in 1909[4] and as an abdominal procedure in 1976,[5] has since been adopted as a laparoscopic procedure.[10] From 1999 onward, we adopted laparoscopic paravaginal repair as our preferred approach for correcting anterior compartment prolapse attributed to lateral defects, followed by later repair of residual central defects if deemed necessary, and started prospective evaluations using the pelvic organ prolapse quantification (POPQ) system.[11] This article reports on our 5-year experience with this approach.

Patients and methods

Two hundred twelve women with symptomatic anterior vaginal prolapse underwent laparoscopic paravaginal defect closure at Flinders Medical Centre, South Australia, from January 1999 through December 2004. The study was approved by the audit subcommittee of the institutional ethical committee.

The median age of the women was 61 years (range31–89); their median weight was 68 kg (range 48–120); andtheir median parity was 3 (range 0–9). More than half of the women had had previous pelvic surgery, with 25% having had previous prolapse surgery, but none had had a paravaginal repair (Table 1).

Preoperative measures

All patients were evaluated by the POPQ system using the Valsalva maneuver to assess prolapse in each compartment. Both the tandem and ordinal POPQ systems were used, ensuring demonstration of the patient's maximal prolapse, and the presence or absence of anterior vaginal rugae and paravaginal sulci was noted. Patients were classified as having attachment defects only (absent sulci and intact rugae) or having both attachment and central fascia defects (absent sulci and rugae). Patients in the latter group (n = 84; 39.6%) were counseled on the potential need for subsequent repair of the central defect.

Table 1 Previous pelvic surgery in 212 women with anterior vaginal wall prolapse

Previous procedure	No.	%
Hysterectomy	108	50.9
Colporrhaphy	44	20.8
Burch colposuspension	2	0.9
Sacrospinous colposuspension	1	0.5
Marshall-Marchetti-Kranz	2	0.9
Ventrosuspension	1	0.5
Any pelvic surgery	113	53.3

Table 2 Results of urodynamic assessment in 103 women with urinary symptoms or POPQ stage 3 or 4 prolapse

Urodynamic test result	No.	%
Mixed incontinence	61	59.2
Detrusor overactivity	19	18.4
Obstructed outflow	5	4.9
Urodynamic stress incontinence	20	19.4
Stable bladder	3	2.9
Occult urethral hypermobility	4	3.9
Intrinsic sphincter deficiency	1	1.0

POPQ = pelvic organ prolapse quantification.

The standard policy consisted of a trial of conservative measures, including local estrogen treatment, pessaries, and formal pelvic floor rehabilitation with a continence nurse or physiotherapist including instruction on non-Valsalva voiding and defecation, and measures to minimize intraabdominal pressure rises. Surgery was considered only when conservative treatment failed or patients explicitly requested it.

Urodynamic studies were undertaken for women (n = 103; Table 2) with urinary incontinence, voiding difficulties, or moderate to severe prolapse (POPQ stage 3 or 4).

Women with detrusor overactivity received conservative management. All patients received preoperative bowel preparation with a laxative mixture the day before surgery and antibiotic prophylaxis and thromboprophylaxis during and after surgery.

Laparoscopic repair

Patients are placed in the steep lithotomy position in Allen stirrups. A 4-puncture transperitoneal video laparoscopic approach is used to free adhesions and facilitate surgical access. Two 12-mm trocars are inserted centrally (infraumbilically and 5 cm above the symphysis), and 2 5-mm trocars are inserted bilaterally at the level of the umbilicus. The bladder is reflected traversing 3 layers: peritoneum, loose areolar tissue, and the thin membrane overlying the ATFP. An arched peritoneal incision is made with electrosurgical scissors centrally between the 2 lateral umbilical ligaments and above the bladder dome. The bladder is then reflected away from the pubic symphysis by blunt dissection of loose, largely avascular areolar tissue.

Thereafter, the membranous layer overlying the ATFP is divided hemostatically along its length. The bladder is bluntly dissected medially to reveal the paravaginal space, remaining anterior to the ischial spines and obturator bundles and clear of aberrant obturator vessels overlying the

Table 3 Concomitant procedures in 212 women undergoing laparoscopic paravaginal repair

Concomitant procedure*	No.	%
Adhesiolysis	96	45.3
Supralevator repair	47	22.2
Hysteropexy/colpopexy	42	19.8
Enterocele excision	16	7.5

*All were laparoscopic procedures.

iliopectineal ligament. With a finger in the vagina the lateral sulcus is approximated to the ATFP to aid defect recognition. The torn lateral edge of the pubocervical fascia is revealed by blunt dissection of the bladder medially with a peanut-shaped swab on a 5-mm grasper. Dissection is kept to a minimum to reduce bleeding.

Paravaginal defects are closed with 4 to 6 sutures of O Ethibond (Ethicon; Johnson and Johnson, Sydney, New South Wales, Australia) starting from the distal point and alternating right and left sides to maintain vaginal symmetry. Up to 2001, 1 bite was taken in the lateral pubocervical fascia and subepithelial vagina and 1 in the ATFP and obturator internus muscle, tying 3 to 4 knots. From 2001 onward, a third bite was taken in the iliopectineal ligament. The commonest configuration is 4 sutures on each side, with the distal 3 as triple-bite sutures and the proximal one taking 1 bite in the vagina and 1 in the iliopectineal ligament, omitting the obturator internus bite because of spatial restriction and the risk of neurovascular injury. Usually the sutures are tied without tension merely to close the defect, but tied more tightly if correction of urethral hypermobility is needed. Concomitant level I defects were addressed by hysteropexy or colpopexy, and all women with posterior fascia defects had a laparoscopic supralevator repair (Table 3).

Screening cystoscopy is performed to exclude intravesical sutures and to ascertain an intact bladder and normal ureteric function. A suprapubic catheter is inserted and secured. It is removed after 2 satisfactory residuals (i.e., both <100 mL and less than half the voided volume) are obtained.

Follow-up and follow-up procedure

All patients were reviewed with POPQ assessments at 6 weeks, 6 months, 12 months, and annually thereafter. Patients with combined defects who remained or became symptomatic had a follow-up anterior colporrhaphy with a full-thickness vaginal graft spanning intact vault and paravaginal supports. These patients received a preoperative enema the day before surgery, a prophylactic dose of a second-generation cephalosporin after induction of anesthesia, and intraoperative and postoperative thromboprophylaxis.

A diamond-shaped vaginal graft is harvested from the redundant part of the anterior vaginal wall by sharp dissection. The bladder is reflected by sharp dissection laterally to intact paravaginal sulci and cranially to intact DeLancey level I supports,[12] and midline plication is made with interrupted 1 polyglactin sutures from the bladder neck to the anterior fornix. The graft is laid back to front over the repair site, securing it at the top to the level I supports, laterally to the arcus tendineus, and suburethrally to the fascia with 2/0 polyglactin. The vagina is closed with locking 2/0 polyglactin, and a vaginal pack and suprapubic catheter are inserted. Prophylactic broad-spectrum antibiotics are given for 5 to 7 days.

Results

Of the 212 women, 128 had lateral attachment defects only, whereas 84 (39.6%) had both attachment and central fascia defects (combined defects). The mean duration of follow-up was 14.2 months, with 132 women having a follow-up of more than 12 months and 10 women lost to follow-up.

Operating time ranged from 50 to 255 minutes; the range being dictated predominantly by concomitant procedures (Table 2). Median blood loss (estimated by "informed guess work" replaced by weighing pads, etc) was 50 mL, and hospitalization duration was with a median of 4 days (range 2–17).

Nine women (4.2%) had major complications, defined as bowel, ureter, or bladder injury, anesthetic complications, unintended laparotomy, or blood loss >1000 mL (Table 4). Seven women (all with previous surgery) sustained bladder injury. Two women underwent unintended laparotomy; 1 for intestinal obstruction when a small bowel loop was strangulated between vault suspension sutures, and 1 for control of bleeding. Three women (1.4%) were subsequently readmitted: 1 each for deep venous thrombosis, prolonged urinary retention, or nonspecific gastrointestinal upset. There were 61 minor complications (Table 4) with prolonged urinary retention, defined as residuals greater than 100 mL by day 7 necessitating catheterization, occurring in 10.4%.

Only 3 women had a failure at the site of paravaginal reattachment, giving a success rate of 98.6% for re-creation of the paravaginal sulci. The objective success rate after laparoscopic repair, defined as a POPQ score less than 2 at all times

Table 4 Operative and postoperative complications

Complication	No.	%
Major		
Blood loss >1000 mL	2	0.9
Bladder injury	7	3.3
Bowel injury	1	0.5
Unintended laparotomy	2	0.9
Minor		
Deep venous thrombosis	1	0.5
Granulation tissue	5	2.4
Pelvic hematoma	7	3.3
Pelvic infection	6	2.8
Prolonged urinary retention	22	10.4
Pyrexia >38°C	2	0.9
Urinary tract infection	18	8.5

Table 5 Preoperative and postoperative POPQ assessments

			Latest postoperative score*			
	Preoperative		After laparoscopic repair only		After correction of the residual central defect†	
POPQ score	No.	%	No.	%	No.	%
0	0	—	119	56.1	133	62.7
1	0	—	43	20.3	46	21.7
2	166	78.3	35	16.5	19	9.0
3	34	16.0	4	1.9	3	1.4
4	12	5.7	1	0.5	1	0.5
Total	212	100	202	95.3	202	95.3

POPQ = pelvic organ prolapse quantification.
*10 women (4.7%) were lost to follow-up.
†18 women (8.5%) had a vaginal surgical correction of the residual central defect.

during follow-up, was 76.4% (Table 5) with most recurrences (23/40; 57.5%) occurring in the anterior compartment in the 84 women with combined defects. Of the 84 women with combined defects, 56 (66.7%) had only a minimal asymptomatic degree of anterior wall prolapse on follow-up. Twenty-three had a recurrence of anterior wall prolapse despite restored sulci, with symptoms occurring on average 14 months (median of 13 months [56 weeks], mean of 14.8 months [64 weeks], range 1.5– 42 months) after surgery. These women were offered an additional vaginal repair. Five declined surgery, and 18 underwent anterior plication that corrected the anterior prolapse in all but one; the only one who had not received a vaginal graft. Two serosal inclusion cysts occurred in the 17 women with a vaginal graft; both resolved on simple aspiration. The compartments responsible for other POPQ scores >2, also occurring with a median of 14 months (range 2–39 months), are shown in Table 6. Of the women with urodynamically demonstrated stress incontinence (Table 2), 75% reported to be fully continent at last follow-up, but no further urodynamic studies were conducted.

Discussion

Anterior compartment prolapse is a major challenge both for the women who have it and for the gynecologists to whom they turn for help. Regrettably, there is no universal cure for this condition,[8] but careful assessment with the POPQ system can go a long way in delineating the problem and seeking appropriate solutions.

Cystoceles were classified into those with lateral attachment defects, diagnosed when the paravaginal sulci became vertical during the supine Valsalva maneuver, and those caused by a combination of attachment and fascia defects. Central fascia defects were suspected when there was a loss of rugosity of the anterior wall on Valsalva and were thought to be due to transverse and midline pubocervical defects. The idea of combining paravaginal repair with anterior colporrhaphy for combined defects was abandoned because midline plication may counteract the paravaginal repair by pulling the lateral attachments away from the pelvic wall.[1] Thus women with combined defects were informed that they might require a further vaginal procedure if they began or continued to have symptoms. This resulted in a 2-staged approach with attachment defects corrected first and residual central defects being addressed later. It has recently been argued, however, that there is a need for a randomized study of anterior repair with paravaginal repair versus anterior repair alone and paravaginal repair alone.[2] Young et al[13] reported on 100 patients treated concurrently with vaginal paravaginal repair and anterior colporrhaphy, noting a paravaginal recurrence in 2% and midline recurrence in 22% within 1 year, but with a high complication rate. In our study, one third of the residual central defects were progressive and became symptomatic within 4 years of the primary procedure, but 64% of the patients with a central defect have thus far not needed a follow-up procedure.

Even patients with unilateral defects underwent bilateral laparoscopic repair as prophylaxis and to maintain vaginal symmetry. Until 2001, defects were closed with 1 bite in the lateral pubocervical fascia and subepithelial vagina and 1 bite in the AFTP and obturator internus muscle. The subjective impression was that the lateral vaginal sulci were being restored bluntly, and therefore a third bite in the iliopectineal ligament was added. This anchoring bite has 2 advantages. First, it suspends the lateral vaginal fornix from the iliopectineal ligament and not from a potentially atrophic obturator internus with poor suture retention and produces a sharper paravaginal sulcus. Second, it provides a standardized repair technique irrespective of urethral hypermobility. Without stress incontinence, the sutures are simply tied to achieve anatomic defect closure without elevation. With urethral hypermobility they are tied more tightly to achieve overcorrection.

Table 6 Failure rate (POPQ >1) at the last assessment during follow-up

Compartment	No.	%
Anterior	7	3.3
Central fascia defect	6	2.8*
Central + paravaginal	1	0.5†
Posterior	6	2.8
Vault	6	2.8
Global	2	0.9†
Not specified	2	0.9
Total	23	10.8

POPQ = pelvic organ prolapse quantification.
*18 women (8.5%) had undergone repair of a central defect of which 1 failed and 5 had declined further surgery.
†Considered failures of laparoscopic paravaginal repair (n = 3; 1.4%).

An obvious weakness in our study is that symptoms and discomfort regrettably were not recorded in the same systematic way as POPQ assessments. Although most patients, including those with POPQ scores of 2 or higher, reported either a cure or marked improvement and 75% with stress incontinence reported resolution of the problem, symptoms were not elicited and documented in a sufficiently standardized manner to accord great validity to the data obtained.

Appropriate assessment of the results of prolapse surgery and paravaginal repair in particular is fraught with difficulties. First, lateral attachment defects often occur in association with other defects, as was the case in 40% of our patients. In fact, it has been argued that women with pelvic support defects rarely have a single site of involvement.[14] Second, the patient groups included in most reports, including ours, are mostly diverse in terms of previous surgery and presence or absence of incontinence. Third, the specified repair procedure is frequently performed with other procedures, making it difficult to judge the relative contribution of each to the end result.[2,13,15] Also in our study, 43% of women simultaneously had a level I procedure to augment anterior support superiorly. Fourth, an excellent anatomical result is not necessarily reflected in a similar functional result and vice versa.[16–18] Fifth, prolapse and anterior compartment prolapse especially has a high recurrence rate.[15–19] Part of this may be due to unrecognized coexisting defects or to newly arising defects in other compartments, but reintervention for the same problem is common.[2,18] Long-term follow-up is therefore essential but not always easy to achieve.

As a result, judging the relative merits of different procedures, whether open, vaginal, or laparoscopic, has a degree of arbitrariness that is difficult to eliminate even when concentrating on studies with random allocation to different procedures.[20] The latter are also hampered by the fact that randomizing among complex procedures does not necessarily guarantee that each is performed with a comparable level of skill and associated conditions.[21,22] No trials involving a laparoscopic approach have been reported, however, and only 1 compared an abdominal with a vaginal approach.[20] Benson et al[18] conducted a randomized trial of abdominal versus vaginal paravaginal repair reporting a reoperation rate of, respectively, 16% and 33% within an average 2.5 years follow-up, but women in both groups had a range of other interventions including anterior colporrhaphy in 33% of the vaginal and 30% of the abdominal group, and results are only available for 80% of the women randomized. In theabsence of firm standardization of procedures and tech-niques[21] and a clear definition of outcome measures,[16] con- trolled trials are not likely to be more informative than our cohort studies[23,24] and many others published thus far.

Despite these limitations in comparing our results with those of others reported in the literature, our results are encouraging, even though the anticipated need for a follow-up procedure in a proportion of women may be perceived as a drawback. The laparoscopic intervention alone achieved restoration of the lateral sulci in 98.6% of patients including those with combined defects. When considering only women with ongoing follow-up and excluding those who declined the follow-up procedure for coexisting central defects, anterior compartment prolapse alone was satisfactorily corrected in 97% (191/197). Nevertheless, prolapse remained or became an issue again for 23 (10.8%) of our patients, mostly because of prolapse in other compartments or because they declined the follow-up procedure. This further emphasizes the need for clear definitions of recurrent prolapse that are evidence-informed and clinically meaningful,[16] particularly because the demand for prolapse surgery is estimated to increase considerably over the next 2 decades.[25]

Conclusion

Laparoscopic paravaginal repair cures anterior compartment prolapse in 76% of patients. Follow-up graft-reinforced anterior colporrhaphy for residual central defects increases the cure rate by 10%.

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Chapter 3: Success Rates and Outcomes of Laparoscopic Mesh Sacrohysteropexy

3.1 Introductory comments

As described in Chapter 2, the history of surgery techniques as well as laparoscopic surgery were reviewed in detail. Also, the result and outcome of laparoscopic paravaginal repair for vaginal prolapse repair durability and success rate has been reported. In seeking to further investigate the outcome and success rate of laparoscopic surgery, success rates and outcomes of laparoscopic mesh sacrohysteropexy are presented in this chapter.

3.2 Aim

Hysterectomy and vaginal repair are conventional treatments to address apical prolapse; however, women are increasingly requesting uterine-preserving alternatives. This study aimed to evaluate the impact of laparoscopic mesh sacrohysteropexy on symptomatic prolapse from an Australian experience.

3.3 Summary

One hundred and thirty-four women had a laparoscopic hysteropexy and concurrent vaginal prolapse repair and four women had an isolated laparoscopic hysteropexy. Out of the 136 patients (98.6%) seen at post-operative 4–6 weeks, all had Stage 0 POP-Q scores. Prolapse recurrence was observed in 22 patients, while 116 patients remained cured at their last follow-up. Laparoscopic mesh sacrohysteropexy is an effective and safe procedure with a high success rate comparable to available international data.

3.4 Publications in this chapter

Success rates and outcomes of laparoscopic mesh sacrohysteropexy.

S Daniels, D Robson, M Palacz, S Howell, T Nguyen, **F Behnia-Willison.**

Australian and New Zealand Journal of Obstetrics and Gynaecology 2020; 60 (2), 244-249.

3.5 Author contribution

I was responsible (100%) for the concept and design of research and (50%) data collection and

analysis forthe publication. Samuel Daniels was responsible (30%) in data collection and analysis and Danielle Robson and Tran T. T. Nguyen were responsible (30% each) for writing, editing, and proof reading. In this research, I was appointed as Australasian Gynaecological Endoscopy and Surgery Society (AGES) supervisor and I had to encourage and provide a platform for my training fellows to publish and to be the first author.

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ORIGINAL ARTICLE

Success rates and outcomes of laparoscopic mesh sacrohysteropexy

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Background: Uterovaginal prolapse is a prevalent gynaecological issue, which canhave a negative impact on the quality of life of women. Hysterectomy and vaginal repair are conventional treatments to address apical prolapse; however, women are increasingly requesting uterine-preserving alternatives.

Aims: This study aimed to evaluate the impact of laparoscopic mesh sacrohysteropexy on symptomatic prolapse from an Australian experience.

Materials and Methods: This retrospective cohort study presents outcomes of 157 patients who underwent laparoscopic mesh sacrohysteropexy at a private practice in South Australia during 2007–2017. Primary outcome is the success rateaccording to the pelvic organ prolapse quantification (POP-Q) system. Secondary measures included complication rates and patients identified as having Stages III-IVprolapse and their outcomes.

Results: The median age was 58 years (27–86 years), median parity was 2 (0–6), andmedian body mass index was 26.8 (23–29.9). One hundred and thirty-four womenhad a laparoscopic hysteropexy and concurrent vaginal prolapse repair and four women had an isolated laparoscopic hysteropexy. The mean pre-operative pointC was 0.60. The mean change from pre-operative point C to post-operative point Cwas 7.6 cm ($P < 0.01$). Of the 136 patients (98.6%) seen at post-operative 4–6 weeks, all had Stage 0 POP-Q scores. Prolapse recurrence was observed in 22 patients, while 116 patients remained cured at their last follow-up. Prolapse recurrence was associated with anterior vaginal mesh, previous prolapse surgery, pre-operative Stage III-IV disease and number of vaginal deliveries.

Conclusions: Laparoscopic mesh sacrohysteropexy is an effective and safe proce- dure with a high success rate comparable to available international data.

KEYWORDS

laparoscopy, pelvic organ prolapse, surgical mesh, uterus, vagina

INTRODUCTION

Uterovaginal prolapse affects 50% of women over 50 years old, and 50% of parous women.[1,2] Prolapse results from defects in the integrity of the uterosacral cardinal ligament complex which can impact quality of life.[3] Hysterectomy with vault suspension and vaginal repair is the standard surgical management of these patients.[4] However, up to 40% of women undergoing vaginal hysterectomy will subsequently develop vault prolapse as hysterectomy does not correct the underlying pathophysiology of pelvic organ prolapse (POP).[3,5] This has led to the emergence of uterine-preserving techniques that provide level one support.

Sacrohysteropexy involves suspension of the uterus from the sacral promontory using either sutures or polypropylene mesh. Laparoscopic approach is becoming increasingly popular, due to shorter recovery time; however, current data from an Australian perspective remain sparse.[6-9] This study reports on the first cohort, to our knowledge, of women undergoing laparoscopic sacrohysteropexy for prolapse within Australia and represents an 11 year retrospective review from a single centre in South Australia. The primary outcome of the study was the objective measurements of pre- and post-operative point C.

MATERIALS AND METHODS

This was a quantitative retrospective study of women who consulted a single Australasian Gynaecological Endoscopic and Surgery Society accredited surgeon in South Australia, between January 2007 and December 2017. Ethical and governance approvals were granted by the Bellberry Hospital Research Ethics Committee and Governance office (Ref: HREC/ 2016-04-293). All patients presenting with symptomatic POP were analysed. The choice of surgery was determined by the patient, after discussion about hysterectomy, future fertility, and uterine conservation. All patients were referred for pelvic floor physiotherapy and offered vaginal pessaries prior to surgery. Exclusions to uterine preservation or complex laparoscopic surgery included significant uterine enlargement (>280 cc), body mass index (BMI) >35, current cervical smear abnormalities, and concomitant medical conditions that would preclude a laparoscopic approach for anaesthetic concerns. Patients electing for laparoscopic sacrohysteropexy were women with symptomatic prolapse wishing to preserve their uterus and had failed conservative measures. All patients underwent detailed pre-operative assessment and further investigations of pelvic organ function as required. Urodynamic studies were performed if there were severe prolapse or symptoms of stress urinary incontinence. A multi-disciplinary team was involved including a pelvic floor physiotherapist, dietitian, and weight-loss management.

Outcomes analysed included patient demographic indices such as age, BMI, parity, previous vaginal surgery, sexual activity, smoking, and menopausal status. Indications for surgical intervention, and pre- and post-operative POP quantification (POP-Q) assessment were collected. Other data included concomitant procedures, length of procedure, estimated blood loss, length of stay, post-operative follow-up, and complications. The primary outcome was point C and the POP-Q stage at post-operative six weeks, and yearly thereafter. Success of the primary outcome was defined as the following criteria: no prolapse in the treated compartment, 1 cm above the hymen.[7] The operat- ing surgeon performed all pre- and post-operative objective assessments. Secondary measures included complication rates as well as patients identified as having Stages III and IV prolapse and their outcomes.

Follow-up

The post-operative follow-up was at four to six weeks, six months to one year, and long-term after 12 months.

Statistical analysis

Data integrity was assessed using a year by year analysis to identify inconsistencies of reporting between years. Where data integrity was questionable with sudden drops in outcomes that could not be accounted for, those variables were excluded from any analysis. Efforts were made to correct missing data and data entry errors through searches of individual patient records. Where data were collected with different degrees of outcomes between years, these variables were collapsed into dichotomous variables to indicate whether the outcome occurred or not. Where data were incomplete or missing with no ability to determine the outcomes, these patients were excluded from analysis.

Categorical measures were summarised as numbers failed (disease recurred) and censored (disease did not recur by final follow-up). Median survival was presented although this could not be calculated in all cases. The impact of demographic and clinical variables on disease-free survival was assessed using Cox proportional hazards models. Pre- and post-operative point C was summarised as means with standard deviations. Changes across the two time points were assessed using paired *t*-tests. All tests were two-tailed and assessed at the 5% alpha level. The analyses were completed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Surgical technique

The technique for the laparoscopic sacrohysteropexy is modified from the 'Oxford hysteropexy'.[10] All patients undertook a clear fluid diet, bowel preparation in the evening prior to surgery, and 400 µg of misoprostol vaginally two hours pre-operatively. Intra-operative antibiotics, paracetamol and parecoxib were administered. An indwelling catheter and Pelosi uterine manipulator (Cooper Surgical) were placed. Pneumoperitoneum was established; 12 mm umbilical and suprapubic ports were placed as well as 5 mm lateral ports. Trendelenburg position was obtained along with five degrees left lateral tilt to facilitate retraction of the sigmoid from the sacral promontory. The anatomy of the sacral promontory was identified; the overlying peritoneum was opened with monopolar scissors and the incision continued caudally, staying medial to the right ureter and aiming toward the right uterosacral ligament in the right pararectal space. The peritoneal incision was carried across to the posterior cervix as far as the insertion of the left uterosacral ligament. A type-1 monofilament, macroporous, lightweight, non-absorbable mesh (Restorelle – Y, Colpoplast and Y mesh by AMS) was used to suspend the cervix from the sacral promontory. A Y-shaped mesh was used as this was the only abdominal mesh which was available and approved by the Therapeutic Goods Administration at the clinician's hospital. The mesh was tailored and cut according to the

distance measured between the umbilicus and the upper border of the symphysis pubis as well as the distance between the ischial spine and introitus. The mesh was attached to the posterior cervix with delayed absorbable sutures (2.0 PDS, Ethicon or 2.0 V-Lok 180, Covidien), and the Y-side of the mesh was trimmed and tacked to the sacral promontory utilising 5-mm helical fasteners (Protack, Covidien) with minimal tension when the cervix was held at the level of the ischial spines. A two-layer fixation of the mesh at the level of the sacral promontory was performed to make the mesh more robust with less possibility of stretch or tear. Excessive tension was avoided to decrease the risk of vaginal deviation, *de novo* stress incontinence, apparent new prolapse and cervical elongation. The peritoneum was closed with absorbable sutures (3.0 Monocryl, Ethicon or 2.0 V-Lok 90, Covidien). Check cystoscopy was performed at the end of the procedure to ensure ureteric patency. Additional vaginal repairs or other procedures were performed as indicated.

RESULTS

A total of 157 patients were included; 19 were removed from statistical analysis due to missing data variables. The median age was 58 (27–86), median parity was 2 (0–6) and the median BMI was 26.8 kg/m^2 (23–29.9). Pre-operatively, 80 (58.0%) had POP-Q Stage II prolapse, 49 (35.5%) had Stage III and nine (6.5%) patients had Stage IV. The majority of patients underwent the procedure due to vaginal laxity, and pelvic discomfort (97.1% and 92.5% of patients, respectively); 83.3% had a prior history of at least one vaginal delivery; 13.8% had at least one previous assisted delivery and 17.4% had at least one previous caesarean section (Table 1). The mean operative time was 86 min with all patients incurring minimal blood loss and there were no conversions to laparotomy.

As shown in Table 2, the mean pre-operative point C was 0.60. The mean change from pre-operative point C to post-operative point C was 7.6 cm ($P < 0.01$). Of the 136 patients (98.6%) seen at post-operative 4–6 weeks, all had Stage 0 POP-Q score. The probability of no recurrence of uterovaginal prolapse was approximately 0.8 at 24 months as depicted in Figure 1.

Prolapse recurrence was not associated with key sociodemographic measures including age ($P = 0.72$), BMI ($P = 0.58$), menopausal status ($P = 0.51$), smoking status or being sexually active ($P = 0.72$). Ninety-three percent of women enrolled in this study were classified as 'overweight' with a BMI between 25–29.9. The hazards of recurrence within the overweight population were increased compared with the control group with a 'normal' BMI of 18.5–24.9 (hazards ratio (HR) = 1.79; 95% CI: 0.23–13.77; $P = 0.576$).

Compliance with immediate follow-up (4–6 weeks post-operative) was 98.6%. Two patients were interstate referrals and chose to be followed up with their local practitioner for convenience. Twenty-one percent underwent intermediate follow-up between 6 weeks and 12 months and 55% were reviewed after 12 months. At their last review up to ten years post-operatively, 84.1% were symptom-free. Recurrence was associated with the number of vaginal deliveries (HR = 1.38; 95% CI: 1.01–1.90; $P = 0.046$) but not with prior operative deliveries.

Concomitant procedures performed with laparoscopic sacrohysteropexy included endometrial ablation, adnexal surgery, adhesiolysis, and urinary incontinence procedures. At the time of surgery, 97% had concomitant vaginal repair which is outlined in Figure 2. Prolapse recurrence was significantly associated with anterior synthetic mesh (HR = 2.82; 95% CI: 1.17–6.79; $P = 0.02$) but not with the other mesh repairs. Vaginal mesh erosions that developed post-procedure were not predictive of prolapse recurrence (HR = 2.27; 95% CI: 0.73–7.04; $P = 0.16$).

Previous prolapse surgery (HR = 3.17, 95% CI: 1.15–8.78); $P = 0.03$) and advanced prolapse (POP-Q Stages III or IV) (HR = 3.22, 95% CI: 1.20–7.99); $P = 0.01$) were strong predictors of an early prolapse recurrence. Recurrence occurred in ten patients (20%) with Stage III prolapse and eight patients (89%) with Stage IV prolapse. Seven of those eight patients (75%) had a hysterectomy and one (11%) patient used a vaginal pessary at 44 months post-sacrohysteropexy.

There were no major complications observed following a laparoscopic sacrohysteropexy. However, there were eight women who experienced vaginal mesh erosion and this was all secondary to vaginally placed mesh for prolapse. One woman was followed up elsewhere; one woman had vaginal mesh exposure (0.5 cm) that was detected at the third year of routine follow-up. She was asymptomatic and cured after treatment with vaginal oestrogen as of her last review at seven years. There were four women who underwent excision of exposed vaginal mesh at nine months, 12 months, and 87 months. The laparoscopic mesh was reattached to the sacrum in three women (2.17%). One woman underwent operative laparoscopy and adhesiolysis for persistent pelvic pain. Three women had wound infections who responded to oral antibiotics.

DISCUSSION

To our knowledge, this is the first study with a large cohort and long-term follow-up from Australia. There is a paucity of data on laparoscopic sacrohysteropexy and much of our knowledge is inferred from open and laparoscopic sacrocolpopexy. Sacrohysteropexy with mesh was first reported by Leron and Stanton in 2001 via an open incision.[11] There have been subsequent reports on the laparoscopic approach to this procedure. Studies by Rahmanou et al.[12] and Jefferis et al.[13] similarly reviewed outcomes following laparoscopic hysteropexy and found a mean change in point C of 6.5 and 7.9 cm, respectively. Our study had similar results with a mean change in point C of 7.6 cm. All women ($n = 138$) in this current study had a Stage 0 POP-Q at the first post-operative assessment, demonstrating an immediate success in anatomical reduction of the prolapse in the short-term.

Figure 1 demonstrates that prolapse recurrence occurred within post-operative 20 months with the probability of survival

TABLE 1 Patient demographics and complications

Patient demographics		Number of patients	Hazards ratios (95% CI)	*P*-value
Age†	57 (27–86)		1.01 (0.97–1.04)	0.72
Body mass index, kg/m^2†	26.8 (23–29.9)			
Normal, 18.0–24.9		9/138 (6.52%)		
Overweight, 25.0–29.9		129/138 (93.5%)	1.79 (0.23–13.77)	0.58
Parity†	2 (0–6)			
Vaginal delivery ≥ 1		115/138 (83.3%)	2.33 (0.54–10.04)	0.25
One previous vaginal delivery		18/138 (13.0%)		
Two previous vaginal deliveries		47/138 (34.0%)		
Three previous vaginal deliveries		37/138 (26.8%)		
Four previous vaginal deliveries		9/138 (6/52%)		
Five previous vaginal deliveries		1/138 (0.72%)		
Six previous vaginal deliveries		3/138 (2.17%)		
			1.38 (1.01–1.90)‡	0.046
Assisted deliveries ≥ 1		19/138 (13.8%)	0.97 (0.32 – 3.01)	0.96
Caesarean sections ≥ 1		24/138 (17.4%)	0.54 (0.13 – 2.33)	0.41
Past prolapse surgery		12/138 (8.70%)	3.17 (1.15 – 8.78)	0.03
Past incontinence surgery		3/138 (2.20%)	2.81 (0.37 – 21.12)	0.32
Postmenopausal		86/138 (62.3%)	1.36 (0.55 – 3.37)	0.51
Sexually active		87/138 (63.0%)	0.85 (0.36 – 2.03)	0.72
Smoker		1/138 (0.72%)		
Degree of uterine prolapse by stageII		80/138 (58.0%)		
III/IV		58/138 (42.0%)	3.22 (1.30–7.99)	0.01
Concomitant procedures				
Adnexal surgery		12/138 (8.70%)		0.24
Incontinence procedures		45/138 (32.60%)		0.35
Mini sling		27/45 (60.0%)		
Transobturator sling		16/45 (35.56%)		
Burch colposuspension		2/45 (4.44%)		
Endometrial ablation		14/138 (10.14%)		0.53
Adhesiolysis		12/138 (8.70%)		0.67
Levonorgestrel intrauterine device (Mirena)		19/138 (13.77%)		0.95
Type of vaginal mesh§				
Anterior fascial repair		68/134	0.69 (0.29–1.61)	0.37
Posterior fascial repair		61/134	0.52 (0.21–1.29)	0.16
Anterior synthetic mesh		24/134	2.82 (1.17–6.79)	0.02
Posterior synthetic mesh		16/134	2.52 (0.83–7.71)	0.10
Anterior biological mesh		15/134	0.42 (0.06–3.11)	0.39
Posterior biological mesh		15/134	1.32 (0.39–4.49)	0.66
Complications				
Vaginal mesh erosions		8/134 (5.8%)	2.27 (0.73–7.04)	0.16
Wound infections		3/138 (2.2%)		
Reattachment of sacral mesh		3/138 (2.2%)		
Voiding difficulties		4/138 (2.9%)		
Constipation		1/138 (0.72%)		
Vaginal infection		4/138 (2.9%)		

(Continued)

TABLE 1 (Continued)

Patient demographics	Number of patients	Hazards ratios (95% CI)	*P*-value
Pain	4/138 (2.9%)		
Bleeding	1/138 (0.72%)		
Perineal wound dehiscence	1/138 (0.72%)		

†Reported as mean and total range.
‡Increase risk per number of vaginal deliveries.
§Sixty-four patients had both anterior and posterior procedures.

TABLE 2 Change in point C

Variable	Mean	STD	Median	Minimum	Maximum	Q1	Q3
Pre-operative point C	0.6	1.7	1.0	−6	5	0.0	1
Post-operative point C	−7.0	0.9	−7.0	−10	-6	-8.0	−6
Change in point C	7.6	1.8	7.5	2	11	6.5	9

STD, standard deviation.

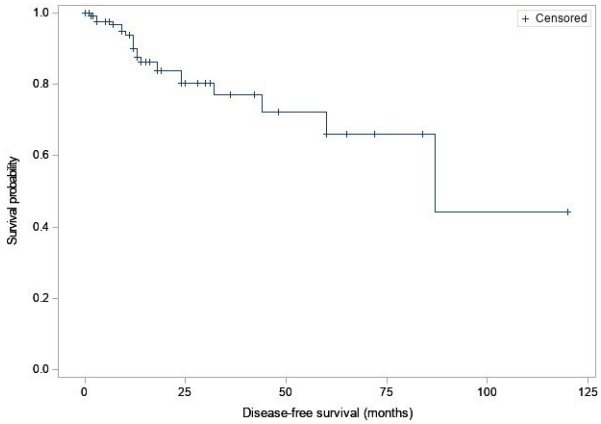

FIGURE 1 Survival analysis to time of uterovaginal prolapse recurrence.

falling to 0.8 after 24 months. This suggests that follow-up in the immediate and intermediate period is imperative.

Earlier this year, the Senate Community Affairs Reference Inquiry Report prompted removal of transvaginal mesh for use in POP from the Australian Register of Therapeutic Goods.[14] Laparoscopic sacrohysteropexy is no longer performed in conjunction with synthetic vaginal mesh procedures. This current study found that the use of anterior vaginal mesh is associated with post-operative complications, and a higher chance of procedure failure in a sacrohysteropexy. Thus, this study reinforces the recommendations recently published by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists to only consider synthetic vaginal mesh for prolapse management in carefully selected cases.[15]

There were no cases of mesh erosion relating to the laparoscopic sacrohysteropexy itself. However, given the controversy of vaginal mesh, we strongly advocate annual follow-up of all patients undergoing laparoscopic sacrohysteropexy to evaluate long-term complications.

Patients who had a pre-operative Stage III or IV prolapse had a higher likelihood of prolapse recurrence at an earlier interval.As such, we would advocate that patients with Stage IV prolapse would benefit from other forms of POP management given the higher failure noted in this study. Similarly, there was higher risk offailure in parous women where prolapse recurrence increased by 38% per vaginal delivery. Alternative surgical management shouldbe considered for women who have had multiple vaginal births.

This current study did not demonstrate a statistically signifi- cant association between BMI and success of procedure, althoughit should be noted that women with a BMI >35 were excluded from this study. If women are physically fit for laparoscopic sacro-hysteropexy, there should be no restrictions placed on eligibility for surgery due to age and obesity if BMI <35. Previous POP sur-gery (P = 0.02) was significant for increased likelihood of prolapserecurrence. This is an important determinant to success and thusshould be outlined when counselling patients. It also suggests that laparoscopic sacrohysteropexy should be considered a first- line surgical intervention prior to any prolapse repair and that initial repair should be performed by trained gynaecologists in pelvic floor reconstructive units who are credentialled as a Level VI Laparoscopic Surgeon.

Limitations of this study include its retrospective nature, heterogeneity of our study cohort and the inconsistent follow-upof patients in the immediate, intermediate, and late follow-upgroups. This study was carried out at a single centre by one skilled pelvic floor surgeon and any associated bias may make the study non-generalisable. Data integrity was strictly maintained; how- ever, these results should be interpreted with caution due to low cell counts for the majority of variables. Multivariable modelling was not undertaken due to the issues with cell counts.

Conversely, the strengths of this study include that it is the firstof its kind in Australia, with standardised pre- and post-operative assessments. This study only reports objective measurable outcomes via the internationally accepted POP-Q evaluations. Future

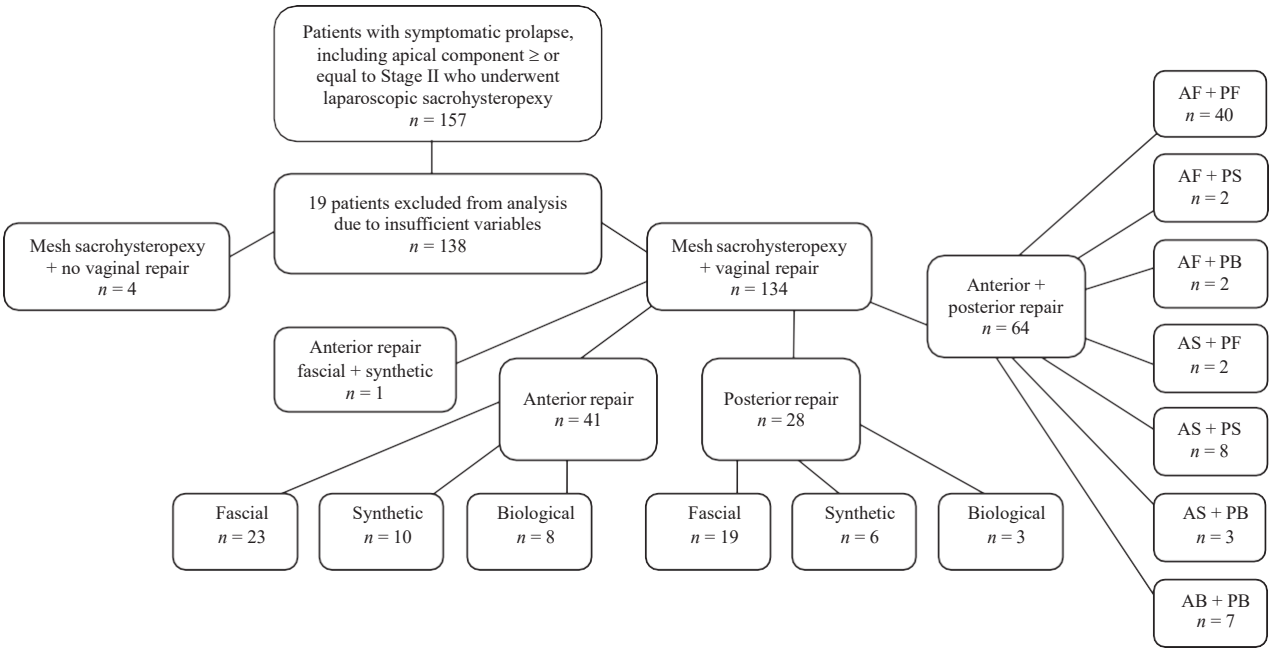

FIGURE 2 Flowchart of the distribution of patients with anterior and posterior vaginal repairs. AB, anterior biological; AF, anterior fascial; AS, anterior synthetic; PB, posterior biological; PF, posterior fascial; PS, posterior synthetic

research in this area should look to include a subjective account ofthe patient symptoms via the validated pelvic floor questionnaire as endorsed by the International Urogynaecological Association. Additionally, follow-up beyond ten years post-procedure wouldprovide additional information for clinicians to advise on lon- ger-term outcomes in these women.

Laparoscopic sacrohysteropexy is a safe, feasible, and well-tol- erated procedure for women with POP. It should be considered asan alternative to hysterectomy in women with a Stage II or III POPas it has a high success rate. It is an innovative uterine-preservingprocedure that can aid in treating these women.

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Chapter 4: Single Incision Laparoscopic Surgery (SILS) In Gynaecology: Feasibility and Operative Outcomes

4.1 Introductory comments

Developments in advanced conventional laparoscopy has led to further minimisations of surgical incision sites, known as Single Incision Laparoscopic Surgery (SILS), which requires one incision at the umbilicus. The SILS method has superior benefits when compared with conventional laparoscopic surgery as it results in decreased blood loss and post-operative pain, faster recovery time, improved cosmesis as well as decreasing the relevant potential complications of multiple accessory ports [1, 2]. It is anticipated this method will soon be replaced by Robotic Single Incision Laparoscopy [2].

To determine the feasibility, safety, and patient satisfaction with the cosmesis of SILS, as well as assess the complexity/difficulty in using this technique, Behnia-Willison et al. [1] conducted a prospective case series analysis of 105 women scheduled to undergo SILS for endometriosis, division of adhesions, hysterectomy, mesh sacrohysteropexy and ovarian cystectomy. This study demonstrated SILS is a feasible and safe technique and can be performed for different gynaecological problems. Patient satisfaction was high (averaged at 8 out of 10) because of the elimination of visible scaring and improved cosmesis, acceptable operative time, and reduced analgesic requirements post-operatively (less pain and complications). Due to the limitations of this study, such as non-comparative design, single-surgeon experience, and short follow-up, future comparative studies and long-term follow-up is required to establish the viability of this new surgical approach in gynaecology.

Following this study, Behnia-Willison et al. [3] described a case study that used SILS for mesh sacrohysteropexy, to correct a global prolapse classified as stage II on the POPQ system. This case report was the first of its kind to be published in the literature. The patient was a 70-year-old woman who underwent SILS mesh sacrohysteropexy followed by anterior and posterior vaginal repair with biological mesh augmentation. Sacrohysteropexy is a technique used to

correct pelvic organ prolapse, that allows women to preserve their uterus, as well as maintain normal sexual function. Conventional sacrohysteropexy is challenging and requires advanced laparoscopic techniques. While the SILS approach was possible, it was more challenging in terms of surgical access, as it required modification of a commercially available single incision port for greater manoeuvrability and took longer (70 minutes) than the conventional approach (~40 minutes). The key advantage of the SILS approach is that the umbilicus serves as the only point of entry, which minimises scarring and incisional pain associated with multiple entry points used for conventional sacrohysteropexy. At the 18 months follow up, the patient was free of symptoms and had no objective prolapse. This outcome is promising as it indicates that SILS can offer surgeons a minimally invasive scarless solution for performing reconstructive vaginal surgeries.

4.2 Aim

To assess the feasibility, safety, cosmesis and outcome of Single Incision LaparoscopicSurgery technique in different gynaecological conditions.

4.3 Summary

A prospective case series analysis of 105 women scheduled to undergo surgery by SILS. The data and parameters such as operative time, estimated blood loss, complications, additional ports and hospital stay were recorded. Post-operative pain and cosmetic outcomes (scar size) were also obtained. Out of 105 women, SILS was performed for 84 (60 excisions of endometriosis, 13 divisions of adhesions, five hysterectomies, two mesh sacrohysteropexies and four ovarian cystectomies). SILS was not undertaken for 21 women because of a number of factors, including the lack of required equipment (e.g., bariatric scope, SILS port, roticulating instruments and diathermy leads). Four women required insertion of additional ports because of surgical difficulties. One intra-operative (uterine perforation) and seven post-operative complications (six wound infections and one vault haematoma) occurred. The outcome shows that SILS is a feasible and safe technique for the surgical management of various

gynaecological conditions. Satisfaction is high because of improved cosmesis and reduced analgesic requirements postoperatively.

4.4 Publication in this chapter

Single incision laparoscopic surgery (SILS) in gynaecology: feasibility and operative outcomes.

F Behnia-Willison, L Foroughinia, M Sina, P McChesney.

Australian and New Zealand Journal of Obstetrics and Gynaecology 2012; 52 (4), 366-370.

4.5 Author contribution

I was responsible (100%) for the concept and design of research and (70%) data collection and analysis for the publication. Leila Foroughinia was responsible for (20%) for the data analysis and 20% of writing and editing. Maryam Sina and Phil McChesney were responsible (20% each) for writing, data entry and proofreading.

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Original Article

Single incision laparoscopic surgery (SILS) in gynaecology: Feasibilityand operative outcomes

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Background: Single incision laparoscopic surgery (SILS) represents the latest advancement in minimally invasive surgery, Combining the benefits of conventional laparoscopic surgery, such as less pain and faster recovery, with improved cosmesis. Although the successful use of this technique is well reported in general surgery and urology, there is a lack ofstudies on SILS in gynaecology.

Aims: To evaluate the feasibility, safety, cosmesis and outcome of SILS in gynaecology.

Methods: A prospective case series analysis of 105 women scheduled to undergo surgery by SILS from August 2010 to November 2011. Intra-operative data such as operative time, estimated blood loss, complications, additional ports and hospital stay were collected. Post-operative pain and cosmetic outcomes (scar size) were also recorded.

Results: Out of 105 women, SILS was performed for 84 (60 excisions of endometriosis, 13 divisions of adhesions, five hysterectomies, two mesh sacrohysteropexies and four ovarian cystectomies). SILS was not undertaken for 21 women because of a number of factors, including the lack of required equipment (eg bariatric scope, SILS port, roticulating instruments and diathermy leads). Four women required insertion of additional ports because of surgical difficulties. One intra-operative (uterine perforation) and seven post-operative complications (six wound infections and one vault haematoma) occurred. Mean operation times were as follows: mesh sacrohysteropexy – 60 min, excision of endometriosis – 55 min, hysterectomy – 150 min, laparoscopic division of adhesions – 62 min and ovarian cystectomy – 40 min.

Conclusions: Our experience shows that SILS is a feasible and safe technique for the surgical management of various gynaecological conditions. Satisfaction is high because of improved cosmesis and reduced analgesic requirements post-operatively.

Key words: adhesiolysis, endometriosis, laparoscopy, single incision laparoscopic surgery.

Introduction

Single incision laparoscopic surgery (SILS) (also known as embryonic natural orifice transumbilical endoscopic surgery (E-NOTES), one-port umbilical surgery (OPUS), laparoendoscopic single-site surgery (LESS) or single-incision multiport laparoscopy (SIMPL)). This approach enables minimally invasive surgery by means of one incision at the umbilicus.[1]

The SILS device is a flexible cylindrical port with multiple channels, which can accommodate up to three blunt trocars with diameters of 5–12 mm, arranged in a triangular configuration. All the required surgical instruments (straight or flexible) as well as a 5–10 mm scope can be passed into the abdominal cavity. A major challenge of this kind of surgery is to minimise the clash between instruments, which can be achieved with careful ergonomic placement of the tip and handle of the instruments.

The SILS method has superior benefits when compared with conventional laparoscopic surgery by resulting in decreased blood loss and post-operative pain, faster recovery time, improved cosmesis as well as decreasing the relevant potential complications of multiple accessory ports.[2]

Single incision laparoscopic surgery was first described in gynaecology by Wheeless for tubal ligation in 1969.[3] A recent literature review[4] reported on studies involving a large variety of laparoscopic surgeries performed through a single incision. According to this review, 9% of the total articles were in gynaecology and the procedures performed by gynaecologists included 4% of total patients.

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Although there is a recent report presenting a total number of 200 women operated via single incision in the Republic of Korea,[5] there are still a limited number of studies of single incision laparoscopic surgery in gynaecology. Most studies carried out in this area are case series or case reports.[6] The prospective study focussed on in this paper presents the outcomes of single incision laparoscopic surgery utilised in a variety of gynaecological procedures. The main aim of the study is to determine feasibility, safety, patient satisfaction with the cosmesis of SILS and also complexity and difficulty in using this technique.

Materials and Methods

To become acquainted with SILS procedures, a formal educational program was completed by the first author. This included dry lab, wet animal lab, advanced animal lab, and 5 insertions of ports prior to surgery on patients. The first SILS procedure on a patient was as a part of an MMIS course (Master of Minimally Invasive Surgery) in the College of General Surgeons, which involved diagnostic laparoscopy.

This prospective study was undertaken from August 2010 to November 2011 and was approved by the ethics committee of the local hospital. All the patients were adequately informed and formally consented for the procedure and for the research. A convenience sample of 105 was scheduled to undergo SILS in South Australia by one surgeon. Women eligible to undergo SILS included those undergoing diagnostic laparoscopy and dye study, possible endometriosis or mild to moderate adhesions, hysterectomy with a normal-sized uterus and low body mass index (BMI), pelvic inflammatory disease (PID), ovarian cysts <5 cm with low risk of malignancy index (RMI < 200) and those patients specifically requesting SILS. Women who had a history of severe adhesions, suspicion of gynaecological malignancy or high BMI (>30) were excluded. Demographic data such as age, BMI, medical history and past surgeries were collected. Patients were reviewed for complications such as wound infection and haematomas one and six weeks post-operatively. All patients were asked to return after one year for evaluation of long-term complications such as umbilical hernia and also for assessing the success rate of operation for diseases such as endometriosis.

Surgical techniques

All procedures were performed under general anaesthesia in lithotomy position. The patients were prepped and draped to hospital standard. A periumbilical nerve block was performed by injecting 5 mL of 0.5% bupivacaine and adrenalin at each of the 3, 6, 9 and 12 o'clock positions. A 15–20-mm vertical skin incision was made within the umbilicus. The rectus sheath was grasped with two implements (eg Rutherford Morrison tissue forceps) and a sharp incision made through the fascia with a scalpel. The incision was extended bluntly using artery forceps before inserting two S retractors. The incision in the fascia was then extended with the scalpel, allowing a 2.5-cm access to the abdomen without extending the skin incision. A Covidien SILS™ port (Tyco Healthcare Pty Ltd, Lane Cove, NSW) was inserted through the incision by grasping the base of the port with two Blake forceps. The Blake forceps were arranged, so the first forceps was positioned from the mid-section of the port to the leading edge and the second from the trailing edge to the mid-section, so the tip of the second clamp met the heel of the first. The port was lubricated with paraffin, and the first clamp was inserted through the incision directed towards the right lateral abdominal wall. When the heel of the first clamp had entered through the sheath, it was removed whilst continued pressure was exerted on the second clamp in an arc-like motion until the lower lip of the port had entered completely through the sheath. The trocars were then inserted. The port was modified by making a Y-shaped cut with a scalpel between the channels, which enabled greater movement of the instruments.

Once pneumoperitoneum was established, the operation commenced with the insertion of a bariatric 5-mm, 30-degree laparoscope and two instruments. The Covidien SILS™ port provides three 5-mm channels, one of which can be upsized to 12 mm. There is also one conduit for CO_2 insufflation (BOC, SA, Australia). The instruments used varied depending on the specific operation in terms of rigidity or roticulation (degree of articulation and extending ability). Each procedure was performed similarly to conventional laparoscopic surgery; however, because of ergonomics and instrument design, crossing of instruments was possible and at times necessary.

At the end of each SILS procedure, intra-operative data such as operative time (time from umbilical skin incision to completion of skin closure of the umbilicus), estimated blood loss, intra-operative complications and conversion to standard multi-access laparoscopy or laparotomy were recorded. Post-operative pain was evaluated in the recovery room and at discharge by the amount of parenteral analgesia, oral analgesia taken by each woman and length of hospital stay were recorded. Moreover, other data such as cosmetic outcomes (scar size) and post-operative complications were collected one week and six weeks after surgery. After one week, women reported a subjective value of satisfaction. Scale scores were weighted by the degree of satisfaction as ranked by the respondents. Women were asked to rate on the scale from 0 (lowest level of satisfaction) to 10 (highest level of satisfaction) to determine patients' satisfaction (including cosmetic perspective, recovery duration and their subjective satisfaction of the overall operation) after their procedure.

Results

SILS procedures were successfully performed on 84 women. Median age of the women who underwent SILS was 40 (range 16–81) and mean BMI was 24.5. This

Table 1 Patient characteristics

Patients' condition	
Age (years)	40 (16–81)
BMI (mean)	24.5
Previous abdominal surgery	
Laparotomy	15 (17.8%)
Laparoscopy	8 (9.4%)
Comorbidities	
Hypertension	7 (8.3%)
Diabetes	1 (1.2%)
Asthma	9 (10.7%)
Neurologic	5 (5.9%)
Total	21 (25%)

BMI, Body mass Index. Data shown as *n* (%). Age presented as mean (range).

procedure could not be performed for a further 21 of the scheduled women because of multiple factors, including unavailability of SILS port itself (five patients); no bariatric scope available for the procedure (six patients); inadequate and damaged bariatric scope discovered at the time of surgery (one patient); absence of reticulating instruments and diathermy leads (four patients); inadequate theatre time (four patients); and assistant who had minimal laparoscopic experience (one patient).

The percentage of SILS patients who had a history of previous abdominal surgery was 27.7 (Table 1). All surgeries were performed under general anaesthesia with <40 mL estimated blood loss. The mean scar length was also measured, which was 12 mm ± 5 in six weeks after the operation. As it has been shown in Table 2, the mean surgery time was 60 min for mesh sacrohysteropexy, 55 min for excision of endometriosis, 150 min for hysterectomy, 62 min for division of adhesions and 40 min for ovarian cystectomy. Most women had other concomitant surgeries such as hysteroscopy, vaginal repair and cystoscopy. The mean hospital stay and the satisfaction score at first post-operative week are shown in Table 2.

Four women required additional ports because of surgical difficulties. In two cases, one additional port(5-mm port for endometriosis and 12-mm port for mesh sacrohysteropexy) was inserted, and another case of endometriosis needed two additional ports, and one was converted to conventional laparoscopic surgery. Twenty-two women (26.2%) needed intravenous (IV) analgesia in the recovery room, 17% were given narcotic analgesia at discharge and 35.6% used only simple analgesia for a short period. Intra-operative and post-operative complications were recorded. One woman with a history of previous caesarean section and laparoscopic excision of endometriosis experienced a uterine perforation and developed a postoperative pelvic abscess, which was drained by a subsequent SILS procedure five days later. She recovered well and was discharged with oral antibiotics. Median follow-up was 7 (2–16) months. The

Table 2 Operative results

SILS	No. of patients	Hospital-stay mean (days)	Operating time – mean (range)	EBL (mL) (mean)	Satisfaction score (mean)	Complication (*n*)		Additional ports	Wound size* (mm) mean (range)
						Intra-OP	Post-OP		
Mesh sacrohysteropexy	2	3	60 (45–90)	<20	8	0	1	1	12
Excision of endometriosis	60	1	55 (30–100)	20	8 (4–10)	1	2	3	10 (8–18)
Hysterectomy	5	3	150 (135–165)	40	8	0	1	0	12 (10–15)
Laparoscopic division of adhesion	13	1	62 (35–90)	<20	8	0	3	0	15
Ovarian cystectomy	4	1	40 (35–85)	<20	9 (8–10)	0	0	0	15 (9–22)

EBL, estimated blood lost; OP, operative; SILS, Single incision laparoscopic surgery.
*Wound size is for six week post-operation.

percentage of women in the cohort who developed a wound infection was 7.1 (n = 6), all of whom responded well to oral antibiotics. One woman experienced a vault haematoma after SILS hysterectomy, which was managed conservatively. No umbilical hernias were observed.

Discussion

Single incision laparoscopic surgery is a relatively new procedure in gynaecology and the literature is limited in this regard. Sixteen articles, including ten case series, two comparative studies, three case reports, and one surgical technique demonstration were presented in a recent literature review.[6] Most reported surgeries that were performed through single incision were hysterectomies and ovarian cystectomies; however, in our case series excision of endometriosis and adhesiolysis were mostcommon.

This study demonstrates that SILS is a feasible and safe technique and can be performed for different gynaecological problems. Patient satisfaction is high because of the elimination of visible scaring and improvedcosmesis and reduced analgesic requirements. The average patient satisfaction score for cosmetic outcomes was high (Table 2), which is an advantage of this technique.

In this study, six women experienced infection after the operation, two of whom had umbilical deposits at the timeof incision; however, in a study by Mereu *et al.*,[7] 16 women with benign adnexal pathologies underwent operation with laparoendoscopic single-site approach withno intra-operative complications. Post-operatively, one umbilical scar wound infection was recorded in the samestudy (one in 16).[7] In another study undertaken by Fader *et al.*,[8] 74 women underwent SILS and the rate of post- operative complications was low and consisted of one pulmonary embolus and two cases of incisional cellulitis.

In our study, one type of port was used throughout the entire sample, which clarifies the function of the particular port in SILS. This factor differentiates the present study from a study undertaken by Park *et al.,*[5] which reported the SILS undertaken by different types of ports. However,the sample size of this study is larger than our survey, which may compensate for variety types of port. Furthermore, both studies were undertaken by one surgeon, which limits generalisabilty.

Although revolutionary new instruments and ports have been designed, there are still technical difficulties in usinga single port. The primary challenges of SILS are the limited degrees of freedom of movement, the number of ports that can be used and the instrument crowdingduring the operation, which increase the complexity and technical difficulty of the operation. Diathermy smoke can be a particular problem with SILS as the original port systems did not include a smoke evacuation valve. However, new port designs may overcome this problem. We have also found that there can be electrical interference when activating monopolar electrosurgical equipment, which obscures the view of the surgical field on the monitor. As described earlier, we modified the portto allow more flexibility and greater range of motion. Covidien has addressed this flexibility issue in the new generation (third-generation) port, which is not yetavailable. The currently available port can also be too short for obese patients, preventing correct positioning in the abdominal wall. Roticulation (angulation) ofinstrument plays an important role in SILS. A number of roticulatory instruments have been developed to overcome these technical difficulties. In the conventional laparoscopic method, a 0 degree scope is often used, whereas with SILS, a bariatric 30-degree scope can enhance the viewing angle and help avoid clashing instruments outside the patient. This can be difficult for some surgeons at first if they are not used to using 30- degree scopes. Use of some innovative laparoscopic instruments such as the Endo Stitch™ (Covidien Surgical) device for suturing also helps to solve some of SILS difficulties. Finally, the current Covidien port provides three channels which does allow only limited cooperation of theassistants. This limitation is more obvious in major cases where four ports or more are used in conventional laparoscopy.

The learning curve for laparoscopic gynaecologic operations[9,10] and robotic gynaecologic surgeries[11] has been reported in the literature. Achieving proficiency with SILS seems to be more challenging as it requires higher level of laparoscopic skills.[6] However, there is also a report about a short learning curve for single incision laparoscopy-assisted vaginal hysterectomy.[12] This surgeryrequires skilled surgeons and operating team. Operative time in SILS has been shown to be decreased when experience is gained by the surgeon. The development of virtual reality models and animal labs has helped make the learning process easier for all novice users.

The most important consideration is the safety of the patient, which should not be compromised at any stage. Therefore adding a port, when it seems necessary, takes precedence over cosmetic considerations. Adding a port should not be interpreted as failure to perform SILS but rather in the context of using the minimum number of ports to conduct safe surgery. One should not compromise optimal patient care under any circumstances and being humble and having a low threshold for adding extra ports can mean a safer and acceptable learning curve with this new surgical technique.

The strengths of this study are its prospective design and the fact that procedures were performed for a variety of gynaecological conditions. The limitations of this study include its non-comparative design, single-surgeon experience, short follow-up and the presence of concomitant surgeries may have had obscured the analgesic requirement and length of stay needed for SILS patients.

The outcomes of this study included a high level of patient satisfaction regarding the cosmetic aspect, as wellas acceptable operative time and low rate of post-

operative pain and complications. However, we strongly believe that future comparative studies and long-term follow-up is required to establish the viability of this new surgical approach in gynaecology. It is conceivable that the utilisation of SILS with robotic surgery will overcome many shortcomings of SILS.

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Chapter 5: Techniques for Single-Port Urogynecology and Pelvic Reconstructive Surgery

5.1 Introductory comments

As previously described in Chapter 4, advancement in conventional laparoscopy has led to Single Incision Laparoscopic Surgery (SILS), which requires only one incision at the umbilicus with the confirmed benefits as significantly less blood loss and post-operative pain, faster recovery time, improved cosmesis and decreasing the chance of potential complications of multiple accessory ports. In seeking to further investigate more advanced techniques, this chapter mainly focuses on laparoendoscopic single-site surgery (LESS) and the application of this technique in gynaecological conditions.

5.2 Aim

The chapter aims to evaluate the instruments, ergonomics and learning curveregarding the technique and description of minimally invasive solutions to prolapse.

5.3 Summary

The article and book chapter confirm that laparoendoscopic single-site surgery is a feasible substitute for conventional laparoscopic sacrohysteropexy. The better cosmetic result and shorter recovery time resulted in high patient satisfaction. As interest in laparoendoscopic single-site surgery grows, the range of surgical procedures that use this approach is also likely to increase. In these publications the feasibility of this technique to resolve complex gynecological problems, such as uterus-sparing prolapse repairs are demonstrated.

5.4 Publications used in this chapter

A laparoendoscopic single-site surgery approach to mesh sacrohysteropexy.

F Behnia-Willison, A Garg, MJNC Keirse.

Case Reports in Medicine 2013; Article ID 641675. doi.org/10.1155/2013/641675.

5.5 Author contribution

I was responsible (100%) for the concept and design of research and 70% data collection and analysis for the publication. Anirudha Garg and Marc J. N. C. Keirse were responsible for

writing (40% each), editing and proofreading of the manuscript.

Techniques for Single-Port Urogynecology and Pelvic Reconstructive Surgery (Book Chapter).

F Behnia-Willison, A Garg.

Atlas of Single-Port, Laparoscopic, and Robotic Surgery, 2014, New York, NY. Springer. pp167-182.

5.6 Author contribution

I was responsible (100%) for the design of research and (70%) data collection and analysis as well as 40% of writing and editing for the book chapter. Dr Anirudha Garg was responsible for (30%) for the data analysis and (60%) of the writing editing, and formatting of the publication.

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Case Report

A Laparoendoscopic Single-Site Surgery Approach to Mesh Sacrohysteropexy

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Although laparoendoscopic single-site surgery (LESS) has spread across surgical disciplines, this has not been the case for the repair of uterovaginal prolapse. We describe the use of this technique for mesh sacrohysteropexy to correct a global prolapse classified as stage II on the pelvic organ prolapse quantification (POP-Q) system. The procedure involved intraoperative modification of a commercially available single incision port. At the 18 months followup, the patient was free of symptoms and had no objective prolapse.

1. Introduction

Laparoendoscopic single-site surgery (LESS), also variously known as single incision surgery or single-port surgery, is a minimally invasive procedure which is based on the premise that the use of a single umbilical incision results in less postoperative pain and better cosmetic results than the traditional, multiport laparoscopic surgery. Single incision laparoendoscopic surgery is increasingly being used for a variety of surgical procedures. Although its use for tubal ligation dates back to more than 40 years [1], compared with other surgical specialties, there is still relatively little literature on outcomes of single-port surgery in gynecological surgery. A recent literature review indicated that only 4 percent of all laparoendoscopic single-site procedures had been performed by gynecologists [2]. Most gynecological procedures performed through single incision, apart from tubal ligation, have been hysterectomies, oophorectomies, and ovarian cystectomies [3]. Here we report on the use of the single-port technique for mesh sacrohysteropexy. To the best of our knowledge, mesh sacrohysteropexy through a single-port approach has not been reported previously.

2. Patient Presentation

The patient was a 70-year-old woman with a body mass index of 26, who was para 3 having had 3 vaginal births. She presented with symptomatic global prolapse and had found no relief from conservative management including pelvic floor exercises and vaginal estrogens. At her request, she was scheduled for a laparoendoscopic single-site mesh sacrohysteropexy followed by anterior and posterior vaginal repair with biological mesh augmentation. Her pelvic organ prolapse quantification (POP-Q) [4], as determined intraoperatively, was GH4 cm,C +1.5, Aa 0, Ba +0.5, Ap 0, Bp −3, D 8, TVL 10, and PB 1.5 cm resulting in a global prolapse stage score of II.

3. Intervention

The procedure was performed under general anesthesia in lithotomy position. After skin preparation and draping, a periumbilical infiltration was made with 5 mL injections of 0.5% bupivacaine and adrenalin at each of the 3, 6, 9, and 12 o′ clock positions. As shown in Figure 1, a 15–20 mm vertical trans-umbilical skin incision was made. The rectus sheath

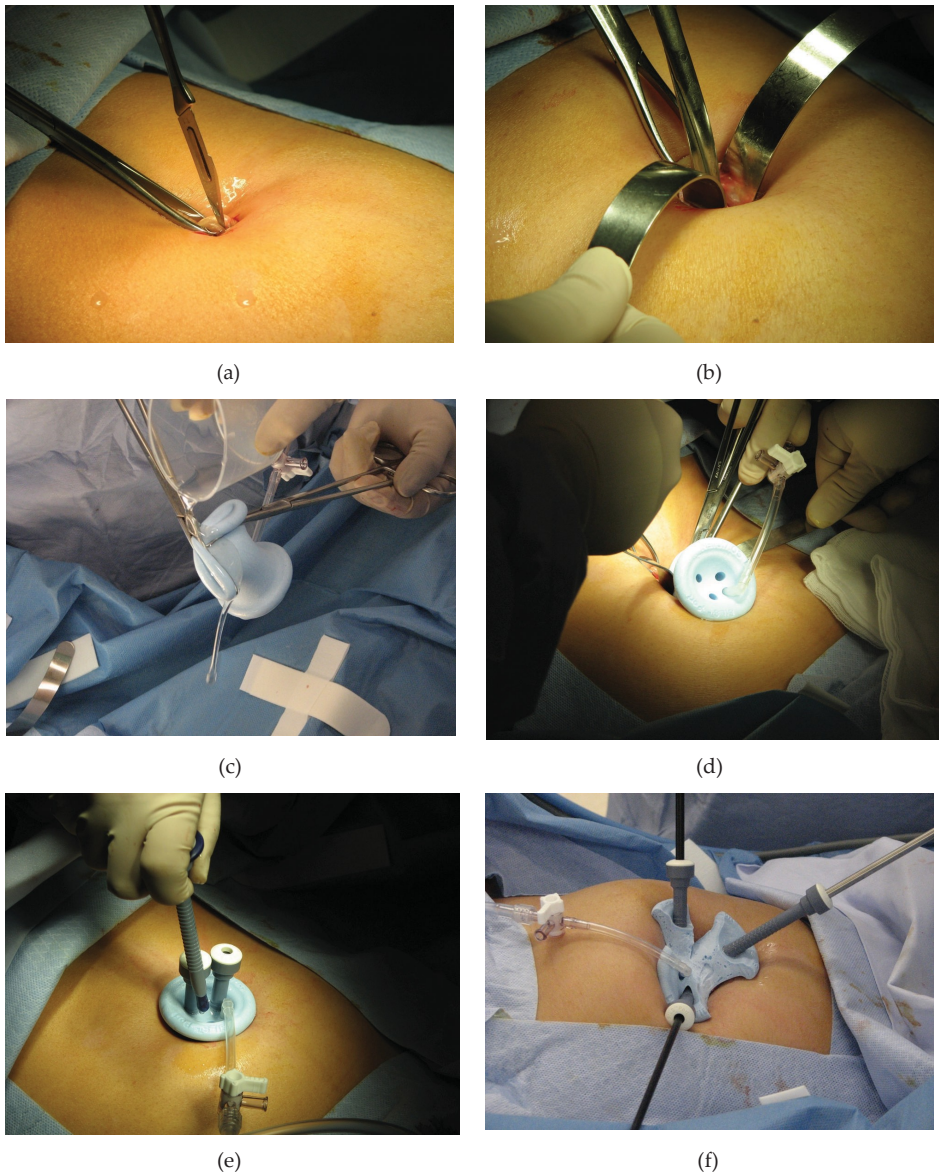

Figure 1: Insertion and modification of the Covidien SILS port: (a) incision to gain access to the peritoneal cavity via the umbilicus; (b) using S retractors to establish pneumoperitoneum; (c) lubricating the SILS port with paraffin wax; (d) grasping the SILS port using two Blake forceps and insertion into the umbilicus with the forceps as a guide; (e) insertion of the trocars and insufflation of the abdomen; and (f) Y-shaped modification of the port by 3 cuts made at an angle of 120 degrees from each other to allow for greater maneuverability.

was lifted and held with two Littlewood's graspers, and the fascia was incised with a scalpel. The incision in the fascia was extended bluntly using artery forceps before inserting two S retractors. A Covidien SILS port (Tyco Healthcare, Lane Cove, NSW, Australia) was inserted through the incision by grasping the base of the port with two Blake forceps. The Blake forceps were arranged so that the first forceps was positioned from the midsection of the port to the leading edge and the second from the trailing edge to the mid-section with the tip of the second clamp meeting the heel of the first. The port was lubricated with paraffin, and the first clamp was inserted through the incision directed towards the right lateral abdominal wall. When the heel of the first clamp had entered through the sheath, it was removed while continuous pressure was exerted on the second clamp in an arc-like motion until the lower edge of the port had entered completely through the sheath. The port was then modified by making a Y-shaped cut with a scalpel between the three channels, at 120 degrees from each other, to enable greater movement of the instruments (Figure 1). This modification not only increased the range of motion of instruments, but it also improved ergonomics and reduced clash of the instruments. The trocars were then inserted.

Once pneumoperitoneum was established, the operation commenced with the insertion of a bariatric 5 mm, 30-degree

laparoscope, and two instruments. The Covidien SILS port provides three 5 mm channels, one of which can be upsized to 12 mm. There is also a conduit for CO_2 insufflation (BOC, SA, Australia). The single-port procedure was performed similarly to conventional laparoscopic surgery. However, because of ergonomics and instrument design, crossing of instruments was possible and at times necessary.

The patient was tilted to the left. The sigmoid colon was gently pushed to the left with a blunt bowel grasper and the right ureter, and iliac vessels were identified. The peritoneum over the sacral promontory was then grasped and lifted, and an incision was made from the top of the sacral promontory to the back of the cervix at the most caudal level of the insertion of the uterosacral ligaments.

Next, a polypropylene type 1 monofilament macroporous nonabsorbable mesh (AMS, USA) was used to suspend the cervix from the sacral promontory. The length of mesh was measured and tailored to the patient (15 cm). The mesh was anchored to the posterior cervix with five absorbable ProTack fasteners (AbsorbaTack Fixation Device, Covidien). The other end of the mesh was then fixed to the sacral promontory utilising 5 mm non-absorbable helical fasteners (ProTack Fixation Device, Covidien) to elevate the uterus. The aim is to lift the cervix at least 6–8 cm above the level of the introitus to allow shortening of the mesh and subsequent fibrosis. The entire length of the mesh was covered with peritoneum closed with Vicryl 2-0 using a Covidien Endostitch device.

Hemostasis was achieved, and the diameter of the ureter was inspected to exclude obstruction-induced dilatation. As is common practice with laparoscopic pelvic floor repairs in our department, a cystoscopy was performed after the procedure to observe ureteric patency before the trocars were removed. The sheath within the trans-umbilical port site was identified and sutured using long-absorbable sutures (PDS) before skin closure. The overall operating time was 70 minutes.

After completion of the hysteropexy, an anterior and posterior vaginal repair was undertaken with biological mesh. A vaginal pack and indwelling catheter were inserted, and the patient was transferred to recovery with calf compressors. Low molecular weight heparin (Enoxaparin) was commenced 8 hours after the operation. There were no intraoperative or postoperative complications. No analgesia was required postoperatively, and the patient was discharged after defecation 2 days after the intervention.

4. Followup

One week post-operatively, the patient had a port site infection, which was treated and resolved with oral antibiotics. She had no prolapse at the 6-week followup, and the size of the umbilical scar was 1.5 cm. At 6-month followup, she remained free of symptoms. The port site had healed to 0.5 cm. Objective evaluation showed GH 2 cm, C −8, Aa −3, Ap −3, Ba −3, Bp −3, TVL 10, PB 3 cm, indicating the absence of any prolapse. At 6 months, the patient still rated her satisfaction as 9 on a 10-point visual analogue scale, mainly, because of the absence of post-operative pain, quick recovery, early return to day-to-day life, and cosmesis.

On followup at 12 months and 18 months there were no symptoms and no objective prolapse on POPQ assessment. There was no evidence of mesh erosion or any other complication. The umbilical scar was no longer visible. The patient used vaginal estrogen cream twice weekly and had regular pelvic floor exercises.

5. Discussion

Studies of nongynecological patients show a comparablerate of minor complications, such as wound infection, with laparoendoscopic single-site surgery as those found with standard laparoscopy [5, 6]. Van den Boezem and Seitses reported 4 cases of wound infection in 50 laparoendoscopic single-site colorectal operations [7]. We observed a similar number of infections: 6 of 100 patients undergoing gynecological laparoendoscopic single-site surgery developed port-site infections [8]. However, this is a minor complication that is easily treated with oral antibiotics. It has been reported that laparoendoscopic single-site procedures require a longer operating time than conventional laparoscopic procedures. This would seem to apply to laparoendoscopic single- site sacrohysteropexy too. In our experience, the time to perform a conventional laparoscopic sacrohysteropexy is 20 to 40 minutes [8], compared with 70 minutes for the laparoendoscopic single-site sacrohysteropexy. However, operating times decrease with increasing experience of the surgeon [8]. So, we postulate that the time for laparoendoscopic single-site sacrohysteropexy will also decrease with experience.

As any procedure, laparoendoscopic single-site surgery has some limitations, such as the necessary surgical skill and the need for careful selection of patients. A relatively low body mass index is required, and there should be no adhesions from previous abdominal surgery. Furthermore, a laparoendoscopic single-site pelvic floor repair is a physically taxing procedure; there can be a crowding of instruments; the relative novelty of the laparoendoscopic single-site instruments means that there is still room for improvement to maximize ergonomics.

6. Conclusion

This paper shows that laparoendoscopic single-site surgery is a feasible substitute for conventional laparoscopic sacrohysteropexy. The better cosmetic result and shorter recovery time resulted in high patient satisfaction. As interest in laparoendoscopic single-site surgery grows, the range of surgical procedures that use this approach is also likely to increase. Currently, most are still confined to specialized centers as the jury is still out on their value and their relative merit compared with conventional laparoscopic surgery in routine clinical practice. Nonetheless, this paper shows the feasibility of this technique to resolve complex gynecological problems, such as uterus-sparing prolapse repairs.

Conflict of Interests

The authors specifically state that there is no conflict of interests, commercial or otherwise, in respect to this paper.

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Techniques for Single-Port Urogynecology and Pelvic Reconstructive Surgery

Fariba Behnia-Willison and Anirudha Garg

This chapter introduces the use of single-port laparoscopy for surgical management of female pelvic floor repair. Degrees and types of pelvic organ prolapse are quantified. Patient care is covered, including preoperative and postoperative care and consent. The instruments, ergonomics, and learning curve are then discussed. Finally, descriptions of minimally invasive solutions to prolapse are described. Specifically, the use of sutures and mesh in apical vaginal vault repair with or without a previous hysterectomy are described.

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14.1 Introduction

Historically, the treatment of genital prolapse dates back to 1500 B.C. to the Ebers Papyrus, which described the treatment of prolapse via the smearing of a mixture of honey and other sticky substances on the prolapsed organ [1]. Hippocrates subsequently described the treatment of uterine prolapse by securing the woman upside-down and shaking her. Management involved the insertion of a half pomegranate soaked in wine into the vagina. Suffice it to say, the treatment of prolapse has significantly improved since then. In the middle to late nineteenth century, surgical intervention to treat uterine prolapse consisted of narrowing the vaginal vault via astringents, colporrhaphy, or cautery. By the end of the nineteenth century, there were several surgical approaches to the treatment of uterine prolapse; however, achieving long-lasting repairs remained elusive [1].

An improved understanding of pelvic floor anatomy as well as aseptic surgical techniques brought about the concept of a vaginal/abdominal surgical approach to treat vaginal prolapse.

Finally, the repair of vaginal prolapse was described in its current form in 1957 by Arthure and Savage, whose original description of abdominal sacrohysteropexy continues to be utilized today [2]. Although the surgical procedure largely remains the same, the approach toward pelvic floor repair has continually moved toward minimally invasive surgical techniques. In 2008, the present author performed one of the first mesh sacrohysteropexies as a laparoendoscopic single-site (LESS) surgery, thus helping to further minimize the invasiveness of prolapse repair.

The primary goals in surgical management of prolapse are not only to correct the prolapse but to correct the symptoms associated with this condition. This includes the reversal of urinary or fecal incontinence, urgency, and improvement of sexual dysfunction if present. There also are significant psychological consequences to prolapse, which may be improved with surgical correction [3].

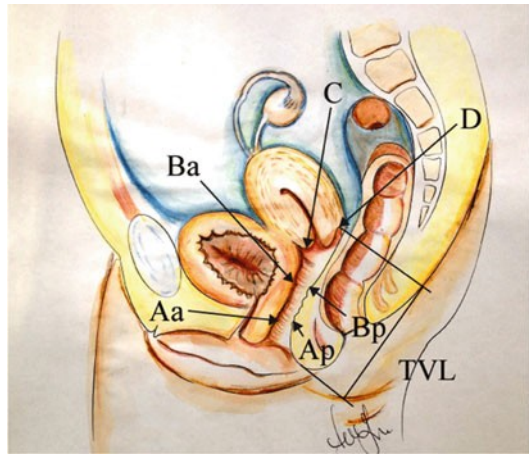


Fig. 14.1 A sagittal view of the female pelvic floor. All measurements are taken with the vaginal orifice (hymen) as the midpoint with a value of 0. Points within the vaginal cavity are negative and points outside the vaginal cavity are positive (From Bump et al. [4]; with permission)

Point	Description	Range of Values
Aa	Anterior vaginal wall 3 cm proximal to the hymen	-3 cm to +3 cm
Ba	Most distal position of the remaining upper anteriorvaginal wall	-3 cm to + tvl
C	Most distal edge of cervix or vaginal cuff scar	
D	Posterior fornix (N/A if post-hysterectomy)	
Ap	Posterior vaginal wall 3 cm proximal to the hymen	-3 cm to +3 cm
Bp	Most distal position of remaining upper posteriorvaginal wall	-3 cm to + tvl

Genital higtus (pb) - Measured from middle of external urethral meatus toposterior midlline hymen

Perineal body (pb) - Measured from posterior margin of to gh middle of analopening

Total vaginal length (tvl) - Depth of vagina when point D or C is reducedto normal position

Table 14.1 Staging criteria for POP-Q

POP-Q staging criteria	
Stage 0	Aa, Ap, Ba, Bp = −3 and C or D ≤ − (tvl − 2) cm
Stage I	Stage 0 criteria not met and leading <−1 cm
Stage II	Leading edge ≥ −1 cm but ≤+1 cm
Stage III	Leading edge > +1 cm but <+ (tvl – 2) cm
Stage IV	Leading edge ≥ +(tvl – 2) cm

From Bump et al. [4]

14.2 Prolapse Quantification

In order to describe pelvic floor dysfunction as it relates to gynecology, an objective system to quantify prolapse has been developed [4]. As described in Fig. 14.1, the Pelvic Organ Prolapse Quantification (POP-Q) system allows for a quick, one-line dissemination of the severity of pelvic organ prolapse, allowing the reader to understand the degree and type of prolapse (anterior versus posterior). Given this quantification system, a staging protocol, as described in Table 14.1, was concurrently developed.

14.3 Patient Care for Single-Port Pelvic Floor Repair

14.3.1 Preoperative

Women typically appear at the clinic with prolapse symptoms, which may include vaginal bulge, pelvic pain, sexual dysfunction (including dyspareunia), and urinary or fecal dysfunction. A standardized, comprehensive history that addresses prolapse, urinary, bowel, and sexual symptoms is completed. A physical examination, including assessment of the pelvic floor utilizing the POP-Q system, a cough test, and a Q-tip test are also performed. Perineal ultrasound analyzing detrusor and bladder neck caliber is carried out. The patient is further investigated with cystometric urodynamic studies, if indicated.

All patients are offered a vaginal support device to reduce vaginal bulge in the form of a ring pessary if they are sexually active or a mushroom pessary if they are not active. Conservative management is recommended initially for a minimum of 3–6 months and includes pelvic floor exercises, the use of estrogen cream if it is not contraindicated, lifestyle changes (including a reduction in caffeine intake and addressing constipation), reducing weight, reducing intra-abdominal pressure by decreasing heavy lifting (modifying gym activ- ities such as lying down when lifting weightsand increasing repetition with decreased load when lifting), and managing asthma or smoking (decreased coughing). Patients are advised to prolong the conservative management period until their family is complete. All patients are given bowel preparation the day before any laparoscopic pelvic floor surgery.

14.3.2 Consent Visit

If the patient's symptoms persist and she desires surgical management, she is asked to speak with the surgeon and her partner or support person about the postoperative period. They are informed about intraoperative prolapse staging, where 29 % of prolapses are upgraded and 9 % are downgraded, and subsequent modifications to the surgery that may be made owing to intraoperative findings [5]. Patients are reminded that pelvic floor repair is a major operation requiring strict and lifelong lifestyle management postoperatively. They are told about the risks of mesh repair as well as the limited data on the use of mesh in gynecology. This is an important aspect of the treatment because women with active lifestyles are prone to organ prolapse and, because the procedure is relatively pain-free postoperatively, they may relapse and compromise successful outcomes. Hence, strict follow-up visits at 1 week for detection of early complications, then 6 weeks, 3, 6, and 12 months, and annually thereafter are required.

14.3.3 Postoperative

An indwelling catheter (IDC) and vaginal pack are inserted immediately after the operation and removed the next day. A deep vein throm- bosis prevention protocol is followed, and laxa- tive medication in the form of a bulking agent is administered. It is recommended that patientsstay in the hospital until there is no significant postvoid residual (<20 %) and the bowels are active.

Good patient selection, sound surgical skills, and postoperative patient lifestyle changes are cornerstones of a successful pelvic floor repair surgery.

14.4 Instruments, Ergonomics, and Learning Curve

14.4.1 Instruments (Commonly Used in LESS Pelvic Floor Repair)

- 30-degree, 5-mm bariatric scopes or 5-mm flexible scopes (Olympus; Center Valley, PA)
- Ligosure roticulating instruments (Covidien; Mansfield, MA)
- Endostitch (Covidien; Mansfield, MA) with Ethibond sutures (Ethicon; Somerville, NJ)or a straight needle-holder utilizing V-loc (Covidien; Mansfield, MA)
- Straight tooth and bowel graspers
- Roticulating graspers
- Smoke evacuator
- Suction irrigation
- Covidien (Mansfield, MA) or GelPOINT single-port surgical device (Applied Medical; Rancho Santa Margarita, CA)

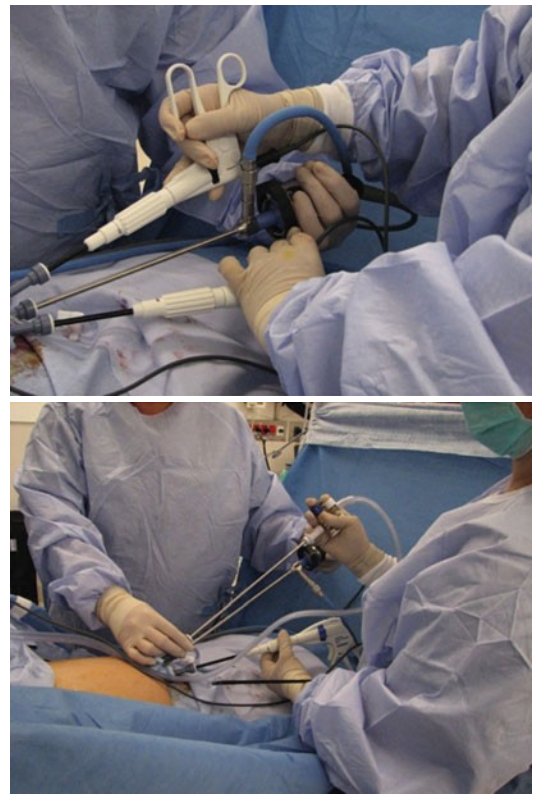


Fig. 14.2 Proper ergonomics are vitally important in a LESS procedure. Because of the single port access to the intra-abdominal cavity, the degrees of freedom are limited compared to those in conventional multiport laparoscopy. A surgical plan taking into account these limitations is important in producing successful outcomes for LESS pelvic floor repair. Note how the surgeons are standing as midline as possible with their arms in neutral positions and bodies facing away from the patient's head

14.4.2 Ergonomics

When using single-site ports of any kind, the ergonomics of the instruments will become crucial in performing the surgery. There are two important points regarding ergonomics in LESS pelvic floor repair. First, the operation can be cumbersome if a proper approach has not been thought through owing to the single fulcrum point at the abdomen as well as crowding of the instruments (Fig. 14.2). Second, there are issues regarding the body positioning of the surgeon and the assistant.

Unlike conventional laparoscopy in which crossing of instruments is discouraged, such a maneuver becomes necessary at times in LESS.

Crossing instruments is safe because of the insulating properties of roticulating graspers. This requires retraining for many conventional laparoscopic surgeons. Furthermore, the surgeon needs to be aware of possible instrument crowding issues. Thus, in order to minimize surgery time as well as reduce frustration, the surgeon needs to plan out the order and positioning of the instruments, taking into account the patient's anatomy, body mass index (BMI), and any surgical procedures performed previously on this patient prior to making an incision.

The operation is easier if a 5-mm bariatric 30° scope is used with a highly experienced assistant who will need to have both hands constantly on the camera and light lead to provide the best possible view. It is advisable to commence with the scope on the right side or most cephalic channel to enable the assistant to push the camera down toward the patient and away from the midline. The surgeon should place the instruments in a way that is physically most comfortable. As the operation proceeds, changing the channels of the instruments or changing the operating side may be required; therefore the surgeon should stand as close as possible to the head of the patient andin the midline. This provides the most accessible plane for operating on the pelvic floor. This is a particularly important point in LESS gynecology because of the limited degrees of freedom with a single-port approach and subsequent problems with needing to lean over patients (Fig. 14.2).

14.4.3 Learning Curve

A short learning curve for LESS requires sound anatomic knowledge, conventional laparoscopic surgical experience, and proficiency with laparoscopic suturing. Furthermore, an understanding of current surgical procedures for pelvic floor repair is highly valued, since the approaches to these do not change significantly with the transabdominal approach (LESS versus multiport laparoscopy).

With regard to LESS versus conventional laparoscopic transabdominal pelvic floor repair surgeries, it has been noted that LESS takes more time (which decreases with experience) and is more strenuous if the ergonomics of the patient or operator have not been properly thought through. Current data are only available as case reports; however, the data from these reports appear encouraging both for patients and for surgeons [6]. This is probably because the surgeries themselves are the same, but the approach to them is simply being modified (single-port) in order to improve cosmesis and minimize invasiveness. Thus, the learning curve for a surgeon when training in LESS mainly deals with port insertion and ergonomics.

Prior to utilizing a LESS approach, as occurred with this chapter's first author, it is beneficial to have advanced skills in conventional laparoscopic pelvic floor repair surgeries utilizing Verress needles to establish the pneumoperitoneum. When switching to LESS, the author required approximately ten port insertions with the Covidien device (Mansfield, MA) in order to demonstrate efficiency and accuracy in the port insertion technique. This was achieved in dry laboratories, animal laboratories, and in the operating theater under supervision. Subsequently, the insertion of the GelPOINT port (Applied Medical; Rancho Santa Margarita, CA) required only one practice insertion with instruction in order to achieve proficiency. This was achieved following approximately 200 LESS procedures utilizing Covidien ports. Initially, port insertion took 7–10 min, but with practice (~25 procedures), this decreased to approximately 3–4 min per insertion.

14.5 Establishing the Pneumoperitoneum and Inserting the Port

14.5.1 Covidien SILS Port

All pelvic floor repair LESS procedures are performed under general anesthesia with the patient in the lithotomy position. Once the patient is prepared and draped, a periumbilical nerve block is performed by injecting 5 mL of 0.5 % bupivicaine and adrenaline at each of the 3, 6, 9, and 12 o'clock positions. A 15–20-mm vertical transumbilical skin incision is made. The rectus sheath is grasped with two graspers and a sharp incision made through the fascia with the tip of a scal- pel, allowing intraperitoneal access. The incision is stretched with an artery clip and opened to its maximum opening width, which should accommodate the insertion of two S-retractors. A scalpel is used to extend the sheath incision to 2.5 cm under the skin without extending the skin incision.

The Covidien SILS port is inserted through the incision by grasping the base of the port with two Blake forceps. The Blake forceps are arranged so that the first forceps is positioned from the midsection of the port to the leading edge, and the second is arranged from the trailingedge to the midsection, such that the tip of the second clamp meets the heel of the first. The portis lubricated with paraffin, and the first clamp is inserted through the incision directed toward theright lateral abdominal wall. When the heel of thefirst clamp enters the sheath, it is removed whilecontinued pressure is exerted on the second clamp in an arc-like motion until the lower lip ofthe port enters completely through the sheath. The trocars are then inserted. The present authorhas modified the Covidien SILS port by cutting it vertically between the channels at 120° angles so that a larger degree of freedom is attained for each trocar insertion port. Figure 14.3 briefly illustrates the process of incising the abdomen and inserting the port.

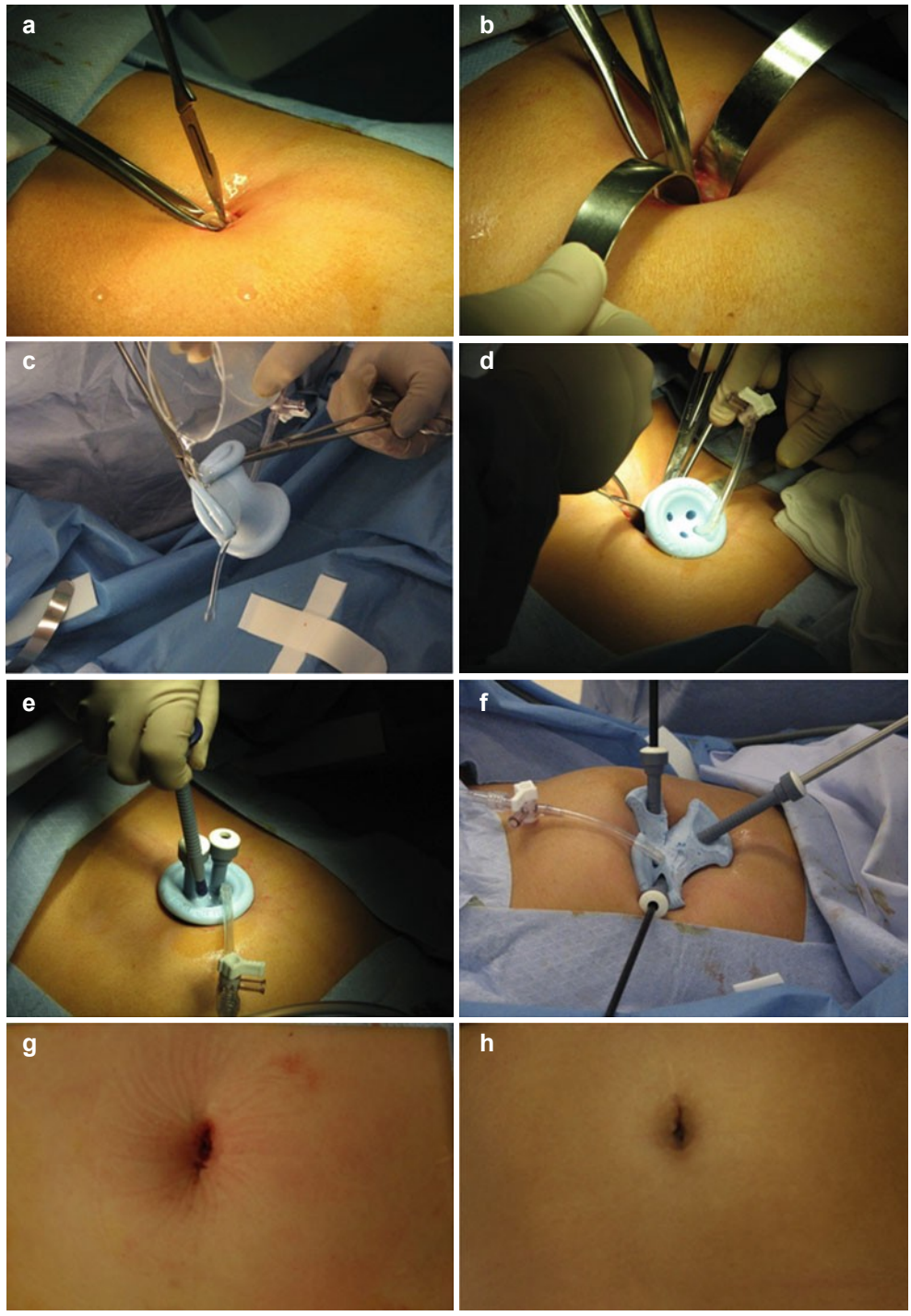


Fig. 14.3 An overview of the insertion, modification of the Covidien port, and postoperative cosmesis. (**a**) Incising and gaining access to the peritoneal cavity via the umbilicus. (**b**) Using S retractors to establish the pneumoperitoneum. (**c**) Lubricating the SILS port with paraffin wax. (**d**) Grasping the SILS port using two Blake forcepsand inserting these into the umbilicus with the forceps as

a guide. (**e**) Insertion of the trocars and insufflation of theabdomen. (**f**) Trocars are then inserted and the port is cut every 120° between the channels of the SILS port to allowfor greater maneuverability. (**g**) The umbilicus is visual- ized immediately postoperatively. (**h**) Six weeks postoperative

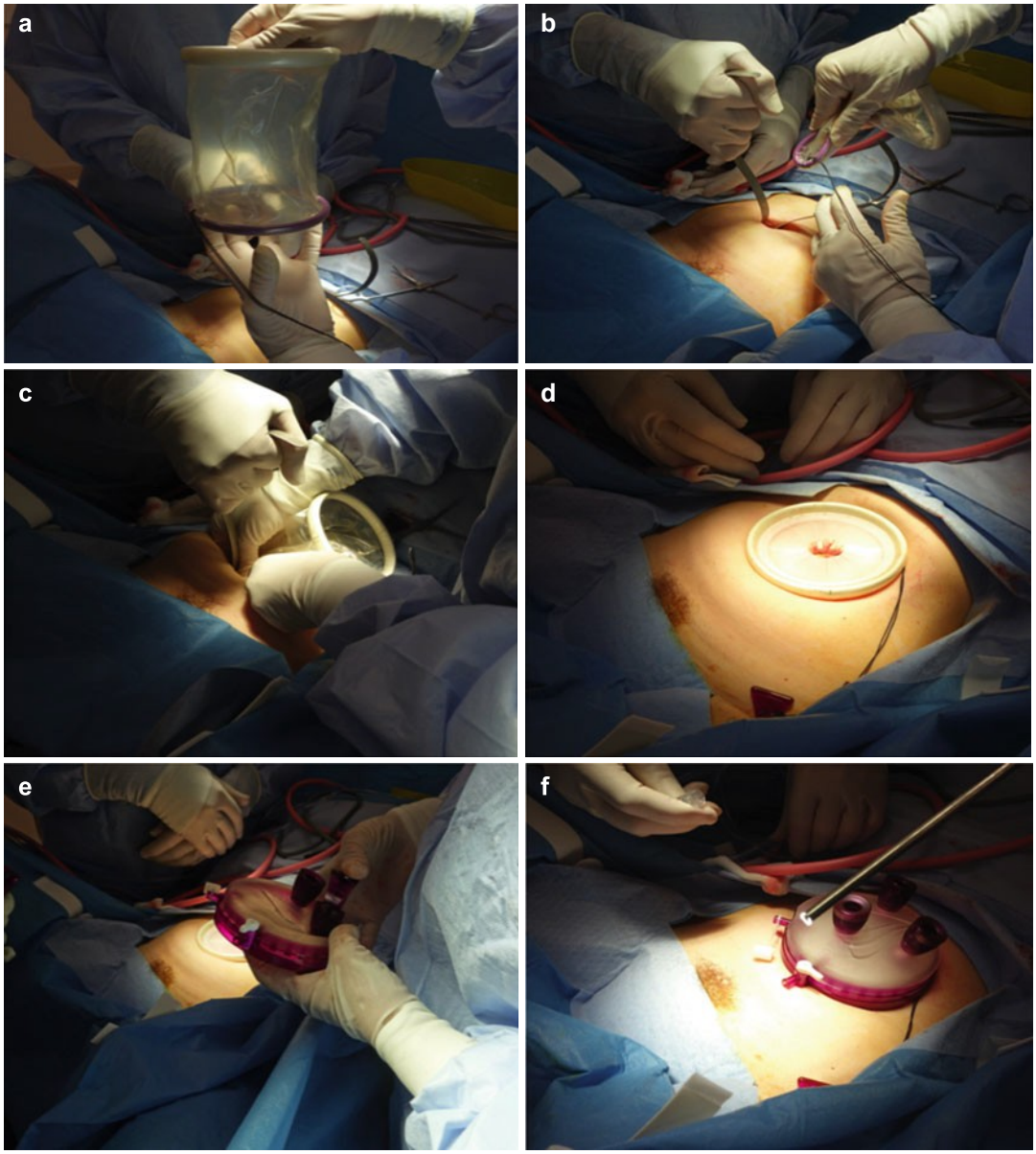


Fig. 14.4 Insertion of the GelPOINT port. (**a**) The purple ring is the intraperitoneal portion of the port, and the white ring remains outside the patient. (**b**) Using S retrac-tors to keep the umbilicus open, the ring is squeezed tightly to allow entry through the umbilicus. (**c**) Fingers are used to move the port intra-abdominally. (**d**) The inserted port is visualized. (**e**) Trocar guides are inserted through the gel head of the port. (**f**) The gel head is attached to the port, and the surgery may now commence

14.5.2 Applied Medical GelPOINT Port

The GelPOINT port is inserted by squeezing one of the purple rings of the Alexis portion of the port system using an S-retractor and inserting it into the transumbilical incision with the force of the surgeon's hands directed toward the pelvis of the patient. A digital examination is then performed to ensure no bowel or omentum is caught between the purple ring and the abdominal wall. The outer ring is twisted inward to achieve more tension; this stretches the incision site and increases the diameter of the opening. The GelPOINT gel cap is pierced with three trocars whose locations are defined by the vertices of a triangle placed horizontally over the gel cap. This is placed over the Alexis part of the port and locked. The insertion of the GelPOINT device is illustrated in Fig. 14.4.

With the GelPOINT device it is easier to use straight instruments than with the Covidien port. In the case of suturing and utilizing conventional needle holders, one needs to learn and practice one-handed suturing technique because it makes the operation and suturing with LESS simpler.

14.6 Apical Compartment Repair Utilizing Nonabsorbable Sutures

Laparoscopic suture colpopexy (also known as vaginal vault suspension or McCall colposuspension) and laparoscopic hysteropexy using nonabsorbable suture material are valuable techniques in providing apical vaginal sup- port dating back to 1957 [7]. Prophylactically, they can be performed after vaginal or laparoscopic hysterectomy or in conjunction with anterior and posterior vaginal wall prolapse repair for further support and reinforcement of the apical compartment with or without uter-ine preservation. In the urogynecology unit at Flinders University, the preferred sutures are Ethibond (Ethicon; Somerville, NJ; nonabsorbable) or PDS (Ethicon; Somerville, NJ) or V-loc (Covidien; Mansfield, MA; absorbable after 6 months) sutures, that promote inflamma- tion and scarring. A 15-cm barbed suture witha small loop at the end of the thread for locking is especially useful in LESS procedures because it eliminates the need for knot tying. These biologic processes act together to reinforce the uterosacral ligament supporting the vaginal vault or uterus in its correct anatomic position. This approach is sometimes preferable to lapa- roscopic mesh sacrohysteropexy because it may have fewer postoperative complications, such as new-onset urinary incontinence, pelvic pain and dyspareunia, damage to the surrounding pelvic floor organs, or subsequent surgical reintervention because of mesh exposure [8].

14.6.1 Typical Patient Presentation

A 65-year-old woman with a BMI of 25 and two prior vaginal deliveries presented with symptomatic global prolapse unresponsive to conservative management such as pelvic floor exercises, vaginal pessary, and estrogen cream. Her intraoperative POP-Q was GH 6 cm, Aa 0, Ba +0.5, Cx +1.5, Ap −1, Bp −0.5, total vaginal length (TVL) 10, resulting in a global prolapse, POP-Q Stage III.

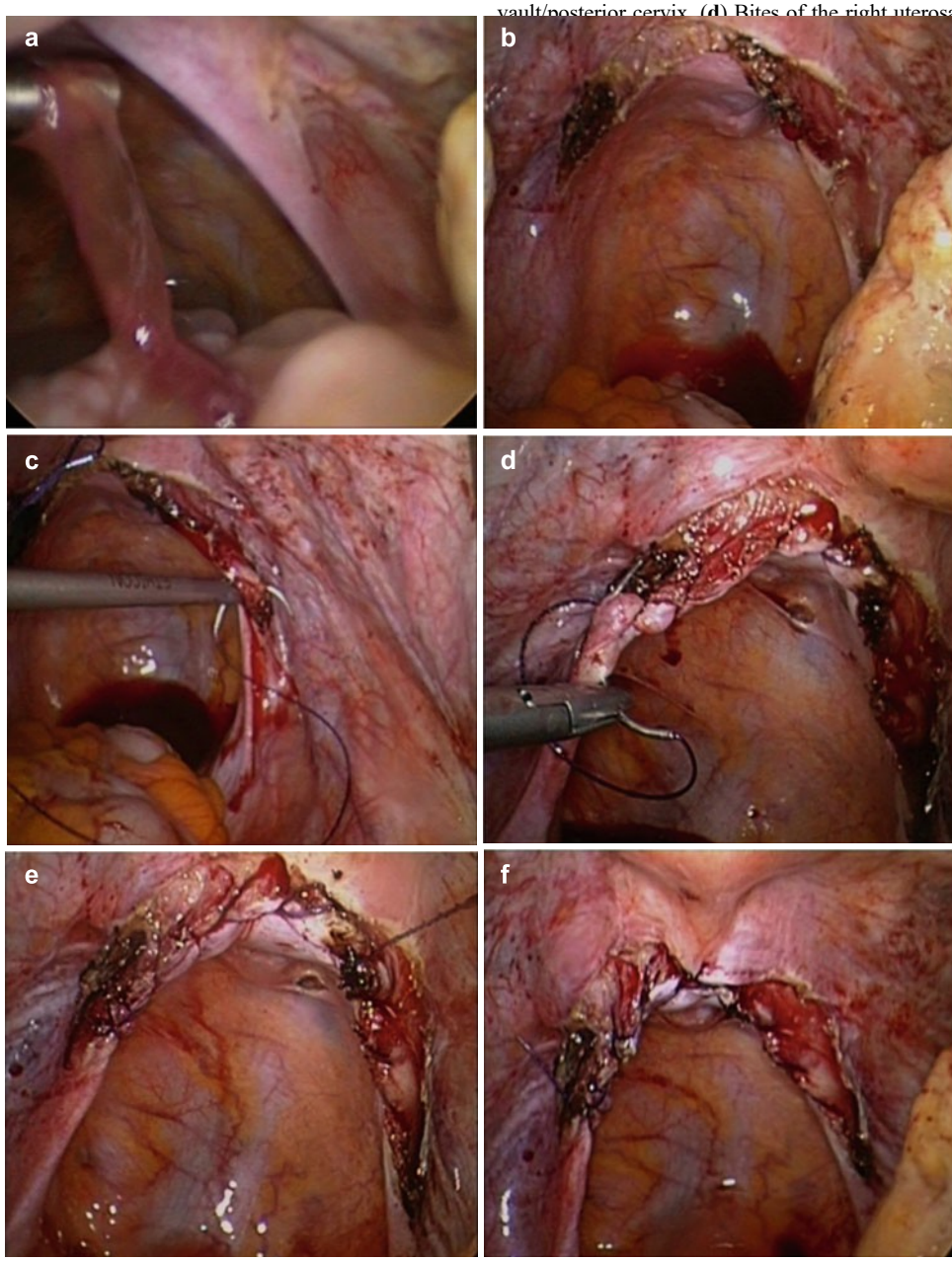


Fig. 14.5 An outline of the use of sutures in apical vaginal prolapse repair using nonabsorbable sutures. (**a**) The uterosacral ligament and ureters are identified on the left and right side. (**b**) 5–6 cm incisions (fenestrations) are made horizontally in the lateral portions of the left and right uterosacral ligaments. These are medial to the ureters and give subperitoneal access for the insertion of the sutures. (**c**) A V-loc suture is placed through the right uterosacral ligament and locked at the proximal end. This method in LESS suturing requires one-handed suturing using the straight needle holder. The surgeon starts at the initial lateral incision site as proximal as possible and continues medially across the pos-terior vault/posterior cervix. (**d**) Bites of the right uterosac-ral ligament

ligament is also incorporated. (**e**) The suture is tensioned once the left-most incision has been reached, bringing the uterosacral ligament and uterus/vault together. (**f**) A second suture is incorporated in the same plane for extra reinforcement of the uterosacral ligament. NB: In the case of usingEndostitch with Ethibond sutures, the same incision is mademedial to the ureter and over the uterosacral ligament. (**g**)The Endostitch is loaded and suturing starts from the proxi-molateral portion of the uterosacral ligaments, moving medially and ending at the level of posterior cervix/vault.
(**h**) An extracorporeal suturing technique is then utilized. The sutures should then be tensioned such that there is a gap of 3–4 cm in the pouch of Douglas. This is done in order to prevent bowel entrapment and possible obstruction

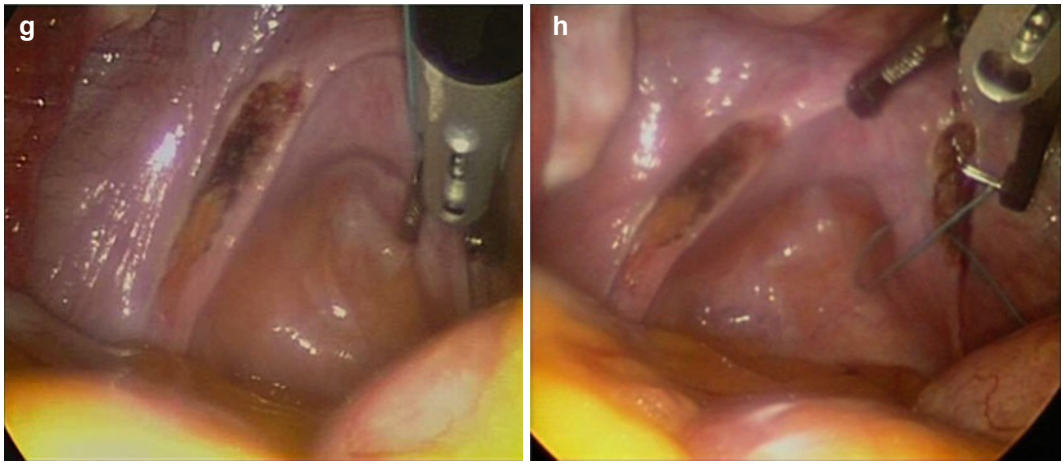


Fig. 14.5 (continued)

14.6.2 Procedure

Of particular importance in the apical repair of a vaginal vault or uterine prolapse is the integrity of the uterosacral ligament close to the uterus/vaginal vault. This important ligament is particularly prone to weakening and lengthening with age and multiparity. The relevant anatomy is shown in Fig. 14.3. Nonabsorbable sutures are used to strengthen and shorten the ligament by continuously suturing it from the lateral ends to the posterior cervix medially. The use of nonabsorbable sutures is important because it causes a local inflammatory reaction as well as providing support to the prolapsed organ. The inflammation causes scarring and fibrosis of the uterosacral ligament and subsequent elevation and correction of the prolapse. The steps to this procedure are outlined in Fig. 14.5.

14.7 Single-Incision Laparoscopic Mesh Sacrohysteropexy

The use of mesh in prolapse repair has been described successfully by Leron and cowork-ers [9] in 13 women who wished to retain their uteri and had significant prolapse. Mesh provides an alternative to suture-based prolapse repair in that it gives greater support to the apical portion of the vagina in the long term and is especially beneficial for women in whom child-bearing is incomplete [10]. Thus, mesh is sometimes

preferred to suture-based prolapse repair, espe- cially in younger, nulliparous women [11].

14.7.1 Typical Patient Presentation

A 70-year-old woman with a BMI of 26, Parity 3,who had always delivered vaginally, presented with symptomatic global prolapse, which was not improved with conservative management such as pelvic floor exercises, vaginal pessary, and estrogen cream. Her POP-Q was GH 4 cm, Aa −1, Ba +1.5,Cx +2, Ap −1, Bp +1, TVL 10, and right levator avulsion, resulting in a global POP-Q Stage III.

14.7.2 Procedure

Once pneumoperitoneum is established, the oper- ation commences with the insertion of a bariatric 5 mm, 30° laparoscope and two instruments. The patient is tilted to the left, and the sigmoid colonpushed to the left side of the patient. In case of dif-ficulty with bowel or ovarian mobilization, a straight needle can be passed through the abdomi- nal wall and through the bowel mesentery or ovar- ian tissue and again through the abdominal wall outside of the body to assist with retraction. The right ureter and vessels as well as the sacral prom- ontory are identified and a small incision is madein the peritoneum, on the top of the sacral promon-tory. There are now two possible approaches to mesh insertion: transperitoneal or retroperitoneal.

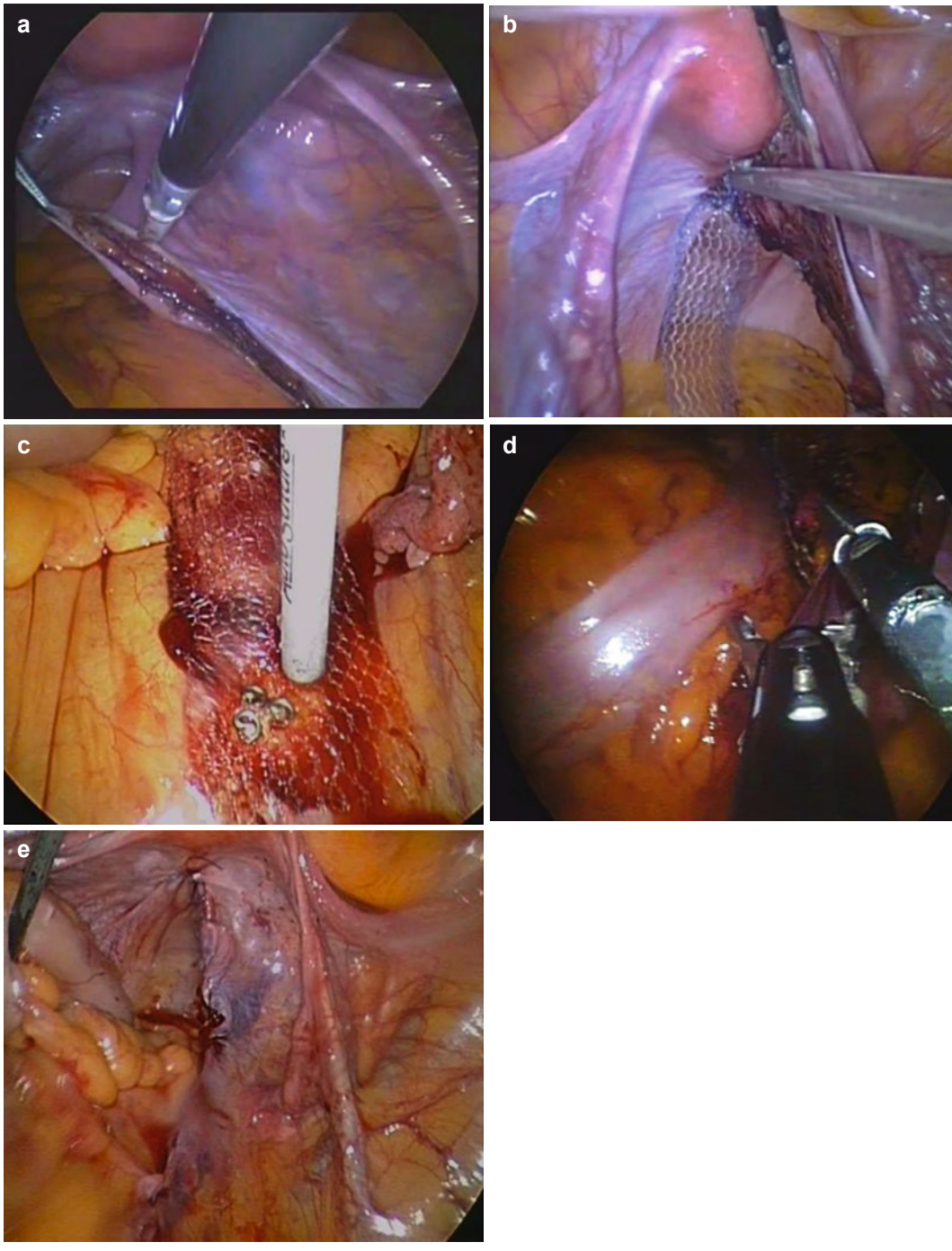


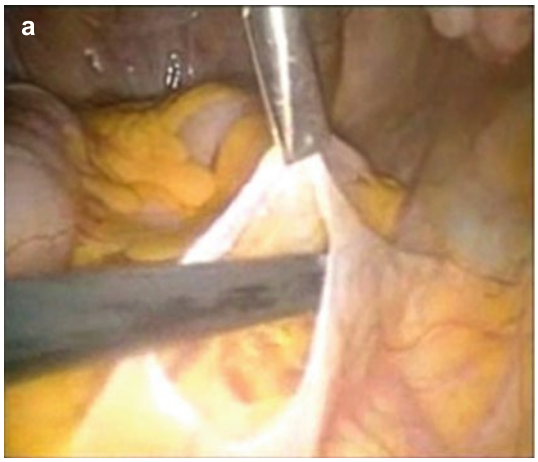
Fig. 14.6 Transperitoneal LESS mesh sacrohysteropexy. (**a**) The peritoneum over the sacral promontory is lifted and incised with Ligosure devices (Covidien; Mansfield, MA), and the incision is extended to the posterior cervix in the right pararectal space, just below the uterosacral ligament. (**b**) The mesh is attached to the posterior cervix using Absorbatack (Covidien; Mansfield, MA).

Alternatively, one can attach the mesh utilizing one-

handed suturing techniques or Endostitch. (**c**) The mesh is then secured to the sacral promontory using Protack fas- teners. (**d**) The peritoneum is sutured over the mesh start- ing from the sacral promontory and moving caudally until the posterior cervix is reached. (**e**) The end product of enclosing the attached mesh in the peritoneum. Note that no mesh should be exposed because it can potentially cause bowel adhesions

14.7.3 Transperitoneal Mesh Sacrohysteropexy

The right ureter is identified, and a peritoneal incision is made from the sacral promontory in the right pararectal space inferior to the uterosacral ligament to the posterior part of the cervix. Next, a polypropylene type-1 monofilament macroporous, nonabsorbable mesh is used to suspend the cervix from the sacral promontory. The length of mesh is measured and tailored to the anatomy of the patient, ensuring that themesh is long enough to avoid tension and thus postoperative pain. The mesh is introduced through the transumbilical port. The distal end of the mesh is anchored to the posterior cervix with five absorbable 5-mm nonabsorbable helical Protack fasteners (Covidien; Mansfield, MA) or V-loc sutures. The mesh is then tacked to the sacral promontory with Protack fasteners. The aim is to lift the cervix at least 6–8 cm above the level of the introitus. The entire length of the mesh is closed and covered with peritoneum using Endostitch and Vicryl absorbable sutures. The use of mesh allows further shortening of the ligament via inflammation-induced fibrosis over time. A description of this procedure is given in Fig. 14.6.



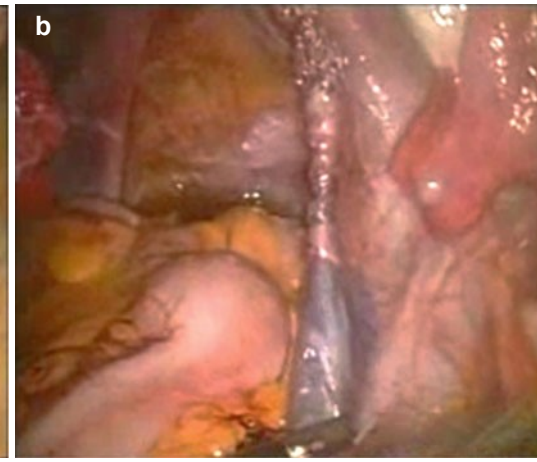


Fig. 14.7 Retroperitoneal LESS mesh sacrohysteropexy. (**a**) An incision is made at the sacral promontory and at the posterior cervix. (**b**) A retroperitoneal tunnel is created from the initial incision in the sacral promontory to the posterior cervix with the assistance of two additional small incisions in the right pararectal space. An Elevate mesh kit wing (American Medical Systems, Inc.; Minnetonka, MN) is then passed through the mesh. (**c**) The portion of mesh protruding from the incision site at the sacral promontory is secured using Protack fasteners. (**d**) Sutures have been used to attach the caudal portion of the mesh to the posterior cervix. (**e**) The peritoneum at the sacral and posterior cervix incision sites is sutured over the mesh. The vaginal vault/uterus is lifted with tightening and subsequent fibrosis of the tissue surround- ing the mesh

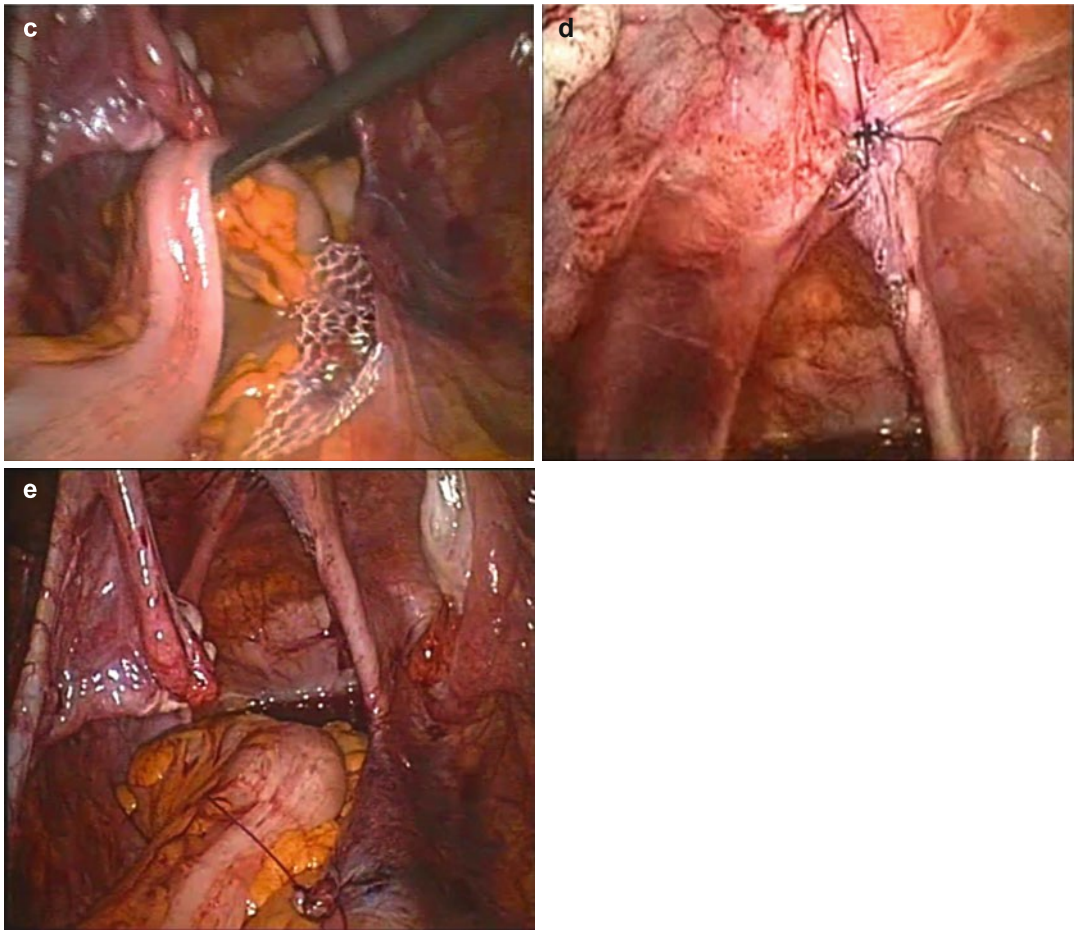


Fig. 14.7 (continued)

14.7.4 Retroperitoneal Mesh Sacrohysteropexy

This approach has been described by Behnia-Willison and colleagues [6] and is briefly covered here. Once the right ureter and vessels as well as the sacral promontory are identified, a small incision in the peritoneum on the top of the sacral promontory is made. Three small incisions into the peritoneum are made at intervals of 5 cm (avoiding complete incision of the peritoneum), and a tunnel is made in the retroperitoneum from the sacrum to the posterior cervix. Elevate mesh kit wings (American Medical Systems, Inc.; Minnetonka, MN) are used to anchor the mesh and feed it bluntly underneath the peritoneal membrane while maintaining patency of the membrane. There are three incisions (5 mm) made in the right pararectal space, and they are used to grasp the rigid portion of the wing and reinsert it again underneath the peritoneum in a linear fashion so that the mesh is fed underneath the peritoneum from the sacral promontory to the posterior cervix. The mesh is then anchored to the cervix and the sacral promontory utilizing Protack and/or V-loc. This particular methodology ensures the patency of the peritoneal membrane and avoids the need to fully dissect the peritoneum via sharp dissection. It is described in Fig. 14.7. The use of a subperitoneal tunneling technique for mesh insertion significantly shortens operation time.

Patients undergo cystoscopy at the end of these procedures to ensure ureteric patency. It is important to note that, following either of the procedures, anterior or posterior transvagi- nal repair with or without mesh is often under- taken in order to further strengthen the pelvic floor.

Acknowledgments The authors of this chapter would like to thank Dr. Marc Keirse for his valuable comments and Ms. Annie Yu for her illustration of Fig. 14.1.

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Chapter 6: Natural Orifice Translumenal Endoscopic Surgery (NOTES)

6.1 Introductory comments

The most advanced technique in minimally invasive surgery is Natural Orifice Translumenal Endoscopic Surgery (NOTES), which offers the possibility of surgery without visible scars [11]. The idea of incisionless surgery is of significant interest to surgeons and others interested in this field of investigation. The NOTES approach has now been used for a variety of operations ranging from diagnostic explorations of the peritoneal cavity to complex organ resections including pancreatectomy, splenectomy, and nephrectomy [1].

In gynaecology, NOTES is performed through the vagina (vNOTES). Transvaginal entry offers potential benefits because it gains access to the peritoneal cavity without the need to open an abdominal viscus, hence it reduces complications associated with abdominal incisions (e.g., bleeding, herination, infection). The potential for vNOTES to revolutionise the treatment of pelvic floor repair and other gynaecological conditions is the result of the design and development of advanced electro-diathermy/ultrasonographic devices for haemostasis. Moreover, with the establishment of simulation and interactive learning centres, gynaecologists now have access to new tools and resources to improve their laparoscopic techniques and suturing skills for pelvic floor repair [1, 2].

Much of the discussion pertaining to vNOTES however, focuses on technical and training issues, with little attention to date, paid to the opinions of women [3]. A study by Strickland et al. [2] sought the perceptions of 300 female health care workers and patients in relation to their views on vNOTES. In all groups and across all ages, significant skepticism was documented for peritoneal access using the transvaginal route [2, 4]. While vNOTES offers women a scarless operation with the possibility of less pain than experienced in standard laparoscopic surgery or SILS, the effect of vNOTES on sexual function was expressed as a particular concern by younger women. In Australia, women remain to be convinced about the potential

advantages of the emerging vNOTES technology [3].

This brief historical outline reveals the shifting role of surgical procedures, with the trend towards minimising invasiveness. Humanity's efforts to understand the human body in regard to the biological processes of healing, disease and pathogenicity has come a long way from ancient times, when brutal methodologies were employed to restore health based on fictious philosophies. The modern world of medicine has developed into a highly progressive domain equipped with the knowledge, skills, techniques, equipment, and technology to treat thousands of health conditions. Over time, surgery has played a shifting role in restoring health. It began as a last line of treatment and then moved to the front-line as new innovative techniques and technologies were developed. Surgery has progressed from its brutal beginnings, where improvements in aseptic practise and infection control revolutionised the success of 'open' surgery. Overtime, with the development of new surgical techniques, high-resolution imagining tools, and microscopic surgical instruments, surgeons have progressively migrated away from the 'open' wound approach and now perform minimally invasive 'keyhole'surgeries to treat the same conditions.

With the development of more sophisticated robots and machines, underpinned by artificially intelligent software and machine learning algorithms, the field of surgery will continue to advance as innovators develop new and novel ways to improve clinical outcomes by making complex procedures and other treatments as minimally invasive as possible. It is my opinion, that medical practitioners of all fields, should obey both adages, '*first, do no harm'* and '*beneficence*', where these maxims can be practised by adopting a minimally invasive approach to treat any health condition. This means, non-surgical routes should be explored first, with minimally invasive surgical interventions serving as last-line approach to treatment. To make 'truly' minimally invasive surgery a reality, future research should focus on the delivery of diagnostic and therapeutic sensory systems through natural orifices, whereby investigation is

under precise remote control and navigation. The articles presented in this chapter focus on minimally invasive gynaecological procedures and, at the time of their publication, were on the leading edge of the minimally invasive surgical trend.

6.2 Aim

A 12-point questionnaire devised by a multidisciplinary group of surgeons interested in minimally invasive surgery. The questionnaire was designed to establish the opinions of women with respect to NOTES surgery versus standard laparoscopic procedures. Responses were de-identified and analysed. Also, for more comprehensive outcomes, this survey was distributed among Middle Eastern women, in the 2nd study to assess the view of more traditional and conservative multi-cultural women in relation to vNOTES as many of these women are Virgo intacta prior to their marriage and may require surgery while not married.

6.3 Summary

Potentially, NOTES surgery offers women a scarless operation with the possibility of less pain than experienced in standard laparoscopic surgery. Few women, however, were troubled about the cosmetic effect of surgery. The effect of NOTES on sexual function was expressed as a particular concern by younger women. In all groups and across all ages, peritoneal access using the transvaginal route was met by significant skepticism. In Australia, women remain to be convinced about the potential advantages of the emerging NOTES technology. In Middle East, vNOTES may hold value for women who have conservative upbringing and/or value cosmesis.

6.4 Publications in this chapter

1. Transvaginal natural orifice translumenal endoscopic surgery (NOTES): a survey of women's views on a new technique.

AD Strickland, MGA Norwood, **F Behnia-Willison**, SA Olakkengil, PJ Hewett.

Surgical Endoscopy 2010; 24 (10), 2424-2431.

6.5 Author contribution

2. I was responsible (20%) for the design of research and data collection and analysis of the obtained data (30%) and writing. Santosh Olakkengil and Peter J. Hewett were designed the research (40% each) and Michael G. A. Norwood was (50%) responsible for academic writing, editing, and English proofreading. This study was a joint effort as a part of my Master of minimally invasive surgery. This study gave me the platform to be the first author of the publication entitled "Middle Eastern women's attitudes and expectations towards vaginal natural orificetransluminal endoscopic surgery (vNOTES): a survey-based observational study".

3. Middle Eastern women's attitudes and expectations towards vaginal natural orifice transluminal endoscopic surgery (vNOTES): a survey-based observational study.
F Behnia-Willison, T Nguyen, A Rezaeimotlagh, J Baekelandt, PJ
Hewett.Surgical Endoscopy, 2021; 1-8 doi: 10.1007/s00464-020-081930.

6.6 Author contribution

I was responsible (100%) for the concept and design of research and (30%) for data collection and analysis.Peter J. Hewett, Tran T. T. Nguyen and Adel Rezaeimotlagh were responsible (20% each) fordata collection and analysis. Tran T. T. Nguyen and Peter J. Hewett were involved with writing(40% each) and editing.

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Surg Endosc (2010) 24:2424–2431
DOI 10.1007/s00464-010-0968-3

Transvaginal natural orifice translumenal endoscopic surgery(NOTES): a survey of women's views on a new technique

Andrew D. Strickland · Michael G. A. Norwood · Fariba Behnia-Willison · Santosh A. Olakkengil · Peter J. Hewett

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Abstract
Background Laparoscopic and minimally invasive surgery has changed the surgical landscape irrevocably. Natural orifice translumenal endoscopic surgery (NOTES) offers the possibility of surgery without visible scars. Transvaginal entry offers potential benefits because it gains access to the peritoneal cavity without the need to open an abdominal viscus. Much of the discussion pertaining to NOTES focuses on technical and training issues, with little attention to date paid to the opinions of women. The perceptions of female health care workers and patients were sought in relation to their views on transvaginal NOTES.
Methods This study surveyed 300 women using a12-point questionnaire devised by a multidisciplinarygroup of surgeons interested in minimally invasive surgery.The questionnaire was designed to establish the opinions of women with respect to NOTES surgery versus standard laparoscopic procedures. Responses were de-identified.
Results Three-fourths of the women surveyed were neu- tral or unhappy about the prospect of a NOTES procedure, and this remained constant even when it was stipulated that laparoscopic cholecystectomy and NOTES had equivalent safety and efficacy. Younger nulliparous women were most concerned about the potential negative effect of NOTES on sexual function. A minority were concerned about the cosmetic effect of surgery, although surgical scars were perceived as more important to younger respondents.
Conclusions Potentially, NOTES surgery offers women a scarless operation with the possibility of less pain than experienced in standard laparoscopic surgery. Few women, however, were troubled about the cosmetic effect of surgery. The effect of NOTES on sexual function was expressed as a particular concern by younger women. In all groups and across all ages, peritoneal access using the transvaginal route was met by significant skepticism. In Australia, women remain to be convinced about the potential advantages of the emerging NOTES technology.

Keywords NOTES · Patient perceptions · Questionnaire · Transvaginal cholecystectomy

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Over the past 20 years, laparoscopic surgery has become the accepted gold standard for many operations previously performed via laparotomy. The commonly noted advantages of a rapid recovery time, a shorter hospital stay, reduced pain, and improved cosmesis after such interventions are widely reported [1–4]. Laparoscopic cholecystectomy (LC) particularly has been embraced worldwide. Many hundreds of thousands of patients undergo LC annually, with acceptably low rates of morbidity and mortality [5].

Recent technological advances in the field of minimally invasive surgery have culminated in the development of natural orifice translumenal endoscopic surgery (NOTES) [6]. This technique allows excision of organs such as the gallbladder, the ovary, and the appendix using instruments introduced into the peritoneal cavity within a flexible endoscope [7–9]. The flexible scope may be introduced into the peritoneal cavity via the vagina, the stomach, or the rectum.

The transvaginal approach to the abdomen has been championed because it would avoid a breach of the

gastrointestinal tract, thereby preventing possible contamination of the peritoneal cavity [10]. In addition, use of the female genital tract to gain access to the peritoneal cavity without transgression of the abdominal wall may further improve recovery times, avoid abdominal scars, and cause less pain than standard laparoscopic operations [11].

The issues surrounding NOTES parallel the debates that took place at the introduction of laparoscopic surgery. Much of this discussion centers around the technical, training, and financial considerations of the procedure [12, 13]. Little significance has been given to acceptance of the practice by the general public.

Transvaginal access to the peritoneal cavity via an incision at the posterior fornix of the vagina clearly is associated with the possibility of complications, but quantification of this risk currently is not possible. In addition, for a variety of different reasons, some women may be reticent to accept surgical exploration of the peritoneal cavity using this route of entry.

Public interest in minimally invasive surgery is high, and the importance of a generally positive perception of this technique is likely to be extremely important to the success or failure of such an intervention. To date, we are unaware of any transvaginal NOTES cholecystectomy procedures undertaken in Australia, and no data exist as to the attitudes of female Australians toward such a concept.

This study first aimed to investigate the opinions of female patients and health care workers at a teaching hospital with respect to their acceptance or rejection of NOTES compared with standard laparoscopic surgery. Second, the study investigated the surveyed population with respect to the effects of age and parity on the opinions expressed.

Materials and methods

The attitudes of females toward the possibility of undergoinga NOTES procedure via the transvaginal route of the peritoneal cavity entry was assessed using an anonymous questionnaire. Three groups were selected in an attempt to investigate whether the setting in which the questionnaire was delivered influenced the results. Group 1 consisted of female health care professionals. Group 2 was composed of patients who were to undergo or had undergone a LC. Group 3 comprised patients attending a gynecologic clinic. Three similar questionnaires (varying only due to the setting of the patient) were constructed. Approval for use by the local ethics committee at the investigating hospital was obtained. Appendices 1, 2, and 3 show these questionnaires in full.

The de-identified questionnaires were collated by a single independent researcher and analyzed using SPSS statistical software, version 17.0 (SPSS Inc., Chicago, IL) to compare responses between groups, ages, and parity.

Results

For this study, 300 individuals were surveyed including 195 health professionals (HP), 37 patients who were undergoing or recently had undergone LC, and 68 gynecologic clinic (GC) patients. The demographics of the three groups did not vary significantly except that the LC group was found to be significantly older (see Table 1 for raw data). The vast majority of the individuals surveyed were Australian or European born. Except for scars after surgery, very similar responses (no statistical differences) were obtained from the three groups.

When asked whether they disliked scars after a surgical procedure 66% replied ‘‘no.’’ This response was similar between the HP (64%) and GC (67%) patients, but more frequent among the LC patients (86%). When the patients were divided according to age, cosmesis appeared to become more of an issue, with 37% of 20- to 39-year-olds disliking scars compared with 29% of 40- to 55-year-olds and 11% of patients older than 55 years ($p = 0.012$, chi-square). The response to the issue of cosmesis was not statistically different between the parous and nulliparous women.

The subsequent question asked whether it would be preferable to undergo an alternative operative method that avoided abdominal scars. To this question, 58% responded ‘‘yes,’’ although this was less likely with increasing age ($p = 0.01$, chi-square). The respondents then were requested to rank how they felt about having an abdominal operation through the vagina. They responded by circling one of five responses: very happy, happy, unsure, unhappy, or very unhappy. Whereas 32% said they would be unhappy or very unhappy to undergo a transvaginal pro- cedure, 18% stated that they would be happy or very happy. The remainder (50%) felt neutral.

These findings were similar among the three different age groups. However, the parous patients were more likely to be happy or very happy with a transvaginal procedure than the nulliparous women ($p = 0.03$, chi-square).

The questionnaire then asked whether the patients would be concerned that a NOTES procedure might have a negative effect on their sexual function. Overall, 42% of the women were concerned with this possibility, although this appeared to be markedly influenced by age ($p = 0.003$, chi-square). Younger respondents were more concerned with this possibility: 50% of the 20- to 39-year-olds, 32% of the 40- to 55-year-olds, and 34% of the patients older than 55 years.

When the patients were asked whether they would prefer NOTES or LC, the majority ($n = 194$, 65%) said they would prefer LC. These results were maintained for the three individual groups and for the patients of different ages and parities. However, the patients who stated that

Table 1 Summary of questionnaire results[a]

	Group			
	All	HP	GC	LC
No. of subjects	300	195	68	37
Mean age (years)	39.9	38.8	38.4	48.9
Dislike scars (%)				
Yes	32	36	33	14
No	68	64	67	86
Would prefer alternative method (%)				
Yes	60	70	46	31
No	40	30	54	69
Happy with vaginal operation (%)				
Very happy	5.4	3.6	9	8.3
Happy	12.5	13.9	9	11.1
Neutral	49.8	44.8	62.7	52.8
Unhappy	17.8	19.1	13.4	19.4
Very unhappy	14.5	18.6	6	8.3
Concerns about sexual function (%)				
Yes	42.4	47.7	35.8	25.7
No	31.5	28.5	32.8	45.7
Unsure	26.1	23.8	31.3	28.6
Would prefer NOTES to LC (%)				
Yes	27.1	16.5	43.9	52.9
No	68.1	78.2	53	41.2
Unsure	4.9	5.3	3	5.9
Would you be happy to consider NOTES for gynecologic surgery (%)				
Very happy	10.1	8.8	14.9	8.3
Happy	34.5	34.2	31.3	41.7
Neutral	37.8	35.8	43.3	38.9
Unhappy	10.5	11.9	7.5	8.3
Very unhappy	7.1	9.3	3.0	2.8
Would surgeon gender influence your decision (%)				
Yes	17.9	18.2	22.4	8.3
No	70	68.4	70.1	77.8
Unsure	12.1	13.4	7.5	13.9

[a] All values are percentages (%) unless stated otherwise

HP health professionals, *GC* gynecology clinic, *LC* laparoscopic cholecystectomy, *NOTES* natural orifice translumenal endoscopic surgery

they minded scars were more likely to want a NOTES procedure ($p = 0.03$, chi-square). The patients were no more likely to prefer NOTES for a gynecologic procedure. Again, no difference was observed among the three different groups (HP, LC, and GC), age groups, or parities. Finally, only 17% of the patients stated that surgeon gender would influence their decision to undergo a NOTES procedure. This decision was not influenced by patient age or parity.

Discussion

Transvaginal NOTES appears to be technically possible. However, the globalization of such a technique may well

depend on the degree of acceptance from the general public. Although safety and efficacy are of primary importance, issues of the patients' perception of abdominal scars and the influence of such surgery on sexual function may well have an impact on the widespread acceptability of such a procedure. This study represents the largest survey of women's attitudes about transvaginal NOTES published to date.

The questionnaires were given to three different groups in an attempt to investigate whether the setting of the survey influenced responses. It was postulated that patients attending a gynecologic clinic would be more open to the possibility of undergoing a NOTES type procedure. Similarly, it was suggested that after an LC, patients would

react more favorably to an option that might cause less pain and leave no visible scars.

The settings, however, did not affect the answers obtained from the groups except for cosmesis. This may well be an effect of the higher mean age of the respondents in the LC group compared with the remaining two sets of responders. The fact that the LC group was not more in favor of the NOTES procedure suggests that postoperative pain relief in this group was adequate. Similarly, the administration of a NOTES questionnaire in a gynecology outpatient setting did not make women more accepting of a transvaginal operation.

The results from this survey suggest that one major incentive for the NOTES procedure, the absence of abdominal scars, might not be such an important factor for many patients. The majority of women (66%) are not concerned about the scars produced by surgery. However, as might perhaps be expected, younger respondents were more concerned with cosmetic issues, although this still remained a minority response. When given the option of an operation that did not produce scars, scarcely more than half of the individuals surveyed responded positively, although this response decreased significantly with increasing age.

These results suggest that cosmesis is very much the province of the younger group, although not exclusively. In this survey, only 1 in 10 respondents older than 55 years were concerned by scars after surgery. It appears that even in the youngest group, only one-third of the patients indicated that they disliked scars produced by routine laparoscopic surgery.

The results of this study appear to be in contrast to those obtained from previously conducted investigations, all conducted in the United States. In the Peterson et al. [14] survey of 100 women, 68% showed a preference toward a NOTES procedure due to the lower risk of abdominal hernia and a possible reduction in postoperative pain. Concern with respect to cosmesis, however, was remark- ably similar to the results presented in this article (34%), with only 39% of the patients highlighting this as an important feature of the NOTES surgery. Perhaps as expected, nulliparous and younger women (\40 years) were more concerned with the possible impact of NOTES surgery on their sexual function and fertility.

A second study conducted by Swanstrom et al. [15], demonstrated that 56% of the 192 patients surveyed would choose a NOTES procedure over an LC. Again, cosmesis was not nearly as important as procedure-related risks,pain, and recovery time. Finally, Varadarajulu et al. [16] in a survey of 100 patients comprising men and women found that 78% preferred that their cholecystectomy be performed with a NOTES procedure. In general, older female patients and those with prior endoscopic experience were more likely to opt for the NOTES option.

Australian women appear to be less convinced about the potential benefits of NOTES procedures than their American counterparts. This may be due to cultural differences, but a more likely explanation is public awareness and perception of the technique. Because much of the NOTES technology has been developed in the United States, itlikely has a much higher profile in both the mass media andthe medical literature. Public interest in minimally invasive procedures is high, and new procedures may thus be championed with little convincing evidence. A number of procedures have now been performed with NOTES technology, although no evidence of potential advantages over standard laparoscopic surgery currently exists.

The results of this study and work conducted previously suggests that younger nulliparous women are most concerned with cosmesis, although this group expresses the greatest concern over any change in sexual function. Such a dichotomy is difficult to resolve because NOTES is ideally suited to this group. However, with a paucity of evidence concerning the results of such procedures, little reassurance with respect to preservation of sexual function can be given.

A prospective study investigating a variety of hysterectomy techniques, including vaginal hysterectomy, concluded that sexual function was not negatively affected by any of the surgical methods investigated [17]. Similarly, it may be more difficult to gain access to the peritoneal cavity in nulliparous women than in parous women because their pelvic floor structures have not undergone the changes associated with vaginal fetal delivery.

Surveyed women appear to be concerned about the possibility of a hernia after laparoscopic surgery, although little emphasis has been placed on the possibility of a vaginal herniation after NOTES surgery. Studies of prolapse after vaginal hysterectomy indicate a low rate for this complication, which occurs when pelvic floor tissues are weak preoperatively [18]. After transvaginal NOTES, because the colpotomy is performed in the posterior fornix, the uterine suspensory ligaments (apical support) remain unaffected by the procedure, so the incidence of prolapse (hernia) likely is low. However, detachment of the posterior vaginal wall fascia from the pericervical ring theoretically may increase the risk of posterior vaginal wall prolapse (enterocoele).

Public perception of new procedures such as NOTES is likely to play a large part in the acceptance or rejection of these techniques. Currently, many questions about NOTES remain, although it is hoped that they will be answered by well-conducted, future trials. It seems that such trials in conjunction with a positive mass media portrayal may be required to change current perceptions of this technique among Australian women.

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Appendix 1: Healthcare Professionals Questionnaire

Questionnaire

Background:

Key hole (laparoscopic) surgery using small incisions, is a well established technique. However, there is now a new concept in surgery known as '*N.O.T.E.S.*' (Natural Orifice Transluminal Endoscopic Surgery). This utilises a natural orifice (e.g. the vagina) to allow entry into the abdominal cavity so that operations such as a cholecystectomy (removal of the gallbladder) can be performed with the use of specialised equipment. In the case of cholecystectomy, the gallbladder would be removed from the body via the vagina, leaving no visible scars. It may also be potentially less painful. In a few specialist centres, this procedure is now being performed although there are no clinical trials to support its use. As a woman, we would be interested to hear your views regarding the utilisation of the vagina as a way of performing this type of surgery.

Your age:_____years

Have you had children? **Y/N**

Are you known to have gall stones? **Y/N**

Have you had a cholecystectomy (removal of gall bladder)? **Y/N**

Have you had an abdominal operation before? **Y/N**

Would you mind abdominal scars as part of an abdominal operation? **Y/N**

Would you find it preferable if you could have the operation (laparoscopic cholecystectomy), using an alternative method resulting in no scars? **Y/N**

If yes, is this because of:
a) Cosmetic reasons
b) Potential for less pain
c) Both
d) Other (please state)……...…….
……..……..

How to you feel about using the vagina as an entry site for an operation? (Please circle)
a) Very happy b) Happy c) Not sure d) Unhappy e) Very unhappy

Would you be concerned that surgery through the vagina (NOTES) may have a negative impact on your sexual function? **a) Yes b) No c) Not sure**

Would you prefer to have a laparoscopic (key hole) cholecystectomy or a NOTES cholecystectomy?
a) Laparoscopic cholecystectomy b) NOTES cholecystectomy

If NOTES cholecystectomy was shown to be as effective and as safe as laparoscopic cholecystectomy which would you prefer? **a) Laparoscopic cholecystectomy b) NOTES cholecystectomy**

If you required a gynaecological procedure such as a sterilisation, how would you feel about this being performed vaginally (NOTES sterilisation), rather than with standard key hole surgery? (Please circle)
a) Very happy b) Happy c) Not sure d) Unhappy e) Very unhappy

Finally, would the sex of the surgeon influence your decision as to whether to undergo a NOTES procedure?
Yes/No/Unsure

Thank you

Appendix 2: Gynecology Outpatient Group

Questionnaire

Background:

Key hole (laparoscopic) surgery using small incisions, is a well established technique. However, there is now a new concept in surgery known as '*N.O.T.E.S.*' (Natural Orifice Transluminal Endoscopic Surgery). This utilises a natural orifice (e.g. the vagina) to allow entry into the abdominal cavity so that operations such as a cholecystectomy (removal of the gallbladder) can be performed with the use of specialised equipment. In the case of cholecystectomy, the gallbladder would be removed from the body via the vagina, leaving no visible scars. It may also be potentially less painful. In a few specialist centres, this procedure is now being performed although there are no clinical trials to support its use. As a woman, we would be interested to hear your views regarding the utilisation of the vagina as a way of performing this type of surgery.

Your age:_____years

Have you had children? **Y/N**

Are you known to have gall stones? **Y/N**

Have you had a cholecystectomy (removal of gall bladder)? **Y/N**

Have you had an abdominal operation before? **Y/N**

Would you mind abdominal scars as part of an abdominal operation? **Y/N**

Would you find it preferable if you could have the operation (laparoscopic cholecystectomy), using an alternative method resulting in no scars? **Y/N**

If yes, is this because of: **a) Cosmetic reasons**
b) Potential for less pain
c) Both
d) Other (please state)……...…….
……..……..

How to you feel about using the vagina as an entry site for an operation? (Please circle)
a) Very happy, b) Happy, c) Not sure, d) Unhappy, e) Very unhappy

Would you be concerned that surgery through the vagina (NOTES) may have a negative impact on your sexual function? **a) Yes b) No c) Not sure**

Would you prefer to have a laparoscopic (key hole) cholecystectomy or a NOTES cholecystectomy?
a) Laparoscopic cholecystectomy b) NOTES cholecystectomy

If NOTES cholecystectomy was shown to be as effective and as safe as laparoscopic cholecystectomy which would you prefer? **a) Laparoscopic cholecystectomy b) NOTES cholecystectomy**

If you required a gynaecological procedure such as a sterilisation, how would you feel about this being performed vaginally (NOTES sterilisation), rather than with standard key hole surgery? (Please circle)
a) Very happy b) Happy c) Not sure d) Unhappy e) Very unhappy

Finally, would the sex of the surgeon influence your decision as to whether to undergo a NOTES procedure?
Yes/No/Unsure

Thank you

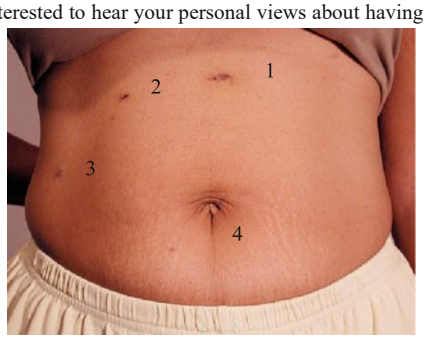
Appendix 3: Laparoscopic Cholecystectomy Group

Questionnaire (Cholecystectomy group)

Background:

You will be having keyhole surgery (laparoscopic cholecystectomy) to remove your gallbladder. This means that you will have 4 small scars as shown in the picture below. New technology has been invented which means that gallbladder operations could now be done via the vagina. This means that you could have the operation with no scars and maybe less pain. This is called *N.O.T.E.S.* surgery.

We would be interested to hear your personal views about having an operation done through your vagina.



Your age:_____years Your country of birth_____

Have you had children? (Please circle one)
Yes/No

Have you had an operation on your belly before? (Please circle one)
Yes/No

Would you mind having scars on your belly as part of an abdominal operation? (Please circle one)
Yes/No

Would you prefer it if you could have an operation, using an alternative method resulting in no scars? (Please circle one)
Yes/No/Not bothered

If yes, is this mainly because: **a) My belly would look better**
b) It may be less painful
c) Other (please state)……...…….
…….

How would you feel about having a belly operation through your vagina? (Please circle one)
a) Very happy, b) Happy, c) Not sure, d) Unhappy, e) Very unhappy

Would you be concerned that surgery through the vagina may have a negative impact on your sexual function? (Please circle one)
Yes/No/Not sure

If a scarless vaginal operation was shown to be as good and as safe as a keyhole operation on the belly, which would you prefer? **a) Keyhole operation** **b) Scarless vaginal operation**

If you required a gynaecological procedure such as a sterilisation, how would you feel about this being performed through your vagina, rather than with standard keyhole surgery? (Please circle one)
a) Very happy, b) Happy, c) Not sure, d) Unhappy, e) Very unhappy

Finally, would the gender of the surgeon influence your decision whether to undergo an operation through your vagina? (Please circle one)
Yes/No/Not sure

Thank you for your time

This questionnaire was prepared by the University of Adelaide, Masters of Minimally Invasive Surgery Group, and has received ethical approval for its conduct. All information is regarded as strictly confidential.

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Middle Eastern women's attitudes and expectations towards vaginalnatural orifice transluminal endoscopic surgery (vNOTES): a survey-based observational study

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Abstract

Background Trans-vaginal natural orifice transluminal endoscopic surgery (vNOTES) is a recently popularised minimally invasive surgical procedure, aimed at minimising abdominal wall scars and improving pain and patient recovery times. Although vNOTES has been studied in the context of post-operative pain and cosmesis, women's acceptance of the technique has only been cursorily examined. In this survey-based observational study, we assessed the acceptability of this technique among a cohort of Middle Eastern women.

Materials and methods A cohort of 175 Middle Eastern women were surveyed using a 13-item questionnaire at a single gynaecology centre. The survey used was a translated version of a questionnaire from a previous study (1) and comprised open-response, five-point Likert Scale and agree-disagree items.

Results Among 175 Middle Eastern women participated in this study most of them holding neutral view on abdominal and gynaecological procedures via vagina. 47% of participants were unsure regarding the effect of surgery via vagina on their sexual function. Although 61% of the participants showed no preference towards vNOTES over laparoscopic cholecystectomy, more than half of them indicated preference if vNOTES shown to be as effective and safe as laparoscopic cholecystectomy. The gender of the surgeon was shown to have no influence on the perspectives of the majority of participants to undergo vNOTES.

Conclusions vNOTES may hold value for women who have conservative upbringing and/or value cosmesis. This study provides information regarding Middle Eastern women's perspectives on vNOTES, which may be of considerable clinical use as the popularity of this surgical technique continues to increase.

Keywords vNOTES · Trans-vaginal · Natural orifice · Minimally invasive surgery · Pelvic surgery · Cholecystectomy

Laparoscopic techniques, which are minimally invasive surgical procedures, have changed the approaches in abdominal surgeries with demonstrated advantages, such as reducing the scarring and post-operative pain, achieving effective short-term outcomes, increasing cosmetic satisfaction, improving cost-effectiveness, and decreasing the hospitalization time [1–4]. Natural Orifice Transluminal Endoscopic Surgery (NOTES) is a novel minimally invasive surgery that has obtained considerable attention in recent years [5]. NOTES utilizes trans-visceral access to the intraperitoneal abdominal cavity via natural orifices, such as mouth (transgastric or gNOTES), urethra (uNOTES), vagina (vNOTES), and anus (transrectal or rNOTES) without causing scars [1–4].

Although NOTES was initially developed on animal models, the number of reported human applications has increased significantly over the past decades from six cases in 2007 to 916 cases in 2011 of which 14% of cases operated in the USA and 86% were operated in other countries including Italy, Switzerland, and Australia [2]. Furthermore, 46% of these cases were pure NOTES and the rest were hybrid.

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Cholecystectomy was known as the main NOTES procedure (75%) and vNOTES approach was the most common one in these cases [3]. vNOTES has been used for various abdominal operations, such as appendectomy, cholecystectomy, nephrectomy, hernia repair, and adrenalectomy [6].

Despite the aforementioned advantages that have been demonstrated by novel minimally invasive surgeries, patient's acceptance plays an important role in the implementation of these approaches. There are limited studies addressing the patient's perspectives on vNOTES and more than half of these studies are broader studies on NOTES perspectives, in which vaginal access was ranked or selected from a list of other possible access sites [3, 6–11]. These studies indicated that the trans-vaginal approach is often the least preferred access site. The remaining five studies delved deeper into specific perspectives on vNOTES and revealed more insight into the female perspective on this new technique. The first study, which was performed in the USA [12] found that 73 of 100 surveyed women would consider having vNOTES, with 68% indicating they would opt for vNOTES if the technique was shown to be equivalent to the laparoscopic approach. The appeal of vNOTES was found to involve a perception that it minimized pain, hernia formation, and improved cosmetic benefits. However, some participants had concerns involving infection and the impact of vNOTES on sexual life and fertility, with younger and nulliparous women being more concerned about the impact on sexual function and fertility.

In Switzerland [13], the study showed 4% of surveyed women would opt for vNOTES cholecystectomy, which also found that age, education, profession, and parity did not influence the preference for vNOTES. Similar findings were seen in the American and Italian studies [14].

Another study showed that 81% of women had concerns about vNOTES impact on their sex life and 58% were concerned about their fertility; both of which were more prevalent in younger and nulliparous women [11]. Two studies from Australia revealed a 'neutral' position from the women surveyed. The first study included 300 women and the majority rated 'neutral' preference towards vNOTES [15]. The second study on vNOTES was for donor nephrectomy [6] and 57% of surveyed patients said that they would prefer an alternative surgical technique with fewer scars. One-third were concerned about the impact on sexual function in this survey.

These findings demonstrated a pertinent cultural influence in women's acceptance of vNOTES, especially inmore traditional and conservative countries. On the other hand, cultures in which cosmetic outcomes are prioritized may facilitate positive attitudes towards the trans-vaginal approach. An interesting dynamic arises when a cohort of women is based within a traditional conservative culture, but also highly value cosmesis.

The aim of this study is to assess the acceptability of vNOTES among Middle Eastern women with a complex cultural background. We considered this demographic to have a complex cultural background given the conservative legal structure currently impacting women in the Middle East, in combination with high rates of cosmetic industry consumption and surgeries.

Methods

This study received ethics approval from Bellberry Limited.

Questionnaire

The perspective of Middle Eastern women towards vNOTES were collected using a translated version from English to Persian of 13-point questionnaire ([5], Appendix 1). This questionnaire was originally developed by a multi-disciplinary group of surgeons interested in minimally invasive surgery and was previously published [5]. It uses cholecystectomy as the surgical procedure for comparison. The English and translated Persian version were initially trialled among a small group of participants fluent in both Persian and English, to ensure an adequate translation was achieved.

Participants

Women attending FBW Gynaecology Plus, a private gynaecology practice in Adelaide Australia, were invited to participate in the study by anonymously completing the questionnaire in Persian. Demographic data are displayed in Table 1. Completed questionnaires were compiled and the

Table 1 Participant demographics

Question	Demographic item		
	Number of participants		175
1	Mean Age (years)		35.7
	Age Range (years)		15–78
2	Had children (%)	Yes	66
		No	34
3	Known to have gall stones (%)	Yes	6
		No	94
4	Had a cholecystectomy (%)	Yes	5
		No	95
5	Had previous abdominal surgery (%)	Yes	50
		No	50
6	Dislike scars as a part of abdominal surgery (%)	Yes	83
		No	17
7	Prefer alternative scarless surgical procedure (%)	Yes	95
		No	5

data entered into an Excel™ Spreadsheet (Microsoft Office 2010).

Statistical analysis

All statistical assessments of the data were performed using IBM SPSS software, version 21.0. Questions 8–13 were analysed for goodness of fit using either binomial or Chi-squared analysis. The associations between variables were analysed using a Chi-squared test of independence. The strength of any subsequent associations found was determined using either Phi or Cramer's V tests. The assumptions underpinning the Chi-squared test were checked and the assessment disregarded if a violation occurred.

This observational study was structured based on strengthening the reporting of observational studies in epidemiology (STROBE) checklist.

Results

As given in Table 1, 175 women aged between 15 and 78 (mean 35.7) participated in this survey, of which 66% had children, 6% known to have gallstones, and 5% had previously done laparoscopic cholecystectomy. Furthermore, half of the participants had previously undergone abdominal surgery. More importantly, 83% of participants stated that they dislike surgical scars and 95% preferred scarless surgical procedures.

The perspective of participants on vNOTES is givenin Table 2. Although most of participants women held a neutral view towards abdominal (Question 8) and gynae- cological (Question 12) surgeries via vagina, the number of women with positive feelings were significantly higher than those with negative feelings in both categories. Sub- sequent analysis indicated that Furthermore, 47% were unsure regarding concerns about sexual function with surgery via vagina (Question 9). Most women (61%) expressed that they would not prefer vNOTES to laparo- scopic cholecystectomy (Question 10). Over half (54%) preferred vNOTES if shown to be as effective and safe as laparoscopic cholecystectomy (Question 11). Finally,a significant majority (67.4%) of women conveyed thatthe gender of the surgeon would influence their decisionto undergo vNOTES (Question 13), which is much higher when compared to 17.9% of Australian women.

The dataset was subsequently analysed with respect to the demographic variables reported within Table 1. Crosstabs of the categorical questions relating to the perception of the participants towards vNOTES (Questions 8–13) were created for age, parity, presence of gallstones, previous cholecystectomy, previous abdominal surgery,

Table 2 Percentage breakdown of all participants' perspectives on trans-vaginal NOTES

Questionnaire item		%	Statistical Analysis	Statistical re-analysis: neutral bias removed	Statistical re-analysis: categories collapsed
Q8: Feeling towards abdominal operation via the vagina	V happy	14	One sample Chi-square test = Significant		
	Happy	25			
	Neutral	39			
	Unhappy	18			
	V Unhappy	5			
Q9: Concerns about sexual function with surgery via the vagina	Yes	29	One sample Chi-square test = Significant		N/A
	No	24			
	Unsure	47			
Q10: Would prefer NOTES to lap cholecystectomy	Yes	39	One sample binomial test = Significant	N/A	N/A
	No	61			
Q11: Would prefer NOTES if shown to be as effective and safe as laparoscopic cholecystectomy	Yes	54	One sample binomial test = Not Significant	N/A	N/A
	No	46			
Q12: Feeling towards gynaecology surgery using vaginal NOTES	V happy	18	One sample Chi-square test = Significant		
	Happy	23	V unhappy 3		
	Neutral	49			
	Unhappy	6			

cant				
Q13: Would surgeon gender influence decision to undergo vaginal NOTES	Yes	39	One sample Chi-square test = Significant	N/A
	No	41		
	Unsure	20		

preference for scars as well as for a scarless surgical procedure. The crosstab assessments are detailed in Tables 3, 4, 5, and 6.

The results showed that younger and nulliparous patients were less likely to accept vNOTES as they were more concerned for their future sexual function. On the other hand, women with previous abdominal surgery were more likely to prefer vNOTES. The preference of laparoscopic cholecystectomy over vNOTES cholecystectomy in the participants was independent of age, parity, previous abdominal surgery, and a dislike for scars from abdominal surgery.

Discussion

This study assessed the perspective of Middle Eastern women towards vNOTES. There were 175 participants in this study with most of them holding neutral view on abdominal and gynaecological procedures via vagina. 47% of participants were unsure regarding the effect of surgery via vagina on their sexual function. Although 61% of the participants showed no preference towards vNOTES over laparoscopic cholecystectomy, more than half of them indicated preference if vNOTES shown to be as effective and safe as laparoscopic cholecystectomy. The gender of the surgeon was shown to have no influence on the perspectives of the majority of participants to undergo vNOTES. To the best of our knowledge, there are no studies available, in which the perspectives of Middle Eastern women on the vagina as an entry point into the peritoneal cavity were explored. Therefore, this study presents the first insight into how this surgical technique is perceived by women from a non-Western, non-Asian, culturally complex background.

The results are consistent with earlier study that Western and Middle Eastern women share a neutral view of the vaginal route as an entry site for both abdominal and gynaecological surgeries. Subsequent analysis, in which age, parity, previous abdominal surgery and scar preference were taken into account showed that vNOTES was less preferred among nulliparous and younger women. This is one of the first studies on the perspective of Middle Eastern women on vNOTES. The second strength of this study is that it can compare a conservative upbringing to the views of Western women, which has been previously studied.

Table 3 Consideration of age on participants' perspectives on trans-vaginal NOTES

Questionnaire item		%	%	%	Statistical analysis—all	Statistical re-analysis: neutral bias removed	Statistical re-analysis: categories collapsed
Age category		<30	>30-<40	>40			
Number of participants		58	57	60			
Q8: Feeling towards abdominal operation via the vagina	V happy	9	7	25	^{2} (8, n=175)=13.738, P=0.089	^{2} (6, n=105)=9.569, P=0.144	^{2} (2, n=105)=5.794, P=0.055 Phi 0.233
	Happy	26	19	28			
	Neutral	40	47	30			
	Unhappy	21	21	12			
	V Unhappy	5	5	5			
Q9: Concerns about sexual function with surgery via the vagina	Yes	40	23	25	^{2} (4, n=175)=9.832, P=0.043 Crammers V 0.168	^{2} (2, n=175)=9.800, P=0.007 Phi 0.326	N/A
	No	10	30	30			
	Unsure	50	47	45			
Q10: Would prefer NOTES to lap chol-	Yes	40	42	37	^{2} (2, n=175) 0.364, P=0.834	N/A	N/A
	No	60	58	63			
Q11: Would prefer NOTES if shown to be as effective and safe as laparoscopic cholecystectomy	Yes	52	54	57	^{2} (2, n=175)=0.291, P=0.865	N/A	N/A
	No	48	46	43			
Q12: Feeling towards gynaecology surgery using vaginal NOTES	V happy	14	18	23	^{2} (8, n=175)=6.109, P=0.635	^{2} (6, n=89)=4.121, P=0.660	^{2} (2, n=89)=3.687, P=0.158
	Happy	19	23	28			
	Neutral	53	53	42			
	Unhappy	9	4	5			
	V unhappy	5	4	2			
Q13: Would surgeon gender influence decision to undergo vaginal NOTES	Yes	33	47	38	^{2} (4, n=175)=2.891, P=0.576	^{2} (2, n=140)=1.623, P=0.444	N/A
	No	43	37	42			
	Unsure	24	16	20			

Table 4 Consideration of parity on participants' perspective on trans-vaginal NOTES

Questionnaire item		%	%	Statistical analysis—all	Statistical re-analysis: neutral bias removed	Statistical re-analysis: categories collapsed
Had children		Yes	No			
Number of participants		115	60			
Q8: Feeling towards abdominal operation via the vagina	V happy	17	7	^{2} (4, n = 175) = 5.434, P = 0.246	^{2} (3, n = 107) = 5.433, P = 0.143	^{2} (1, n = 107) = 3.689, P = 0.055 Phi 0.186
	Happy	25	23			
	Neutral	38	40			
Q9: Concerns about sexual function with surgery via the vagina	Unhappy	15	23	^{2} (2, n = 175) = 9.100, P = 0.011 Crammers V 0.168	^{2} (1, n = 92) = 9.147, P = 0.002 Phi − 0.315	N/A
	V Unhappy	5	7			
	Yes	23	40			
	No	30	12			
Q10: Would prefer NOTES to lap cholecystectomy	Unsure	47	48	^{2} (1, n = 175) = 0.192, P = 0.662	N/A	N/A
	Yes	38	42			
Q11: Would prefer NOTES if shown to be as effective and safe as laparoscopic cholecystectomy	No	62	58	^{2} (1, n = 175) = 0.019, P = 0.891	N/A	N/A
	Yes	54	55			
	No	46	45			
Q12: Feeling towards gynaecology surgery using vaginal NOTES	V happy	20	15	^{2} (4, n = 175) = 2.991, P = 0.559	^{2} (3, n = 89) = 1.852, P = 0.604	^{2} (1, n = 89) = 1.681, P = 0.198
	Happy	26	18			
	Neutral	46	55			
	Unhappy	5	7			
	V unhappy	3	5			
Q13: Would surgeon gender influence decision to undergo vaginal NOTES	Yes	44	30	^{2} (2, n = 175) = 3.402, P = 0.183	^{2} (1, n = 140) = 2.827, P = 0.093	N/A
	No	37	47			
	Unsure	19	23			

Women who had undergone previous abdominal surgery with a visible scar were more likely to report a positive feeling towards vNOTES for the same abdominal surgery but scarless. This association did not alter after reanalys- ing the data by removing the neutral bias; however, it did alter by condensing the responses into positive or negative.By analysing the data in this way, it was possible to iden- tify two additional significant associations; older women and/or multiparous women expressed significantly more positive attitudes towards vNOTES for scarless abdominal surgery than younger and/or nulliparous women.

Conversely, there were no significant associations between 'feeling towards vNOTES for gynaecological surgery' and age, parity, previous abdominal surgery or dislike of scar as a part of abdominal surgery. This indicates that Middle Eastern women are favourable towards vNOTES for gynaecological surgery.

These findings indicate that women feel differently towards vNOTES depending on the purpose of the sur- gery. Interestingly, 83% women surveyed disliked scars, but this did not alter their perception towards vNOTES, whether for abdominal or gynaecological purposes. This highlights the cultural and personal significance attached

to a woman's vagina, which may be the major hurdle to address if surgeons wish to pursue the field of vNOTES.

As the results indicated, young and nulliparous participants were more concern regarding their future sexual function. The sexuality of Middle Eastern women is a controversial and complex topic given the substantial cultural and religious implications of sexual expression. Themes of sexual obedience and power make it difficult to clearly identify how Middle Eastern women view sexuality [7]. Nevertheless, the results of this study indicated that Middle Eastern women have a collective opinion regarding their future sexual functioning following vNOTES surgery, with the more frequent response being unsure.

Sexual function can have various meanings and value. Younger women may value their sexual response differently than older women due to fertility potential. However, the sexually active parous women do not feel that vNOTES will interfere with their sexuality [8]. This study suggests that Middle Eastern women share the same concern for future sexual function following vNOTES as expressed by other women around the world [5, 9–11]. It would therefore seem that this concern is important to explore if this surgical technique were to become more routinely offered. This has

Table 5 Consideration of previous abdominal surgery on participants' perspective on trans-vaginal NOTES

Questionnaire item		%	%	Statistical analysis—all	Statistical re-analysis: neutral bias removed	Statistical re-analysis: categories collapsed
Had previous abdominal surgery		Yes	No			
Number of participants		87	88			
Q8: Feeling towards abdominal operation via the vagina	V happy	18	9	^{2} (4, n = 175) = 11.280, P = 0.024 Crammers V 0.254	^{2} (3, n = 107) = 6.926, P = 0.074	^{2} (1, n = 107) = 6.702, P = 0.010 Phi 0.250
	Happy	32	17			
	Neutral	31	47			
	Unhappy	15	20			
	V Unhappy	4	7			
Q9: Concerns about sexual function with surgery via the vagina	Yes	28	31	^{2} (2, n = 175) = 2.737, P = 0.255	^{2} (1, n = 92) = 1.768, P = 0.184	N/A
	No	29	18			
	Unsure	43	51			
Q10: Would prefer NOTES to lap cholecystectomy	Yes	37	42	^{2} (1, n = 175) = 0.508, P = 0.476	N/A	N/A
	No	63	58			
Q11: Would prefer NOTES if shown to be as effective and safe as laparoscopic cholecystectomy	Yes	57	51	^{2} (1, n = 175) = 0.707, P = 0.400	N/A	N/A
	No	43	49			
Q12: Feeling towards gynaecology surgery using vaginal NOTES	V happy	25	11	^{2} (4, n = 175) = 7.204, P = 0.125	^{2} (3, n = 89) = 6.531, P = 0.088	^{2} (1, n = 89) = 3.638, P = 0.056
	Happy	23	24			
	Neutral	46	52			
	Unhappy	3	8			
	V unhappy	3	5			
Q13: Would surgeon gender influence decision to undergo vaginal NOTES	Yes	48	31	^{2} (2, n = 175) = 5.893, P = 0.053 Crammers V 0.184	^{2} (1, n = 140) = 5.614, P = 0.018 Phi 0.200	N/A
	No	33	48			
	Unsure	19	21			

begun to be investigated [12–15], and it does not appear that vNOTES negatively impacts on sexual function, further reinforcing the need to examine the perspective of consumers with the development of new surgical techniques.

In this study, the preference of vNOTES was directly compared to laparoscopic surgery, such as cholecystectomy and it was revealed that the participants preferred laparoscopic surgery. More importantly, age, parity, having had previous abdominal surgery or a dislike of scars from abdominal surgery, did not impact their perspective towards vNOTES. A similar finding was reported in a previous study assessing the preference of Australian women, who also preferred laparoscopic surgery over vNOTES [5]. Due to cultural and religious background, Middle Eastern women may have difficulty accepting vNOTES if not sexually active or have gone through childbirth. Considering the Australian [5] and current studies, it appears that the vaginal route is a global taboo subject and needs further awareness and patient education.

This study also considered the influence of the surgeon's gender on the acceptance of vNOTES. Historically, the prevalence of male gynaecologists was far higher than female gynaecologists (80:20); however, there has been a

shift towards training female gynaecologists globally specifi-cally in the Middle East. The impact of the surgeon's genderoffering the procedure is likely to be a concern to Middle Eastern women.

Unfortunately, it was not possible to perform bivariate analyses on women known to have gallstones, who had a cholecystectomy or who prefer an alternative surgical technique that was scarless, due to the sub-categories being too unequal in size. Although 32% of this cohort would be unhappy to have vNOTES, there were 95% of the women surveyed indicated they would prefer an alternative surgical technique that was scarless and further indicated that this was primarily due to the assumption of it resulting in less pain and producing a better cosmetic outcome. This finding supports the intention of the authors to survey a cohort of women who are believed to value cosmesis and be limited be culture and religion. However, this indicates that the cosmetic outcome of a scar-free surgical procedure was not sufficiently attractive enough to overcome the surveyed women's concerns regarding vaginal access and their beliefs, whether that be cultural, personal, religious, or otherwise. This may indicate that gynaecologists for Middle Eastern women may benefit further addressing vNOTES technique

Table 6 Consideration of scar preference on participants' perspectives on trans-vaginal NOTES

Questionnaire item		%	%	Statistical analysis—all	Statistical re-analysis: neutral bias removed	Statistical re-analysis: categories collapsed
Minds Abdominal scars		Yes	No			
Number of Participants		146	29			
Q8: Feeling towards abdominal operation via the vagina	V happy	16	3	^{2} (4, n = 175) = 4.733, P = 0.316	^{2} (3, n = 107) = 2.810, P = 0.422	^{2} (1, n = 107) = 1.095, P = 0.295
	Happy	25	21			
	Neutral	36	52			
	Unhappy	17	21			
	V Unhappy	6	3			
Q9: Concerns about sexual function with surgery via the vagina	Yes	41	21	^{2} (2, n = 175) = 1.299, P = 0.522	^{2} (1, n = 92) = 0.528, P = 0.468	N/A
	No	29	24			
	Unsure	30	45			
Q10: Would prefer NOTES to lap cholecystectomy	Yes	36	55	^{2} (1, n = 175) = 3.608, P = 0.058	N/A	N/A
	No	64	45			
Q11: Would prefer NOTES if shown to be as effective and safe as laparoscopic cholecystectomy	Yes	59	31	^{2} (1, n = 175) = 7.572, P = 0.006 Phi = 0.208	N/A	N/A
	No	41	69			
Q12: Feeling towards gynaecology surgery using vaginal NOTES	V happy	20	10	^{2} (4, n = 175) = 1.587, P = 0.811	^{2} (3, n = 89) = 1.559, P = 0.669	^{2} (1, n = 89) = 0.134, P = 0.714
	Happy	23	28			
	Neutral	49	52			
	Unhappy	5	7			
	V unhappy	3	3			
Q13: Would surgeon gender influence decision to undergo vaginal NOTES	Yes	40	34	^{2} (2, n = 175) = 0.519, P = 0.772	^{2} (1, n = 140) = 0.153, P = 0.695	N/A
	No	40	41			
	Unsure	20	24			

in a culturally sensitive manner to mitigate any post-surgical physical or emotional concerns, and/or that this cohort may be less suitable for this surgical approach regardless of any desired positive surgical outcomes.

Conclusion

vNOTES is a new form of minimally invasive surgery. This advancement appears impressive and may potentially improve patient's surgical experience. This study indicated that vNOTES may be a potential preferred surgical option for older and/or multiparous Middle Eastern women and that the impact on future sexual function may be a prohibiting concern for younger and/or nulliparous women. In the conclusion, Middle Eastern women appear to be in favour of vNOTES for gynaecologic surgery over cholecystectomy.

Disclosures

Fariba Behnia-Willison, Tran Nguyen, Adel Rezaeimotlagh, Jan Baekelandt, and Peter J. Hewett have no conflicts of interest or financial ties to disclose for this study.

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Appendix 1 Patient Questionnaire

Background

Key hole (laparoscopic) surgery using small incisions, is a well-established technique. However, there is now a new concept in surgery known as '*N.O.T.E.S.*' (Natural Orifice Transluminal Endoscopic Surgery). This utilises a natural orifice (e.g. the vagina) to allow entry into the abdominal cavity so that operations such as a cholecystectomy (removal of the gallbladder) can be performed with the use of specialised equipment. In the case of cholecystectomy, the gallbladder would be removed from the body via the vagina, leaving no visible scars. It may also be potentially less painful. In a few specialist centres, this procedure is now being performed although there are no clinical trials to support its use. As a woman, we would be interested to hear your views regarding the utilisation of the vagina as a way of performing this type of surgery.

1. Age:_____years.

2. Have you had children? Y/N.

3. Are you known to have gall stones? Y/N.

4. Have you had a cholecystectomy (removal of gall bladder)? Y/N.

5. Have you had an abdominal operation before? Y/N.

6. Would you mind abdominal scars as part of an abdominal operation? Y/N.

7a. Would you find it preferable if you could have the operation (laparoscopic cholecystectomy), using an alternative method resulting in no scars? Y/N.

7b. If yes, is this because of:

a) Cosmetic reasons.

b) Potential for less pain.

c) Both.

d) Other (please state).

8. How do you feel about using the vagina as an entry site for an operation? (Please circle)

a) Very happy, b) Happy, c) Not sure, d) Unhappy, e) Very unhappy.

9. Would you be concerned that surgery through the vagina (NOTES) may have a negative impact on your sexual function?

a) Yes b) No c) Not sure.

10. Would you prefer to have a laparoscopic (key hole) cholecystectomy or a NOTES cholecystectomy?

a) Laparoscopic cholecystectomy b) NOTES cholecystectomy.

11. If NOTES cholecystectomy was shown to be as effective and as safe as laparoscopic cholecystectomy which would you prefer?

a) Laparoscopic cholecystectomy b) NOTES cholecystectomy.

12. If you required a gynaecological procedure such as a sterilisation, how would you feel about this being performed vaginally (NOTES sterilisation), rather than with standard key hole surgery

a) Very happy, b) Happy, c) Not sure, d) Unhappy, e) Very unhappy.

13. Finally, would the sex of the surgeon influence your decision as to whether to undergo a NOTES procedure?

Yes/No/Unsure.

Thank you

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Chapter 7: Potential Role of Platelet- Rich-Plasma (PRP) In the Treatmentof Lichen Sclerosus

7.1 Introductory comments

Lichen Sclerosus (LS) is a chronic inflammatory autoimmune skin disorder that affects the skin around the vulva or anus. The condition makes patches of skin look white, thickened, andcrinkly, which are often itchy and painful. If not treated, LS is associated with a greater degreeof scarring and an elevated risk of cancer in the genital area [1]. LS affects around one in 80 women, where ~4% of women with LS will go on to develop vulvar cancer [2]. LS can happenat any age but is most common in middle-aged and elderly women. LS is clinically diagnosedfollowing a colposcopy biopsy. Since the cause of LS remains unknown and there is no cure, treatment with cortisone ointments and barrier creams only improve quality of life by alleviating symptoms. Treatment success is determined by a reduction in reported symptoms such as vulva itching, soreness and/or dyspareunia. It is best practise for anyone diagnosed with LS to undergo yearly colposcopy biopsy to screen for pre-cancerous changes. Surgery may be required to remove any cancerous or pre-cancerous skin, and can also be performed toremove scarring or adhesions that cover the vaginal entrance [3].

While the use of ultrapotent topical steroids can successfully help with the management of symptoms, they can have adverse effects such reddening and thinning of the skin, burning discomfort, vaginal atrophy, and vulvovaginal thrush. Like with many other gynaecological conditions, limited treatment options often result in prolonged suffering and the frustration of having to trial different options to find something that offers some relief. Frustrated patients and discontent clinicians drive the field to discover new treatment options.

For LS, PRP therapy could be used as an alternative method to current conventional treatments.The biological rationale for the clinical use of PRP resides in the local delivery GFs, cytokines, chemokines, proteins, and mediators (in physiological proportions), which contribute to tissue

healing and regeneration. In particular, they play an important role in phagocytosis of fibrotictissue, inflammation reduction, angiogenesis stimulation, and collagen III synthesis [1, 4, 5].

The downside to PRP therapy lies with the need to inject the prepared PRP into the target area,which may cause some momentary discomfort to the patient. This discomfort may be reducedby using vaginal laser to cause microtrauma to the vaginal tissue and rather pouring the PRP to avoid PRP injection. The PRP preparation procedure is also known to have a marked effecton the quality of the PRP product, specifically regarding cell types and quantify and thereforeGF and cytokine content. Platelet activation is also a critical step that influences the availabilityof these bioactive molecules. Prior to PRP administration, thrombin and/or calcium chloride ($CaCl_2$) is often added to activate the platelets. Some physicians however, prefer to inject PRPin its resting form, relying on spontaneous platelet activation occurring after exposure to the native collagen present in the connective tissues [1, 3]. The challenge is developing the right preparation protocol that yields high concentrations of PRP, and a platelet activation method that achieves optimal release of bioactive molecules. Since little is known about the concentration of thrombin and/or $CaCl_2$ needed to trigger optimal release of GFs, this makes ithard for clinicians to achieve the clinical potential of PRP for LS.

The paper presented in this chapter [6] describes an early yet important study into the use of PRP for the treatment of LS. Over two years, 28 patients clinically diagnosed with LS and unresponsive to topical steroid treatment were treated with PRP. The findings showed that PRP therapy can regenerate normal skin and can be used as an alternative to steroid treatments, as nearly all patients showed clinical improvement in the size of their lesions, and in eight cases,the lesions disappeared completely. The concluding remarks is that PRP presents a potential alternative to topical steroids for the treatment of vulvovaginal autoimmune conditions such as LS. A larger pilot and/or randomised controlled trial study is required however, to evaluate thisfinding further.

7.2 Aim

To evaluate the safety, symptom resolution, and objective improvement in patients with the autoimmune condition genital LS after treatment with PRP.

7.3 Summary

Over a 2-year period at FBW Gynaecology Plus, we had a total of 28 patients with confirmedLS on biopsy, unresponsive to topical steroid treatment. Almost all of our patients showed clinical improvement in the size of their lesions, and in 8 cases, lesions totally disappeared aftertreatment with PRP. Symptoms disappeared in 15 of the 28 patients after treatment, with no need for further steroid therapy in 23 patients. Thirteen women experienced partial symptom relief. Based on our limited findings, we hypothesize that PRP presents a potential alternativeto topical steroids for treatment of vulvovaginal autoimmune conditions such as LS.

7.4 Publication used in this chapter

Use of platelet-rich plasma for vulvovaginal autoimmune conditions like lichen sclerosus.

F Behnia-Willison, NR Pour, B Mohamadi, N Willison, M Rock, IW Holten, R O'Shea, J Miller.

Plastic and Reconstructive Surgery Global Open 2016; 4 (11) e1124.

7.5 Author contribution

I was responsible (100%) for the concept and design of research and data collection and 30% of writing forthe publication. Prof O'Shea was responsible for (30%) of writing and editing. Behrang Mohammadi (100%) was responsible for the data analysis and Nadia Willison was responsiblefor (40%) writing and editing and proofreading.

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Original article

Use of Platelet-rich Plasma for Vulvovaginal Autoimmune Conditions Like Lichen Sclerosus

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Background: Lichen sclerosus (LS) is an inflammatory dermatosis with autoimmune pathogenesis. Although relatively common, its true incidence is unknown and likely underestimated. LS is usually anogenital, but in around 10% of patients, it can present as extragenital lesions. Continuous administration of topical corticosteroids is the mainstay of medical treatment. Other treatments are available but are only occasionally prescribed along with or instead of topical steroids. Injection of platelet-rich plasma (PRP) into affected areas has been reported to result in the regeneration of normal skin. In this study, we aimed to evaluate the safety, symptom resolution, and objective improvement in patients with autoimmune condition like genital LS after treatment with PRP.

Methods: Over a 2-year period at FBW Gynaecology Plus, we had a total of 28 patients with confirmed LS on biopsy, unresponsive to topical steroid treatment. After acquiring informed consent, patients' own blood was centrifuged on site and injected under local anesthesia to the external genitalia.

Results: Almost all of our patients showed clinical improvement in the size of their lesions, and in 8 cases, lesions totally disappeared after treatment with PRP. Symptoms disappeared in 15 of the 28 patients after treatment, with no need for further steroid therapy in 23 patients. Thirteen women experienced partial symptom relief.

Conclusions: Based on our limited findings, we hypothesize that PRP presents a potential alternative to topical steroids for treatment of vulvovaginal autoimmune conditions such as LS. A larger pilot and/or randomized controlled trial study is required to evaluate this finding further. *(Plast Reconstr Surg Glob Open 2016;4:e1124; doi: 10.1097/GOX.0000000000001124; Published online 23 November 2016.)*

Lichen sclerosus (LS) is a chronic autoimmune inflammatory dermatosis characterized by a lymphocytic response that has a predilection for the genital skin in both sexes and an association with several other autoimmune diseases.[1] Women are 6 to 10 times more often affected than men.[2] LS may involve complications of erosions, atrophy, and scarring as a result of inflammation and altered fibroblast function, leading to fibrosis of the upper dermis. There can also be purpura, hyperpigmentation, fissures, and edema.[3] LS mainly affects the anogenital area of the skin, in more than a 5:1 ratio when compared with extragenital skin.[4]

LS is relatively common although the true incidence is unknown and possibly underestimated, in part, due tothe distribution of patients among different clinical specialities and to the fact that it can be asymptomatic.[1] The etiology of LS is uncertain although there is evidence for linkages between autoimmune mechanisms and the pathogenesis of LS.[5]

LS is a scarring process and may cause loss of the labia minora, sealing of the clitoral hood, and burying of the clitoris. In women, vulvar LS can present with progressive pruritus, dyspareunia, dysuria, or genital bleeding.[4] These symptoms may also occur in postmenopausal women due to the lack of estrogen in the vaginal area. LS has a considerable impact on affected patients physically, emotionally,

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and psychologically, affecting their quality of life through pain and embarrassment and having a significant impact on their sexual lives, which can affect their intimate relationships.

Severe introital stenosis (ie, narrowing of the vaginal opening) occurs rarely.[1] LS can also be associated with squamous cell carcinoma (SCC); there is a 4% lifetime risk of developing SCC among LS sufferers.[6] Histopathological examination of vulval SCC cases shows that over 60% have a background of LS.[7] In the presence of typical clinical features, confirmation with colposcopy and exclusion of conditions such as vulvar intraepithelial neoplasia, a biopsy is not always necessary for the diagnosis of LS.[8] However, histological examination is recommended given the presentation of atypical features and mandatory if the disease fails to respond to treatment and second-line therapy is to be used.[1]

There is no current cure for LS nor is there a comprehensive treatment to cover all patients. Much of the management of LS is aimed at controlling symptoms, such as pruritus in extragenital LS. Current guidelines aim at treating patients with ultrapotent topical corticosteroids, which are symptomatically effective in 90% of women and show variable objective improvement.[9] Corticosteroids require continuous administration and present complications.[10] Furthermore, for the 40% to 57% of postmenopausal women experiencing symptoms resulting from atrophic vaginitis[11] due to menopausal estrogen deficiency and natural aging of the vagina, corticosteroids can worsen the atrophy.[12] As most patients with LS are of postmenopausal age,[13] corticosteroids are a problematic treatment option.

In Australia, the guidelines for treatment of LS are for betamethasone dipropionate ointment (0.05%) to be used twice daily for 1 month, then daily for 2 months, and gradually reduced as needed (ideally 1–2 times per week[14]). This high-maintenance treatment regime canlead to relapse by patients who are not compliant or whofind it to be a difficult regime to uphold. A study by Ren-aud-Vilmer et al[15] investigated remission and recurrence rates of 85 patients with 0.05% clobetasol proprionate ointment and found that 72% of women under age 50 showed complete remission, 23% of women between 50 and 70 years old had complete remission, and no women over 70 years old had complete remission. These results highlight the impact of age on the success of topical corticosteroids as treatment for LS.[15]

A variety of other treatment options are available, including calcipotriol, retinoids, systemic steroids, tacrolimus, and pimecrolimus. Photodynamic therapy has also been reported to be beneficial.[16] Surgical treatments involve vulvectomy, cryosurgery, and laser ablation.[1] These procedures pose the risk of scarring to damaged tissues and present high recurrence rates.[17] Less invasive techniques are therefore of interest.

In recent years, many scientists have shown the existence of cells in the adult body that are capable of repairing and regenerating damaged tissue. By extracting and processing blood through a sophisticated extraction system, it is possible to produce platelet-rich plasma (PRP), a type of plasma that contains several major growth factors, nutrients, minerals, and monocytes with the potential to assist in wound healing.

PRP has been used clinically for tissue regeneration, reconstructive and plastic operations, and surgery, including wound hemostasis, wound sealing, augmentation of bone grafts periodontics, and treatment of tendonitis.[18–20] In addition, PRP has promoted tendon healing in acute tendon injury and repair models. Increased epithelialization has been demonstrated in both acute traumatic wounds and chronic diabetic wounds through the use of PRP.[20] PRP injection with or without needling has been described as a new and promising modality for the treatment of atrophic acne scars.[21] Activated platelets release growth factors that contribute to cell migration, proliferation, differentiation, angiogenesis, removal of tissue debris, and regeneration of appropriate type of tissue.[22] PRP has a high safety level and can be obtained relatively noninvasively through a venous blood draw where the blood is then mechanically centrifuged to extract a concentrate of PRP, which allows repeated administration.[17,23]

One study investigated a new regenerative approach based on grafting of adipose-derived stem cells and injection of PRP that removed symptoms and reduced atrophy and sclerosus in 15 female patients with a histologic diagnosis of LS who were unresponsive to topical steroid therapy.[17] However, the need for all patients to undergo liposuction to isolate the adipose-derived stem cells means that the process still requires day surgery, thereby having a significant impact on the health system and patients' lifestyles. The aim of this study was to investigate the efficacy of injecting PRP alone as a treatment for LS, so that the need for surgery may be eliminated or rendered as mini-mally invasive as possible for patients who do not respond to topical steroid treatment.[17]

The potential adoption of PRP for autoimmune skin conditions such as LS has been discussed in the literature.[5,17] However, it still remains unclear whether PRP is a sufficiently effective treatment to replace topical steroids. The aim of this article is to present a new regenerative approach that removes symptoms and reduces atrophy and sclerosus in patients diagnosed with LS. This method is based on injection of PRP.[17]

PATIENTS AND METHODS

Patients were 28 women aged 22 to 88 years (M = 60) who attended FBW Gynaecology Plus from 2013 to 2016 (Table 1). Twenty-six of the 28 patients had confirmed LS on biopsy, with histopathological data indicating possible LS for 1 patient and no LS for one other patient. However, colposcopic examination suggested the presence of LS in

all patients. Symptoms were unresponsive to topical steroid treatment in all cases. Those patients who had been using steroids for management of LS symptoms discontinued their use throughout the duration of the study.

After providing written informed consent, patients' ownblood (10 mL) was centrifuged (Regens Lab, New York, N.Y.) on site and injected under local anesthesia (ligno-caine, 23%; tetracaine, 7%) to any affected areas of the ex-ternal genitalia, including the labia majora, labia minora,

Table 1. Baseline Patient Characteristics

	Value (%)
Age range, y	
<45	2 (7.1)
46–55	6 (21.4)
56–65	14 (50)
66–75	3 (10.7)
>76	3 (10.7)
Histopathology of LS	
Yes	26 (92.9)
No	1 (3.6)
Unclear	1 (3.6)

LS, lichen sclerosus.

clitoris, and clitoral hood. The injection was carried out using a 27-gauge needle in a fanning motion to break the scar and fibrotic tissue and retrograde injection of PRP in the tissue. Patients received 3 PRP treatments 4 to 6 weeks apart and again at 12 months. Patients were verbally interviewed about their symptoms (eg, soreness, discomfort, and dyspareunia) after each treatment session, and lesions were evaluated at each session by colposcopy. Patients with vulval intraepithelial neoplasia (n = 2) were excluded from the study. Posttreatment pain scores were measured after each treatment using a verbal scale from 0 to 10. Patients were asked to complete the Australian Pelvic Floor Questionnaire 24 at baseline and at 2 to 3 months after the final PRP treatment, with higher scores indicating greater frequency of symptoms on each variable. The questionnaire was used to assess symptoms of urinary incontinence, general bladder function, prolapse, and sexual function.

Statistical Analyses

Changes in lesion size, symptoms, and need for topical steroid use were compared from pre- to posttreatment using the Wilcoxon signed-rank test. Statistical analyses were performed using SPSS Statistics version 21.0 (IBM, Chicago, Ill.), and values of P less than 0.05 were considered to be statistically significant.

RESULTS

Nearly all patients exhibited clinical improvement in the size of their lesions (Table 2), and in 8 of the 28 patients (28.6%), lesions disappeared completely after treatment with PRP. A Wilcoxon signed-rank test indicated that there was a statistically significant decrease in the number of patients with lesions after PRP treatment ($Z = -4.562$; $P < 0.001$).

Pretreatment symptoms included severe itch (requiring steroid treatment), soreness, discomfort, and/or dyspareunia. As shown in Table 2, more than half the sample had become free of symptoms after the final PRP treatment at 12 months or more. A Wilcoxon signed-rank test showed a statistically significant decrease in the presence

Table 2. Presence of Lesions and Symptoms after Platelet-rich Plasma Treatment

	n (%)
Presence of lesions	
Lesion not seen	8 (28.6)
Lesion became smaller	17 (60.7)
Lesion the same	3 (10.7)
Presence of symptoms	
No symptoms	15 (53.6)
Intermittent symptoms	13 (46.4)

of symptoms after treatment ($Z = -4.768$; $P < 0.001$).

After the final treatment (at 12 months or more), 82.1% of patients (n = 23) no longer needed to use steroids; the remaining 17.9% (n = 5) continued to use them intermittently. A Wilcoxon signed-rank test showed a statistically significant decrease in steroid use after treatment with PRP ($Z = -4.963$; $P < .001$).

Although there was a generally declining trend for responses to items on the Australian Pelvic Floor Questionnaire from pre- to posttreatment, none of the changes were statistically significant, likely due to the very small sample size for pelvic floor disorders.

Patients reported minimal to moderate pain. During the 24 hours after the procedure, 26 patients (92.9%) reported pain scores of 2 to 3; the remaining patients reported scores of 5 and 7, respectively. There were 0 cases of infection, bleeding, hematoma, or other adverse outcomes.

DISCUSSION

In this study, we found that the majority of patients with LS reported significant improvement in their symptoms, with no need for further steroid therapy after PRP treatment.

Furthermore, the majority of patients' lesions disappearedor became smaller after treatment. Based on these limitedfindings, we hypothesize that PRP can be used as a possiblealternative to topical corticosteroids for the treatment of LSor at least in cases where steroids have ceased to work. ThePRP procedure is minimally invasive and safe and can beperformed in an office setting under local anesthesia. Our findings lend support to those of Casabona et al[17] by demon-strating that PRP injection may be an effective treatment forLS, without the need for further surgery and associated risks.The study possessed several limitations. First, our sam- ple size was limited, and a subsequent pilot study or ran-domized controlled trial (RCT) with a larger sample sizeis required to further evaluate the efficacy of PRP. Second,the vast majority of patients were postmenopausal, making it difficult to generalize the current findings to women ofreproductive age. However, it should be considered thatLS occurs most frequently in postmenopausal women.[25] Fi-nally, it is conceivable that the observed improvements in LS symptoms after PRP treatment were partially or wholly due to the tissue needling involved in the PRP injection process rather than to a simple effect of the PRP in and of itself. Subjecting tissues to microtrauma can instigate the tissue repair cascade, and in the present circumstances, this cannot be ruled out as a therapeutic mechanism. For this reason, we intend to conduct a double-blind RCT in which one group is randomized to a saline injection, with a second group randomized to PRP treatment.

CONCLUSIONS

Growth factors released by platelets, monocytes, and nutrients have an important role in phagocytosis of fibrotic tissue, inflammation reduction, angiogenesis stimula-

tion, and collagen III synthesis. The injection of PRP can therefore be considered effective therapy for LS.

It remains unclear whether needling with saline can result in the same outcome as PRP due to the breakdown of sclerotic tissue, allowing the local stem cells and monocytes to improve tissue healing. There is a need for further RCTs to compare outcomes between these 2 treatment methods and to elucidate the precise mechanism whereby PRP treatment seems to benefit patients with skin conditions like LS.

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Chapter 8: Safety and Long-Term Efficacy of Fractional CO2 Laser Treatment in Women Suffering from Genitourinary Syndrome of Menopause

8.1 Introductory comments

Gynaecological conditions are major contributors to the morbidity and mortality of women worldwide. The level of priority and research efforts allocated to finding solutions to better treat these conditions, however, is far from equal with other conditions. For example, uterine, endometrial, ovarian,and cervical cancers are the most common malignancies of the female genital tract and are given top priority within the Australian health care system, because of their high prevalence, high risk of recurrence and relatively poor prognosis [1]. Other more common 'benign' conditions are often overlooked, simply because they are not considered 'life threatening'. This disparity in priority is unacceptable as many benign gynaecological conditions have a high prevalence and are often associated with debilitating symptoms that have a negative consequence on physiological health and psychological wellbeing and in turn a significant reduction in quality of life. To provide women with the best chance of living a fulfilling life, the priority assigned to a particular illness/condition needs to consider both mortality and morbidity. Four common benign gynaecological conditions that are significantly overlooked by the Australian health care system are genitourinary syndrome of menopause (GSM), vaginalprolapse, stress incontinence, and urge incontinence.

8.2 Genitourinary Syndrome of Menopause

Life expectancy for women has increased significantly during the past century and many women will now spend more than one-third of their lives in menopause. Many of these postmenopausal women, expect to maintain good health and a high quality of life into their postmenopausal years, and consider sexual health and relationship satisfaction to be of paramount importance [37-39]. The sexual health of postmenopausal women can be undermined by the progressive ageing of the body, as well as by GSM [40].

GSM is a relatively new term for the condition previously known as atrophic vaginitis (AV).

A review by Angelou et al. [2] define GSM as “a chronic, progressive, vulvovaginal, sexual, and lower urinary tract condition characterised by a broad spectrum of signs and symptoms, most of which can be attributed to the lack of estrogen that characterizes menopause”. GSM mainly affects postmenopausal women, but it is also seen in premenopausal women, often due to prolonged use of the oral contraceptive pill, other prescribed medications, or external factors such as smoking or alcohol abuse [3]. It is estimated 8-22% of premenopausal women and 40-57% of postmenopausal women experience symptoms resulting from GSM [4], however, only 1 in 5 women experiencing these symptoms will consult a physician on issues related to GSM [2].

GSM is the consequence of women existing in an hypoestrogenic state, which leads to dramatic hormonal, anatomical and physiological changes in the genitourinary tract, such as shortening and narrowing of the vagina, loss of rugae, and flattening and keratinization of the epithelial surface [3]. Many women with GSM/AV suffer from persistent irritation/itchiness, sensitivity/pain, burning sensation, and dyspareunia (painful sexual intercourse). The discomfort associated with sexual intercourse often leads to a vicious cycle of decreased desire, arousal, orgasm, and frequency of coitus, resulting in loss of self-confidence and depression [5]. Dyspareunia ensues because estrogen deficiency causes a loss in dermal collagen in the dense connective tissue of the vagina, bladder, and urethra. This causes the vaginal wall to become thinner and less elastic, resulting in the vagina becoming shortened and narrowed and the epithelium becoming thin and atrophic, and thus easily prone to trauma [6].

Women with GSM experience pain and burning and are at an increased risk of developing vaginal infections and/or UTIs largely due to disruption of the pH and normal microbiota of the vaginal milieu. The vaginal mucosal ecosystem is comprised of stratified squamous non-keratinized epithelium overlaid by a mucosal layer, continuously lubricated by cervicovaginal fluid [7]. Estrogen is very important as it induces these epithelial cells to fill with glycogen,

which when released from exfoliated and lysed epithelial cells is catabolised by α-amylase and

subsequently metabolised to lactic acid by beneficial *Lactobacillus* spp. [7]. The lactic acid acidifies (reduces pH to 3.5-4.5) [8] the vaginal milieu to favour proliferation of *Lactobacilli* and inhibit the growth of opportunistic pathogens. In essence, the normal acidic vaginal pH in women is driven by oestrogen, glycogen, and *Lactobacilli spp.*

In the case of GSM, decreased glycogen availability due to reduced oestrogen, results in reduced synthesis of lactic acid by *Lactobacilli*. This changes the vaginal milieu to an alkaline pH of ≥5.0, which impairs the viability of healthy vaginal flora and promotes growth of opportunistic pathogens such as Group B streptococci, staphylococci, coliforms, and diphtheroids [8]. Women who develop infections, will often require systematic antibiotic treatment.

8.3 Current treatments for GSM

The primary goal of the treatment of GSM is to achieve the relief of symptoms, and the earlier the condition is diagnosed the better the prognosis. First-line treatment often consists of non-pharmacological therapy such as moisturisers and lubricants, complementary medicines, and lifestyle modifications, which are often effective for mild cases. For severe cases, the 'gold standard' approach is hormonal therapy with oestrogen alone (ET) or with oestrogen-progestin (EPT). The goal of estrogen therapy is to prevent loss in dermal collagen and induce glycogen uptaketo restore *Lactobacilli* dominance in the vaginal milieu. While these therapies may be effectivein increasing vaginal lubrication and reducing dyspareunia, they have not been shown to consistently increase sexual desire or activity [9].

Furthermore, there is a concern that estrogen therapy is contraindicated in women on adjuvant aromatase inhibitors (AIs), which are being increasingly used in early breast cancer. Postmenopausal women (with oestrogen-dependant breast cancer) being treated with AIs can

experience worsening symptoms of GSM/AV due to profound oestrogen suppression. Generally, vaginal estradiol (E2; type II estrogen) preparations (as a tablet, ring, or cream) are perceived to have a low systemic absorption of oestrogen and have been shown to result in

significant symptomatic benefit, superior to that of non-hormonal preparations. Vagifem (a vaginal E2 tablet) is commonly used due to good compliance and efficacy in treating AV. In a study by Kendal et al. [8], the effect of Vagifem on E2 serum levels in a small number of women with severe GSM/AV and receiving AI therapy was assessed. For this cohort of women, it was found Vagifem significantly raises systemic E2 levels in the short term, which in effect reverses the estrogen suppression achieved by AIs in women with breast cancer, such that Vagifem in combination with AIs is contraindicated. Until more research is done, it is recommended that women with a current or prior history of estrogen-dependent breast cancer and are experiencing GSM symptoms are offered non-hormonal preparations. Vaginal estrogen should be reserved for patients who are unresponsive to non-hormonal remedies. Ultimately, treatment should be individualised based on each woman's risk–benefit ratio and clinical presentation. In the instance that the decision is made to use vaginal estrogen, it should be prescribed at the lowest dose to affect vaginal symptoms and for a limited period until symptoms are improved [8, 10].

8.4 Fractional Microablative CO2 Laser for the treatment of GSM

Currently, ET or ETP therapy is considered the 'gold standard' for treating GSM, but as mentioned, it is not applicable to all women. The effectiveness of this therapy is also compromised by a lack of patient compliance, and it is difficult to accurately measure efficacy due to significant variance in subjective impression of symptom repression amongst patients. Furthermore, the literature largely reports on the short-term efficacy of this treatment. A significant knowledge gap exists regarding the use of this therapy long-term.

Early detection and individually tailored nonpharmacologic and/or pharmacologic treatment is

paramount for not only improving quality of life but also for preventing exacerbation of symptoms in women with GSM. For women with symptoms related to sexual activities, a

lubricant may be sufficient. If urinary and genital symptoms exist, a local, low-dose estrogen therapy may be effective. Women who currently have (or have a history) of hormone-sensitive cancer will need to be treated with more caution. Newer therapeutic approaches have been developed more recently, which include selective-estrogen receptor modulators, synthetic steroids, oxytocin, vaginal dehydroepiandrosterone, and laser therapy [4, 11]. Further research is required however, to investigate the viability and scope of their implementation in day-to-day clinical practice.

Fractional microablative CO_2 laser ($FxCO_2$) represents one potential non-pharmacological approach to GSM. The CO_2 laser was first used in gynaecology in 1973 for the treatment of cervical erosions [12], and later for the treatment of cervical intraepithelial neoplasia, as well as for microsurgery of the fallopian tube [13, 14]. Over the past 20 years, use of the CO_2 laser in gynaecology has gained momentum and as a result, has gathered a good safety record. This is largely due to its limited depth of penetration (0.1-0.5mm) and lateral dermal damage (0.5mm), which allows $FxCO_2$ to be used in delicate areas such as the bladder, lateral side wall near the ureter and bowel serosa [15]. The laser can also be used for excision or incision by increasing the power density. $FxCO_2$ targets both the epidermis and dermis, which is achieved by delivering a laser beam into the skin at microthermal treatment zones (MTZ). Within each MTZ, old epidermal pigmented cells are expelled and the penetration of collagen in the dermis activates heat shock proteins that in turn activate growth factors. This results in an increase in vascularity, collagen, extracellular matrix production, and thickness of vaginal epithelium [4, 11].

Despite $FxCO_2$ having received FDA approval for incision, excision, ablation, vaporisation,

and coagulation of body soft tissues in various medical specialties, GSM is not specifically listed as an indication for treatment [4, 11]. CO_2 laser therapy for GSM has however, been tested in smaller, uncontrolled clinical trials with positive results. For example, Pagano et al. [16]. used $FxCO_2$ to treat GSM/AV in 26 women with breast cancer, who were undergoing

hormonal treatment and chemotherapy, which inherently induces a transient or permanent menopause status. The study evaluated the effects of $FxCO_2$ on sexual function and in relieving symptoms of AV. The conclusions of the study were that $FxCO_2$ is associated with a significant improvement in AV symptoms in women affected by hormone-driven breast cancer. This outcome is promising as it appears FCO_2L has the advantage of relieving AV symptoms without having to resort to contraindicated estrogen preparations. In a more recent study by Pagano et al. [17], researchers assessed the histological changes related to $FxCO_2$ in vulvar tissue from 20 GSM patients. The results were promising as the $FxCO_2$ treatment led to restoration of the normal architecture of vulvar tissue, with significant improvement in GSM-related signs and symptoms. From the small-scale studies conducted, $FxCO_2$ appears to hold promise as an effective minimally invasive, non-hormonal treatment for GSM. Further studiesare required however, to examine long-term safety and efficacy of $FxCO_2$ in comparison withestrogen therapy and proper controls.

The objective of the paper presented in this chapter was to conduct a prospective panel design study to evaluate the safety and long-term efficacy of $FxCO_2$ treatment of 102 women (ranging 51-86 years) presenting with symptomatic GSM, and not responsive to (or not able to take) conventional treatments. Each participant underwent a series of vaginal treatments with the MonaLisa Touch, DEKA system at intervals of six or more weeks. Each patient was asked to complete the Australian Pelvic Floor Questionnaire at three time-points across the study period to gather data on sexual function and side-effects and Wilcoxon signed-rank tests were used to detect statistically significant clinical changes in sexual function and side-effects occurring

from pre- to post-treatment.

The primary outcome of this study was that ~84% of the patients who suffered from moderate or severe GSM experienced an improvement in symptoms. Statistically significant improvements were observed for all variables assessed, including scores on sexual function, painful intercourse, vaginal dryness, and reduced libido. Although not the primary outcome of this study, the improvement in prolapse symptoms, impaired bladder function, urge and stress incontinence were interesting outcomes. The key limitation of this study was the high attrition rate, as participant responses decreased by less than half from the third treatment to the 12–24-month follow-up, making it difficult to be confident in the soundness of comparisons from baseline to the final follow-up. A larger number of participants were intentionally recruited in anticipation of patient attrition during follow-up. Another weakness was the absence of a control group receiving either a placebo or hormonal treatment. Nevertheless, the study demonstrates that $FxCO_2$ treatment can provide long-term improvements in the GSM symptoms for postmenopausal women, and the data combined with other short-term studies provide sufficient evidence to warrant a randomised controlled trial.

From my experience as a gynaecologist, I find the results of this study encouraging as I am often faced with the challenge of treating many women with age-related GSM who are unresponsive to oestrogen therapy. If the short- and long-term safety and efficacy of $FxCO_2$ can be adequately ascertained, I believe this will revolutionise the treatment of GSM and other gynaecological issues that rely on hormonal and/or surgical treatments.

8.5 Aim

To evaluate the impact of trans-vaginal fractional CO_2 laser treatment on women suffering from genitourinary syndrome of menopause.

8.6 Summary

102 women presenting with symptomatic GSM were treated with the fractional CO2 laser system across a series of treatments delivered at intervals of minimum six weeks. TheAustralian

Pelvic Floor Questionnaire was used to obtain the data on sexual function and side-effects. The primary outcome of this study was an improvement of the symptoms of GSM. Thesecondary outcome included bladder function and prolapse symptoms. Results: A total of 102women suffering from moderate to severe GSM were recruited. Eighty-four percent

experienced significant improvement in their symptoms after CO2 laser treatment. Scores on measures of sexual function, dyspareunia, and bothersomeness of sexual issues were improved from pre-treatment to long-term (12–24 month) follow-up. In this study, fractional microablative CO2 laser treatment was associated with an improvement in symptoms of GSM and sexual function.

8.7 Publication in this chapter

Safety and long-term efficacy of fractional CO2 laser treatment in women suffering from genitourinary syndrome of menopause.

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8.8 Author contribution

I was responsible for (100%) the concept and design of research and data collection and (20%) of writing for the publication. Alan Lam was responsible for (30%) of writing and editing. Behrang Mohammadi (100%) was responsible for the data analysis and Nadia Willison was responsiblefor (50%) writing and editing and proofreading.

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Full length article

Safety and long-term efficacy of fractional CO_2 laser treatment in women suffering from genitourinary syndrome of menopause>

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ABSTRACT

Objectives: To evaluate the safety and long-term efficacy of fractional CO_2 laser treatment in reducing the severity of symptoms of genitourinary syndrome of menopause (GSM) in menopausal women.
Study design: 102 women presenting with symptomatic GSM were treated with the fractional CO_2 laser (MonaLisa Touch, DEKA) system across a series of treatments delivered at intervals of six or more weeks. The Australian Pelvic Floor Questionnaire was used to gather data on sexual function and side-effects at three time-points across the study period (prospective panel design study). Wilcoxon signed-rank tests were used to detect statistically and clinically significant changes in sexual function and side-effects occurring from pre- to post-treatment. The primary outcome of this study was an improvement of the symptoms of GSM. The secondary outcome included bladder function and prolapse symptoms.
Results: A total of 102 women suffering from moderate to severe GSM were recruited. Eighty-four percent experienced significant improvement in their symptoms after CO_2 laser treatment. Scores on measures of sexual function, dyspareunia, and bothersomeness of sexual issues were improved from pre-treatment to long-term (12–24 month) follow-up. Furthermore, there were improvements on measures of bladder function ($P = 0.001$), prolapse ($P = 0.001$), vaginal sensation ($P = 0.001$), vaginal lubrication ($P < 0.001$) and urge incontinence ($P = 0.003$) from the pre-treatment assessment to the second assessment (i.e. after the third treatment).
Conclusions: In this study, fractional microablative CO_2 laser treatment was associated with an improvement in symptoms of GSM and sexual function.

Introduction

Life expectancy for women has increased significantly during the past century and many women will now spend more than one third of their lives in menopause [1,2]. Many of these postmenopausal women, who expect to maintain good health and a high quality of life into their postmenopausal years, consider sexual health and relationship satisfaction to be of paramount importance.

The sexual health of postmenopausal women can be undermined by the progressive ageing of the body, as well as by genitourinary syndrome of menopause (GSM) [3]. GSM, previously known as atrophic vaginitis, is a multifaceted oestrogen-dependent condition which often occurs as a manifestation of meno-

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pause [4]. The fall in oestrogen resulting from menopause causes the vaginal epithelium to become thin and pale [1], lose vascularity, collagen fibres, leading to decreased engorgement, lubrication, and reduced elasticity. Vaginal smears of patients suffering from GSM demonstrate a unique morphology whereby superficial cells are scant and there is an increase in intermediate and parabasal cells in hypoestrogenemic conditions, which, along with decreased glycogen-rich cells, promotes increased vaginal pH [5]. These conditions increase the risk of developing symptoms such as dryness, burning, itching, irritation, abnormal discharge,recurrent thrush and dyspareunia, which are likely to cause an altered response to sexual stimuli [4]. This discomfort associated with intercourse often leads to a vicious cycle of decreased desire, arousal, orgasm and frequency of coitus, resulting in loss of self-confidence and depression throughout the pre- and postmeno- pausal stages [6].

It is estimated that about 8–22% of premenopausal women and 40–57% of postmenopausal women experience symptoms result-ing from GSM [7]. However, only 1 in 5 women experiencing these symptoms will consult a physician on issues related to GSM [1]. Current therapies for GSM include hormonal therapy with oestrogen alone (ET) and oestrogen-progestin therapy (EPT).Whilst these therapies may be effective in increasing vaginal lubrication and reducing dyspareunia, they have not been shown to consistently increase sexual desire or activity [8].

Due to embryological origin, the lower one third of the vagina(like the urethra and bladder) has fewer oestrogen receptors thanthe upper two thirds, which may impact the effect of hormonal therapy on the lower third [7,9]. For this reason, hormonal therapy is not particularly effective as a treatment for superficial dyspareunia. In addition, a subgroup of women demonstrates contraindications to hormonal therapy or experiences relapse shortly after treatment [8]. The rate of medical adherence to this line of therapy is quite variable (52–74%) mainly due to safety concerns, inconvenience, and inadequate symptom relief from available treatments [10,11]. There is a lack of long-term safety datafor vaginal hormonal therapy and the important question of whether it is safe to use local oestrogen treatment in cancersurvivors remains unanswered [2]. Regardless, patients diagnosed with breast cancer are often reluctant to use oestrogen treatment. Therefore, the need to consider non-pharmacological approaches is essential.

Fractional micro-ablative CO_2 laser represents one potential non-pharmacological approach to GSM. Broadly speaking, laser treatments employ heat to improve the collagen structure of tissue [12]. Fractional micro-ablative CO_2 laser achieves its effects by

Table 1
Summary of results from studies investigating fractional CO_2 laser as a treatment for GSM.

First author (year of publication)	Study population (n)	Treatment	Measures	Results
Salvatore [18]	Postmenopausal women (n = 50)	Fractional CO_2 laser	Vaginal dryness, vaginal burning, vaginal itching, dyspareunia, dysuria Vaginal Health Index (VHI)	At 12-week follow-up, statistically significant improvements in - VHI score ($p < 0.001$) - Vaginal dryness, burning, itching, dyspareunia, dysuria ($p < 0.001$).
Filippini [23]	Cancer patients and natural menopausal participants (n = 46)	Fractional CO_2 laser	Vaginal burning, vaginal dryness, vaginal itching, dyspareunia, heat, pain	Two months after the first treatment, improvements recorded in - symptoms of burning, dryness, dyspareunia, itching, heat, and pain (decreases ranged from 73.76% to 88.85%; statistical significance not reported).
Perino [22]	Postmenopausal women (n = 48)	Fractional CO_2 laser	Vaginal dryness, vaginal burning, vaginal itching, dyspareunia VHI	30 days after final laser application, statistically significant improvements in - VHI score ($p < 0.0001$) - Vaginal dryness, burning, itching, dyspareunia ($p < 0.0001$).
Pieralli [24]	Postmenopausal breast cancer survivors (n = 50)	Fractional CO_2 laser	VHI Dyspareunia	After three sessions, statistically significant improvement in - dyspareunia ($p < 0.0001$) At thirty days post-treatment, statistically significant improvement in - VHI score ($p < 0.0001$).
Sokol [25]	Women of mean age 58.6 (+/− 8.8 y; n = 30)	Fractional CO_2 laser	Vaginal burning, vaginal dryness, vaginal itching, dyspareunia, dysuria, pain VHI Female Sexual Function Index	At three-month follow-up, improvements in - vaginal burning, itching, dryness, dyspareunia, dysuria and pain (statistical significance not reported) - VHI score ($p < 0.001$) - Female Sexual Function Index ($p < 0.001$).
Pitsouni [21]	Postmenopausal women (n = 53)	Fractional CO_2 laser	Vaginal Maturation Value (VMV), VHI, sexual function, symptoms of GSM, Female Sexual Function Index (FSFI), International Consultation on Incontinence Questionnaire of Female Urinary Tract Symptoms (ICIQ-FLUTS) and Urinary Incontinence Short Form (ICIQ-UI SF), Urogenital Distress Inventory (UDI-6) and King's Health Questionnaire (KHQ).	At 12 week follow-up, MV, VHIS and FSFI increased significantly. Dyspareunia, dryness, burning, itching, dysuria, frequency, urgency, urgency incontinence, stress incontinence and scores on the ICIQ-FLUTS, ICIQ-UI SF, UDI-6 and KHQ decreased significantly

thermally altering only a fraction of the epidermal and/or dermal architecture, leaving intervening areas unaltered [13]. These intact areas allow for rapid healing of the tissue [13]. Modern fractionalmicroablative CO_2 lasers incorporate trains of very short high peak power pulses with long interpulse intervals; this modification allows for cleaner incision or ablation with less charring becauseeach pulse is shorter than the thermal relaxation time of the target tissue, so that optimum ablation and heat deposition is achievedwith minimal heat build-up in the adjacent tissue [14].

Fractional micro-ablative CO_2 has proved to be safe in remodelling tissue properties of many body regions, such as the skin of the face, neck and chest, and has the ability to produce new collagen and elastic fibres [15]. Within the atrophic vagina, fractional micro-ablative CO_2 treatment has been reported toproduce a thicker epithelium along with larger diameter epithelial cells rich in glycogen [16]. Further, this therapy has been shown to increase *Lactobacillus* and reduce vaginal pH [17].

To date, a handful of studies have investigated the short-termeffects of fractional CO_2 laser as a treatment for GSM (Table 1). These studies have demonstrated short-term improvements in Vaginal Health Index (VHI) scores, vaginal dryness, burning, itching, dyspareunia and dysuria, generally in postmenopausal samples.

The pilot study of 50 women conducted by Salvatore et al. [18] demonstrated that treatment with fractional CO_2 was feasible, safe and resulted in significant improvement of symptoms related to atrophy at 12 weeks' follow-up. These outcomes are reported to significantly improvement overall sexual satisfaction and qualityof life [18]. However, no study has assessed the long-term efficacy of fractional CO_2 laser treatment. The purpose of this study was toinvestigate the safety, feasibility and long-term efficacy (12–24 months) of fractional micro-ablative CO_2 treatment in a cohort ofpostmenopausal women suffering dyspareunia and/or other symptoms due to GSM. The primary objective focussed on improvement of GSM symptoms and sexual satisfaction. As a secondary end-point, we investigated any potential side-effects associated with the treatment, with a focus on bladder function symptoms of prolapse.

Materials and methods

Women with symptoms of genitourinary syndrome of meno-pause (GSM) who were not responding to or not able to take conventional treatments (such as oestrogen therapy for postmen-opausal women) were recruited to the study and underwent vaginal treatment with fractional CO_2 laser.

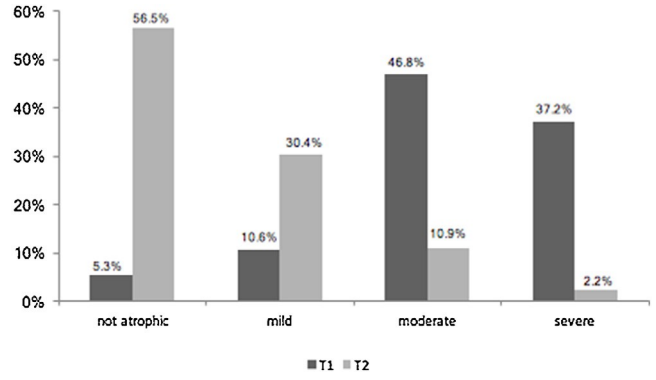

Fig. 1. Changes in severity of GSM symptoms between pre-treatment (T1; n = 94) and post-treatment assessment (T2; n = 92). Women were scored for GSM symptom severity pre- and post-treatment. Symptom severity was rated in the following categories: not atrophic, mild atrophy, moderate atrophy, or severe atrophy. The percentage of women in each category is shown.

Inclusion criteria included postmenopausal women aged between 51 and 86 years, and complaint of at least one of the following GSM symptoms: (1) vaginal dryness, and/or (2) dyspareunia. Exclusion criteria included unexplained bleeding, abnormal pap-smear, active genital infections or any kind of active cancer within the urogenital area. Patients undergoing any concomitant treatment throughout the study period were excluded.

At the first consultation, all the women were asked to provide written informed consent for their clinical data to be collected for the purpose of clinical quality study, and where applicable, for scientific presentation and/or publications. They were also asked to complete a validated interviewer-administered pelvic floor questionnaire (the Australian Pelvic Floor Questionnaire) [19] which integrates bladder, bowel, sexual function, pelvic organ prolapse, severity, bothersomeness and condition-specific quality of life, on a scale of 0–3 (see attached survey). A gynecologist (FBW) performed a colposcopy and graded the atrophy according to elasticity, fluid volume, epithelial integrity and moisture as per Bachmann to define atrophy on a modified four-point scale (not atrophic, mild, moderate and severe atrophy).

For analysis of treatment outcomes, intensity of GSM symptoms (vaginal dryness, vaginal dyspareunia, vaginal tightness, prolapse symptoms, bladder function and urge and stress incontinence) was recorded using measures of frequency and severity. Questionnaires were completed anonymously. Nurses collected each question-naire after completion and labelled it using a random computer-generated enrolment number. Clinical data and the questionnaire were collected at baseline before the first treatment (T1), between 2 and 4 months from initial treatment (T2), and between 12 and 24 months after the initial laser treatment (T3). The study received Human Research Ethics approval from Bellberry Limited (Applica-tion ID: 2016-04-293). Patients were not compensated for participation in this study.

Study protocol

Prior to laser treatment, all patients underwent colposcopy to stage and confirm atrophic vaginitis and to exclude other underlying pathology such as vulvar intraepithelial neoplasia (VIN) and lichen sclerosus. Pelvic ultrasound was carried out at baseline to assess and record endometrial thickness. Patients with a past medical history of genital herpes were given prophylactic antiviral medication. Each participant was treated with the fractional microablative MonaLisa Touch CO_2 laser system (SmartXide2 V_2LR, DEKA, Italy) with the following settings: power 30 W, dwell time 1000 ms, DOT spacing 1000 mm, SmartStak parameter 2, and D- pulse mode. The laser beam was emitted after the vaginal probe was inserted to the top of the vaginal canal, then rotated and withdrawn in order to provide complete 360^0 coverage of the vaginal wall. The vestibule and fourchette were treated with a 90^0 probe, with the following settings: power 20 W, dwell time 1000 ms, DOT spacing 1000 mm, SmartStak parameter 1, and D- pulse mode.

A silicon-based balm was used post-procedure to enhance wound healing and aid hydration of the skin. The balm was not used vaginally; rather, it was applied to the fourchette of the vagina. The balm contained a combination of physiologic lipids and botanical sterols and has been previously shown to reduce post-operative swelling, aid healing and reduce the risk infection following laser treatment [20].

Each patient received three fractional CO_2 vaginal laser treatments at intervals of six or more weeks. Follow-up was approximately 12 months after the initial treatment. The proce- dure was performed by one gynaecologist. Participants did not require any specific analgesia or anaesthesia. They were advised to

Table 2
Scores on sexual variables at pre-treatment (*T1*), after the third treatment (*T2*), and at the 12–24 month follow-up (*T3*). Changes are represented using Wilcoxon's signed-rank test scores.

	Median scores			Changes							
	T1	*T2*	*T3*	*Change T1-T2 (improvement% (n), Z, r, p)*				*Change T1-T3 (improvement%, Z, r, p)*			
				% (*n*)	*z*	*r*	*p*	% (*n*)	*z*	*r*	*P*
Sexual function	1	0	0	62 (66)	−4.66	0.40	<0.001	44 (25)	−2.82	0.39	0.005
Painful intercourse	2	1	1	66 (78)	−5.16	0.41	<0.001	71 (34)	−3.11	0.37	0.002
Sexual issues	2	1	1	50 (85)	−6.04	0.46	<0.001	48 (40)	−4.20	0.47	<0.001

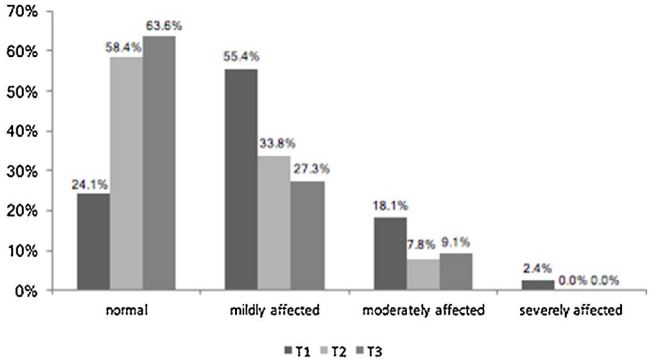

Fig. 2. Change in participants' sexual dysfunction scores at pre-treatment (T1;n = 83), after the third treatment (T2; n = 77), and at 12–24 month follow-up (T3; n = 33). Women rated their level of sexual dysfunction in the following categories:normal, mildly affected, moderately affected and severely affected. The percentageof women in each category is shown.

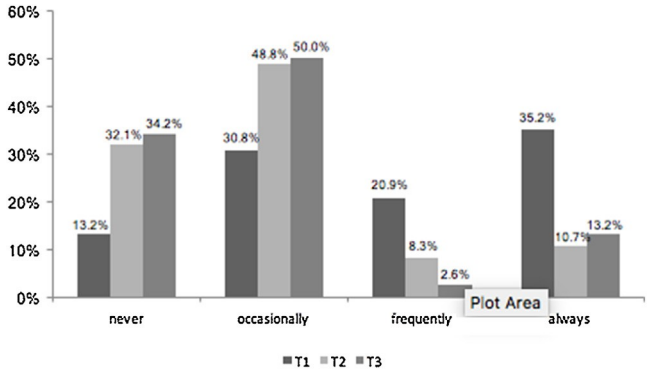

Fig. 3. Changes in the frequency of self-reported pain during intercourse at pre- treatment (T1; n = 91), after the third treatment (T2; n = 84), and at 12–24 month follow-up (T3; n = 38). Women rated the frequency of pain during intercourse in thefollowing categories: never, occasionally, frequently, and always. The percentage ofwomen in each category is shown.

avoid vaginal intercourse, bathing, and using the bath for at least5 days after each laser application, so as to allow tissue healing.

Statistical analysis

Based on the study by Pitsouni et al. [21] a sample size of 47 participants would be required to achieve 5% significance, 90% power and a hypothetical effect size of 0.5 (medium effect). Withthe expectation that there would be 50% attrition from the timeof recruitment to follow-up, we needed a minimum of 94 patientsenrolled in the study. Wilcoxon signed-rank tests were used to detect any statistically and clinically significant differences occurring from pre- to post-treatment. Statistical significance was set at 0.05. Data were analyzed using IBM SPSS software, version 21.0 (IBM, New York, NY).

Results

In this study, we recruited 102 postmenopausal women experiencing symptoms of GSM with an age ranging from 51 to 86 ($M = 61.00$; SD = 7.00). All the cases were postmenopausal.

Among women in study, common reasons given for discontinuing oestrogen therapy include (i) local side-effects (e.g. irritation, a sensation of burning), (ii) a desire to find out whether climacteric symptoms have ended, (iii) fear of breast cancer and (iv) fear of thrombo-embolism.

Changes in severity of GSM symptoms

Approximately 84% of the patients who suffered from moderate or severe GSM experienced an improvement in symptoms, moving into the 'mild' or 'not atrophic' categories following treatment (Fig. 1). A Wilcoxon signed-rank test revealed a statistically significant improvement in GSM symptoms following participa- tion in treatment, $z = 7.75$, $p \leq 0.001$, with a large effect size ($r = 0.57$). The median severity score decreased from pre-treatment (Md = 2) to post-treatment (Md = 0).

Sexual function

Median scores on sexual function variables at pre-treatment (T1), after third treatment (T2; 2–4 months after initial treatment), and at 12–24 month follow-up (T3) are shown in Table 2. Due to patient attrition, sample sizes are reported for each time-point. There were statistically significant improvements for all variables assessed, including scores on sexual function, painful intercourse, and other sexual issues including vaginal dryness and reduced libido.

There was an overall reduction in the participants' sexual dysfunction scores from T1 to T2, with an increase in the number of patients reporting "normal" sexual functioning from 24.1% at T1 to 58.4% at T2 (Fig. 2). This trend remained stable (63.6%) at T3 (12–24 month follow-up). The percentage of participants reporting mild, moderate and severe sexual dysfunction tended downwards from T1 to T3 (insert data?).

There was an overall improvement in participants' self-reported pain during intercourse (i.e. dyspareunia; Fig. 3), with an increase from 13.2% at T1 to 32.1% at T2 in the percentage of participants who self-reported "never" experiencing painful intercourse. The trend remained stable (34.2%) at T3.

This trend was mirrored by the percentage of participants self-reporting "bother" with sexual intercourse issues (Fig. 4).

Secondary effects

While the focus of the study was on GSM and sexual function, we also investigated several effects of the laser treatment among

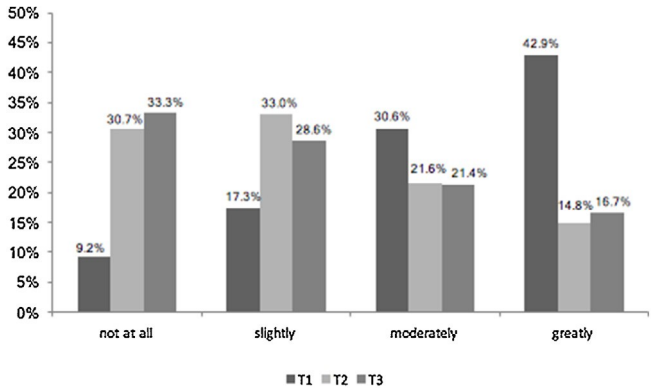

Fig. 4. Extent to which patients reported that sexual issues were bothering them at pre-treatment (T1; n = 98), after the third treatment (T2; n = 88), and at 12–24month follow-up (T3; n = 42). Women rated how bothersome sexual issues were according to the following categories: not at all, slightly, moderately or greatly. Thepercentage of women in each category is shown.

women with urinary incontinence issues or prolapse. Other variables from the Australian Pelvic Floor Questionnaire were analysed using Wilcoxon's signed-rank test (Table 3). There were significant improvements from T1 to T2 on indices of prolapse, vaginal sensation, vaginal lubrication, bladder function, and urge incontinence. These improvements were also observed at T3.

We observed complications in a small number of patients. Following treatment, three women experienced post-coital urinary tract infections and two experienced vaginal discharge/infection; all of them required antibiotic treatment. Three women experienced lower pelvic pain for two to three days, and required simple analgesia (such as ibuprofen). One patient (who had failed to inform us about her past medical history of genital herpes) had a genital herpes breakout following treatment. Finally, two women presented with postmenopausal bleeding following their third laser treatment (at 4 months and 6 months respectively). Investigation of the endometrial thickness revealed and increase in their endometrium from 3 mm to 5 mm. Their endometrial biopsies were benign. The increase in endometrial thickness may be coincident, or may be related to revitalisation and rejuvenation occurring beyond the vagina following laser treatment.

Discussion

Fractional CO_2 laser treatment has displayed a good safety profile [13,22] though there is a need for larger-scale studies to assess the risk/benefit profile of this treatment in patients with GSM [18]. This study is the first to assess the long-term effects of fractional microablative CO_2 laser treatment on GSM symptoms, sexual function, bladder-related issues, and prolapse in postmenopausal women who had failed to respond to oestrogen therapy. Previous pilot studies of fractional microablative CO_2 laser in GSM patients have tended to adopt the Vaginal Health Index (VHI) and/or a Visual Analogue Scale (VAS) to measure symptom intensity.

To the best of our knowledge, this is the first study of its kind to employ the Australian Pelvic Floor Questionnaire, to record changes in general bladder function, sexual function, urge incontinence and prolapse following fractional microablative CO_2 treatment.

In the short term (2–4 months after the initial treatment), we observed significant improvements in sexual function, dyspareunia, sexual issues, bladder function, prolapse symptoms, vaginal sensation and lubrication, and urge incontinence. From baseline to long-term follow-up (between 12 and 24 months), we recorded statistically significant improvements in all above mentioned variables. This indicates that the improvements observed in the short term were maintained at long-term follow-up.

It is likely that these positive effects observed at follow-up in postmenopausal women were due to the alleviation of urogenital symptoms and the restoration of genital tissue viability. Our current data provide evidence for the efficacy of fractional microablative CO_2 laser treatment in improving symptoms associated with GSM and quality of life at short- and long-term follow-up. These results are consistent with those of Salvatore et al. [18], Filippini & Farinelli [23], Perino et al. [22], Pieralli et al. [24], and Sokol et al. [25]. The size of the cohort within this study adds strength to the findings, and the long-term follow up demonstrates long-term efficacy of this therapy [18,22–25]. To the best of our knowledge, this is the first study of its kind to be completed in Australia.

The high rate of women with improved sexual function as well as the reduction in pain and irritation experienced by patients following intercourse further supports the use of fractional microablative CO_2 laser as a treatment for GSM in postmenopausal women. Specific factors related to sexual function, such as vaginal lubrication and vaginal tightness, improved following treatment. This demonstrates the multi-modal ability of this technique to treat a wide range of symptoms. Although not the primary outcome of this study, the improvement in prolapse symptoms, impaired bladder function, urge and stress incontinence were interesting outcomes of this study. It is possible that fractional microablative CO_2 laser is also improving the general comfort and self-confidence of patients, thus further contributing to their enhanced sexual function.

One limitation of our study was the high attrition rate; participant responses decreased by less than half from the third treatment to the 12–24 month follow-up, making it difficult to be confident in the soundness of comparisons from baseline to the final follow-up. However, we recruited a larger number of participants that previous studies in anticipation of patient attrition during follow-up. Another weakness of this study is the absence of a control group receiving either a placebo or hormonal treatment. However, these data combined with the other short-term studies using fractional CO_2 laser treatment provide evidence to warrant a randomised controlled trial. Furthermore, it would be of interest to extend the use of fractional CO_2 lasers to women with severe contraindications to hormonal treatments, such as cancer survivors who lack long-term safety data for hormonal therapy.

Table 3
Description of positive side-effects at pre-treatment (*T1*), after the third treatment (*T2*), and at the 12–24 month follow-up (*T3*).

	Median scores			Changes							
	T1	*T2*	*T3*	*Change T1-T2 (improvement% (n), Z, r, p)*				*Change T1-T3 (improvement% (n), Z, r, p)*			
				% (*n*)	*z*	*r*	*p*	% (*n*)	*z*	*r*	*p*
Prolapse symptoms	0	0	0	69 (86)	−3.26	0.25	0.001	82 (38)	−3.08	0.36	0.002
Vaginal sensation	0	0	0	61 (96)	−3.24	0.23	0.001	63 (46)	−2.69	0.28	0.007
Vaginal lubrication	1	0	0	26(78)	−3.90	0.31	<0.001	36 (34)	−2.53	0.34	0.011
Bladder function	0	0	0	77 (74)	−3.27	0.27	0.001	77 (39)	−2.17	0.25	0.029
Urge incontinence	1	0	0	51 (97)	−2.92	0.29	0.003	53 (48)	−3.64	0.37	0.000

Nevertheless, this study demonstrates that fractional CO_2 laser treatment can provide long-term improvements in the GSM symptoms for postmenopausal women, and these data combined with the other short-term studies using fractional CO_2 laser treatment provide sufficient evidence to warrant a randomised controlled trial. The results of this study are encouraging in that women with age-related GSM who are normally unresponsive to oestrogen therapy experienced noticeable improvements in their sexual function, dyspareunia and the overall severity of symptoms associated with this condition.

In conclusion, the present study demonstrates that fractional micro-ablative CO_2 laser promises to offer an effective, safe and non-invasive treatment alternative for GSM, with improvements in sexual function, reduced symptoms of dyspareunia following intercourse and an overall satisfaction with sexual life in postmenopausal women suffering from GSM. This study adds to the current literature by providing pioneering evidence into the long-term effects of ongoing treatment with fractional micro-ablative CO_2 lasers. The results of this study are encouraging in that they present an alternative treatment to topical estrogen in women who are nonresponsive and/or noncompliant, as well as women who have been advised not to use E2 or those high-risk women who are worried about possible side effects.

Disclosures

The authors have not conflict of interest. FBW is a preceptor for Monalisa and runs laser workshops for the company. FBW is paid to run these teaching workshops but received no support, financial or otherwise, to run this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejogrb.2017.03.036.

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Chapter 9: Fractional CO2 Laser forTreatment of Stress Urinary Incontinence

9.1 Introductory Comments

Two common forms of urinary incontinence are urge urinary incontinence (UUI) and stress incontinence (SUI). As discussed in detail in **Chapter 1**, UUI is characterised by the involuntary loss of urine associated with urgency, frequency, and nocturia, triggered by a hypersensitive detrusor muscle. Patients often report triggers of UUI by events such as running water, handwashing, orgasm, changes in posture or position, and even changes in temperature [1, 2]. SUI is the unintentional loss of urine, as a result of physical movement or activities that put pressure on the bladder such as, coughing, laughing, sneezing, heavy lifting, jumping and running. SUI is the consequence of weakened or damaged urethral sphincter and/or the pelvic floor muscles, such that they cannot dependably hold urine [3, 4]. In women, childbirth is a common cause of SUI due to tissue and nerve damage sustained during delivery. Other factors include chronic coughing, menopause, obesity, constipation, and engaging in high-impact activities such as running and jumping [1, 3, 5]. Both UUI and SUI can have a profound impact on a woman's quality of life, and it often results in avoiding social activities out of fear of incontinence related embarrassment. The gold standard for diagnosis is to perform a urodynamic study. A helpful tool in diagnosis is to also have the patient keep a bladder diary.

Treatment options for UUI and SUI are listed in Table 1. Treatment efficacy and success is measured by a patient's report on the reduction of symptoms and subsequent urodynamic studies. Unfortunately, the clinical success of available treatments is highly variable and largelydependent on patient compliance and cooperativity, especially for first-line treatments. Furthermore, when there is the need to pursue second- to last-line treatments, this involves theuse of hormonal preparations and surgical procedures that become increasingly invasive in their nature. From my years of experience as gynaecologist and from my review of the literature, it is clear new first-line minimally invasive solutions are needed. The focus of the studies presentedin this thesis investigate the efficacy and safety of Platelet-Rich-Plasma (PRP) therapy and Fractional CO_2 Laser ($FxCO_2$) as potential minimally invasive first-line solutions for treatingUUI and SUI.

Fractional CO_2 Laser ($FxCO_2$) as potential minimally invasive first-line solutions for treating UUI and SUI.

Table 1: Treatment options for UUI and SUI.

	UUI	**SUI**
First-line	*Lifestyle modifications:* reduce intake of caffeine, alcohol, andacidic foods, take supplementalmagnesium. *Behavioural techniques:* Kegalexercises, double voiding, scheduled toilet trips, bladder training. Hormone replacement therapy: low-dose topical estrogen,	*Lifestyle modifications:* quit smoking, weight loss, treating a chronic cough, reduced caffeine andalcohol intake, high-fibre diet (to avoid constipation), low-impact exercise. *Behavioural techniques:* Kegalexercises, bladder training
Second-line	Anticholinergics: oxybutynin (Ditropan XL), tolterodine (Detrol), darifenacin (Enablex)	Vaginal pessary Urethral inserts
Third-line	Percutaneous Tibial NerveStimulation (PTNS) Intravesical botulism toxin	

	A(‘Botox’) injections	
Last-line	Sacral Neuromodulation (SNM) *Major surgery:* detrusor myomectomy, augmentation cystoplasty, urinary diversion, continent urinary diversion	*Major surgery:* Sling procedure,Laparoscopic Burch colposuspension (LBC)

9.2 Aim

To evaluate the impact of trans-vaginal fractional CO2 laser treatment on symptoms of stress urinary incontinence (SUI) in women.

9.3 Summary

Study design: Women clinically diagnosed with SUI preferring non-surgical treatment were recruited to the study. Fractional CO2 laser treatments were utilised trans-vaginally every 4–6 weeks for a total of three treatments. Response to treatment was assessed at baseline (T1), at 3 months after treatment completion (T2) and at 12–24-month follow-up (T3) using the Australian Pelvic Floor Questionnaire (APFQ). The primary outcome was changes in reported symptoms of SUI. Secondary outcomes assessed included bladder function, urgency, urge urinary incontinence (UUI), pad usage, impact of urinary incontinence on quality of life (QOL) and degree of bothersome bladder. This study suggests that fractional CO2 laser is a safe, feasible, and beneficial treatment for SUI.

9.4 Publication used in this chapter:

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9.5 Author contribution

I was responsible for (100%) the concept and design of research and data collection and 40% of writing forthe publication. Alan Lam was responsible for (30%) of writing and editing. Behrang Mohammadi (100%) was responsible for the data analysis and Tran T.T. Nguyen was responsible for (50%) writing and editing and proofreading.

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Fractional CO_2 laser for treatment of stress urinary incontinence

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ABSTRACT

Objectives: To evaluate the impact of trans-vaginal fractional CO_2 laser treatment on symptoms of stress urinary incontinence (SUI) in women.
Study design: Women clinically diagnosed with SUI preferring non-surgical treatment were recruited to the study. Fractional CO_2 laser system (MonaLisa T, DEKA) treatments were administered trans-vaginally every 4–6 weeks for a total of three treatments. Response to treatment was assessed at baseline (T1), at 3 months after treatment completion (T2) and at 12–24-month follow-up (T3) using the Australian Pelvic Floor Questionnaire (APFQ). The primary outcome was changes in reported symptoms of SUI. Secondary outcomes assessed included bladder function, urgency, urge urinary incontinence (UUI), pad usage, impact of urinary incontinence on quality of life (QOL) and degree of bothersome bladder.
Results: Fifty-eight women were recruited and received the study treatment protocol. Eighty-two percent of participants reported an improvement in symptoms of SUI at completion of treatment (mild to no SUI) ($p = <0.01$). Treatment effect waned slightly when assessed at follow-up. Nevertheless, 71% of participants reported ongoing improvement in SUI symptoms at 12–24 months ($p < 0.01$). All secondary outcome measures were improved after treatment compared to baseline.
Conclusions: This study suggests that fractional CO_2 laser is a safe, feasible, and beneficial treatment for SUI and may have a role as a minimally-invasive alternative to surgical management.

Introduction

Urinary incontinence (UI), defined as the complaint of any involuntary leakage of urine, affects nearly 40% of women; stress urinary incontinence (SUI) accounts for approximately half of all UI [1]. UI significantly impacts on quality of life, affecting the woman's physical, mental, social and sexual well-being and leading to avoidance of intimacy, depression and social isolation [2–4]. In addition, the economic impact of UI was estimated to be $710 million in 1998 and was projected to be $1.6 billion by 2009 in Australia [5].

Surgical options for SUI include trans-vaginal insertion of amid-urethral sling (MUS) and the more invasive, traditional gold-standard Burch colposuspension procedure, requiring an abdominal approach (laparotomic or laparoscopic). With similar success rates of 74–90% and similar longevity, the choice of one procedure over the other often depends on surgical training, experience, and preference [6]. A systematic review suggests MUS to be a superior surgical treatment, which has rapidly become the procedure of choice for SUI due to shorter operating time and quicker patient recovery; there are nevertheless inherent surgical risks applicable to both procedures, including bleeding, infection, bladder and urethral injury, voiding dysfunction and pain [7].

In 2016, the US Food and Drug Administration (FDA) reclassified the use of mesh kits in urogynaecology as Class III medical devices requiring pre-market approval [8]. The resultant media attention and class actions against manufacturers of these devices has resulted in the withdrawal of most pelvic organ prolapse (POP) mesh devices from the market [9]. Thus, there is strong publicinterest in and a clinical need for a minimally-invasive, non- hormonal, effective treatment for SUI.

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Fractional micro-ablative laser therapy has been shown to be a potential non-surgical treatment alternative for SUI [10,11]. The subclinical thermal tissue effect from the laser beam induces human dermal fibroblasts to initiate an inflammatory healing cascade, stimulating de novo collagen and elastin synthesis resulting in a thicker vaginal epithelium with larger diameter, glycogen-rich epithelial cells [12–14].

The aim of this study is to evaluate the change in SUI symptoms after trans-vaginal fractional micro-ablative CO_2 laser in women at baseline, compared to follow-up at 3 months and 12–24 months post-treatment.

Materials and methods

This is a prospective observational study on women with SUI symptoms who were treated with trans-vaginal fractional CO_2 laser. The study received Human Research Ethics approval from Bellberry Limited (Application ID: 2016-04-293). All participants provided informed, written consent; participants were not compensated for their participation.

Study population

During 2014–2017, all women aged 18 years or more being treated by a single gynaecology consultant at FBW Gynaecology Plus were invited to participate in the study. Inclusion criteria were no/unsatisfactory response to conservative treatments and a preference for non-surgical management of bothersome SUI symptoms. The women also demonstrated a positive cough test and urethral hypermobility on ultrasound. All women that participated were offered urodynamic studies and encouraged to continue with topical oestrogen therapy and pelvic floor muscle exercises. Women with stage II pelvic organ prolapse quantification system (POPQ) score, acute or recurrent urinary tract infections, pregnancy, current malignancy, known cervical dysplasia or undiagnosed abnormal uterine bleeding were excluded. All participants were asked to complete the bladder function section of the Australian Pelvic Floor Questionnaire (APFQ) (Appendix A) at baseline (T1), 3 months after third treatment (T2), and at 12–24 months' follow-up (T3). The APFQ is a validated self-administered pelvic floor questionnaire utilised for quantification of clinical and research outcomes [15]. The primary outcome of this study is to describe the change in self-reported SUI symptoms based on question 6 of APFQ.

The secondary outcomes were bladder function, urgency, urge incontinence, pad usage, quality of life, degree of bothersome bladder score as assessed by APFQ. Improvement of SUI was calculated based on severity scoring 0-3. Bladder function score was calculated by adding all 15 questions in the bladder subsection of APFQ, with maximum score of 45. Scores 0–11.25 was normal bladder function, 11.26–22.5 was mild bladder dysfunction, 22.6–33.75 was moderate bladder dysfunction, and 33.76–45 was severe bladder dysfunction. Questionnaires were distributed to participants and collated by practice staff; the identity of individual respondents remained blinded to the investigators.

Intervention

The intervention was carried out at the FBW Gynaecology Plus office. Participants were pre-treated with topical anaesthetic cream at the level of vestibulum. After 10 min, they were treated with trans-vaginal fractional micro-ablative CO_2 laser system (MonaLisa Touch, SmartXide2 V2LR, DEKA, Italy) using the following settings: power 40 W, dwell time 1000 ms, DOT spacing 700 mm, SmartStak parameter 3 and D-pulse mode. The laser beam was emitted from a 90 vaginal probe gently inserted up to the level of the bladder neck, then rotated and withdrawn in order to provide treatment of the anterior lower one third of the vagina and external urethral meatus. Each patient also received three total vaginal length laser treatments with a 360-degree probe as per Salvatore et al. [15]. Three treatments were delivered at intervals of 4 to 6 weeks.

Patients were advised to abstain from vaginal intercourse for 5 days after laser application and avoid heavy lifting (>1 kg) for 6 weeks. Participants with a past history of genital herpes were given antiviral prophylaxis 2 h prior to laser treatment.

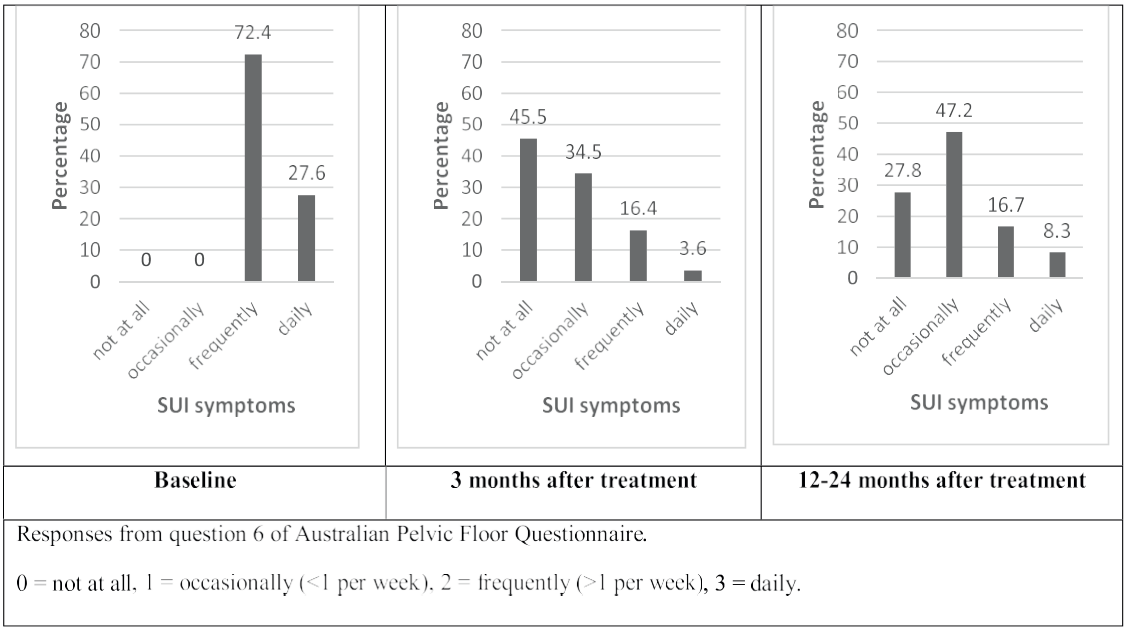

Fig. 1. Changes in stress incontinence symptoms in women who underwent fractional CO_2 laser at pre-treatment (T1; n = 58), 3 months post-treatment (T2; n = 55), and 12–24-month post-treatment (T3; n = 36).

Statistical analysis

Power analysis showed that a sample size of 29 participants would be required to achieve 5% significance, 80% power. Wilcoxon signed-rank tests were used to detect differences for the primary and all secondary outcomes. The threshold for statistical significance was set at 0.05. Data were analysed using IBM SPSS software, version 21.0 (IBM, Chicago, Illinois)

Results

Fifty-eight women were recruited to the study with an average age of 57.4±11.4 years (30–85 years); 45 (77.6%) were postmenopausal, 44 (75.9%) women were on vaginal oestrogen and 33 (56.9%) women underwent urodynamic studies, which confirmed SUI. There were 54 women who were followed-up at 3 months (T2) and 36 at 12–24 months (T3).

In relation to the primary outcome (question 6 of APFQ), Fig. 1 illustrates the reduction in SUI symptoms reported by women at follow-up (T2 and T3) compared to baseline (T1). At T1, all 58 participants reported frequent or daily SUI symptoms. At T2, 80% (44 of 55) reported an improvement in SUI symptoms, which included 45.5% (25 of 55) participants reporting no SUI symptoms, 16.4% (9 of 55) participants reported frequent symptoms, 3.6% (2 of 55) reported daily symptoms. These changes were also reflected in the median score reduction for Q6 ($p < 0.01$).

At T2 (3 months); 27 of the 36 women (75%) that returned reported SUI symptoms 'not more than occasionally,' including 10 of the 36 (27.8%) (T3) who reported no symptoms. These women also had a negative cough test at the time of clinical examination. The remaining 9 of the 36 (25%) women experienced a return of occasional SUI symptoms.

Similar results were demonstrated for secondary outcomes of bladder function (APFQ questions 1–15), urge incontinence (APFQ question 5) and bothersome bladder (APFQ question 15). Normal bladder function increased from 31% (18 of 58) at T1 to 72.2% (39 of 54) at T2. This trend decreased to 69.4% (25 of 36) at T3. There was an overall improvement in participants' urge incontinence scores from T1 to T2, with an increase in the number of patients reporting "never" leaking urine when they rush to the toilet from T1 to T2 (19% to 60%, $p < 0.01$); this trend decreased slightly to at T3 (44.4%, $p < 0.01$). There was an improvement in the participants' degree of bothersome bladder from T1 to T2; more women reported "not at all (bothersome)" from T1 to T2 (3.4% to 50%, $p < 0.01$); this trend reduced at T3 (36%, $p = 0.01$). The results are summarised in Table 1.

Women lost to follow-up were contacted to offer review. Upon phoning 22 of the 58 patients to arrange the 12-month follow-up, 5 participants reported no further SUI symptoms (cured) and 3 participants reported 50–60% improvement of their SUI symptoms which they deemed manageable. There were another 14 women who did not improve after 3 sessions of CO_2 laser treatment, 4 of whom opted for MUS surgery and some women desired to avoid surgery by undergoing autologous cell therapy, such as platelet-rich plasma (RegenPRP+).

There were no serious adverse events as a result of the treatment protocol. Out of 58 participants, 3 (5.4%) participants noticed a change in vaginal discharge diagnosed as thrush, which resolved with treatment; 2 (3.4%) participants reported symptoms of urinary tract infections (both of these patients had previous history of post-coital UTIs) and were treated with appropriate antibiotics; 1 (1.7%) participant developed a recurrence of genital herpes and required antiviral therapy.

Comments

This study describes the change in prevalence of SUI symptoms before and after fractionated CO_2 laser to treat both pre- and post-menopausal women with SUI. The study showed that following 3 treatments at 4–6-week intervals, SUI symptoms improved in 80% of participants at 3 months ($p < 0.01$) and that these benefitspersisted in 75% of participants at 12 months ($p < 0.01$).

SUI is a significant condition affecting women with their physical, mental and social well-being [1,2]. Women who seek non-surgical treatment are presented with a limited range of low-risk treatment options, such as pelvic floor muscle strengthening and vaginal pessaries [17]. For women who are sexually active, vaginal pessaries can pose coital problems. In addition, pessaries can be problematic for women with severe vaginal atrophy and mobility issues, as the need for regular examinations can be traumatising, painful and requiring concomitant topical oestrogen therapy.

Topical oestrogen therapy has been shown to provide modest treatment benefits for women experiencing UI, mostly improving urinary urgency and frequency related symptoms [18]. Recent literature suggests that topical oestrogen does not increase incidence of oestrogen-dependent malignancies, cardiovascular or thromboembolic complications [19]. However, women with a personal history of these conditions, especially breast cancer, are often advised to avoid any hormonal treatment and many others still decline, leaving them with few alternatives for management of their SUI. Furthermore, topical oestrogen benefits only last while the product is being applied, which requires patient compliance.

Since the 1990s, surgical management of SUI has shifted from the more invasive traditional Burch colposuspension to increasing use of the MUS, due to shorter operating time and fewer complications (except for bladder injury) with improved outcomes

Table 1
Outcomes for women who underwent fractional CO_2 laser at pre-treatment (T1) compared to 3 months after treatment (T2) and 12–24 months after treatment (T3).

	APFQ	Improvement % (n)	Median T1	Median T2	p-value	Improvement % (n)	Median T1	Median T3	p-value
Primary outcome									
Stress incontinence	6	80 (55)	2	1	<0.01	75 (36)	2	1	<0.01
Secondary outcomes									
Bladder Function	1-15	67 (54)	1	0	<0.01	87.5 (36)	1	0	<0.01
Urge incontinence	5	79 (55)	2	0	<0.01	63 (36)	2	1	<0.01
Urgency	4	65 (55)	2	1	<0.01	45 (36)	2	1	<0.01
Wearing pads	10	54 (55)	2	0	0.01	46 (36)	2	0	0.01
Impact of urinary leakage on QOL	14	63 (55)	1	0	<0.01	44 (36)	1	0	0.01
Degree of bothersome bladder	15	56 (54)	2	1	<0.01	45 (36)	2	1	<0.01

APFQ = Australian Pelvic Floor Questionnaire.
STD = Standard deviation.
$p < 0.05$ as statistically significant.
Differences were assessed by Wilcoxon sign-rank testing.

[7]. Furthermore, recent FDA statements, TGA withdrawal of mesh products, class actions, and media focus on mesh in urogynaecological procedures has seen a strong public reaction against mesh. There is a 2.4–9.8% risk of mesh erosion after MUS insertion with higher erosion rates after use of transvaginal mesh in POP surgery [20–23].

Trans-vaginal fractionated CO_2 laser treatment has been shown to improve vaginal tissue health in women with vaginal atrophy [12]. Since 2014, a growing number of studies have been published exploring the use of trans-vaginal laser treatment for gynaecogical conditions such as SUI, mixed UI (MUI) and genitourinary symptoms of menopause (GSM) [16,25]. Salvatore et al. first published a pilot study of 50 women with GSM who were dissatisfied with topical oestrogen therapy. Following three treatments with fractional CO_2 laser, the outcomes were assessed with the Vaginal Health Index Score (VHIS) and Short Form-12 Quality of Life (SF-12 QOL) survey. They found significant improvements in the symptoms and impact of GSM on QOL by all measures assessed at 12 weeks [15]. Behnia-Willison et al. showed in a study treating 102 women with GSM with fractional CO_2 laser having improvements up to 24 months by colposcopic examinations and responses to APFQ [24].

Regarding use of laser for UI, Ogrinc et al. recruited 175 women with symptoms of SUI or MUI. Their treatment protocol included an erbium-doped yttrium-aluminium-garnet (Er:YAG) laser to deliver both non-ablative full circumferential vaginal and fractionated anterior vaginal wall treatment; this significantly improved symptoms in 77% of women with SUI and 34% of women with MUI [26]. Two other prospective cohort studies using Er:YAG laser to treat SUI showed similar positive results [26,27]. This study builds on data from other prospective cohort studies showing that Er:YAG vaginal laser treatment was able to significantly improve symptoms of SUI short-term (up to 12 months) as assessed by the International Consultation on Incontinence Questionnaire (ICIQ) and the Incontinence Severity Index (ISI) [27]. Similarly, Isaza et al. demonstrated long-term benefits up to 36 months after CO_2 laser for women with mild SUI and GSM [28]. Hence, the treatment poses minimal risks and this study also adds to data demonstrating a good safety profile with trans-vaginal use.

The purpose of this study was to include women who were still symptomatic after first line conservative treatment, including pelvic floor exercises and vaginal oestrogen therapy, and desired to have an alternative non-surgical therapy. Whilst a blinded RCT would be ideal, data from this observational study suggests that fractionated CO_2 laser treatment of the vagina results was able to produce comparable outcomes to MUS procedures, with ongoing improvement of SUI symptoms at 12–24 months. It is most likely that maintenance CO_2 laser therapy is required. Due to individual ageing pattern and menopause effect and uncertain treatment intervals after T3, further studies are required.

Limitations of the study include the study design and attrition rate. We experienced a high attrition rate for responses from T1 (n = 58) to T3 (n = 36), which introduces a possibility of attrition bias and can weaken the strengths of our findings. At T2, all patients attended follow-up but 3 patients did not complete the data. At T3, there was 62% of women who attended follow-up. Another limitation was our primary outcome being based on a subjective measure reported by participants and objective biases. In addition there are well known placebo effects with the use of new medical devices. However, the strength of this study is the potential to develop a another non-surgical treatment option for symptomatic SUI. The first line treatment includes oestrogen cream for vaginal atrophy, pelvic floor muscle training, and lifestyle optimisation. The second line treatment includes CO_2 laser treatment +/- platelet-rich plasma (PRP). Then third line treatment would be surgery.

In summary, micro-ablative fractional CO_2 laser treatment appears to be a promising, non-surgical, non-hormonal, minimally invasive, durable, low risk treatment option for women with SUI. The safety this treatment modality and the reduced prevalence as per self-reported SUI symptom reduction from baseline suggests a possible alternative for women with SUI who are unwilling to accept the inherent risks of MUS and Burch colposuspension, or whose medical comorbidities exclude surgical treatment. Further research should compare the use of fractionated CO_2 laser with placebo and/or established treatments, as well as determine whether booster treatment is required to sustain improvements in SUI symptoms longer term.

Disclosures

The authors have no conflict of interest. FBW is a preceptor for MonaLisa Touch and runs laser workshops for the company. FBW is paid to run these teaching workshops but received no support, financial or otherwise, to run this study.

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Conflict of interest

The authors have no conflicts of interest to declare.

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Appendix A. Australian Pelvic Floor Questionnaire – Bladder Function Items

Questionnaire item	Response options			
APFQ1. How many times do you pass urine in the day?	(0) Up to 7	(1) Between 8-10	(2) Between 11-15	(3) More than 15
APFQ2. How many times do you get up at night to pass urine?	(0) 0–1	(1) 2 times	(2) 3 times	(3) More than 3 times
APFQ3. Do you wet the bed before you wake up at night?	(0) Never	(1) Occasionally–less than once per week	(2) Frequently–once or more than per week	(3) Always–every night

APFQ4. Do you need to rush or hurry to pass urine when you get theurge?	(0) Never	(1) Occasionally	(2) Frequently	(3) Daily

cough test and bladder neck funnelling by the treating specialist; only 33 participants agreed to undergo urodynamic studies. The remaining participants declined this test due to invasiveness and social circumstances, such as cost and insurance cover. There were

APFQ5. Does urine leak when you rush or hurry to the toilet? i.e. You can't make it in time?	(0) Never	(1) Occasionally–less than once per week	(2) Frequently–more than once per week	(3) Daily

4 participants who underwent urodynamics and surgical management which had resolved their SUI symptoms. Another limitation is that this is an uncontrolled study and subjected to the usual

APFQ6. Do you leak urine with coughing,	(0) Not at all	(1) Occasionally	(2) Frequently	(3) Daily

(*Continued*)

Questionnaire item	Response options			
sneezing, laughing or exercising?				
APFQ7. Is your urinary stream (urine flow) weak, prolonged or slow?	(0) Never	(1) Occasionally–less than once per week	(2) Frequently–more than once per week	(3) Daily
APFQ8. Do you have a feeling of incomplete bladder emptying?	(0) Never	(1) Occasionally–less than once per week	(2) Frequently–more than once per week	(3) Daily
APFQ9. Do you need to strain to empty your bladder?	(0) Never	(1) Occasionally–less than once per week	(2) Frequently–more than once per week	(3) Daily
APFQ10. Do you wear pads because of urinary leakage?	(0) None-never	(1) As a precaution	(2) When exercising/ during a cold	(3) Always
APFQ11. Do you limit your fluid intake to decrease leakage?	(0) Never	(1) Before going out/ socially	(2) Moderately	(3) Daily
APFQ12. Do you have frequent bladder infections?	(0) No	(1) 1–3 per year	(2) 4–12 per year	(3) More than once per month [16]
APFQ13. Do you have pain in your bladder or urethra when you empty your bladder?	(0) Never	(1) Occasionally–less than once per week	(2) Frequently–more than once per week	(3) Daily
APFQ14. Does the urine leakage affect your routine activities like recreation, socialising, sleeping, shopping, etc.?	(0) Not at all	(1) Slightly	(2) Moderately	(3) Greatly
APFQ15. How much does the bladder problem bother you	(0) Not at all	(1) Slightly	(2) Moderately	(3) Greatly

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Chapter 10: Promising Impact of Platelet Rich Plasma and Carbon Dioxide Laser for Stress UrinaryIncontinence

10.1 Introductory Comments

As previously mentioned in Chapter 9, treatment options for UUI and SUI are listed were presented in detail. This chapter describes the potential role of combined PRP and FxCO2 laser for SUI.

10.2 Platelet-Rich-Plasma Therapy and Fractional CO2 Laser

PRP therapy and/or $FxCO_2$ laser are appealing options for the treatment of SUI, as it may be possible to prevent the need for surgical intervention. PRP and $FxCO_2$ laser are thought to create a better support around the neck of the bladder by repairing and regenerating the surrounding tissue. Stimulation of collagen is thought to create a 'biological' sling andimproved connective tissue quality, enabling better support of the bladder neck, and normalising the anatomy to prestress incontinence states and thus preventing involuntary leakage of urine.

The use of PRP therapy and/or $FxCO_2$ laser are also appealing options for the treatment of UUI, as it removes the need for multiple treatments while also being suitable for those patientsthat cannot use HRT. While it is not fully understood as to how PRP therapy and/or $FxCO_2$ laser stimulate tissue repair for UUI, it is thought that by correcting the vaginal mucosa thickness, improving lubrication, and reducing the vaginal pH, this may alleviate some of the irritation and subclinical infection that could give rise to urgency.

Together, PRP therapy and $FxCO_2$ laser have synergistic properties that can accelerate tissue repair, fibroblast proliferation, and increase collagen production [75]. The combination of PRP therapy and $FxCO_2$ laser is superior to individual treatments due to antibacterial and anti-inflammatory properties of PRP as shown for treatment of wrinkles, scars, and hyperpigmentation [76]. Combinational $FxCO_2$ laser and PRP therapy has achieved effective repigmentation, while $FxCO_2$ laser alone, showed poor improvement [1, 2]. Furthermore, $FxCO_2$ laser and PRP therapy followed by sun exposure could be used to effectively and safely

treat refractory nonsegmental vitiligo Recently, the application of combining of these two therapies showed promising effect in treating GSM and SUI symptoms [3, 4].

The UUI (2021) paper presents the results of a single-centre prospective cohort study to evaluate the safety, feasibility, and efficacy of transvaginal $FxCO_2$ laser in combination with PRP for the treatment of 121 women with refractory UUI, with urinary function and sexual function as secondary outcome measures. Each participant underwent three sessions of transvaginal $FxCO_2$ laser and PRP treatment, administered at 4–6-week intervals. Outcomes were assessed using the bladder function section of the Australian Pelvic Floor Questionnaire (APFQ) at baseline, 3-6 months, and 12 months follow-up. A statistical analysis of the APFQ responses, revealed a significant reduction in the average severity of all self-reported measures of primary and secondary outcomes from baseline to 3-6 months. Improvements in all bladder function outcomes remained statistically significant at 12 months follow-up, and no adverse events were recorded for this cohort. The conclusion was that $FxCO_2$ laser with PRP appears to be a safe, feasible, and effective treatment for UUI, bladder function, and sexual function, such that it may have a role as an alternative therapy for severe and refractory UUI.

10.3 Aim

To evaluate the safety, feasibility, and efficacy of trans-vaginal fractional micro-ablative CO2 laser therapy in combination with platelet rich plasma (PRP) for the treatment of stress urinary incontinence (SUI) in women.

10.4 Summary

The SUI (2020) paper presents the results of a small-scale study to evaluate the safety, feasibility, and efficacy of transvaginal $FxCO_2$ laser in combination with PRP for the treatment of SUI in 62 women. Each participant underwent three sessions of transvaginal $FxCO_2$ laser and PRP treatment, administered at 4–6-week intervals. Outcomes were assessed using the bladder function section of the Australian Pelvic Floor Questionnaire (APFQ) at baseline, 3 months, and 12 months follow-up. 66% of participants reported improved SUI symptoms from

baseline to 3 months and at 12 months, 62% reported improved SUI symptoms. From baseline to 3 months, all bladder function variables improved significantly, and at 12 months, significant improvements were maintained for all bladder function variables, except pad usage. The conclusion was that $FxCO_2$ laser with PRP might be a beneficial treatment for SUI, such that it may have the potential to be a minimally invasive and low-risk alternative to surgery, with reduced recovery time.

10.5 Publications in this chapter:

Promising impact of platelet rich plasma and carbon dioxide laser for stress urinary incontinence.

F Behnia-Willison, TTT Nguyen, AJ Norbury, B Mohamadi, S Salvatore, A Lam.

European journal of obstetrics & gynecology and reproductive biology: X 2019; 5: 100099. doi: 10.1016/j.eurox.2019.100099.

10.6 Author contribution

I was responsible for (100%) the concept and design of research and data collection and (40%) of writing forthe publication. Alan Lam was responsible for (30%) of writing and editing. Behrang Mohammadi (100%) was responsible for the data analysis and Tran T.T. Nguyen was responsible for (50%) writing and editing and proofreading.

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Promising impact of platelet rich plasma and carbon dioxide laser for stress urinary incontinence

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ABSTRACT

Objectives: To evaluate the safety, feasibility and efficacy of trans-vaginal fractional micro-ablative CO_2 laser therapy in combination with platelet rich plasma (PRP) for the treatment of stress urinary incontinence (SUI) in women.

Study design: Participants with SUI underwent three sessions of transvaginal CO_2 laser and PRP treatment, administered at 4-6-week intervals. Outcomes were assessed using the bladder function section of the Australian Pelvic Floor Questionnaire (APFQ). The primary outcome was changes in the participants' symptoms of SUI. Secondary outcomes were related to general bladder function. Outcome differences from baseline (T1) to 3 months (T2) and 12 months (T3) were analysed using Wilcoxon signed-rank tests. Subjective verbal scales were used to assess the degree of pain associated with PRP injections and laser treatment.

Results: Sixty-two women with SUI were enrolled into this study. There were 66% (41/62) of participants who reported improved SUI symptoms from T1 to T2 ($p < 0.001$) and at T3, 62% (23/37) of patients reported improved SUI symptoms ($p < 0.001$). From T1 to T2, all bladder function variables were improved significantly ($p < 0.002$). At T3, significant improvements ($p < 0.03$) were maintained for all bladder function variables, except pad usage ($p = 0.073$).

Conclusions: Combining transvaginal fractional CO_2 laser with PRP might be a beneficial treatment for SUI. It may have the potential to be a minimally-invasive and low-risk alternative to surgery, with reduced recovery time.

Introduction

Urinary incontinence (UI) has a prevalence of 45% in women [1]. UI can impact on one's social, physical, mental and sexual wellbeing, and lead to depression and social isolation [2,3]. Many women are reluctant to seek medical help due to the associated embarrassment and social stigma [4]. UI is projected to cost $1.27 billion by 2018 in Australia [5].

Stress urinary incontinence (SUI) refers to the involuntary leakage of urine accompanying physical exertion (i.e. coughing, exercise, sneezing) [2]. It is commonly acquired after pregnancy and childbirth due to weakening of the pelvic floor muscles that support the urethra against the anterior vaginal wall [2,4]. Current SUI treatment includes surgery to re-establish sufficient urethral resistance in order to prevent urine leakage during increased intra-abdominal pressure [2].The mid-urethral sling (MUS) has become the preferred procedure, as it is less invasive than the Burch colposuspension [6]. However, the MUS procedure has a 5–20% failure rate and carries risks such as infection, voiding dysfunction, haemor- rhaging, pain, bladder/urethral injury, and mesh erosion [7,8]. Internationally, there has been a shift away from transvaginal implants, with the Therapeutic Goods Administration (TGA) in Australia withdrawing their approval for certain transvaginal mesh products [9]. Hence, there is a need for alternative efficacious, outpatient SUI treatments.

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Researchers have recently explored transvaginal laser as a less invasive treatment option for SUI [10,11]. By inducing thermal changes to tissues, the laser can instigate an inflammatory healing cascade, resulting in various histological, cytological, metabolic and gene expression changes that can restore and remodel tissues by promoting collagen synthesis and structural remodelling of collagen fibres [12–14]. In SUI patients, the laser applied to vaginal wall may improve pubo-cervical fascial collagen content and structure as well as the mucosal thickness, thus reinforcing urethral/bladder neck support [4,15,16]. Salvatore et al demonstrated that transvaginal laser reduced UI symptoms in women with vaginal atrophy [11]. Furthermore, Ogrinc et al and Gambacciani et al recorded significant improvements in SUI in women treated with Er:YAG non-ablative laser [10,17]. Currently, there are no published larger-scale studies investigating the long-term effects of micro-ablative CO_2 laser treatment for SUI.

Platelet-rich plasma (PRP) can drive cell migration, proliferation, differentiation, angiogenesis and removal of tissue debris, through growth factors and chemical mediators released by platelets. As a result, PRP can assist in tissue repair, healing and regeneration [18–21]. Clinically, PRP has effectively treated burns, skin disorders, lichen sclerosus, problematic wounds and tendonitis [14,18,20,21].

The primary reason for combining PRP with laser is based on the potential synergistic therapeutic effect [21]. The fibroblasts and collagen content were higher in the skin when PRP was used in conjunction with fractional CO_2 laser to promote healthy tissue healing [21]. The PRP may also reduce inflammation of laser treated areas to expedite tissue remodelling by stem cell activation, migration, and proliferation [14]. Gaspar et al investigated the combined application of fractional CO_2 laser and PRP for vaginal atrophy and found histological evidence of vaginal regeneration and subjectively, the patients reported reduced vaginal dryness and dyspareunia [22]. Moreover, water is the chromophore for CO_2 laser, meaning that dehydrated tissues would respond poorly to the laser. PRP can hydrate and optimise the tissues (i.e. vaginal mucosa) [22].

This study sought to investigate the feasibility and efficacy of transvaginal CO_2 laser with PRP for the treatment of SUI, in women. The primary outcome measured was symptoms of SUI, cough test, and bladder neck funnelling on ultrasound and urodynamics study. Secondary outcomes included symptoms of general bladder function, level of bother with bladder issues, and quality of life (QoL).

Materials and methods

This single-centre prospective observational pilot study enrolled 62 women suffering from SUI who were treated with transvaginal CO_2 laser and PRP. Participants provided written informed consent prior to treatment. This study was approved by the local ethics committee in adherence with the Declaration of Helsinki. Patients were not compensated for participation.

Participants

Inclusion criteria for this study included women who exhibited clinically significant symptoms of SUI (judged by pad usage and had a negative impact on QOL from SUI symptoms), a positive cough test, urethral hypermobility as detected by translabial ultrasound, who did not respond or responded unsatisfactorily to previous therapies and were opting for non-surgical treatment. Exclusion criteria included prolapse stage II as per the Pelvic Organ Prolapse Quantification (POPQ) system, current malignancy, known cervical dysplasia, acute or recurrent urinary tract infections, previous pelvic reconstructive surgery, current pregnancy, undiagnosed abnormal uterine bleeding, concurrent use of anti-platelet or anti-coagulant medications and any psychiatric disorder precluding informed consent. Women were encouraged to continue conservative SUI treatments, such as topical oestrogen therapy and pelvic floor exercises.

Study protocol

All participants underwent transvaginal laser treatments (MonaLisa Touch, SmartXide2 V2LR, DEKA, Italy), with the following settings applied: power 40 W, dwell time 1000 μs, DOT spacing 700 μm, SmartStak parameter 3, and double pulse mode. Prior to treatment, a topical anaesthetic cream was appliedto the vulva. A 90° vaginal laser-emitting probe was then inserted up to the level of the bladder neck, rotated and withdrawn, exposing the anterior lower one-third of the vagina to the laser. Participants were also subjected to total vaginal length laser treatments with a 360° probe, as described by Salvatore et al [26]. Overall, patients received three treatments, four to six weeks apart, conducted at FBW Gynaecology Plus. Patients were advised toavoid vaginal intercourse for five days after each laser treatment and to avoid lifting loads >10 kg for two weeks. Patients with a pasthistory of genital herpes were given antiviral prophylaxis two hours prior the laser treatments. A hydrating silicone-based balm was applied to the vulvo-vestibular area to minimise dryness post- laser.

Participants also received the same amount of RegenPRP$^+$ treatment immediately after each vaginal laser treatment. The 10 mL blood sample was drawn and prepared on site with a RegenLab$^+$ centrifuge. After topical local anaesthetic cover, the PRP was injected into the anterior lower one-third of the vagina and periurethral area. Post-treatment pain scores were measured after each treatment using a verbal scale from 0 to 10.

The primary treatment outcome and the secondary treatment outcomes (symptoms relating to general bladder function, such as nocturia, urge urinary incontinence and pad usage) were measured using the participant's scores from relevant items of the Australian Pelvic Floor Questionnaire (APFQ), which is a validated quality of life questionnaire (see Appendix 1). The 15 bladder function variables were added to calculate an overall bladder function score out of 45 [27]. Questionnaires were completed at baseline (T1), three months after the third treatment (T2) and at a 12–24 months after treatment (T3). Additionally, sociodemographic data was gathered from the practitioner's medical records (including records of patient POPQ scores) [25].

Statistical analysis

Statistically significant differences in all primary and secondary outcomes occurring between T1-T2 and T1-T3 were detected using Wilcoxon signed-rank tests. The threshold for statistical significance was set at 0.05. IBM SPSS software, version 21.0 (IBM, Chicago, Ill) was used for data processing and analysis.

Results

This study recruited 62 women, ranging from 32 to 86 years of age (mean = 55.98; SD = 11.27), 48 (77.4%) were postmenopausal. Most women (92%, 57/62) were multiparous with 72.6% (45/62) having an average of 2.3 vaginal births. Most women were Caucasian (95.2%, 59/62). There were 65.2% (28/43) obese women in this cohort. All women were candidates for urodynamic assessment. However, 56.5% (35/62) women proceeded to have baseline urodynamics. There were 39.3% (24/62) of women who used vaginal oestrogen despite all women were recommended this treatment if not contraindicated.

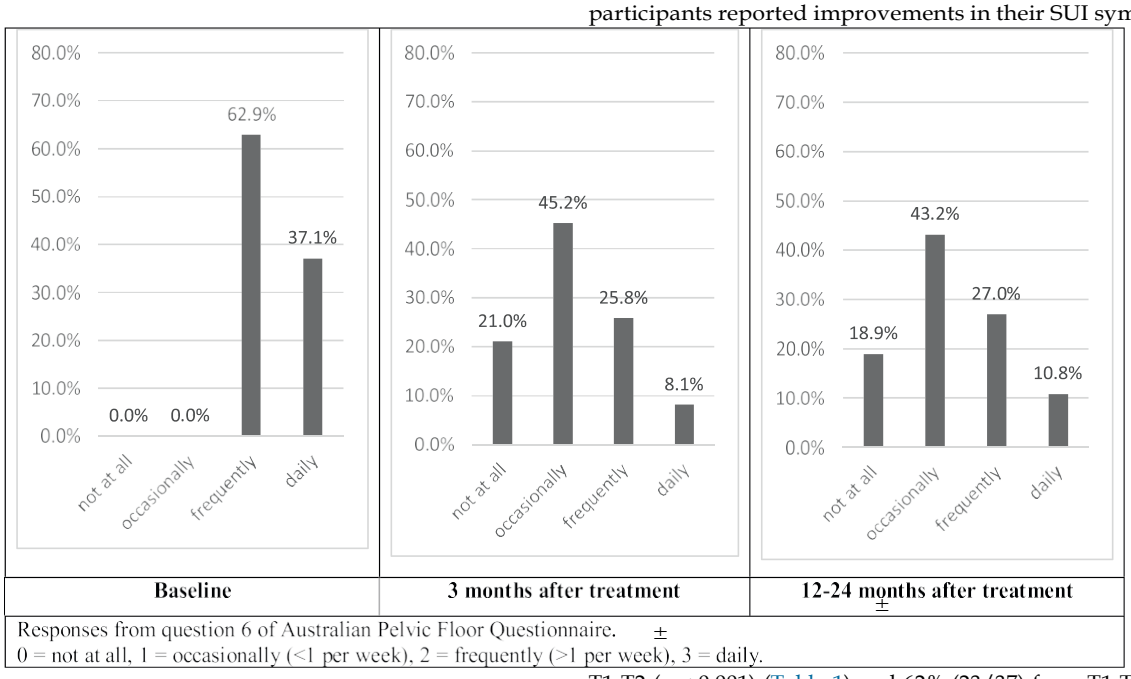

Fig. 1. Changes in stress incontinence symptoms in women who underwent PRP and fractional CO2 laser at pre-treatment (T1; n = 62), 3 months post-treatment (T2; n = 62),and 12–24-month post-treatment (T3; n = 37). The vertical and horizontal axes show the frequency percentages and the disease status respectively.

Stress urinary incontinence

Fig. 1 reveals changes in SUI symptoms, as measured by APFQ item 6 at 3 months follow-up (T2) and at 12–24 month follow up (T3), compared to baseline (T1). At T1, 100% (62/62) of participants reported either frequent or daily SUI symptoms, compared to 25.8% (16/62) for frequent symptoms and 8.1% (5/62) for daily symptoms at T2. At T1, no participants reported that they experienced either occasional or no SUI symptoms. Whilst at T2, 66.2% (41/62) of participants reported either occasional or no symptoms of SUI. At T3, 18.9% (7/37) reported no SUI symptoms, 43.2% (16/37) reported occasional symptoms, 27% (10/37) reported frequent symptoms and 10.8% (4/37) reported daily symptoms.

These improvements are also reflected in the decrease in mean and median scores, from 2.3 0.4 and 2 (T1), to 1.2 0.8 and 1 (T2),to 1.3 0.9 and 1 (T3) for APFQ item 6. Overall, 66% (41/62) of participants reported improvements in their SUI symptoms from T1-T2 ($p < 0.001$) (Table 1) and 62% (23/37) from T1-T3 ($p < 0.001$) (Table 2).

Secondary outcomes relating to bladder function

Fig. 2 reveals lower levels of patient-reported bother with their bladder symptoms after the treatment protocol. At T1, 3.3% of participants reported that their bladder symptoms didn't bother them. At T2 and T3, these numbers improved to

Table 1
Outcomes for women who underwent PRP and fractional CO2 laser at pre-treatment (T1) compared to 3 months after treatment (T2). Changes are represented using Wilcoxon's signed-rank test scores.

APFQ	Change between T1-T2					
	Improvement % (n)	z	r	p	Mean ± STD	Median
Primary outcome						

Stress incontinence	6	66 (62)	5.9	0.54	<0.001	T1 = 2.3 ± 0.4 T2 = 1.2 ± 0.8	T1 = 2 T2 = 1
Secondary outcomes							
Bladder Function	1-15	86 (57)	5.2	0.49	<0.001	T1 = 1.0 ± 0.8 T2 = 0.3 ± 0.5	T1 = 1 T2 = 0
Urge incontinence	5	73 (62)	4.7	0.43	<0.001	T1 = 1.6 ± 0.9 T2 = 0.8 ± 0.7	T1 = 2 T2 = 1
Urgency	4	62 (62)	4.5	0.40	<0.001	T1 = 1.7 ± 1 T2 = 1 ± 0.8	T1 = 2 T2 = 1
Wearing pads	10	48 (62)	3.5	0.32	0.001	T1 = 1.4 ± 1.2 T2 = 0.9 ± 1.0	T1 = 2 T2 = 1
Impact of urinary leakage on QOL	14	67 (58)	4.5	0.41	<0.001	T1 = 1.4 ± 1 T2 = 0.6 ± 0.9	T1 = 1 T2 = 0
Degree of bothersome bladder	15	58 (60)	5.4	0.50	<0.001	T1 = 2 ± 0.8 T2 = 1.1 ± 0.9	T1 = 2 T2 = 1

APFQ = Australian Pelvic Floor Questionnaire.
STD = Standard deviation.
z = Z value = standard scores.
r = Effect size = z / square root of N = total number of cases. r > 0.35 is medium effect. r > 0.5 is strong effect.
p = Probability value: statistically significant is set at p < 0.05 and statistically highly significant as p < 0.001.

Table 2
Outcomes for women who underwent PRP and fractional CO_2 laser at pre-treatment (T1) compared to 12–24 months after treatment (T3). Changes are represented using Wilcoxon's signed-rank test scores.

	APFQ	Change between T1-T3					
		Improvement % (n)	z	r	p	Mean ± STD	Median
Primary outcome							
Stress incontinence	6	62 (37)	4.3	0.50	<0.001	T1 = 2.3 ± 0.4 T2 = 1.3 ± 0.9	T1 = 2 T2 = 1
Secondary outcomes							
Bladder Function	1-15	57 (17)	3	0.52	0.002	T1 = 1 ± 0.8 T2 = 0.4 ± 0.6	T1 = 1 T2 = 0
Urge incontinence	5	46 (37)	2.5	0.29	0.012	T1 = 1.6 ± 0.9 T2 = 1.1 ± 0.9	T1 = 2 T2 = 1
Urgency	4	44 (37)	3.1	0.36	0.002	T1 = 1.7 ± 1 T2 = 1.1 ± 0.9	T1 = 2 T2 = 1
Wearing pads	10	41 (37)	1.7	0.20	0.073	T1 = 1.4 ± 1.2 T2 = 1 ± 1.1	T1 = 2 T2 = 1
Impact of urinary leakage on QOL	14	70 (37)	3.7	0.43	<0.001	T1 = 1.4 ± 1 T2 = 0.6 ± 0.9	T1 = 1 T2 = 0
Degree of bothersome bladder	15	57 (37)	3.9	0.46	<0.001	T1 = 2.0 ± 0.8 T2 = 1.1 ± 1.1	T1 = 2 T2 = 1

APFQ = Australian Pelvic Floor Questionnaire.
STD = Standard deviation.
z = Z value = standard scores.
r = Effect size = z / square root of N = total number of cases. r > 0.35 is medium effect. r > 0.5 is strong effect.
p = Probability value: statistically significant is set at p < 0.05 and statistically highly significant as p < 0.001.

26.2 % and 37.8%, respectively. The number of participants reporting moderate or great bother decreased from T1 to T2 and T3. The mean and median scores for degree of bothersome bladder at T1 were 2 0.8 and 2. They fell to 1.1 0.9 and 1 atT2 and 1.1 1.1 and 1 at T3. Overall, from T1-T2 and T1-T3, 58% and 57% of participants, respectively, experienced improve- ments in the degree to which their bladder issues bothered them (p < 0.001) (Tables 1 and 2).

Similarly, improvements were also seen from T1-T2 in urge incontinence, urgency, pad usage, impact of urine leakage on quality of life and overall bladder function (p < 0.02) (Table 1).These improvements remained significant at T3 (p < 0.03), except for pad usage (p = 0.073) (Table 2). Additionally, the mean and median scores for every secondary outcome (Tables 1 and 2) decreased from T1 to T2 and T3.

No participants experienced any adverse events due to these treatments. There were five participants who proceeded to have MUS surgery following the study. Nevertheless, PRP and fractional CO_2 laser treatment yielded pre-operative benefits in these women to increase mucosal thickness and quality [13,15].

In our cohort, two women (aged 70 and 78 years) who proceeded with SUI surgery consented for histological evaluation post-treatment of PRP and laser. They originally presented with severe GSM and SUI not responding to vaginal estrogen and other conservative measures. The histology at surgery demonstrated healthy non-atrophic vaginal mucosa.

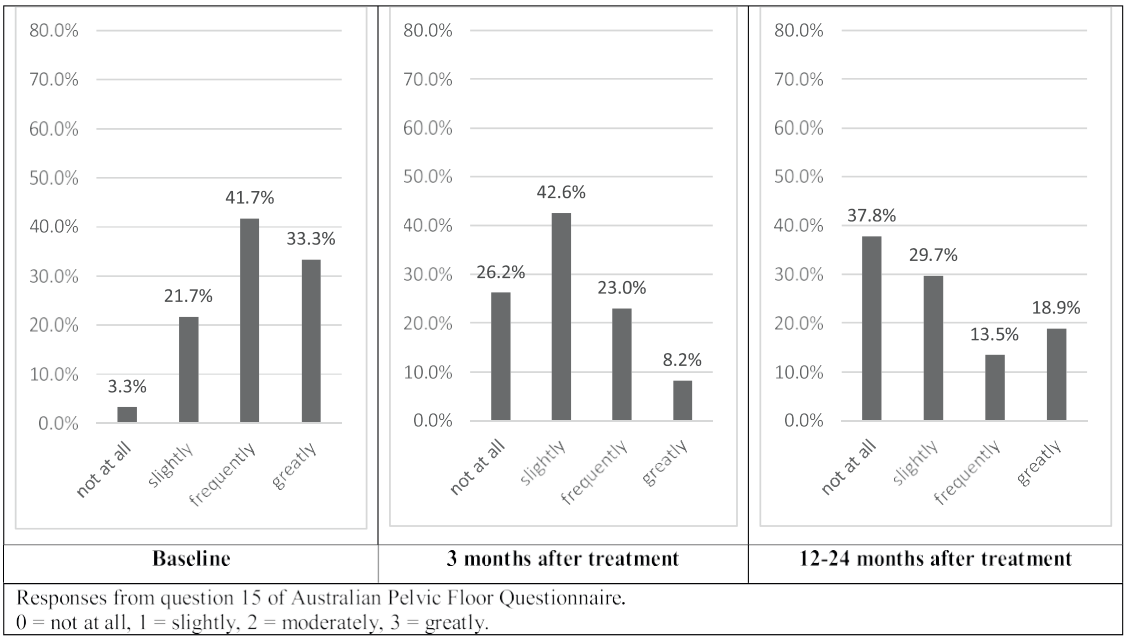

Fig. 2. Changes in bothersome symptoms in women who underwent PRP and fractional CO2 laser at pre-treatment (T1; n = 60), 3 months post-treatment (T2; n = 36), and 12–24-month post-treatment (T3; n = 37). The vertical and horizontal axes show the frequency percentages and the disease status respectively.

Comment

This study was based on the recently published study on transvaginal laser on SUI treatment, where the non-responders to transvaginal were treated with adjuvant PRP and had a successful outcome [28]. This study is the first to investigate short- and long-term effects of transvaginal PRP and laser for SUI treatment. A number of participants reported improvements in SUI symptoms at T2 and T3, both with statistically significant changes compared with T1. Moreover, mean and median scores for item 6 on the APFQ (Tables1 and 2) decreased from T1 toT2 and T3. These results suggest that the combined use of PRP and fractional micro-ablative CO_2 laser may be an effectivetreatmentfor SUI, and that it may yield long-term improvements in SUI symptoms (up to 12–24 months).

SUI is burdensome both on a personal and national economic level [3,5]. In terms of treating SUI, surgery is currently the most effective option, with MUS being the standard procedure [7,8]. However, the invasiveness, recovery time and risks associated with MUS are drawbacks of this procedure [7,8], and due to recent comments made by regulatory bodies such as the TGA on the use of transvaginal mesh in gynaecological procedures, there has been widespread negative publicity surrounding procedures involving such materials [9]. Consequently, many SUI patients refuse to consider MUS. This is reflected by a considerable decline in SUI surgery in Australia since 2012 [6–8]. Aside from this, some women are unable to undergo complex laparoscopic surgery for urinary incontinence due to medical comorbidities. Hence, there is a profound need for an effective minimally-invasive treatments.

Whilst there are several conservative treatment strategies available, most rely on patient motivation [26,27]. Such strategies include behavioural modifications (i.e. moderating fluid intake and pelvic floor muscle training), pessaries (an intravaginal device which elevates the vesico-urethral angle) and pharmacological agents, like serotonin and noradrenaline reuptake inhibitors (SNRIs) and topical oestrogen, which can increase urethral sphincter muscle tone [26,27]. However, there is often poor compliance with behavioural-based therapies, side effects of the medications, and considerable costs associated with the pessaries as well as discomfort associated with the necessary insertion and removal of the devices on a regular basis [26,27].

PRP and laser may offer a minimally invasive, non-surgical, low-risk and efficacious treatment alternative for SUI. The findings from this study support and build upon previous research, such as the small prospective cohort study from Ogrinc et al, which demonstrated the short-term efficacy (up to 12 months) of Er: YAG non-ablative laser in treating UI (including SUI) [10], and the study from Salvatore et al, which demonstrated improvements in SUI symptoms following three fractional micro-ablative CO_2 laser treatments [11]. Studies have also shown PRP to be effective in treating gynaecological conditions, such as lichen sclerosus and GSM [18]. Additionally, combined application of PRP and laser has yielded benefit in vaginal rejuvenation [22].

Another benefit of the PRP and laser combination treatment is that the patient opt to urodynamic (UD) studies prior to surgical treatment if indicated. UD studies are an added expense to national health and patient, which can be time-consuming, invasive and uncomfortable for the patient [27]. Overall, rates of urodynamic studies at this centre were reduced by 43% and surgery also reduced by 92%, which may have a cost benefit to the patient and national health system.

There were several weaknesses associated with this study. Firstly, there was no comparison of the patients receiving PRP and laser to other participants receiving single modality treatment (PRP or laser alone). Therefore, this study could not reveal the individual contributions of PRP and the laser treatments to the improvements in SUI symptoms. It would be important to assess

the impact of topical estrogen use on vaginal mucosa with the study treatment. Similarly, there was also no direct comparison with othercurrent standard treatments such as the MUS procedure, or with a control group. A randomised control trial (RCT) is desirable to confirm the findings of this study. It would also be valuable to assessthe treatment effects beyond 24 months. Additionally, 22.6% of women in this study were pre-menopausal. Future studies should attempt to better represent this demographic. Finally, there was a high attrition rate from pre-treatment (T1) to the 12–24 month follow up (T3). This creates a potential for bias.

In conclusion, this study suggests that the combined use of transvaginal PRP and CO_2 laser is a novel treatment option for SUI. This treatment protocol is minimally-invasive, requires negligible recovery time and is comparatively lower risk than surgery. These findings warrant further investigation into this treatment, ideally as an RCT comparing PRP and laser to a placebo and/or current treatments, including surgery. Future research should also assess the individual contributions of the PRP and laser to the improvement of symptoms,and maintenance of treatment benefit beyond 24 months.

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Declaration of Competing Interest

The authors have no conflict of interest and have not receivedany support (financial or otherwise) to conduct this study. However, SS is a consultant for DEKA laser.

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Chapter 11: Feasibility, Safety, and Efficacy of Fractional Micro-Ablative CO2 Vaginal (Fxco2) Laser Treatment and Platelet-Rich Plasma (PRP) in Women with Urge Urinary Incontinence

11.1 Introductory Comments

In Chapter 10 the efficacy, safety and feasibility of combined PRP and $FxCO_2$ laser for treatment of SUI are demonstrated. In this chapter it is shown that the use of PRP therapy and/or $FxCO_2$ laser are also appealing options for the treatment of UUI, as it removes the needfor multiple treatments while also being suitable for those patients that cannot use HRT. Whileit is not fully understood as to how PRP therapy and/or $FxCO_2$ laser stimulate tissue repair forUUI, it is thought that by correcting the vaginal mucosa thickness, improving lubrication, andreducing the vaginal pH, this may alleviate some of the irritation and subclinical infection thatcould give rise to urgency.

Together, PRP therapy and $FxCO_2$ laser have synergistic properties that can accelerate tissue repair, fibroblast proliferation, and increase collagen production [75]. The combination of PRPtherapy and $FxCO_2$ laser is superior to individual treatments due to antibacterial and anti- inflammatory properties of PRP as shown for treatment of wrinkles, scars, and hyperpigmentation [76]. Combinational $FxCO_2$ laser and PRP therapy has achieved effective repigmentation, while $FxCO_2$ laser alone, showed poor improvement [1, 2]. Furthermore, $FxCO_2$ laser and PRP therapy followed by sun exposure could be used to effectively and safelytreat refractory nonsegmental vitiligo Recently, the application of combining of these two therapies showed promising effect in treating GSM and SUI symptoms [3, 4].

11.2 Aim

To evaluate the feasibility, safety, and efficacy of FxCO2 vaginal laser treatment and PRP in women with refractory UUI with urinary function and sexual function as secondary outcome measures.

11.3 Summary

The UUI (2021) paper presents the results of a single-centre prospective cohort study to evaluate the safety, feasibility, and efficacy of transvaginal $FxCO_2$ laser in combination with

PRP for the treatment of 121 women with refractory UUI, with urinary function and sexual function as secondary outcome measures. Each participant underwent three sessions of transvaginal $FxCO_2$ laser and PRP treatment, administered at 4–6-week intervals. Outcomes were assessed using the bladder function section of the Australian Pelvic Floor Questionnaire (APFQ) at baseline, 3-6 months, and 12 months follow-up. A statistical analysis of the APFQresponses, revealed a significant reduction in the average severity of all self-reported measuresof primary and secondary outcomes from baseline to 3-6 months. Improvements in all bladderfunction outcomes remained statistically significant at 12 months follow-up, and no adverse events were recorded for this cohort. The conclusion was that $FxCO_2$ laser with PRP appears to be a safe, feasible, and effective treatment for UUI, bladder function, and sexual function, such that it may have a role as an alternative therapy for severe and refractory UUI.

11.4 Publication used in this chapter:

Feasibility, safety, and efficacy of fractional micro-ablative CO2 vaginal (FxCO2) lasertreatment and platelet-rich plasma (PRP) in women with urge urinary incontinence.

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11.5 Author contribution

I was responsible for (100%) the concept and design of research and data collection and (40%) writing forthe publication. Alan Lam was responsible for (30%) of writing and editing. Sanja Krneta (100%) was responsible for the data analysis and Tran T.T. Nguyen was responsible for (50%) writing and editing and proofreading.

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Feasibility Safety and Efficacy of Fractional Micro-Ablative CO_2 Vaginal ($FxCO_2$) Laser Treatment and Platelet-Rich Plasma (PRP) in Women with Urge Urinary Incontinence

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Abstract

ackground: Urge urinary incontinence (UUI) is the involuntary loss of urine associated with urgency, frequency, and nocturia. Current management involves behavioural therapies, which can be time-consuming and costly to the patient, and medications, which can have side effects. Fractional micro-ablative CO2 laser (FxCO2) and platelet-rich plasma (PRP) are two novel approaches that may offer symptomatic relief for women with UUI.

Objectives: To evaluate the feasibility, safety, and efficacy of FxCO2 vaginal laser treatment and PRP in women with refractory UUI with urinary function and sexual function as secondary outcome measures.

Study Design: This was a single-centre prospective cohort study. Participants with UUI underwent three treatments of transvaginal FxCO2 laser and PRP, administered at 4-6-week intervals. Outcomes were assessed with the Australian Pelvic Floor Questionnaire (APFQ) at baseline (T1), 3-6 months (T2), and ≥12 months follow-up (T3). The 12-month follow up data were obtained by face-to-face visit or follow up telephone call. The primary outcome was change in UUI symptoms. Secondary outcomes were related to overall bladder function and sexual function. Outcomes were assessed using Wilcoxon signed-rank test.

Results: In this study, 121 participants underwent treatment with FxCO2 laser and PRP for UUI. There was a significant reduction in the average severity of all self-reported measures of primary and secondary outcomes from T1 to T2 ($p<0.02$). Improvements in all bladder function outcomes remained statistically at T3 ($p<0.04$). There were no adverse events in this cohort.

Conclusion: This study suggests that FxCO2 laser with PRP appears to be a safe, feasible, and effective treatment for UUI, bladder function, and sexual function. FxCO2 laser and PRP may have a role as an alternative therapy for severe and refractory UUI.

Keywords: Urge Urinary Incontinence; Fractional Carbon Dioxide Vaginal Laser Therapy; Platelet Rich Plasma; Bladder Function; Urinary Incontinence; Urinary Urgency

Abbreviations: UUI: Urge Urinary Incontinence; PRP: Platelet-Rich Plasma; APFQ: Australian Pelvic Floor Questionnaire; PTNS: Percutaneous Tibial Nerve Stimulation; SUI: Stress Urinary Incontinence; MUI: Mixed Urinary Incontinence; VVA: Vulvovaginal Atrophy; GSM: Genitourinary Syndrome of Menopause; OAB: Overactive Bladder.

Condensation

Combined fractional micro-ablative CO2 vaginal laser therapy and platelet-rich plasma is a safe and effective treatment of urge urinary incontinence in women with moderate to severe vaginal atrophy.

Introduction

Urge urinary incontinence (UUI) is involuntary leakage of urine accompanied or immediately preceded by urgency. Women who experience UUI may also complain of frequency and nocturia, symptoms which are attributed to detrusor muscle over activity [1]. Women suffering from troubling UUI may avoid seeking treatment due to embarrassment, misunderstanding of the cause and treatment of urinary incontinence (UI), or fear of social exclusion. Therefore, the prevalence of up to 45% of UUI in Australian women may be underestimated [2,3]. The estimated national yearly cost of UI in Australia is upwards of $1.27 billion [4]. Behavioural therapy, weight loss, pelvic floor exercises, and bladder training are first line therapy for UUI. Second line therapy includes medical treatments such as vaginal estrogen, antimuscarinics, and beta-agonists. Third line treatment includes percutaneous tibial nerve stimulation (PTNS), cystoscopic intra-detrusor injections of botulinum toxin and sacral neuromodulation [5].

The high prevalence of urinary incontinence as well as the costs and side-effects associated with current treatments has opened the door to more novel approaches [6], which include $FxCO_2$ laser and PRP.

Study Aim

This study hypothesises that women with UUI who are treated with $FxCO_2$ laser and PRP will exhibit improvements in bothersome urinary symptoms as well as other secondary outcomes.

Material and Methods

This was a prospective cohort study of women with moderate to severe UUI. They were treated with $FxCO_2$ laser (MonaLisa Touch, DEKA) and PRP (RegenLab). The Australian Pelvic Floor Questionnaire (APFQ) was used for quality-of-life assessment, which has been demonstratedto have good discriminant validity, convergent validity, and internal consistency. APFQ was completed at baseline (T1), at 3-6-month follow-up (T2), and at 12- month follow-up (T3). Subjective verbal scales were used to assess the degree of pain associated with PRP injections and laser treatment.

Participants: Inclusion criteria are patients with moderate to severe UUI with or without stress incontinence or prolapse. Exclusion criteria included urinary tract infection, current urogenital tract cancer, pregnancy, untreated cervical dysplasia, abnormal uterine bleeding, active genital herpes, and immunosuppressed patients.

Written informed consent was obtained and the study was approved by Bellberry Ethics Committee, Adelaide, South Australia, in adherence to the Declaration of Helsinki (Application ID: 2016-04-293).

Study Protocol

$FxCO_2$ laser: Participants were treated with $FxCO_2$ laser using the following settings: power 40 watts, dwell time 1,000, spacing 700, stack 3, and double pulse. Each patient received FxCO2 laser treatments with a 360-degree probe. An additional treatment with a 90° vaginal probe at the level of the bladder neck, then rotated and withdrawn in orderto provide treatment of the anterior lower one-third and vestibule of the vagina as per Behnia-Willison, et al. [7-10].

Platelet-rich plasma (PRP): Patient had 10mLs of blood drawn and centrifuged on site. The PRP from the 10mLs syringe was injected to the anterior lower one-third of the vaginal subepithelial and peri-urethral areas and rolled-up 28 x11cm PRP- impregnated gauze was inserted into vagina for 2 hours.

Treatments were delivered at intervals of four to six weeks. Patients were advised to avoid vaginal intercourse for five days after each laser application to prevent infection and pain.

Data Collection

Demographics were gathered from patients at the time of their first consultation. Data assessing aspects of UUI and related symptoms were initially gathered from patients using the APFQ and entered into an electronic medical record that was used for reference throughout the study.

Statistical Analysis

Descriptive statistics were used to describe the clinical characteristics of the patient population and study outcomes

were assessed based on responses to the APFQ at T1, T2, and T3. The responses were entered into a private database by members of the research team and later analysed using SPSS. The responses to each question at the 3 time-points were described using the median and interquartile range. Sign-rank test was used to test for differences in paired medians for each question between T1 and T2, and T1 and T3. A Bonferroni correction was applied to account for multiple comparisons, with statistical significance assessed using a 2-sided Type 1 error rate of alpha=0.002.

Results

This study involved 121 women with a mean age of 56.23 years (±14.26) and mean BMI of 27.51. Of the women, 90% (109/121) were multiparous, 71.7% (86/121) were postmenopausal, and 50% (57/114) used some variety of oestrogen treatment. Table 1 of the appendix summarisesthe demographics of the cohort.

Figure 1 (Appendix) shows changes in UUI symptoms. All participants experienced frequent or daily UUI symptoms at baseline. There were 89 women who were followed-up at 3 months (T2) and 58 at 12-24 months (T3). At T2, 80.9% (72 of 89) reported no or occasional UUI symptoms. These changes were also reflected in the median score reduction for UUI from pre-treatment score of 2 to post-treatment score of 1 as seen in Table 2 (Appendix). At T3 67.2% of women reported no or occasional UUI symptoms. Of the remaining 32.8%, 24.1% reported frequent and 8.6% reported daily UUI symptoms. The median post-treatment score of 1 at T2 remained the same at T3 as seen in Table 3 (Appendix).

Figure 2 (Appendix) shows 88% of the patients with moderate to severe UUI experienced symptomatic improvement, reporting 'mildly affected' or 'normal' bladder function. At T1 69.3% of women reported normal or mildly affected bladder function, with the remaining 30.7% reporting moderately and severely affected bladder function. At T2 96.4% of women reported normal or mildly affected bladder function, 3.6% reported moderately affected, and zero reported having severely affected bladder function. AtT3

95.6% of women reported normal or mildly affected bladder function, 4.4% reported moderately affected bladder function, and zero reported severely affected bladder function.

There were self-reported improvements in 13 out of 15 bladder function parameters at T2 and T3 as seen in Figure 3 (Appendix).

Discussion

To the best of our knowledge, this is the first prospective cohort study to investigate $FxCO_2$ laser and PRP as a treatment for UUI in women with moderate to severe vaginal atrophy as $FxCO_2$ laser is dependent on water content of tissue. Therefore, adjuvant treatment with PRP was aimed to correct moderate to severe vaginal atrophy so that $FxCO_2$ laser can be more effective.

$FxCO_2$ laser is a potential non-surgical treatment for mild to moderate vaginal atrophy and various gynaecological conditions [7-12]. The subclinical thermal tissue effect from the laser beam induces dermal fibroblasts to initiate an inflammatory healing cascade, stimulating de novo collagen and elastin synthesis, resulting in a thicker vaginal epithelium with larger diameter, glycogen-rich epithelial cells [7-10]. There has not been a correlation found between non-ionising lasers such as those used for $FxCO_2$ laser and an increased rate of malignancy [13].

Promising results have arisen from investigations intothe use of $FxCO_2$ laser in the treatment of stress urinary incontinence (SUI) [14-18], mixed urinary incontinence (MUI) [15,17], vulvovaginal atrophy (VVA) [19] genitourinary syndrome of menopause (GSM) [18, 20-26], and overactive bladder (OAB) [27]. Salvatore et al. determined $FxCO_2$ laser to be safe in remodelling tissue properties of many body regions and effective in promoting the growth of new collagen and elastic fibres [28]. They also concluded the technique to be effective in reducing symptoms of UUI in a small sample of patients with vaginal atrophy [29].

PRP treatment involves injecting autologous plasma containing concentrated platelets and growth factors to promote growth and repair damaged tissue [8,9,29-33]. PRP acts as a scaffold, stimulates angiogenesis, fibroblast synthesis, and collagen formation. Furthermore, PRP reduces healing time by 40-50% by inducing migration, proliferation and differentiation of stem cells and reducing inflammation [33]. PRP is associated with reduced treatment burdenin conditions such as SUI [7,8,34,35], GSM [32], lichen sclerosus [30] and other pelvic floor disorders [9] and could be appropriate for women who are unable to use current mainstream treatment options.

Gaspar et al. noted PRP to be an effective treatment for symptoms of VVA in combination with $FxCO_2$ laser treatment through both subjective and objective measures [32]. Of the 92 participants, 40 received three $FxCO_2$ laser and PRP treatments and 52 received only PRP injections. All women continued with pelvic floor exercises. There was a significant

difference between the groups, with the former group reporting a 62.5% decrease in dyspareunia when compared to 15.4% in the latter group. The histological findings also showed a dramatic difference between the two groups, with a significant increase in the thickness of vaginal epithelium, fibroblast activity, and fibrin concentration within the cellular matrix of the former group [32].

A prospective observational study by Behnia-Willison, et al. explored $FxCO_2$ laser and PRP for the treatment of SUI in 62 women [7,8]. Each patient received three $FxCO_2$ laser and PRP treatments with 4-6-week intervals. Patient outcomes were measured using the Australian Pelvic Floor Questionnaire (APFQ) at three points in time; baseline, 3-month follow-up, and 12-month follow-up. The 3-month follow-up showed a 66% improvement in incontinence symptoms and the improvement was 62% by the 12-month follow-up suggesting a need for annual booster treatments [7].

Laser							
Author year [Reference]	**Laser**	**Condition**	**No**	**Study type**	**Follow-up (months)**	**Assessments**	**Main findings**
Behnia-Willison, et al. [7]	Microablative fractional CO_2 laser (MonaLisa)	SUI	58	Prospective observational		APFQ	80% and 75% of patients reported improvement in SUI symptoms at 3-6 -month and 12-24-month follow-up respectively ($p<0.01$). Statistically significant improvements were seen in all secondary outcomes.
ajafian, et al. [14]	IDS Fractional CO_2 laser	SUI	55	Clinical trial		SUI severity, Visual analogue scale	Reduction of SUI severity score from 8.56±0.62 at baseline to 7.87±0.93 at 6-month follow-up ($p<0.0001$).
Menachem, et al. [15]	Ablative vaginal pixel CO_2 laser (FemiLift CO2 laser-Alma Lasers)	SUI	133	Retrospective multicentre evaluation	03-Dec	Pelvic floor distress inventory (PFDI), visual analogue scale (VAS), VVA symptoms questionnaires.	80.6% reported not using pads following treatment compared to 47.8% prior to treatment. Over 97% of patients reported no or mild urgency compared to the initial results of 7.9% and 5.3% respectively.
Fistonic, et al. [16]	Non-ablative Vaginal Erbium:Yag (Fotona)	SUI	39	Labelled, prospective, single centre pilot study	6	International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form (ICIQ-UI SF), Q tip test, Short form 12 questionnaire (SF-12q), perineometry	Post-treatment evaluation showed significant improvement ($p< 0.05$) in all the domains tested.

Franic, et al. [17]	Fractional vaginal pixel CO_2 laser (FemiLift CO_2 laser-Alma Lasers)	SUI	85	Prospective twocentre study	6	ICIQ-UI SF, cough test, VAS.	Mean ICIQ-UI-SF score reduced from 12.0 (baseline), 7.0, (post first treatment), and 3.5 (post-second treatment) (P = 0.001). ICIQ UI SF score was 5 at 6-month follow-up. SUI symptoms were improved with 53.5% of women experiencing moderate to severe SUI symptoms at 6-month follow-up compared to 73% at baseline, 2.4% of which experienced very severe symptoms.
Perino, et al. [27]	Microablative fractional CO_2 laser (MonaLisa)	OAB	30	Prospective observational	1	VHI, VVA symptoms on VAS, micturition diary, OAB questionnaire (OAB-q)	Improvements at T1 (1 month) were seen in VVA symptoms, VHI score, micturition diary, urge episodes, and OAB-q ($p<0.0001$)
Behnia-Willison, et al. [10]	Microablative fractional CO_2 laser (MonaLisa)	GSM	102	Prospective observational		APFQ, GSM symptoms	84% of patients reported significant improvements in GSM symptoms. Secondary outcomes showed statistically significant improvement ($p>0.003$).
Sokol, et al. [26]	Microablative fractional CO_2 laser (MonaLisa)	GSM	30	Prospective observational	12	VAS for dryness, pain, itching or burning, dyspareunia, dysuria. VHIS, FSFI, SF-12q	Significant improvements were seen in VAS for all symptoms as well as in the VHI and FSFI ($p<0.001$). 92% satisfied or very satisfied with treatment outcomes.
Isaza, et al. [18]	Microablative fractional CO_2 laser (MonaLisa)	GSM	161	Prospective observational	36	1-h pad test, ICIQ-UI SF	Significant improvement in ICIQ-UI SF scores and 1-h pad weight test at 12 months (both $p<0.001$), 24 months (both $p<0.001$) and 36 months (both $p<0.001$). Improvements remained statistically significant at 36-month follow-up.

Athanasiou, et al. [23]	Microablative fractional CO_2 laser (MonaLisa)	GSM	94	Retrospective observational	12-Jan	VAS, ICIQ-UI SF, International Consultation on Incontinence Questionnaires-Female Urinary Tract Symptoms (ICIQ-FLUTS), Urogenital Distress Inventory-6, FSFI	There was significant improvement in symptoms severity at 1 month post final treat. Dyspareunia and dryness decreased from 9 and 8 at baseline to 0 for both symptoms (P<0.001) FSFI and frequency of sexual intercourse increased from 10.8 and 1 at baseline to 27.8 and 4 (P<0.001). These benefits remained unchanged at 12-month follow-up.
Paraiso, et al. [24]	Microablative fractional CO_2 laser (MonaLisa) vs vaginal oestriol cream	GSM	69	RCT	6	VAS vaginal dryness score, patient global impression of improvement (PGI-I)	As per PGI-I, 85.8% of laser participants rated their improvement as "better or much better" and 78.5% reported being either satisfied or very satisfied" compared to 70% and 73.3% in the estrogen group.
Pitsouni, et al. [22]	Microablative fractional CO_2 laser (MonaLisa)	GSM	53	Prospective observational	3	VHI, FSFI,vaginal maturity value (VMV),ICIQ-FLUTS, ICIQ-UI SF, Urogenital Distress Inventory (UDI-6), King s Health Questionnaire (KHQ).	VMV, VHIS, and FSFI increased significantly. Significant improvement was seen in symptoms of dyspareunia, dryness, burning, itching, dysuria, frequency, urgency, urgency incontinence, stress incontinence and scores on the ICIQ-FLUTS, ICIQ-UI SF, UDI-6 and KHQ at 3 -month follow up.
Cruz, et al. [19]	Microablative fractional CO_2 laser (MonaLisa) vs vaginal oestriol vs Microablative fractional CO_2 laser (MonaLisa) and vaginal oestriol	VVA	45	RCT	5	Vaginal health index (VHI), VAS, female sexual function index (FSFI)	Significant improvements were seen in VHI in all study groups (laser, vaginal oestriol, and laser with vaginal oestriol). Improvements in dryness, dyspareunia, and burning were seen in laser plus oestriol and laser only (p<0.009). Laser plus oestriol had significant improvement in FSFI score (p<0.004).

Salvatore, et al. [28]	Microablative fractional CO_2 laser (MonaLisa)	VVA, vaginal laxity, UI	38	Prospective observational	1	VAS for dryness, vaginal laxity, itching or burning, and dyspareunia, histological examination	Reduction in mean VAS values for dysuria (1.3 to 0.4), urinary urgency (2.6 to 0.8), UI (1.6 to 0.7), and SUI (3.1 to 1.3) at baseline and after 3 sessions respectively. Histology showed growth of new collagen and elastic fibres.
Salvatore, et al. [29]	Microablative fractional CO_2 laser (MonaLisa)	VVA	50	Prospective observational	3	FSFI, SF-12q	VVA symptoms -vaginal dryness, vaginal burning, vaginal itching, dyspareunia, dysuria-improved at 12-week follow-up $p < 0.001$). VHIS increased from 13.1± 2.5 (baseline) to. 23.1 ± 1.9 (12-week follow-up) ($p < 0.001$). Significant improvement in quality of life($p<0.001$).
PRP							
Author year [Reference]	**Combined therapy**	**Condition**	**No**	**Study type**	**Follow-up (months)**	**Assessments**	**Main findings**
Behnia-Willison, et al. [30]	Nil	Lichen Sclerosus	28	Prospective observational	Dec-24	Verbal interview on symptom severity, colposcopy	On colposcopy at 12 months, lesions were not seen in 8, lesions were smaller in 17, and lesions were the same in 3 women. 15 women experienced no associated symptoms and 13 had intermittent symptoms including itch, pain, dyspareunia.
Laser and PRP							
Author year [Reference]	**Laser**	**Condition**	**No**	**Study type**	**Follow-up (months)**	**Assessments**	**Main findings**
Behnia-Willison, et al. [8]	Microablative fractional CO_2 laser (MonaLisa)	SUI	62	Prospective observational	Dec-24	APFQ	66% (41/62) women reported improved SUI symptoms at 3-6-month follow-up ($p<0.001$). Of the women reached for 12-month follow-up, 62% (23/37) reported maintained improvements in SUI symptoms.
Gaspar, et al. [32]	Microablative fractional CO_2 laser (MonaLisa)	VVA	92	Case control	3	Sexual health, histology	Decreased discomfort during sex and improvement in vaginal mucous histology.

Table 1: Summary of the critical literature survey for the specific application of PRP and $FxCO_2$ laser in conditions such as SUI, GSM, VVA and UI.

This study suggests that $FxCO_2$ laser is a potential beneficial treatment for UUI and related bladder issuesin women. Following treatment with $FxCO_2$ laser and PRP, patients reported short-term improvements in self- reported measures of bladder function, urge incontinence,frequency, nocturia, urgency, pad use, UTI, daily activities effects, bothersome bladder problems, and limiting fluid. All symptom improvements remained statistically significant at the long-term (≥12-month) follow-up. These findings emerge in the context of a need for alternatives to conventional treatments for UUI, which may be costly, have side effects, and be sometimes unsuitable for patients. As UUI affects up 45% of women [1], it is important thatpatients are provided with options. A trend towards re- emergence of some symptoms at ≥12-month follow-up suggests the need for a booster treatment to maintain long-term symptomatic relief. The timing of a booster treatment depends on the aging process and menopause status. Interestingly, all improvements remained statistically significant at T3. Although vaginal estrogen was offered toall the women with vaginal atrophy only 50% of the cohort were compliant. Vaginal estrogen appears to maintain the symptom control in the group with improved urinarysymptoms as seen at Cruz, et al. [19]. A study limitation was the attrition rate during COVID pandemic, with half of the women participating in the ≥12-month face-to-face follow- up, making it difficult to form comparisons from baseline to the final follow-up. However, through teleconsultations many of women who did not return for 12-month follow-up were found to have symptom resolution and successful conservative management measures. Secondly, symptom improvements following PRP treatment might be due to the tissue needling involved in the injection process, rather than to the bio-regenerative effects of the PRP. Subjecting tissue to micro-trauma may instigate the tissue repair cascade [36], and in the present circumstances, this cannot be ruled outas a confounding factor. Future studies should attempt to control for these potential treatment mechanisms in theirdesign, which would include a placebo PRP and sham arm of laser therapy.

Conclusion

$FxCO_2$ laser and PRP may improve UUI, sexual function, and overall bladder function. These treatments appear to be safe, tolerable, and have minimal downtime as theycan resume their normal daily activities immediately after treatment with the exception of abstinence for three days. The treatment effects may diminish significantly by 12-18months and may require a booster treatment to maintainsymptom relief. Further randomised control trials are warranted to confirm the efficacy of these treatment modalities for UUI.

Disclosures

The authors have no conflict of interest and have not received any direct support (financial or otherwise) toconduct this study.

Conflicts of Interest

Dr Behnia-Willison worked as a consultant for Regenlab® for 6 months in 2018. The other authors have no conflictof interest and have not received any support (financial or otherwise) to conduct this study.

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Appendix

	N	Mean	Percent
Postmenopausal women	86/121		71.10%
Anti-cholinergic use	28/112		25%
Physiotherapy	35/113		31%
Estrogen treatment	57/114		50%
BMI		27.51	
Underweight (BMI <20)	9/96	9.4	
Normal (BMI 20-25)	34/96	35.4	
Overweight (BMI 25-30)	27/96	28.1	
Obese (BMI >30)	26/96	27.1	

Table 1: Patient Characteristics.

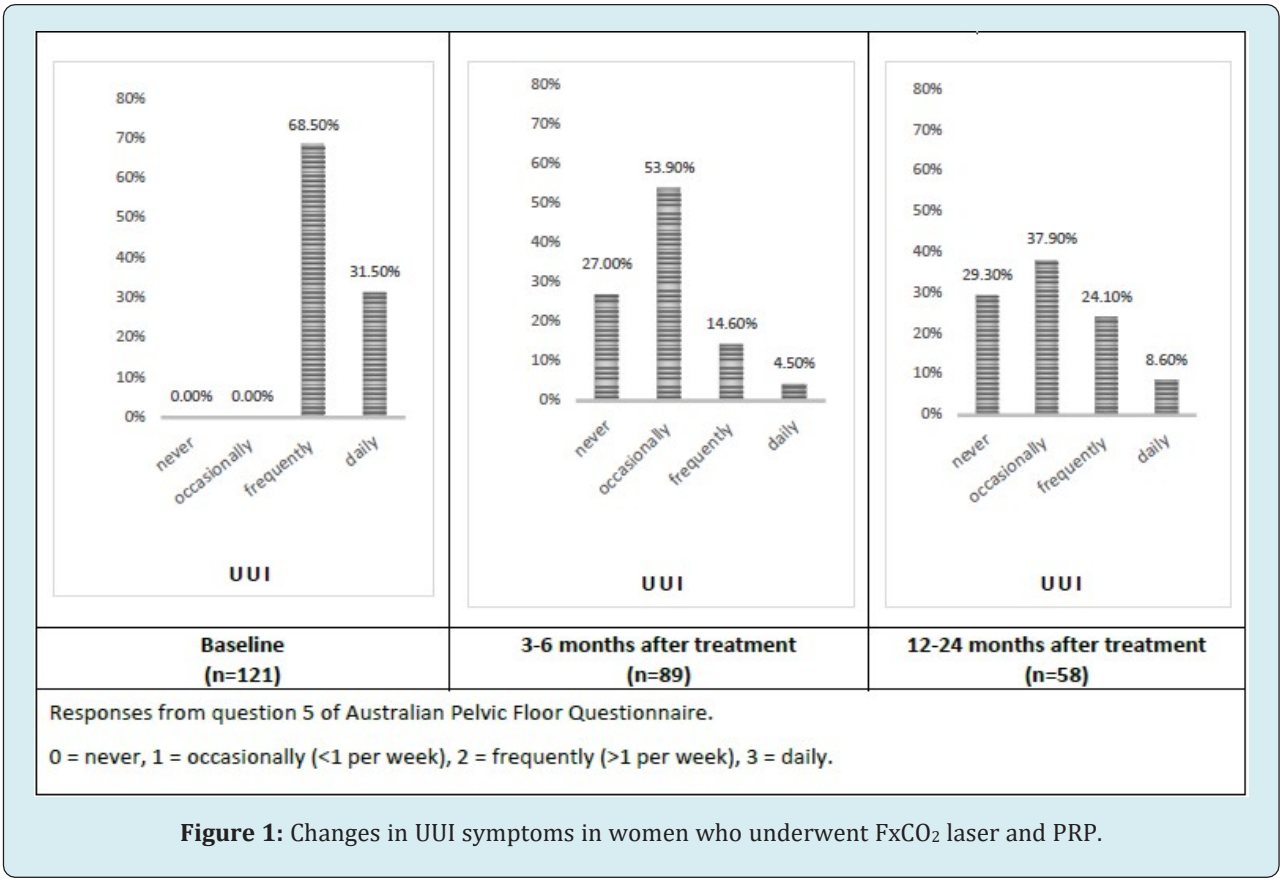

Figure 1: Changes in UUI symptoms in women who underwent $FxCO_2$ laser and PRP.

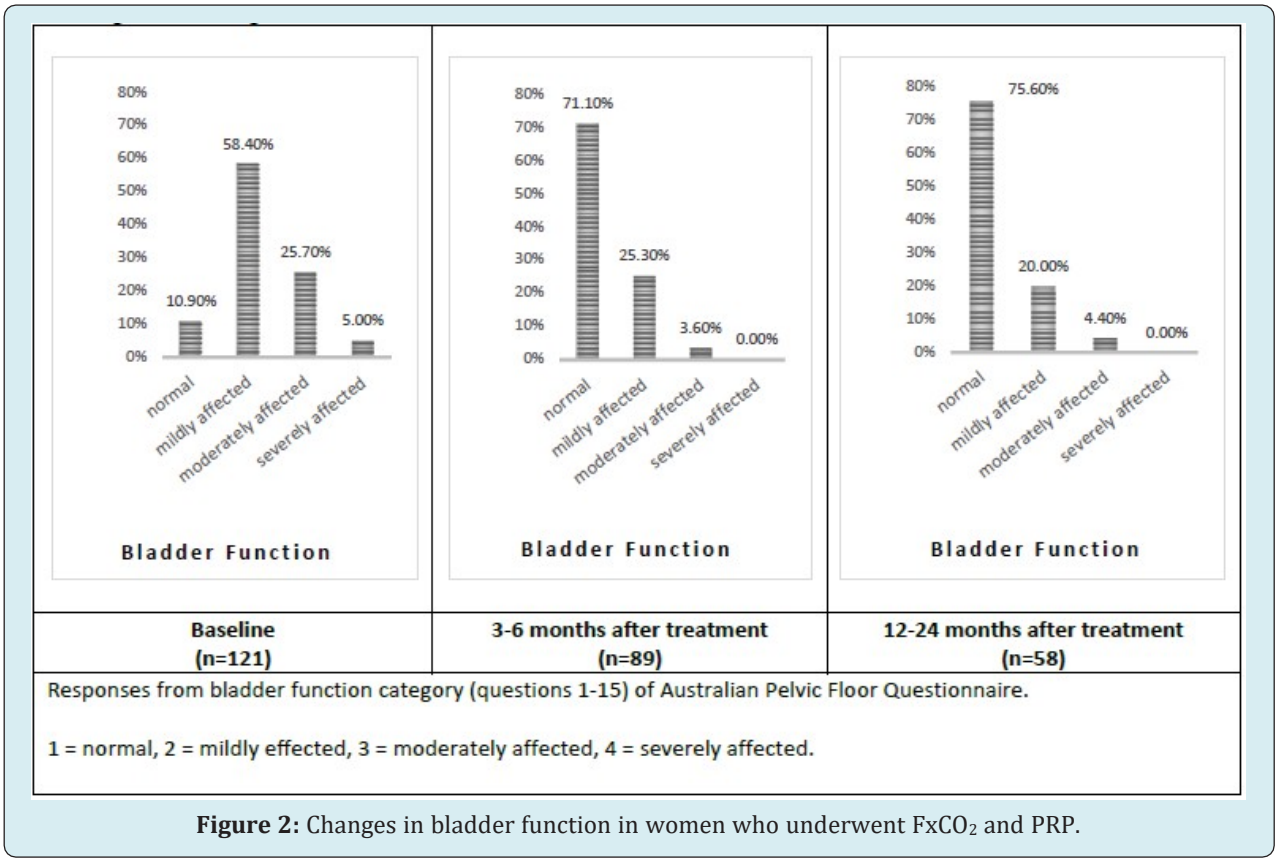

Figure 2: Changes in bladder function in women who underwent $FxCO_2$ and PRP.

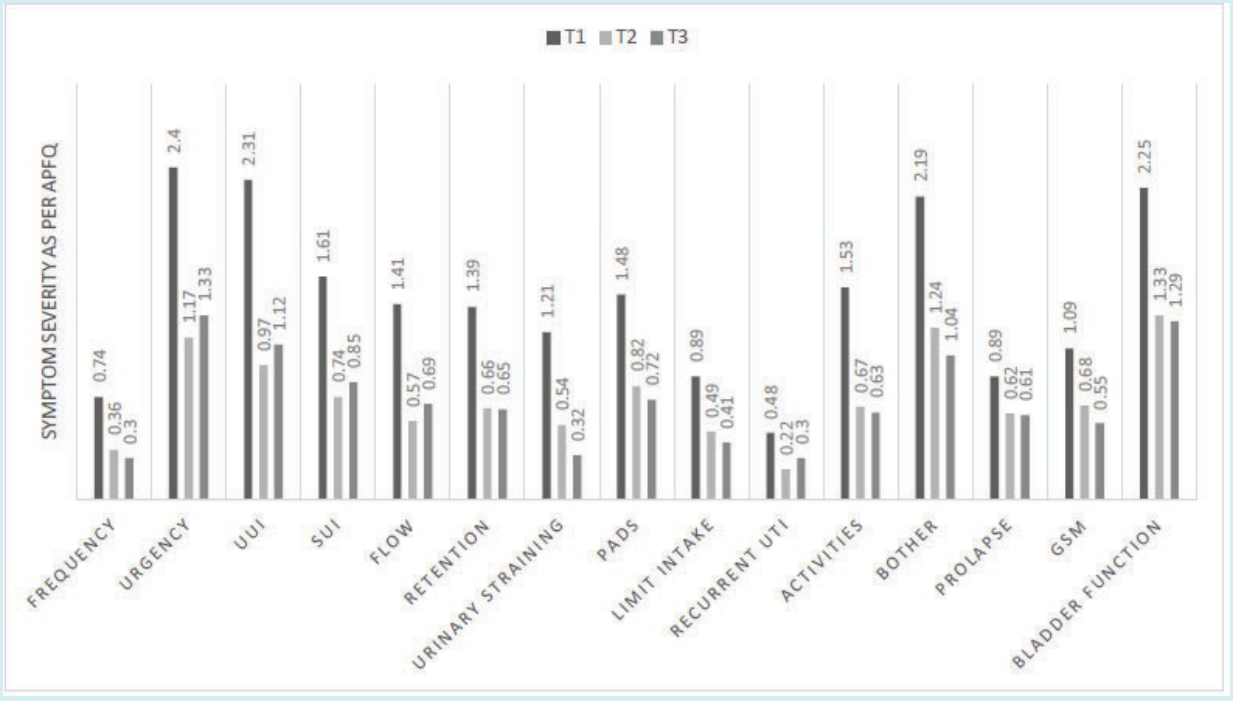

Figure 3: Mean bladder function symptom severity at each timeframe

	APFQ	Change between T1-T2							
		Improvement %	n	z	r	P value <0/05	Mean	± STD	Median
Frequency	1	70.67	85	-4.085	0.31	0	T1 = 0.74	± 0.772	T1=1
							T2 = 0.36	± 0.644	T2 =0
Nocturia	2	51.9	89	-2.333	0.17	0.02	T1 = 0.65	± 0.956	T1=0
							T2 = 0.47	± 0.709	T2=0
Enuresis	3	60.71	89	-1.833	0.14	0.067	T1 = 0.23	± 0.539	T1=0
							T2 = 0.09	± 0.358	T2 =0
Urgency	4	67.34	88	-6.95	0.52	0	T1 = 2.40	± 0.733	T1=3
							T2 = 1.17	± 0.895	T2=1
Urge	5	80.9	89	-7.64	0.57	0	T1 = 2.31	±0.466	T1=2
							T2 = 0.97	± 0.775	T2 =1
Incontinence Stress	6	68.42	88	-6.013	0.45	0	T1 =1.61	± 1.143	T1=2
							T2 = 0.74	± 0.886	T2=1
Incontinence Flow	7	75.58	85	-5.171	0.4	0	T1 = 1.41	±1.126	T1=1
							T2 = 0.57	± 0.848	T2=0
Retention	8	72.11	87	-4.753	0.36	0	T1 = 1.39	± 1.103	T1=1
							T2 = 0.66	± 0.852	T2=0
Urinary	9	73.11	95	-5.255	0.38	0	T1 = 1.21	±1.146	T1=1
							T2 = 0.54	± 0.830	T2=0
straining Pads	10	59.19	87	-4.394	0.33	0	T1 = 1.48	± 1.298	T1=1
							T2 = 0.82	± 0.989	T2=1
Limit intake	11	63.86	81	-3.893	0.31	0	T1 = 0.89	± 0.994	T1=1
							T2 = 0.49	± 0.745	T2=0
Recurrent UTI	12	91.67	82	-3.157	0.25	0.002	T1 = 0.48	± 0 .833	T1=0
							T2 = 0.22	± 0.441	T2 =0
Dysuria	13	84.25	82	-4.653	0.36	0	T1 = 0.84	± 0.838	T1=0
							T2 = 0.15	± 0.418	T2 =0
Activities	14	73.91	82	-5.886	0.46	0	T1 = 1.53	± 1.083	T1=1
							T2 = 0.67	± 0.787	T2=1
How bothersome (QoL)	15						T1 = 2.19	± 0.891	T1=2
		57.37	81	-6.28	0.49	0	T2 = 1.24	± 0.902	T2=1
Prolapse	28	56.62	71	-3.305	0.28	0.001	T1 = 0.89	± 1.149	T1=0
							T2 = 0.62	± 0.968	T2=0
GSM	39	60.63	55	-2.797	0.27	0.005	T1 = 1.09	± 1.085	T1=1
							T2 = 0.68	± 0.805	T2=1
Bladder function	Scale	88.27	71	-6.427	0.54	0	T1 = 2.25	± 0.713	T1=2
							T2 = 1.33	± 0.543	T2=1

Table 2: Outcomes for women who underwent $FxCO_2$ and PRP at T1 compared to T2. Changes are represented using Wilcoxon's signed-rank test scores.

	APFQ	Change between T1-T3							
		Improvement %	n	z	r	P value <0/05	Mean	± STD	Median
Frequency	1	85.33	45	-3.622	0.38	0	T1 = 0.74	± 0.772	T1=1
							T 3= 0.3	± 0.511	T 3= 0
Nocturia	2	79.52	46	-2.045	0.21	0.041	T1 = 0.65	± 0.956	T1=0
							T 3= 0.41	± 0.580	T 3= 0
Enuresis	3	100	46	-0.535	0.06	0.593	T1 = 0.23	± 0.539	T1=0
							T 3= 0.17	± 0.383	T 3= 0
Urgency	4	53.8	46	-4.921	0.51	0	T1 = 2.40	± 0.733	T1=3
							T 3= 1.33	± 0.871	T 3= 1
Urge	5	67.3	58	-5.505	0.51	0	T1 = 2.31	±0.466	T1=2
							T 3= 1.12	± 0.938	T 3= 1
Incontinence Stress	6	65.79	46	-3.929	0.41	0	T1=1.61	± 1.143	T1=2
							T 3= 0.85	± 0.894	T 3= 1
Incontinence Flow	7	57.05	49	-2.847	0.29	0.004	T1 = 1.41	±1.126	T1=1
							T 3= 0.69	± 0.895	T 3= 0
Retention	8	69.83	48	-3.362	0.34	0.001	T1 = 1.39	± 1.103	T1=1
							T 3= 0.65	± 0.838	T 3= 0
Urinary	9	84.91	47	-3.815	0.39	0	T1 = 1.21	±1.146	T1=1
							T 3= 0.32	± 0.594	T 3= 0
straining Pads	10	65.92	46	-3.463	0.36	0.001	T1 = 1.48	± 1.298	T1=1
							T 3= 0.72	± 1.026	T 3= 0
Limit intake	11	61.75	43	-2.81	0.3	0.005	T1 = 0.89	± 0.994	T1=1
							T 3= 0.41	± 0.748	T 3= 0
Recurrent UTI	12	50.76	43	-2.296	0.25	0.022	T1=0.48	± 0 .833	T1=0
							T 3= 0.3	± 0.591	T 3= 0
Dysuria	13	84.93	43	-3.566	0.38	0	T1 = 0.84	± 0.838	T1=0
							T 3= 0.15	± 0.420	T 3= 0
Activities	14	68.53	43	-4.3	0.46	0	T1 = 1.53	± 1.083	T1=1
							T 3= 0.63	± 0.853	T 3= 0
How bothersome (QoL)	15	59.6	41	-4.607	0.51	0	T1 = 2.19	± 0.891	T1=2
							T 3= 1.04	± 1.074	T 3= 1
Prolapse	28	39.74	37	-3.816	0.44	0	T1 = 0.89	± 1.149	T1=0
							T 3= 0.61	± 0.945	T 3= 0
GSM	39	51.92	23	-2.913	0.43	0.004	T1 = 1.09	± 1.085	T1=1
							T 3= 0.55	± 0.736	T 3= 0
Bladder function	Scale	85.67	40	-5.245	0.59	0	T1 = 2.25	± 0.713	T1=2
							T 3= 1.29	± 0.549	T 3= 1

Table 3: Outcomes for women who underwent $FxCO_2$ and PRP at pre-treatment (T1) compared to 12-24 months after treatment (T3). Changes are represented using Wilcoxon's signed-rank test scores.

Behnia-Willison F, et al. Feasibility, Safety and Efficacy of Fractional Micro-Ablative CO_2 Vaginal ($FxCO_2$) Laser Treatment and Platelet-Rich Plasma (PRP) in Women with Urge Urinary Incontinence. J Gynecol 2021, 6(1): 000213.

Discussion, Conclusions, andFuture Work

Discussion

Pelvic floor disorders (PFD), such as Pelvic Organ Prolapse (POP), Urinary Incontinence (UI), Genitourinary syndrome of Menopause (GSM) and Lichen Sclerosis (LS) are common conditions among women globally, with POP and UI affecting 40-60% across their lifetime [1,2]. These disorders are associated with major psychosocial and financial burdens, and impact heavily on national health systems [3].

Standard conservative treatments for PFD such as physiotherapy, pessary devices, hormone replacement therapy, weight loss and lifestyle changes are dependent on patient compliance and are only partially effective [4, 5]. This may explain why only 20-30% of women with symptomatic prolapse seek treatment. If conservative measures are unsuccessful some of theseconditions such as POP and UI can be treated with surgical procedures. These procedures oftenrequire significant down-time, possible complications, with emotional, social, and financial impacts for individuals and the healthcare system [6].

There is a void between the current first-line and second-line treatments. First-line treatments are 100% reliant on the patient while the new scheme is reliant on surgical skills, available technology, and approach[7]. Based on the facts, there is a need to establish alternatives to exhaust all the possible non-surgical and non-invasive options.

My research has demonstrated to be safe and effective is regenerative medicine modalities suchas the use of fractional CO2 (FxCO2) laser and Platelet Rich plasma (PRP)[8-11]. $FxCO_2$ laserin combination with PRP has a unique synergistic effect to reduce inflammation and promote wound healing [12]. Anabolic effects of PRP, combined with the micro-trauma and heat fromFxCO2 laser, has proven effective in improving neovascularisation, cell regeneration,elasticity, and collagen synthesis, allowing no surgical regeneration of the tissues. These effectsalso are essential for tissue healing after any surgery [13-18].

Symptoms of PFDs are often overlapping and include itching, irritation, urinary urgency, dysuria, excessive discharge, vaginal dryness, and superficial dyspareunia[19]. These symptoms prompt women to seek treatment and traditional first-line conservative managementoptions often fail to address these issues. Some of the conventional first-line treatments such as steroid cream for LS may exacerbate other conditions such as vaginal atrophy, leading to worsening or development of new symptoms[20, 21]. Other first-line treatments may be cost prohibitive for conditions such as urge incontinence (UI) such as posterior tibial nervestimulation (PTNS), medications and neuromodulation [22, 23]. Additionally, treatment of atrophy with vaginal oestrogen may be contraindicated or unacceptable for some women due to hormonal interactions and possibility to increase the chance of breast cancer [24, 25].

When first-line treatments fail, surgical treatment can improve the clinical exam findings of POP and UI but fail to address these common symptoms, cause new onset of symptoms and may even exacerbate them [26]. I have found and demonstrated in this thesis that FxCO2 laserand PRP can improve many of these symptoms using treatment that is non-hormonal and less reliant on patient compliance [9-11, 27, 28]. The aforementioned regenerative medicinemodalities also improve the effectiveness of first-line treatments [29, 30].

Introducing regenerative medicine modalities as a new and innovative second-linemanagement may reduce the symptoms and improve patient's quality of life without the need for surgery [29]. Additionally, if surgery is indicated, outcomes are dependent on surgical skillsand techniques, tissue characteristics, and use of tissue-enhancing materials [4, 31]. Given that the first surgery for a patient's PFD is the most critical repair for long-term success, pre- operative treatment with regenerative medicine may improve tissue quality and hence outcomes of surgery. My published work has shown improved surgical outcomes with correction of the vaginal mucosa and new collagen formation of the underlying connective tissue with pre-operative FxCO2 and PRP treatment [8-11, 27, 28].

Over the past decades, gynaecologists have conducted procedures to treat PFDs with traditionalnative

tissue repair with sutures, augmenting it with patient's own skin/fascia, later utilising porcine or bovine biological graft and more recently, synthetic mesh in an increasingly ageingpopulation [32-34].

Biological grafts and synthetic mesh have been associated with some severe and irreversible complications forcing the Therapeutic Goods Administration (TGA) and the United States Food and Drug Administration (FDA) to withdraw them from the market in many countries, including Australia [35]. The action resulted in surgeons resorting back to native tissue repair and no tissue augmentation modality and possible higher failure rate [36, 37].

In the height of mesh controversy, gynaecologists' hands were forced to be innovative and learn from the past lessons about mesh, particularly to follow strict rules and regulations whenintroducing new devices and technology for maximising patient safety [4, 38].

FxCO2 and PRP are an innovative method which can augment repairs in a non-hormonal andnon-synthetic way. I have conducted multiple studies investigating the safety, efficacy, and feasibility of these regenerative techniques post-operatively leading to long term success, enhanced recovery, and low rates of symptom recurrence as published in the peer-reviewed journal [8-11, 27, 28]. Based on the work presented in this thesis, both FxCO2 and PRP can be used as a stand along second-line conservative management option, as a pre-operative adjuvantto establish quality tissue, or as a booster treatment to maintain the success of initial conservative and/or surgical management.

At the end of discussion, my current work is investigating the effect of autologous graft from patient's own blood to be administered at the time of surgery. The formula of blood volume, platelet concentration, calcium ratio, equipment such as centrifuge, container sizes, time for centrifugation, and additional biological material, such as hyaluronic acid, adipose cells, and stem cells have been trialed over the last three-years in dry and animal laboratories. The currentformula has been utilised in 105 patients reproducibility, and patient outcomes were recorded.Our findings from this work demonstrates

significant improvement in subjective, objective, and patient satisfaction scores following vaginal repair using novel autologous graft. This study also demonstrated that the novel use of autologous graft at the time of native tissue vaginal repair is safe and efficacious.

Conclusions and contribution of the thesis

The thesis is composed of eleven chapters, the sequence of which highlights the chronology ofthe knowledge development and research undertakings to meet the defined aims. The Introduction gives an overview of the subject as well as my personal and professionalbackground, and motivation for undertaking this work and describes the existing gaps in the knowledge regarding women's health. The objective and the aims of the thesis are also definedin the introduction. Chapter one provides a comprehensive critical and updated literature review and explains the gaps in knowledge as well as the significance of the research in more details. The main body of the thesis, chapters 2 to 11 is a collection of twelve manuscripts thathave been published in peer-reviewed journals [9-11, 27, 28, 32, 39-44]. These publications present the progress made during this work and details the impact of this research. Finally, theconclusions of the research performed in addition to the recommendations for future works aregiven in the Conclusions. In the following paragraphs the content of each chapter and the alignment of the research with the specified aims are explained.

Chapter 1 provides a critical review of the literature on Pelvic Floor Disorders (PFDs) including urge urinary incontinence (UUI), stress urinary incontinence (SUI), pelvic organ prolapse (POP), genitourinary syndrome of menopause (GSM) and Lichen sclerosus (LS) followed by advanced laparoscopic surgery techniques in PFDs and the evolution of the techniques from advanced laparoscopic to single incision laparoscopic to trans-vaginal naturalorifice transluminal endoscopic surgery (vNOTES) [39]. The emphasis of the chapter is on therole and mechanism of different regenerative medicine modalities in treatment of PFDs, the physical fundamentals, the current challenges, and the associated compensation strategies followed by current requirements and challenges of the PFD treatments.

The advancement of the laparoscopic techniques in gynaecological conditions and the innovative approaches are presented in **Chapters 2 to 6**. The chapters start with laparoscopic paravaginal repair of anterior compartment prolapses followed by graft-reinforced anterior colporrhaphy for central defects, the anatomic cure rate greater than 80% was achieved and moving towards the single incision laparoscopic surgery (SILS) on a cohort of 84 out of 105 women [42]. This research illustrated the feasibility and safety of the technique because of significant improvement of cosmesis and reduced analgesic needs post-operation. The evolution and success of the advanced surgical techniques was further demonstrated with SILSin mesh sacrohysteropexy in different publications and finally the chapter moves to the most advanced technique;" Transvaginal natural translumenal endoscopic surgery (NOTES)". The research includes case reports, survey-based observational study and the feasibility and challenges involved.

Chapter 7 investigates the potential role of regenerative medicine (PRP) in treatment of LichenSclerosus (LS). Twenty-eight patients with confirmed LS during a two-year time were treatedwith PRP. It is concluded that almost all the cohort study showed the signs of improvements in the symptoms [10].

Chapters 8 and 9 present the potential role, efficacy, and safety of fractional CO2 (FxCO2) laser, as another regenerative medicine modality, in treatment of genitourinary syndrome of menopause (GSM) and stress urinary incontinence (SUI) in long-term in two publications [9, 27]. The outcomes of the studies confirmed that the micro-ablative FxCO2 laser treatment shown promising non-surgical, non-hormonal, low risk treatment option for women with LS and SUI. In **Chapters 10 and 11**, the efficacy and safety of combined FxCO2 laser and PRP for treatment of SUI and UUI are analysed. These innovative studies suggested that the combined utilisation of transvaginal PRP and FxCO2 laser is a novel approach towards the application of regenerative medicine in treatment of gynaecology conditions [9, 11]. These studies suggest that the combined use of transvaginal PRP and CO2 laser are a novel treatmentoption for SUI and UUI and provide a solid foundation for further investigations for

utilisationof regenerative medicine for treatments of gynaecological conditions.

Finally, the **Conclusions** summarises the main outcomes and the conclusions from this research along with recommendations for further research and feasibility studies towards the step change strategy from the uncertainty requiring determine patient compliance to doctor control. Based on the work in this thesis the below points can be concluded:

1. Regenerative medicine can be employed as second-line treatment for symptoms of PFDs shifting treatment from patient compliance to gynaecologist control.
2. In the case of surgery, regenerative medicine can be used as preoperative preparation to improve the quality of tissue at the time of operation.
3. Regenerative medicine can be employed as a post-operative treatment for improve healingprocess and as booster treatment to overcome and post-menopausal effect and reverse theaging process of the tissue in order to improve the longer-term outcome of the surgery.

Recommendations for future research

This doctoral thesis provides a solid foundation for future studies and follow and developmentof protocols of the use of regenerative medicine in PFDs. Larger studies, in multi-centre settings involving randomised control trials need to further evaluate the role of these modalitiesand establish the protocol and timing and frequency of booster treatment.

4. Regenerative medicine can be deployed to produce PRP graft to augment tissue intra- operatively with bio-identical, non-synthetic autologous graft with biological and mechanical properties. This formula has been developed over the last 3 years and utilised in 100 patients with success rate of 90%. Further studies need to be conducted to improvethe mechanical properties such as tensile strength, module of elasticity and tear resistanceof this graft. This prospective cohort study demonstrates that the use of this novelautologous graft in augmentation of pelvic native tissue repair is safe, feasible and effectiveat 12 months. Further randomised control trial is required to compare the effectiveness of this

technique versus standard native tissue repair alone.The autologous graft research and study is limited by the prospective cohort design. Whileit allows for demonstration of safety and feasibility, there is further research required to establish an improvement in patient outcomes and satisfaction in a randomised control trialof anterior or posterior repair with or without autologous graft and with larger cohort and longer follow up.

5. Ongoing follow-up of the patients used the autologous graft continues to assess the longer-term success or otherwise of the pelvic organ repair using the developed autologous graft is required to determine the duration of effect.

6. Future study designs will need to account for the type and route of apical repair, whether laparoscopic or vaginal suspension as well as suspension suture material and incorporationof mesh. However, this autologous graft is mainly for correcting level 2 prolapsecorrection but will improve vaginal tissue to allow more successful level 1 surgical correction with mesh that is utilised abdominally to avoid infection and associated complication seen with vaginal mesh.

7. Considering the official warning issued by FDA and TGA regarding the use of laser and PRP, all gynecologists need to conduct their own audit and quality assurance research when it comes to new technologies, devices, or methods. Individual practitioners should learn from their mistakes in the past regarding the use of vaginal mesh, which involved companiesfalsifying results and marketing unproven technologies [36, 45-47] to some underskilled surgeons who were keen to be early adopters. Each device and new technology must undergo research and development with transparent findings. No results from one device should be carried to the other similar devices.

8. Clinicians should perform studies on individual modalities, new devices and introduce the product in safe and regulated mannerin both public and private settings (research should not be limited to university medical centers) and store the data and related analysis on a national database or register that provides assessment of safety, efficacy, and complication rate in a standardised manner.

Closing remarks

Taken together, the findings of the studies encased in this doctorate provide substantial evidence about the potential of regenerative therapies, such as $FxCO_2$ laser, and PRP to serve as new non-surgical, first-line/conservative management approaches for PFDs, as well as GSM and LS. In my opinion, regenerative medicines have significant potential to revolutionise the way in which we treat people. Future research needs to focus on conducting large-scale randomised controlled trials to appropriately establish the safety and efficacy of these therapies, such that they can be accepted as standard practice as first-line treatments for conditions not just within gynaecology, but across many fields of medicine.

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