Surgery for pelvic organ prolapse: the quest to reduce failure rates

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Statement of Originality

This is to certify that to the best of my knowledge, the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is a product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Dr Vivien Wong

Abstract

Female pelvic organ prolapse is a common problem, which can be debilitating and life altering. From a pathophysiological point of view, pelvic organ prolapse can be considered as the herniation of pelvic organs through the levator hiatus, the largest potential hernia portal in the human body, into the vaginal canal. This condition commonly affects parous women. In the Australian population, a women's lifetime risk of requiring surgical treatment for prolapse is in the order of 19%, with a recurrence rate as high as 40 – 60% in the anterior compartment. It appears to be the most challenging compartment to successfully support. Given the high surgical failure rate, one of the main tasks for clinicians is to improve surgical treatment. This thesis is aimed at identifying methods of improving our surgical outcomes, utilising translabial ultrasound as the principal study method.

Due to the unacceptably high rates of prolapse recurrence, mesh augmentation was introduced as part of surgical treatment in 2003 – 2004 to Australia, in the hopes of improving treatment success. Despite limited data on safety and efficacy, there was a rapid and widespread adoption of mesh kits; however, the impact of this injudicious use of foreign material did not become apparent until recent years. Whilst in a retrospective analysis anterior mesh proved to have a lower recurrence rate compared to native tissue repair, it became evident that anterior anchored mesh, such as the Perigee™ (American Medical Systems, Minnetonka, USA) was of maximum benefit only in women who had sustained pelvic floor muscle trauma secondary to vaginal delivery. This form of trauma, termed 'levator avulsion', has

been shown to be a risk factor for prolapse development and prolapse recurrence. In particular, recurrence seems to affect primarily the anterior and apical compartments.

Over the years, there was also increasing emphasis on the importance of apical support especially when performing a repair of the anterior compartment. As such, mesh kit systems with apical anchoring such as the Anterior Elevate™ (American Medical Systems, Minnetonka, USA) were introduced approximately eight years ago. However, in a retrospective analysis of Anterior Elevate™, which utilises anchors into the sacrospinous ligament, it was found to be inferior in anatomical outcomes compared to the Perigee™, a transobturator anchoring mesh fixation device. Whilst conceptually, it would make sense to provide apical anchoring, the optimal method of anchoring remains unproven. The findings from this study, where the Anterior Elevate™ was inferior to the Perigee™ may plausibly be explained by inferior mechanical integrity or poorer load-bearing capability of the self-fixating anchors in the Anterior Elevate.

In another attempt to evaluate the importance of apical support, a surgical audit was conducted on laparoscopic sacrocolpopexy. Sacrocolpopexy has been recognised as the gold-standard surgical treatment for apical prolapse, which involves the placement of a piece of mesh from the vaginal vault to the anterior longitudinal ligament over the sacral promontory. Despite being a robust procedure, a surgical audit assessing the outcome of this treatment found that although the apex was well supported, there was still a very high rate of anterior compartment prolapse recurrence of above eighty percent. The results suggest that despite successfully

supporting the apex, it is important to also be providing support in the mid-vaginal level in order to achieve successful anatomical outcomes for cystocele repair.

Regardless of anchoring methods, mesh repair does not seem to be able to completely compensate for the effect of levator avulsion. Furthermore, it has been shown that transvaginal mesh augmentation did not confer additional benefit in women with excessive levator hiatal area ballooning, i.e. an abnormally distensible hiatus, which on its own is a risk factor for prolapse recurrence. The ongoing disenchantment with surgical outcomes led to the development of a novel surgical technique designed to reduce the size of the hernia portal, the levator hiatal area. The 'Puborectalis sling' procedure involves the placement of a strip of polypropylene mesh lateral to the levator ani muscle, i.e., in the infralevator space of the buttocks, with the aim of restricting hiatal enlargement. The procedure is based on the hypothesis 'The smaller the hernia portal, the less likely it is for the pelvic organs to descend through it'. A phase II clinical observational surgical trial was performed as a pilot study including over a hundred and ten women requiring prolapse surgery. A mean reduction of the levator hiatal area by 12cm^2 was achieved and sustained for over two years, achieving 'proof of concept'. A randomised controlled trial of the puborectalis sling is currently ongoing to evaluate its efficacy in reducing surgical recurrence.

During the course of this work, there has been rapid development in the field of pelvic floor medicine. The rise in vaginal mesh procedures saw a dramatic increase in mesh related complications, which led to heated debates over the use of transvaginal mesh.

Treatment of pelvic organ prolapse with polypropylene mesh shifted from being the ‘silver bullet’ of transvaginal prolapse repair to withdrawal of mesh products from the market - products that had been clearly shown to be effective. Regrettably, political and legal developments outside medicine have left too little time for researchers to investigate the risks and benefits in individual patients to develop criteria for patient selection.

This work hopes to contribute to the evolving literature of mesh use in pelvic reconstructive surgery, to investigate different types of meshes and their anchoring methods, and to outline an alternative operative approach in women at high risk of prolapse recurrence.

Acknowledgement

I would like to thank Prof Hans Peter Dietz for his invaluable support and encouragement throughout my urogynaecology training and also throughout the process of this thesis. It has been a long and arduous journey, but you have made it an amazing and truly fulfilling voyage. You have been awe-inspiring and in my mind, a true legend. I am extremely grateful for your guidance and I know that I couldn't have done it without you. Your determination and wisdom have left a permanent footprint not just on my path but also on the medical fraternity. Your understanding of women's pelvic floor dysfunction and the role imaging plays in this has been a "light bulb" moment for me and I am extremely grateful that you have shared your knowledge so generously, not just with me, but with the world. You have indeed left a legacy!

Thank you to my parents, Patrick and Patricia, without whom all this would not have become a reality. The sacrifices that you have both made to enable me to reach this destination and the constant support that you have given me have been the proverbial wind beneath my wings. I am forever indebted to you both.

Thank you to Prof Clara Shek, who has not only been an awesome co-supervisor, but a true friend who has provided me with guidance, a shoulder to cry on and great friendship. You have also been extremely inspiring and without you, I would be a forever PhD candidate! I am enormously grateful for all you have done for me throughout this journey.

Thank you to Prof Kate Moore, who guided me during my urogynaecology training and provided the opportunity for me to understand how the research world works.

Thank you to Dr Rodrigo Guzman Rojas, with whom I share a truly one-of-a-kind camaraderie. I have enjoyed working with you and will always look on the time we spent scanning chimpanzees at Taronga Zoo with equal fondness and apprehension!

Thank you to Susanne Langer, for all your help in tirelessly following up on patients and keeping things in order! To Andrew Martin and Kirsty Mann, thank you for all the biostatistical help and the tips and tricks in navigating the world of statistical analysis. Thank you to all my family and friends whose support and encouragement have provided the fuel for me to continue on this journey. It has been a long road!

Thank you to Karen, Kelly, Jeremy and Cameron for always being there for me. Your help during my times of need have made this possible. Thank you for the free accommodation, food and love!

To all the amazing patients who have voluntarily participated in our studies and for being so willing to help advance medical learning, I would like to sincerely thank you all. Your participation has given us a better understanding of how to help women with prolapse.

Last but not least, to my incredible husband Benson and son Nicholas for being so patient, understanding and supportive of my endeavours. Without you both being such amazing people, I would not have been able to begin, much less complete this rollercoaster journey. It has truly been one hell of a ride! Thank you for putting up with me and for so kindly accepting my shortcomings. You have both been my pillar and rock, thanks for keeping me upright this whole time!

Authorship Attribution Statement

This thesis contains studies that have been published:

1. **Wong V**, Shek KL, Goh J, Krause H, Martin A, Dietz HP. Cystocele recurrence after anterior colporrhaphy with and without mesh use. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014;172:131-5.

2. **Wong V**, Shek K, Rane A, Goh J, Krause H, Dietz H. Is levator avulsion a predictor of cystocele recurrence following anterior vaginal mesh placement? Ultrasound in Obstetrics & Gynecology. 2013;42(2):230-4.

3. **Wong V**, Shek K, Rane A, Lee J, Rosamilia A, Dietz H. A comparison of two different mesh kit systems for anterior compartment prolapse repair. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2014;54(3):212 - 7.

4. **Wong V**, Guzman Rojas R, Shek K, Chou D, Moore KH, Dietz HP. Laparoscopic sacrocolpopexy: how low does the mesh go? Ultrasound in Obstetrics & Gynecology. 2017;49(3):404-8.

5. **Wong V**, Shek KL, Korda A, Benness C, Pardey J, Dietz HP. A pilot sutdy on surgical reduction of the levator hiatus – the Puborectals Sling, *in process of submission to International Urogynaecology Journal.*

6. **Wong V**, Shek KL. The mesh debate: Transvaginal anterior anchored mesh should not be abandoned. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2017;57(1):105-7.

For publications 1, 2, 3 and 5; I performed data collection, data analysis and interpretation as well as prepared the manuscript for submission to peer-reviewed journals. For publication 4, I also co-designed the study, collected the data and performed data analysis/interpretation as well as prepared the manuscript and was responsible for final approval, under the supervision of Professor HP Dietz. For publication 6, I prepared the manuscript and was responsible for final approval for submission.

Dr Vivien Wong

List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
4D	Four-dimensional
ATFP	Arcus tendineus fasciae pelvis
BMI	Body mass index
DICOM	Digital Imaging and Communications in Medicine
FPOP	Female pelvic organ prolapse
Gh	Genital hiatus
ICS	International Continence Society
MRI	Magnetic Resonance Imaging
OR	Odds ratio
Pb	Perineal body
PFMC	Pelvic floor muscle contraction
PFMT	Pelvic floor muscle training
POP	Pelvic organ prolapse
POPQ	Pelvic organ prolapse quantification
PR	Puborectalis
RCT	Randomised control trial
ROC	Receiver Operator Curve
ROI	Region of interest
SSL	Sacrospinous ligament
SSF	Sacrospinous fixation
TUI	Tomographic ultrasound imaging
TOT	Transobturator
TVM	Transvaginal mesh
US	Ultrasound

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Chapter 1: Introduction

1.1 Pelvic organ prolapse: Scope of the problem

Female pelvic organ prolapse (FPOP) can be considered as a form of hernia, where female pelvic organs herniate into the vaginal canal through the levator hiatus, the largest potential hernia portal in the human body. Herniation of the bladder into the vaginal canal is known as a 'cystocele' or anterior vaginal wall prolapse, herniation of the rectum is termed a 'rectocele' or posterior vaginal wall prolapse and herniation of the uterus is known as 'uterine prolapse' or 'procidentia' if the uterus is entirely exteriorised. In women who have had a hysterectomy, vault prolapse may occur. In the case of vault prolapse, the apex of the vagina descends into the vaginal canal, most often due to herniation of the small bowel into the vagina, otherwise known as 'enterocele'. Complete exteriorisation of the vagina is termed 'vault eversion'. Amongst the various types of prolapse in Caucasians, cystoceles appear to be the most common followed by rectoceles, and apical prolapse (1).

FPOP is a common condition. In a study assessing women who presented to an outpatient clinic for routine gynaecological care, approximately fifty percent of women had an anatomical finding of prolapse at the level of the hymen (2). Of 1004 women between 18 and 83 years old, 38% were diagnosed with stage 1, 35% with stage II and 2% with stage III pelvic organ prolapse (3). In another study, approximately 40% of women aged between 45 and 85 years old had clinical evidence of a prolapse (4).

FPOP can be asymptomatic (5, 6). In symptomatic patients, the condition may give rise to a vaginal lump or a dragging sensation (7), sexual dysfunction, urinary frequency/urgency, urinary incontinence, voiding difficulties and/or bowel symptoms including obstructive defecation or faecal incontinence (8-10). These symptoms can be debilitating and can significantly impair a women's quality of life, both socially and physically (11).

Apart from pessary management, surgery is the mainstay of treatment for FPOP. A women's lifetime risk for prolapse surgery ranges between 10 – 20% (5, 12). In the United States, the annual cost of outpatient care for pelvic floor dysfunction between 2005 to 2006 was in the order of $300 million (13) and between 1979 to 2006, surgical repair for prolapse was amongst the most common inpatient procedure performed in women over the age of 70 (6). As the population continues to age in developed countries, pelvic organ prolapse and its related morbidities will place an increasing burden on the healthcare system (14).

Apart from the high prevalence of primary pelvic organ prolapse, prolapse recurrence after surgical repair is another significant clinical issue. It has been estimated that one third of patients require reoperation (5). Amongst the different forms of FPOP, cystocele seems to be the most difficult condition to manage with a recurrence rate after traditional anterior vaginal wall repair between 40 and 63% (15-18) and up to 90% in some women (19). Due to the high rate of prolapse recurrence, clinicians continually search for repair methods that would render stronger and more robust

support to the pelvic organs whilst retaining or restoring the functionality of the vagina for intercourse as well as normal bladder and bowel function.

1.2 Pelvic organ prolapse: Theories of aetiology

Over the years, a number of authors have published on aetiology and risk factors for pelvic organ prolapse and prolapse recurrence. However, the mechanisms leading to the development of FPOP remain poorly understood. The causation of FPOP is likely multifactorial, a result of a combination of risk factors which may vary between patients. Conceptually, different levels of pelvic organ support have been described, with complex interactions between the levator ani muscle, the vagina, the fascia and ligaments of the pelvic floor contributing to pelvic organ support. There have been several postulated theories of pelvic organ prolapse development.

Bonney (20) first suggested the possibility of pelvic organ descent secondary to the forces placed on the pelvic floor by increased abdominal pressures whilst DeLancey proposed the 'Ship in the Dock' hypothesis, where the interaction between pelvic floor muscles and pelvic ligaments was believed to play an important role in pelvic organ support (21). In this hypothesis, intact pelvic floor muscles help to maintain near-closure of the levator hiatal area, thus minimising the load and tension placed on pelvic ligaments and fascia, which attach the organs to the pelvic sidewall. A defective pelvic floor muscle in this scenario would allow the hiatus to widen, thus allowing the weight of the pelvic organs to put excessive loads on pelvic ligaments and fascia. These might fail over time, leading to FPOP.

DeLancey further described three levels of anatomical support of the pelvic structures suspending the pelvic organs (see Fig 1). These three levels of support were: Level 1, which consisted of the uterosacral and cardinal ligaments. They contribute to suspension of the upper vagina by attaching it to the pelvic sidewall; Level 2 contributes to support of the mid-portion of the vagina, where the paracolpium attaches the vagina laterally and more directly to the pelvic sidewall/ arcus tendineus fasciae pelvis (ATFP); Level 3 involves supports to the lower 1/3 of the vagina, where it directly attaches to the surrounding structures without any intervening paracolpium. It was believed that failure at different levels of pelvic musculo-fascial support may result in the development of different forms of pelvic organ prolapse (21). For instance, failure of Level 1 support may lead to uterine or vault prolapse while failure of Level 2 support may contribute to cystocele formation. The DeLancey view of prolapse aetiology clearly seems to have merit in explaining cystocele and uterine support; it is however quite insufficient to explain posterior compartment prolapse.

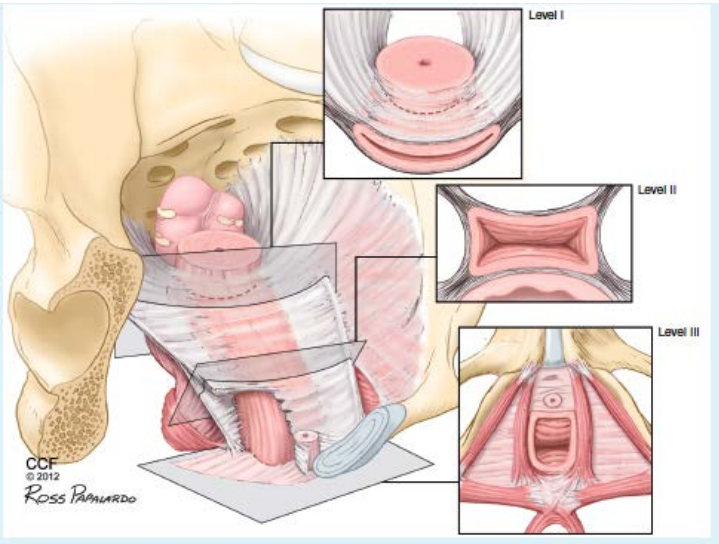

Fig 1: Current anatomical consideration for prolapse. From Lim VF et al, Recent studies of genetic dysfunction in pelvic organ prolapse: The role of collagen defects. Aust NZ Journal Obstet Gynecol. 2014;54(3):198 – 205 with permission.

Richardson, on the other hand, described potential mechanisms for prolapse development based on the theory of defects within the fibromuscular layer, the endocervical fascia between the vagina, bladder and the rectovaginal septum or Denonvillier's fascia between the vagina and rectum. He postulated that cystoceles or rectoceles developed due to isolated defects within these connective tissue structures. He claimed that closure of the defect was associated with successful surgical treatment of prolapse in 91.7% at 3 to 48 months after surgery (22). Site-specific defect repair of the rectovaginal septum in particular was shown to have high surgical success in the treatment of rectoceles (23). The latter has been confirmed in a recent publication of the unit by the author on a surgical audit of the technique in rectocele repair where anatomical cure reported in 85% on clinical examination and 80% on ultrasound assessment (24). It appears that for posterior compartment prolapse the Richardson hypothesis of prolapse pathophysiology does indeed hold true. However, this does not seem to be the case for the anterior and central compartments.

1.3 Pelvic organ prolapse: risk factors

There have been multiple studies on potential risk factors for FPOP. FPOP is likely multifactorial secondary to a combination of risk factors. Risk factors for POP may include aging, menopause, ethnicity, genetic predisposition and connective tissue disorders. Other risk factors may include body mass index, parity, mode of delivery, birth weight of the baby, length of second stage, constipation and other conditions

that are associated with a chronic elevation of intra-abdominal pressures, such as chronic lung diseases.

1.3.1a Age and Menopause

There seems to be an assumption that older women are at a higher risk of prolapse (25) and that menopause may contribute to poorer tissue elasticity and quality contributing to prolapse symptoms (26). However evidence in the literature is conflicting. Epidemiological studies have shown associations between age and prolapse (1, 27); however a study by Nygaard et al found that the rate of symptomatic prolapse was lowest in young women and then the rate plateaus in patients over the age of 40. The rate of prolapse was 1.6% in those 20 – 39 years old, 3.8% in 40 – 59, 3% in 60 – 79 and 4.1% in over 80 (28). In a study by Handa et al (29), 412 women were assessed every 2 years for over 8 years and the authors found the incidence of a new cystocele was 9%, rectocele was 6% and uterine prolapse was 2%. Interestingly, Handa et al also found a relatively high probability of regression of POP in their cohort. The annual rates of regression from stage 1 were 24% for cystocele, 22% for rectocele and 48% for uterine prolapse. In a large cohort of women symptomatic of pelvic floor disorders, an increase in organ descent was noted in premenopausal women; however, the relationship between age and anterior or posterior compartment prolapse was reversed after menopause (30). In studies on the association between age and prolapse recurrence, Whiteside et al have shown prolapse recurrence was more commonly seen in younger women (<60 years) and in those with more advanced preoperative pelvic organ prolapse staging (31). Diez-Itza

et al confirmed these findings in a study on women 5 years after vaginal prolapse repair (31, 32).

In regards to menopause, in a retrospective study on 311 women seen in a tertiary urogynaecological centre, there was no evidence for menopausal age as an independent predictor of any symptom and sign of pelvic organ prolapse and pelvic floor muscle function (33). Current use of hormonal therapy was shown to have a minor negative effect on pelvic organ support (34). These findings suggest that menopause is unlikely to play a major role in FPOP.

1.3.1b Ethnicity

Ethnicity has been thought to play a role in the pathogenesis of pelvic floor dysfunction for several decades (35-41). Data from epidemiological studies and from cadaver dissection suggested that African and Asian women might be less susceptible to FPOP compared to Latina and Caucasian women. African-American women were shown to be four to five times less likely to present with symptomatic prolapse and when compared with Caucasian, African-American women had 1.4-fold less risk of stage 2 pelvic organ prolapse (42). In a cadaveric study, Zacharin demonstrated superior anatomical pelvic support in Chinese compared to Caucasian women (37). Ultrasound studies have also confirmed less pelvic organ mobility in Asians compared to Caucasians (41, 43). The latter study further showed that the levator hiatal area was significantly smaller, and the pubovisceral muscle significantly thicker in Asians compared to Caucasians. Contrary to available data, a comparative

pelvic floor ultrasound study of young nulliparous Ugandans and Caucasians found that all measurements of hiatal dimensions and pelvic organ descent were significantly higher among the Ugandans despite no significant difference between the two groups in pelvic floor muscle thickness and levator hiatal area measurements (44). In a South African study on women symptomatic of pelvic organ prolapse, Black South Africans were shown to have significantly greater levator hiatal area size and greater pelvic organ decent on ultrasound as compared to other ethnic groups (45).

The role of ethnic contribution to prolapse development is complex. Factors such as genetics, lifestyle, diet and nutrition may also play a role. Differences in social background, educational level, degree of bother by prolapse (46), health-seeking behaviour and ease to access medical facilities might further contribute to the racial differences in relation to FPOP reported in the literature.

Interestingly, ethnicity was not shown to be a risk factor for reoperation after surgery for POP recurrence or urinary incontinence (47, 48).

1.3.1c Genetic predisposition and collagen dysfunction

Women with a strong family history of POP appeared to be at an increased risk of prolapse compared to those without (OR 2.58, 95% CI 2.12 – 3.15) (49). Certainly, in studies of twin siblings, there was strong evidence to demonstrate that heritability

contributed to the occurrence of pelvic organ prolapse (50). In a recent meta-analysis, family history was also shown to be a risk factor for recurrence (51).

There is a known correlation between collagen-associated disorders, such as Ehlers-Danlos and Marfan's syndrome, and increased prevalence of pelvic organ prolapse and prolapse recurrence (52-54). Women with prolapse were at significantly greater risk of abdominal hernias compared to controls (31.6% vs 5%, n = 120, p = *0.002*) (55). It appeared that alteration in the quality of collagen metabolism and tissue integrity might give rise to weaker fascial support (56); hence, it is plausible for genetics to play a part in POP development. Studies that analysed collagen components within the uterosacral and cardinal ligaments of women with prolapse found a decrease in total collagen structure but an increase in collagen III/I ratio. Type III collagen is more flexible and elastic while type I collagen has higher tensile strength due to its longer and thicker fibres (57). It has been suggested that increased elasticity of the pelvic floor tissues may lead to impaired pelvic organ support. However, this and similar claims based on studies such as the one quoted remain hypothetical as it is impossible to determine whether the observed changes reflect the cause or effect of POP.

1.3.2 Modifiable risk factors for pelvic organ prolapse

1.3.2a Obesity and Chronic increase in intra-abdominal pressures

Conditions associated with a chronic increase in intra-abdominal pressure e.g. constipation, chronic pulmonary disease and obesity, may increase load bearing on the pelvic floor and in turn, may impair pelvic organ support in the long term. Chronic pulmonary disease and constipation have been shown to be associated with pelvic floor dysfunction (58-60). It has also been suggested that repeated straining on defecation may cause stretching of the pudendal nerve, leading to possible progressive neuropathy and dysfunction in patients with chronic constipation (61, 62). However, the role of these conditions in the pathogenesis of POP remains unclear with conflicting results shown in the literature (3, 63).

As opposed to the ambiguity of the effect of chronic straining and prolapse development, obesity has been shown to be a risk factor for FPOP. The risk of FPOP in women with a body mass index (BMI) ≥ 30kg/m^2 was shown to increase by 2.5-fold compared to women with a normal BMI (1, 28, 64-66). It was shown that of those with a BMI between 25 – 30kg/m^2, the rate of pelvic organ prolapse was approximately 30 – 40% whilst in those whose BMI was greater than 30kg/m^2, the rate of FPOP was in the order of 40 – 75% (1). A recent meta-analysis (67) of over 20 studies evaluating the effect of BMI and pelvic organ prolapse has shown the risk ratios of developing prolapse to be at least 1.36 (95% confidence interval, 1.20 – 1.53) in those who were overweight, and at least 1.47 (95% confidence interval, 1.35 – 1.59) in obese women .

There was also some evidence for the association between obesity and prolapse recurrence (32, 51).

The association between prolapse and obesity however, is likely to be complex. There is evidence that being either primarily or exclusively overweight affects the posterior compartment (68).

1.3.2b Childbirth

Epidemiological and observational studies have shown that parity and vaginal delivery are significant risk factors for pelvic organ prolapse (3, 65, 66). Multiple studies have identified childbirth as the single most reliable predictor of FPOP in later life (1, 58, 69, 70). In a prospective study of 17,032 women who attended family planning clinics, childbirth was the strongest risk factor for FPOP and the risk increased with parity (27). Women with one child were 4 times and those with two children were 8.4 times more likely to require hospital admission for prolapse. The association between parity and FPOP may be partially due to the mechanical and/or hormonal effects of pregnancy on pelvic floor function. It is plausible that the gravid uterus may cause increased distension of the levator hiatus and pelvic organ descent. Furthermore, prolonged exposure to pregnancy hormones such as progestogens and relaxin may favour elastolysis and ultimately result in pelvic floor dysfunction (71). Collagen remodelling in response to pregnancy may also alter the mechanical strength of the pelvic floor and contribute to pelvic floor dysfunction (72). Unfortunately to date, the role of pregnancy in the pathogenesis of FPOP remains unclear and continues to require ongoing research.

Current data in the literature suggests that vaginal delivery may result in significant pelvic floor trauma, especially as the fetus passes through the birth canal. The disruption of pelvic musculature and fascia through this process clearly contributes to the pathogenesis of pelvic organ prolapse. Several long-term population studies found caesarean section to confer a reduced risk of pelvic organ prolapse in later life (66) compared to vaginal birth (65, 73, 74). Forceps delivery, on the other hand, was associated with an increased risk of FPOP (73-76). Trauma to the pelvic floor secondary to vaginal delivery, especially after forceps, may be the underlying explanation. There is now growing evidence to suggest that levator ani muscle injury is probably the missing link between childbirth and FPOP (77).

1.3.2c Levator trauma

The levator ani muscle plays an important role in pelvic organ support. The main component of the muscle and the most important for pelvic organ support seems to be the puborectalis muscle. This muscle structure forms a V-shaped sling around the anorectum posteriorly and attaches to the inferior pubic rami on both sides. The area bordered by the puborectalis muscle posteriorly and the symphysis pubis anteriorly is known as the levator hiatus, which is the largest potential hernia portal in the human body, through which pelvic organs herniate to cause FPOP. Both the integrity of the puborectalis muscle and the size of the levator hiatus are important determinants of pelvic organ support (78).

Abnormal levator ani anatomy in women with genital prolapse was first described by Halban and Tandler in 1907 (79); the first illustration of levator trauma is found in a textbook by De Lee published in 1938 (80). Over a decade later, Howard Gainey reported detachment of the pubococcygeus muscle (which we would call the puborectalis muscle and the condition, levator avulsion) on clinical examination in approximately 20% of patients following vaginal delivery (81). Dietz et al were the first to show levator avulsion was a result of vaginal delivery in a peripartum imaging

study (82, 83). The first case report of levator avulsion diagnosed in the delivery suite was published in 2007, when the same author showed the clinical and imaging documentation of a right-sided levator avulsion in a patient with a large vaginal tear (82), see Fig 1.1. It was in 2009 when the first anatomical confirmation of levator muscle damage was reported. In this study, a gross unilateral levator muscle defect was demonstrated on MRI and serial histological and histochemical stained sections of the pelvis in a 69-year-old multiparous patient (84).

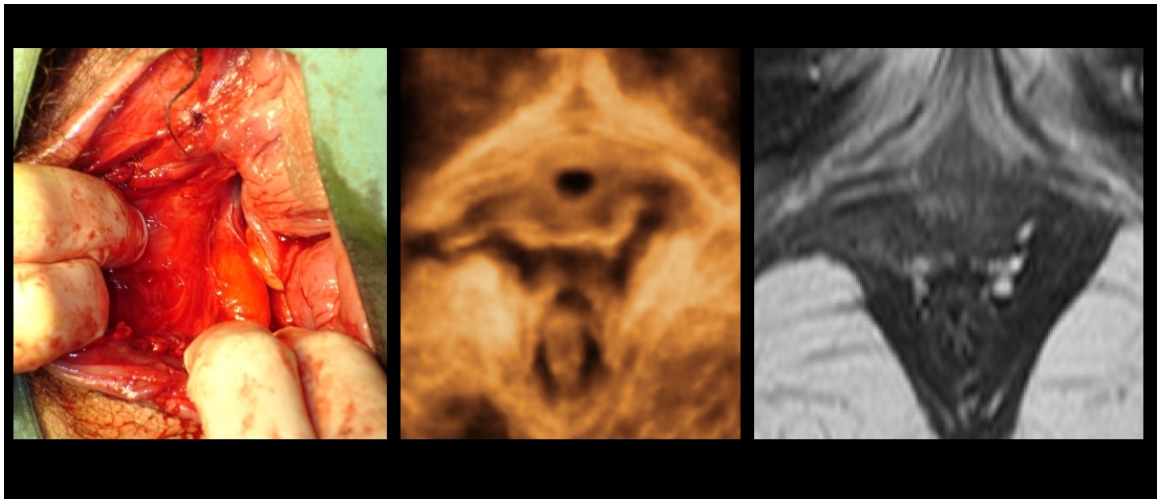

Fig 1.1: Major levator trauma as seen through a large vaginal tear after vaginal delivery (left), on ultrasound (middle) and on MRI (right) 3 months post-partum. Reproduced with permission from Dietz et al, ANZJOG 2007.

Computer modelling studies of childbirth have shown that the puborectalis muscle has to stretch 2 – 3.5 times its resting length during crowning of the baby's head (85, 86). An imaging study using the 3D ultrasound data of 224 pregnant nulliparous women showed that the required muscle stretch at vaginal delivery might in fact vary widely in the general population. The stretch ratio was reported to range from 0.62-2.76 for dimensions at rest and 0.24-2.42 for dimensions on maximal Valsalva (87). Hence, it is not surprising that up to 36% of women may sustain levator avulsion after vaginal birth (77). Reported risk factors of levator avulsion include increasing maternal age, increasing head circumference and the length of 2nd stage (88-90). Forceps is an important risk factor and was shown to be associated with a 3 – 4 fold increased risk of levator avulsion (91, 92). Ventouse delivery, on the other hand, confers a risk comparable to that of normal vaginal delivery (77).

In addition to macroscopic muscle injury, vaginal delivery may also result in microscopic or occult pelvic floor muscle trauma. Research in muscle physiology showed that substantial ultrastructural trauma, up to and including disruption of sarcomeres, was likely to occur if skeletal muscle distended to beyond 1.5 times its original length (93). Given the degree of muscle lengthening at vaginal delivery, it would therefore be plausible to accept that some form of occult muscle injury might occur even if the muscle remained grossly intact. In a peripartum ultrasound study, the hiatal area was shown to enlarge by >20% on Valsalva in 28.5% of primiparae 4 months after vaginal delivery (94) and this change to the levator distensibility might be irreversible (95). Increasing the length of 2nd stage was reported to be a risk factor for abnormal levator distensibility and epidural block might have a protective effect (92). Studies in young healthy nulliparous women and in women symptomatic of

pelvic floor dysfunction have shown an association between hiatal area and pelvic organ descent (96, 97). Microscopic levator trauma may cause an abnormally distensible hiatus or 'ballooning' and this injury may be another mechanism to explain the association between childbirth and FPOP.

Both levator avulsion and an abnormally distensible hiatus or hiatal ballooning have been shown to be independent risk factors for POP (98). A growing body of evidence has demonstrated an association between levator avulsion and POP, especially the anterior and central compartments (76, 99-102). Depending on the types of prolapse, it was reported that unilateral avulsion conveyed an odds ratio between 1.88 and 2.87 for symptoms and signs of prolapse, and between 2.22 and 5.31 in those with bilateral avulsion. Levator avulsion was found to be associated with increased muscle distensibility, an abnormally distensible hiatus or ballooning and reduced muscle contraction (103). These mechanisms are likely to underlie the association between avulsion and FPOP.

FPOP is a form of hernia and the levator hiatus is the hernia portal. The bigger the hernia portal is, the more likely that women will have signs and symptoms of POP as shown in several studies (98, 104-106). It was estimated that for each cm^2 of hiatal area enlargement on Valsalva, the risk of symptoms and signs of prolapse may increase by 6-11% (98).

1.4 Pelvic organ prolapse: Treatment options

1.4.1 Conservative therapy

Conservative treatment is usually regarded as the appropriate first step in the management of FPOP. It encompasses non-surgical methods including lifestyle intervention, weight loss, use of vaginal pessaries as well as pelvic floor physiotherapy (107). Randomised controlled trials have found patients with FPOP experienced improvement in their overall symptom of prolapse following intensive individualised pelvic floor physiotherapy (108-110). In a study of 109 women with pelvic organ prolapse ranging from stage 1 to 3, 19% of patients demonstrated one POPQ stage improvement as well as sonographic improvement in pelvic organ support with individualised pelvic floor muscle training sessions by a trained physiotherapist (111). In a meta-analysis of 13 trials assessing the impact of PFMT, the findings suggested a reduction in prolapse symptoms as well as an improvement in objective prolapse stage (risk ratio 1.7, 95% CI 1.19 – 2.44) (112).

Insertions of objects and devices into the vagina for prolapse reduction have been used for millennia. A Greek physician recommended insertion of half a pomegranate into the vagina to aid support whilst Soranus advocated insertion of a linen tampon soaked in vinegar and a piece of beef (113). Only in the early sixteenth century did medical doctors start to utilise purpose-made pessaries and these ranged from oval to round shapes. To date, there are a variety of pessaries of different kinds ranging from simple ring and donut shapes to more complex structures such as the Gellhorn or Shelf pessaries. In general, pessary treatment has been regarded to be

acceptable, both by clinicians as well as by patients (114). Patients who are more likely to fail pessary treatment tend to be of younger age (114, 115), those with advanced prolapse (115) or have had previous hysterectomy (116) and those with a larger levator hiatal area and levator avulsion (117). Pessary treatment appears to be successful (118, 119) however, the rate of long term use of pessaries remains low (120). In a study of 273 women fitted with a ring pessary, only 14% continued with pessary use for 7 years or longer (120). More than 50% of patients experienced complications such as bleeding, expulsion, vaginal discharge, pain and constipation and approximately 30% of patients elected for surgical treatment.

1.4.2 Pelvic organ prolapse – surgical treatment

Surgery is commonly employed for the management of symptomatic POP if conservative treatment is not desired or if it has failed. The earliest surgical treatment for POP was relatively simple, including suturing the labia together or removing pieces of vaginal mucosa prior to suturing the edges together to reduce vaginal calibre. The advent of anaesthesia and antimicrobials in the mid-19th century led to improved safety of surgery, such that it became feasible to surgically fix uterovaginal prolapse (121). Surgical management of FPOP evolved over the years with the aim to improve surgical outcomes. Synthetic materials were introduced to augment prolapse repair back in 1955 when Moore et al first used tantalum mesh for anterior compartment prolapse repair (122). In spite of this effort, recurrence remained common with approximately one third of prolapse procedures performed for recurrence (5).

Among the different forms of POP, cystocele can be a particularly difficult condition to manage with a recurrence rate after traditional repair between 40 to 63% (17, 19, 20). In 2003-2004 anterior vaginal meshes anchored via the transobturator route (Anterior Prolift™ Ethicon, Sommerville, NJ USA and Perigee™ AMS, Minnetonka, MN, USA) were invented in France by Prof Bernard Jacquetin and in Australia by Prof Ajay Rane and Prof Malcolm Frazer and marketed through US biomedical corporations.

During the research into mesh kit development, I had the opportunity to interview the co-creators of the transobturator mesh kit anchoring system, Prof Malcolm Frazer and Prof Ajay Rane. These two senior urogynaecologists were determined to improve the surgical repair methods for women with cystocele. The innovation of using transobturator anchoring was based on the concept of the transobturator midurethral slings, introduced in 2002. Placement of a Monarc™ sling involved passage of a helical needle trocar through the infero-medial aspect of the obturator foramen to retrieve a strip of polypropylene mesh, fed through a suburethral incision that allowed the creation of paraurethral tunnels. The sling sat midurethrally, between the urethra and vagina. This development had familiarised gynaecologists worldwide with the obturator foramen as a surgical field, and had established the safety of using this area for the passage of mesh arms.

According to Prof Rane, in the year 2000 he was in Clermont-Ferrand, France, where he observed Prof Bernard Jacquetin's insertion of a Monarc™ sling and subsequent cadaveric dissection. In 2003, Prof Frazer and Rane developed the idea of bilateral transobturator anchoring arms for an anterior compartment mesh,

improving on the concept of suture fixation to the pelvic sidewall, a clearly ineffective method. Initially, the Monarc^{TM} sling was intended to provide the inferior anchoring arms, while an additional superior strip of mesh would provide the cranial anchoring mechanism.

This was initially called Total Anterior Wall Shelf or Total Anterior Reconstruction System (TAWS/TARS, Frazer) or Transobturator Anterior Repair Approach (TARA, Rane), see Fig 1.2. A further novel surgical idea was the 'Obtuledge', a specifically designed mesh strip that allowed for paravaginal repair to the mesh, see Fig 1.3. The intention of Frazer and Rane was to design a commercially produced mesh kit system that provided a robust and easily learned technique for pelvic floor reconstructive surgeons, combining a low degree of invasiveness with ease of insertion. It involved the placement of 4 limbs attached to a central mesh patch supporting the bladder base from the bladder neck to the apex, with the four arms traversing the obturator foramen. The concept was submitted to American Medical Systems, Minnetonka, Minnesota USA, in 2003.

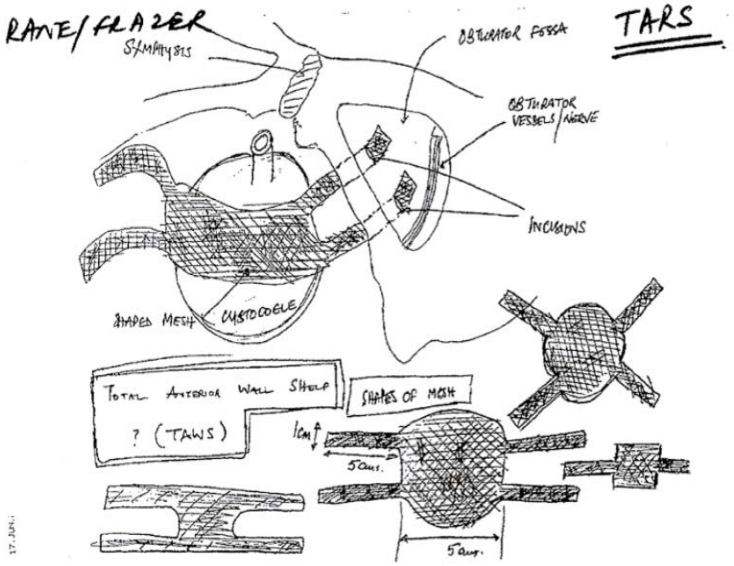

Fig 1.2: Original drawing of a transobturator anchoring mesh kit system by Frazer and Rane in 2003, used with permission by M Frazer.

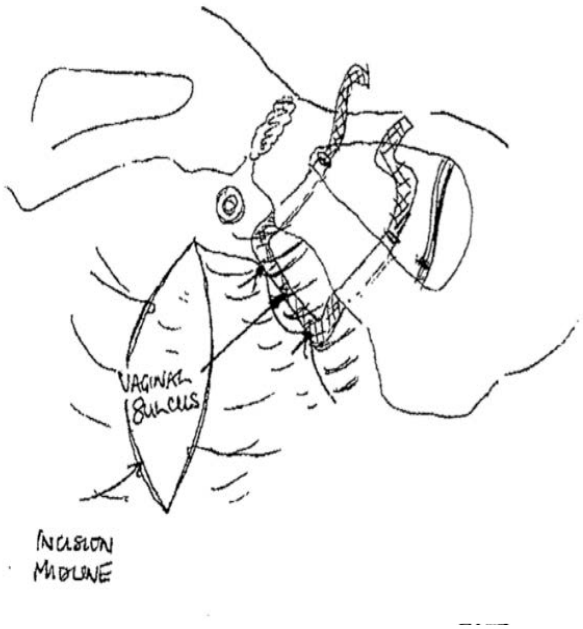

Fig 1.3: Original drawing of a side-wall mesh anchoring device, called the "Obtuledge" by Prof Frazer and Rane, as a form of paravaginal mesh anchoring technique in 2003, used with permission by Prof Frazer.

A patent application was submitted by American Medical Systems in 2004 (see Fig 1.4). Over several months of negotiations, full recognition was given to Prof Frazer and Rane by American Medical Systems later that year.

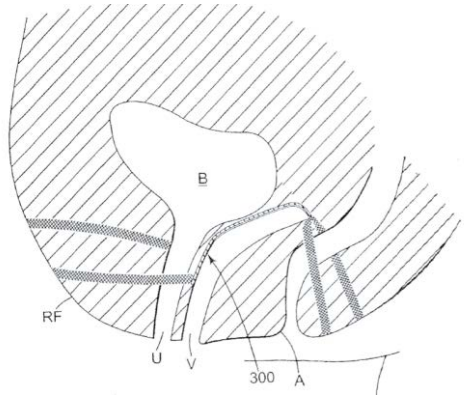

Fig 1.4: Drawing by engineers of the American biomedical company, patent application publication lodged in Feb 2004, US 2004/0039453, Fig 13.

The Perigee™ system (Fig 1.5) became available in Australia in 2004. Prof Rane performed the first 40 Perigee™ mesh kits in Australia with Therapeutic Goods Australia (TGA) special Access Scheme permission, and this series was performed under local HREC approval.

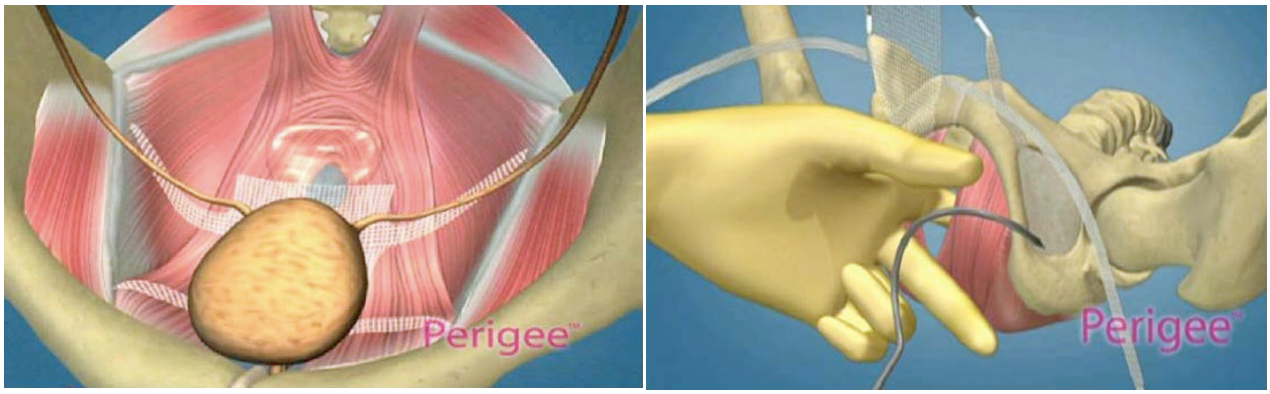

Fig 1.5: The Perigee™ mesh kit system by American Medical Systems. Used with permission from Moore R and Miklos J, "Vaginal Repair of Cystocele with Anterior Wall Mesh via Transobturator Route: Efficacy and Complications with Up to 3-Year Follow-up," Advances in Urology, vol. 2009, doi.org/10.1155/2009/743831.

In France, Bernard Jacquetin also developed the idea of an anterior mesh hammock. Prior to the year 2000, due to ongoing suboptimal prolapse repair outcomes, Jacquetin began to explore the concept of paravaginal defect repairs. Initially, by suturing to the ATFP with disappointing efficacy. He established the Transvaginal mesh (TVM) group to test a "TVM" mesh concept, that is, a trapezoidal mesh to support the bladder base, with a lateral transobturator arm. Originally, the concept was a single-arm design (Fig 1.6); however, due to poor stability a second transobturator arm was added, creating the basis for the anterior Prolift™ mesh kit.

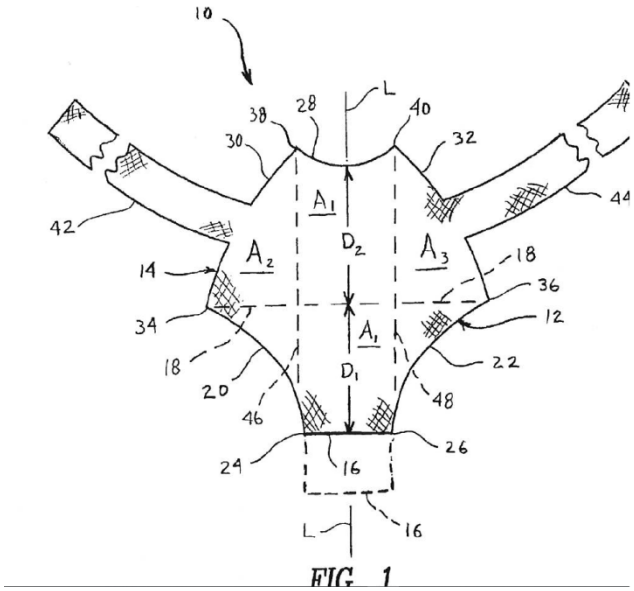

Fig 1.6: Anterior mesh kit system with single arm (with permission from B Jacquetin).

Between 2000 and 2005, anterior mesh kit prototypes developed by Jacquetin were tested on animals and cadavers by the "TVM" group, both in Clermont-Ferrand and in Paris. A first patent application was lodged in 2002. In collaboration with engineers from Ethicon, the anterior and posterior Prolift™ mesh kit systems were patented in 2003 (Fig 1.7).

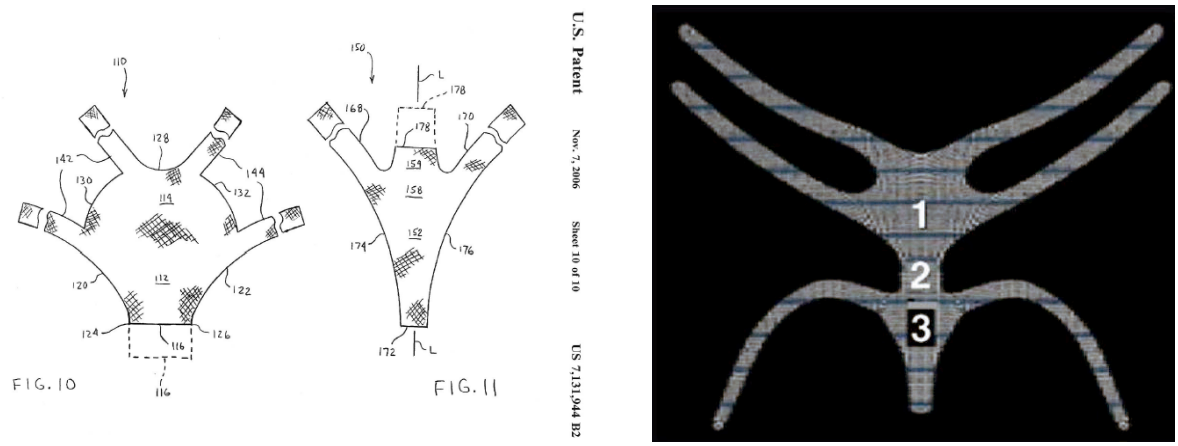

Fig 1.7: Anterior and Posterior Prolift™ mesh kit systems. Figure on the left, reproduced with permission from Prof Jacquetin. Figure on the right, reproduced with permission from Fatton et al, Int Urogynae Journal 2007.

In the following years, multiple medical device companies developed mesh kits along similar design lines. The most substantial deviation from the original concept of transobturator anchoring was the replacement of lateral transobturator arms with plastic anchors designed to perforate the arcus tendinous of the pelvic fascia and / or the obturator internus muscle and its fascia (Anterior Elevate™, introduced in 2008), an approach that has not been successful. Another design change was the incorporation of apical anchoring to the sacrospinous ligaments as in the Anterior Elevate™ and Uphold™ (introduced in 2008) kits.

The primary aim of all anterior anchored mesh kits was to provide better load resistance and thus, improved anatomical outcome through a minimally invasive approach. As a result of effective global marketing the introduction of these mesh kits into clinical practice was rapid. Widespread adoption occurred in spite of limited data

on safety and efficacy. While randomised controlled studies later found a higher objective cure rate with transobturator mesh repair compared to anterior colporrhaphy (123-125); recurrent cystocele was not uncommon and was reported in 13% of patients at 10-month follow up in a surgical audit on the Perigee™ transobturator mesh. In this study, recurrent cystocele was observed to occur dorsal to the anchored mesh in five women on ultrasound imaging. This was seen to be associated with a marked change in the mesh axis on Valsalva, which implied dislodgment of the superior anchoring arms (126). It was the first documentation of mesh failure using imaging in literature, and it also provided insight into the mechanisms of mesh success. Understanding both advantages and disadvantages in individuals was important as its use requires the balancing of both risks and benefits. This was because mesh augmentation surgery is not innocuous and can lead to serious complications (127).

Anatomical studies performed in the early 2000s pointed out the strong association between cystocele and apical prolapse (128). Some authors subsequently claimed that apical anchoring was essential for fixing anterior compartment descent, which led to the introduction of mesh kits such as the Anterior Elevate™ (American Medical Systems, Minnetonka, USA) in 2008. The Anterior Elevate™ is an anterior anchored mesh that utilised tissue anchors to the arcus tendineus fascia pelvis (ATFP) and sacrospinous ligaments (SSL). A different method of apical suspension is the use of mesh inserted through an abdominal incision called a sacrocolpopexy, which is a surgical procedure for vault or uterine prolapse. This procedure was shown to be highly effective in providing apical support but less effective for the anterior and posterior compartment (129), challenging the concept that apical support is important

for cystocele repair. This has also led to the question of whether mesh location, i.e. how far down the mesh is on the vaginal wall, is important for anatomical outcome.

It is generally assumed that etiological factors for pelvic organ prolapse may also be risk factors for POP recurrence after surgery. However, there is limited literature reviewing the risk factors for prolapse and prolapse recurrence and even a fewer number of updated meta-analysis on this topic. Friedman et al recently reviewed twenty-five studies with a total of 5082 patients and an average prolapse recurrence rate was found to be 36%. The authors performed a meta-analysis on body mass index (BMI), age, preoperative stage, levator avulsion, parity, constipation/straining, number of compartments involved, prior hysterectomy and family history. They showed that levator avulsion [odds ratio (OR) 2.76, $P < 0.01$], preoperative stage 3–4 (OR 2.11, $P < 0.001$), family history (OR 1.84, $P = 0.006$), and hiatal area (OR 1.06/cm^2, $P = 0.003$) were significant predictors for recurrence (51).

The findings of this meta-analysis suggested that secondary repair of levator avulsion may offer benefit. This procedure involves reconnecting the puborectalis muscle back to the os pubis. Dietz et al were the first to report the outcomes of a pilot study on surgical repair of levator avulsion in 17 women who had concomitant prolapse repair for symptomatic POP. The authors showed that while direct surgical repair of levator avulsion was feasible at the time of prolapse repair, its effect on prolapse recurrence and hiatal dimensions was relatively disappointing (130). Five patients had prolapse recurrence beyond the hymen and the mean hiatal area on Valsalva was reduced

from 36.84cm^2 to 30.71cm^2 (p< 0.001), still well above the limit of normal at 25cm^2 (96, 97).

The findings of an association between hiatal area and prolapse recurrence can be explained by basic physical considerations. As Pressure = Force / Area, the forces acting on pelvic support structures are directly proportional to the size of the hiatus (see Fig 1.8). In other words, the forces acting on pelvic floor structures are likely to be directly proportional to intra-abdominal pressure and hiatal area. The wider the levator hiatus is, the more load is placed on pelvic organ support, which may be formed by native tissue, surgical sutures or mesh structures in prolapse repair. Hence, traditional repair techniques may fail, resulting in prolapse recurrence. It is plausible that surgical measures aimed at reducing the hiatal area might decrease prolapse recurrence by reducing the load on pelvic organ support.

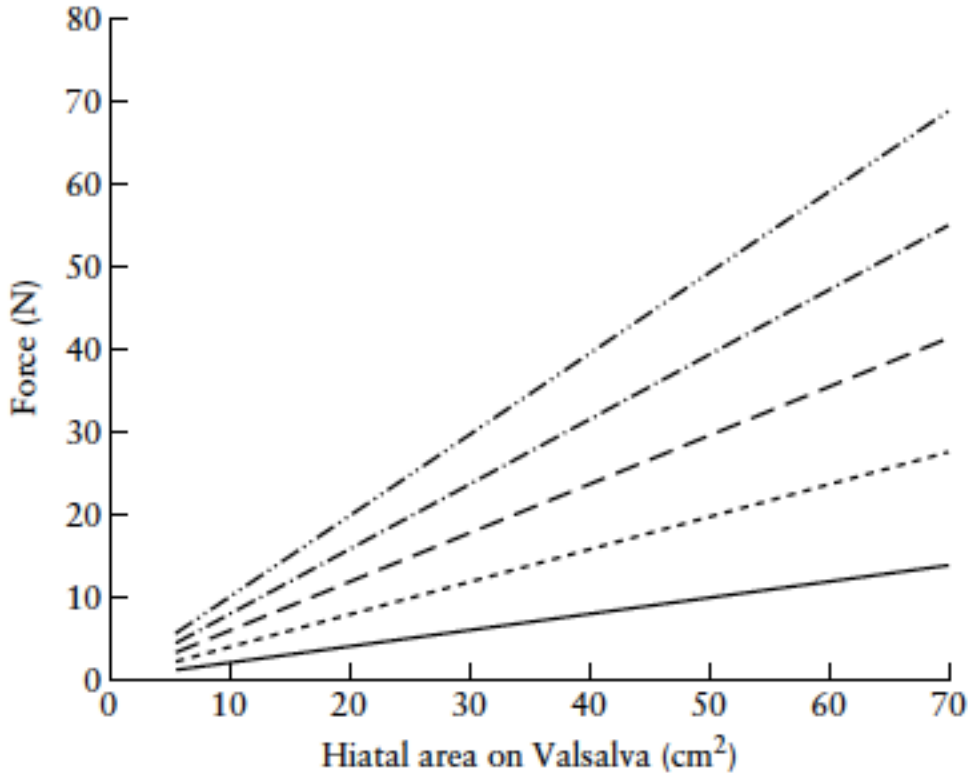

Fig 1.8: Modelling of pelvic floor loading relative to abdominal pressure and hiatal area on Valsalva. The force generated by a given intra-abdominal pressure will vary markedly, depending on hiatal area on Valsalva. ——— 20 cmH_2O; - - - - - 40 cmH_2O; – – – -60 cmH_20; — · — · 80 cm H_20; — · · — · · 100 cmH_20. Reproduced with permission from Dietz, UOG 2012; 40: 495 – 503.

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1.6 Aims of thesis

From the previous discussion, it is evident that successful surgical treatment of FPOP is challenging. This may be largely due to a lack of understanding of the pathophysiology of FPOP, and resulting problems with matching a given patient to the most appropriate procedure. The constant drive to improve surgical outcomes among pelvic reconstructive surgeons led to the adoption of mesh technology without sufficient safety and efficacy testing. In the past this would have been remedied by ongoing development, much of it by trial and error, over decades, as occurred with other innovative medical technologies such as hip replacements. The increasing risk-adversity of Western society has however made such an approach quite unacceptable.

It is evident that a different approach should have been followed, taking into account modern research ethics and regulations. Unfortunately, the ever-increasing compliance burden associated with human research and the adversarial and highly lucrative nature of Western, (especially US) tort law have now cut short efforts at optimisation of mesh design and patient selection, at least for the time being.

Several RCTs have confirmed the efficacy of anterior transvaginal mesh in improving anatomical outcomes compared to traditional native tissue repair; however, insufficient efforts were made to optimise patient selection. This led to the widespread, nonselective use of transvaginal mesh in prolapse surgery without

appropriate diagnostic efforts in order to balance the risks and benefits in individual patients.

There is a growing body of evidence identifying the role that the levator ani muscle has for pelvic floor support. Levator avulsion and hiatal ballooning have been identified to be important risk factors for POP recurrence. Hence any novel surgical technique should first be tested in women at high risk of recurrence, that is, in those with an abnormal pelvic floor. Surgical techniques that compensate for the effects of abnormal levator ani muscle structure would be expected to improve surgical outcomes; hence the development of such techniques should have a high priority.

This work was undertaken to test the following hypotheses:

1. **Augmentation for anterior compartment prolapse is associated with better outcome as compared to traditional anterior colporrhaphy.**

Hypothesis 1 is tested in Chapter 3. In this retrospective cohort study, subjective and objective outcomes including ultrasound quantification of prolapse, following anterior colporrhaphy with and without mesh use for anterior compartment prolapse were assessed. The study further evaluated the efficacy of anterior anchored mesh in women with and without levator avulsion. The study resulted in Paper 1: Wong V, Shek KL, Goh J, Krause H, Martin A, Dietz HP. Cystocele recurrence after anterior

colporrhaphy with and without mesh use. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014;172:131-5.

2. **Levator avulsion is a risk factor for prolapse recurrence after anterior mesh repair.**

Hypothesis 2 is tested in Chapter 4. In this retrospective analysis of data obtained through clinical audits on anterior transobturator mesh procedures (Perigee™ system, American Medical Systems, Minnetonka, MN, USA and Anterior Prolift™ system, Gynecare/Ethicon, Somerville, NJ, USA) performed at three tertiary urogynaecology centres. Levator avulsion was investigated as a risk factor for prolapse recurrence following anterior colporrhaphy with mesh reinforcement. The study resulted in Paper 2: Wong V, Shek K, Rane A, Goh J, Krause H and Dietz H. Is levator avulsion a predictor of cystocele recurrence following anterior vaginal mesh placement? Ultrasound in Obstetrics & Gynecology 2013; 42: 230-234.

3. **Vaginal mesh with apical anchoring to the sacrospinous ligament is associated with improved outcomes compared to mesh implant with sidewall fixation.**

Hypothesis 3 is tested in Chapter 5. In an observational study using data obtained in one internal and two external surgical audits of anterior compartment mesh conducted at three tertiary urogynaecological centres, subjective and objective outcomes of two mesh kits, the Perigee™ and Anterior Elevate™ were compared.

This resulted in Paper 3: Wong V, Shek K, Rane A, Lee J, Rosamilia A and Dietz H. A comparison of two different mesh kit systems for anterior compartment prolapse repair. Australian and New Zealand Journal of Obstetrics and Gynaecology 2014; 54: 212 – 217.

4. **Abdominally placed mesh for apical or uterine prolapse is effective for anterior compartment support.**

Hypothesis 4 is tested in Chapter 6. In an external surgical audit of laparoscopic sacrocolpopexy performed by an experienced laparoscopic surgeon, the efficacy of the procedure in anterior compartment support was evaluated. The correlations between mesh location and mobility and prolapse recurrence on ultrasound imaging were studied. This study resulted in Paper 4: Wong V, Guzman Rojas R, Shek K, Chou D, Moore KH and Dietz HP. Laparoscopic sacrocolpopexy: how low does the mesh go? Ultrasound in Obstetrics & Gynecology 2017; 49: 404-408.

5. **Surgical placement of a piece of mesh sling around the puborectalis muscle safe and effective to reduce levator hiatal area.**

This hypothesis is tested in Chapter 7. In a pilot study on women with symptomatic POP and hiatal ballooning, the safety and efficacy of a novel technique, the Puborectalis Sling, in reducing hiatal area was evaluated. This study resulted in Paper 5: A pilot study on surgical reduction of the levator hiatus - the Puborectalis Sling. Wong et al, in process of submission for publication.

6. **Should mesh continue to be made available to pelvic reconstructive surgeons?**

This question was investigated in Chapter 8. In an opinion piece, current evidence for the use of transvaginal anterior anchored mesh in pelvic reconstructive surgery is detailed. I opposed a ban of mesh since it is now quite clear that women with levator avulsion are likely to benefit with mesh augmentation for prolapse repair. This opinion was published as Paper 6: Wong, V., & Shek, K. L. (2017). The mesh debate: Transvaginal anterior anchored mesh should not be abandoned. Australian and New Zealand Journal of Obstetrics and Gynaecology, 57(1), 105-107.

Chapter 2: Methodology

This work, apart from Paper 6, incorporates several studies on patients after prolapse repairs. Paper 6 is an opinion piece, part of an invited debate in the pages of the premier journal in the field of urogynaecology that is based on a literature search of the current scientific evidence to examine the role of anterior transvaginal mesh in pelvic reconstructive surgery. Patients in Papers 1 to 4 were seen in the context of surgical audits. Paper 5 is a prospective observational study on women enrolled in an experimental surgical multicentre trial. All studies were approved by local human research ethics committees as stated in the corresponding publications.

Patients in this work were seen at multiple centres in Australia including Nepean Public Hospital, Penrith NSW; Royal Prince Alfred Hospital, Newtown NSW; St George Private Hospital, Kogarah NSW; Waverley Private Hospital, Melbourne VIC; Greenslopes Private Hospital, Brisbane QLD and Mater Hospital, Pimlico, Townsville QLD. They all underwent a standardised interview, clinical examination and translabial ultrasound imaging as detailed below. Patients enrolled in the prospective surgical trial in Paper 6 were also interviewed and assessed preoperatively.

2.1 Interview

During the interview, basic demographic data including past obstetric history, height, weight, history of previous pelvic surgery and surgery performed after the index procedure were obtained. Patients were asked about recurrent symptoms of prolapse defined as a vaginal lump or a dragging sensation. Lower urinary tract and bowel

symptoms including stress and urge urinary incontinence, urinary frequency, voiding difficulties, constipation, obstructed defecation and faecal incontinence were also investigated. Sexual dysfunction, in particular dyspareunia, was noted. Patients were asked if they were satisfied with the surgical outcome and to rate overall symptomatic outcome as cured, improved, same, worse or uncertain. A datasheet used to evaluate patient outcome can be found in Appendix 1.

2.2 Clinical examination

Over the years, a number of staging systems have been described to quantify FPOP clinically, starting with the one by Porges in 1963 (1-4). These systems, however, share the same problem in that they are only a description of changes in surface anatomy and in that they provide no information as to the nature of the prolapse. As an example, a posterior compartment prolapse can either be due to a true rectocele, an enterocele, perineal hypermobility or rectal intussusception (5). Unfortunately, none of those systems have been evaluated properly as a test for the prediction of symptoms of prolapse, nor have they been validated against imaging until recently. Nevertheless, the last such system, the prolapse quantification system of the International Continence Society (POP-Q) has been widely adopted and has become the standard method of describing and assessing clinical prolapse, see Fig 2.1 (6). It is also the quantification system used in this thesis. Using the POPQ, gh (genital hiatus), pb (perineal body) and maximal descent of six points on the vaginal surface were measured relative to the hymenal remnant on Valsalva, in the dorsal lithotomy position after bladder emptying.

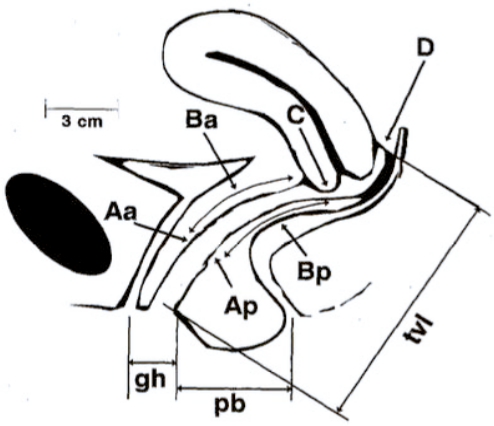

Fig 2.1: The POPQ system involves assessment of six points (points Aa, Ba, Ap, Bp, C, D) as well as points gh (genital hiatus), pb (perineal body) and tvl (total vaginal length). Each points are assessed on Valsalva except for TVL. Reproduced with permission from Bump et al, Am J Obstet Gynecol 1996; 175 (1): 10-7.

Until recently, there was a lack of a definition of significant POP (i.e. degree of pelvic organ descent) that is predictive of symptoms. The National Institutes of Health (NIH) Workshop on Standardisation of Terminology for Researchers in Pelvic Floor Disorders recommended an arbitrary definition using POPQ stage 2, i.e. pelvic organ descent to 1cm above to 1cm below the hymen as the cut-off to define significant POP (7). In this thesis, the same cut-off was used to define significant POP and recurrent pelvic organ prolapse. However, it is acknowledged that there is no general consensus on the definition yet, and that it is very unlikely to be optimal. Using Receiver Operator Characteristic statistics, Dietz et al recently showed that a cut-off of 0.5cm above the hymen in the anterior and posterior compartment, and 4cm above the hymen in the apical compartment were most predictive for symptoms of prolapse, i.e. a lump/dragging sensation (8). Barber et al. gives absolute priority to subjective outcomes and argues that definitions of treatment success should require patients be free of symptoms of prolapse postoperatively (9). However, as many patients with

recurrent POP are asymptomatic (10), POP symptoms do not seem to be optimally sensitive as outcome measures of surgical success. Furthermore, the basic principle of prolapse repair is to restore normal anatomy. We have therefore used a stricter definition based solely on anatomical assessment on clinical and on ultrasound examination to define surgical success in this work.

2.3 Pelvic floor ultrasound imaging

2.3.1 Technique

The advent of ultrasound technology has revolutionised the assessment of the pelvic floor. Use of imaging in Urogynaecology has a history that dates back to the 1920s. Radiological techniques were first used to describe bladder appearance and descent, and later for prolapse. The introduction of B mode real-time ultrasound offered an alternative for pelvic floor assessment. Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) were more recently developed for the same purpose (11). As compared to other imaging modalities, ultrasound is advantageous as it is inexpensive, safe, easy to perform, has high patient acceptance and is easily accessible to clinicians. It has superior spatial and temporal resolution compared to all other imaging methods. Furthermore, ultrasound is the only imaging modality that allows synthetic implants (e.g. meshes) to be visualised, a benefit that is of great relevance to this work. As compared to the transvaginal route, translabial / transperineal ultrasound imaging is non-invasive, allowing real time imaging on dynamic manoeuvres, e.g. Valsalva or pelvic floor muscle contraction, for the assessment of pelvic floor functional anatomy. Today, ultrasound is increasingly used

in the evaluation of pelvic floor disorders especially in women with pelvic organ prolapse, urinary and/or faecal incontinence (11, 12). 3D/4D ultrasound has further facilitated pelvic floor assessment by allowing imaging in the axial plane. This results in the capability to assess the integrity of the levator ani muscle, its insertion to the pubic symphysis and the levator hiatus. The technology allows acquisition of sequences of volume data blocks for archiving and later retrieval for assessment. As there is no 3D or 4D DICOM (Digital Imaging and Communications in Medicine) standard presently, proprietary software is required for post processing analysis of volume data. Over the last twenty years, the technique and the methodology of performing translabial ultrasound has been established and standardised. This work was performed according to the published methodology as detailed elsewhere (13).

Translabial ultrasound imaging is performed with the patient in the supine position using GE Voluson systems (730 expert, 730 Pro, S6, S8, E8 and Voluson i) with RAB 8–4-MHz transducers (GE Medical Systems, Zipf, Austria). It is imperative that imaging is performed after bladder emptying. Prior defecation can also be helpful as it has been shown that a full bladder or a full rectum may hinder pelvic organ descent which may lead to a false negative assessment (14). Figure 2.2 shows placement of the transducer on the perineum for translabial scanning and the corresponding schematic representation of the image obtained in the mid-sagittal view on the ultrasound monitor. Volume acquisition is obtained at rest, on maximum Valsalva and on maximum pelvic floor muscle contraction. During data acquisition on Valsalva, care is taken to ensure patients do not co-activate the levator ani muscle. Levator co-activation is common especially in young nulliparous women (15). It occurs when there is triggering of a pelvic floor muscle contraction when the patient is asked to

bear down and is evident as shortening in the anteroposterior diameter of the hiatus and/or elevation of the bladder neck (16). Levator co-activation is a confounder of pelvic organ descent and may lead to false negative findings. During imaging, attention is also paid to ensure the Valsalva manoeuvre is of adequate duration. To achieve near maximal pelvic organ descent, a Valsalva manoeuvre should last for at least 5-6 seconds (17). There have been suggestions to standardise the Valsalva manoeuvre that involved invasive pressure measurement, for example by asking patients to blow into spirometer-like devices. The technique required an open glottis and may explain why pressures generated were very low (18, 19). In fact, it does not appear necessary to standardise Valsalva pressure. In a study on 75 women, Mulder et al showed that virtually all patients were able to generate intra-abdominal pressures resulting in near maximal pelvic organ descent if properly coached (20) arguing against the need to standardise the Valsalva pressure.

It is important however that dynamic manoeuvres are repeated. At least 3 Valsalva manoeuvers are performed and archived. Volume data showing maximum descent is used for the assessment of pelvic organ prolapse and hiatal area. Post processing is performed at a later date, typically months or even years after image acquisition, using the proprietary software 4D View (GE Medical Kretz Ultrasound, Zipf, Austria), on a desktop personal computer blinded to all clinical data. It has been shown that the published technique for translabial ultrasound imaging is highly repeatable, both in US volume data acquisition and in offline assessment of US parameters (21-23). Furthermore, translabial ultrasound measures of pelvic organ descent are strongly associated with symptoms of FPOP (24, 25) and have a good correlation with POPQ coordinates (26) further validating the technique and the methodology.

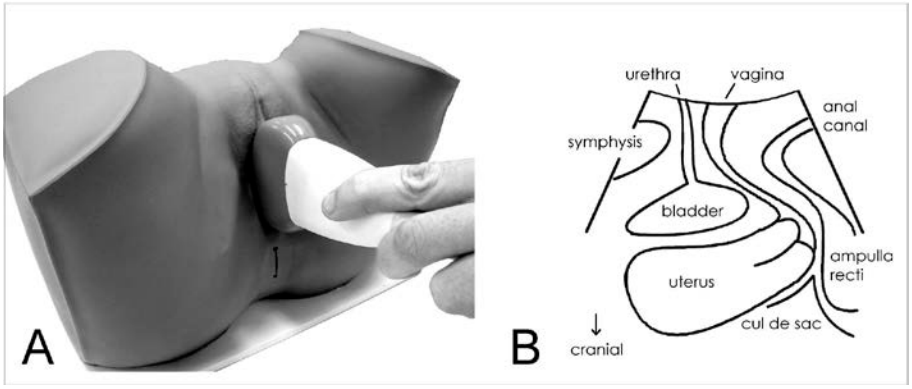

Fig 2.2: Transperineal placement of the ultrasound transducer (image A) and a schematic representation of the pelvic organs obtained in the mid-sagittal plane (image B). From Dietz H. Pelvic Floor ultrasound: a review. Am J Obstet Gynecol. 2010; 202 (4): 321 – 34, with permission.

2.3.2 Pelvic organ descent assessment

Volume data showing the most pelvic organ descent on Valsalva is used for the assessment of pelvic organ descent. Pelvic organ descent is measured against a reference line drawn horizontally from the infero-posterior margin of the symphysis pubis (see Fig 2.3). Organ descent below the reference line has a negative value and above the reference line, a positive value.

Using Receiver Operator Characteristic (ROC) statistics, Dietz et al have defined optimum cut-offs to predict symptoms of prolapse on translabial ultrasound as -10mm and -15mm for cystocele and rectal descent respectively (a minus sign represents descent ***below*** the pubic symphysis) (8). There had been no studies to determine the optimal cut-off for central compartment descent and zero i.e. descent to the level of the pubic bone, was used to define significant central compartment descent until

recently. In 2015, the same group showed that +15mm was the optimum cut-off to predict prolapse symptoms for uterine descent using ROC statistics (a plus sign implies descent to above the pubic bone) (25). We have adopted the same definitions for significant anterior and posterior pelvic organ descent or recurrent prolapse. In Paper 4 the old definition, i.e. descent to the level of the pubic bone, was used to define central compartment prolapse.

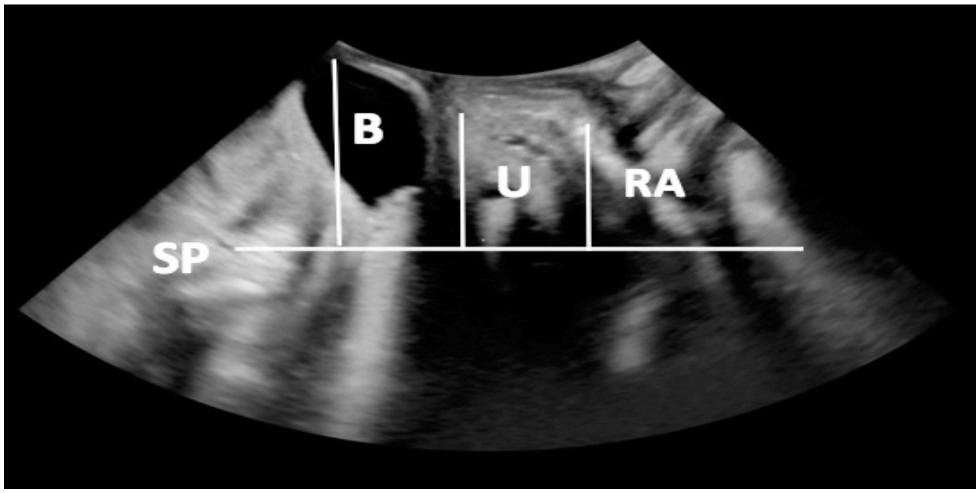

Fig 2.3: Translabial ultrasound imaging in the mid-sagittal image on Valsalva manoeuvre. Orientation: top of the image is caudal; bottom is cranial, left of the image is ventral and right is dorsal. Pelvic organ descent is measured with the most dependent part of the bladder, the leading edge of the uterus and the most caudal part of the rectal ampulla and/or small bowel, from a reference line drawn horizontally through the infero- posterior margin of the symphysis pubis. SP = symphysis pubis, B = bladder, U = uterus, RA = rectal ampulla.

2.3.3 Assessment of mesh implant

In Paper 4, the location and mobility of the mesh used in laparoscopic sacrocolpopexy was accessed. Mesh is identified on ultrasound as a highly echogenic structure in all three orthogonal planes (mid-sagittal, coronal and axial; Figure 2.4), at rest and on maximum Valsalva.

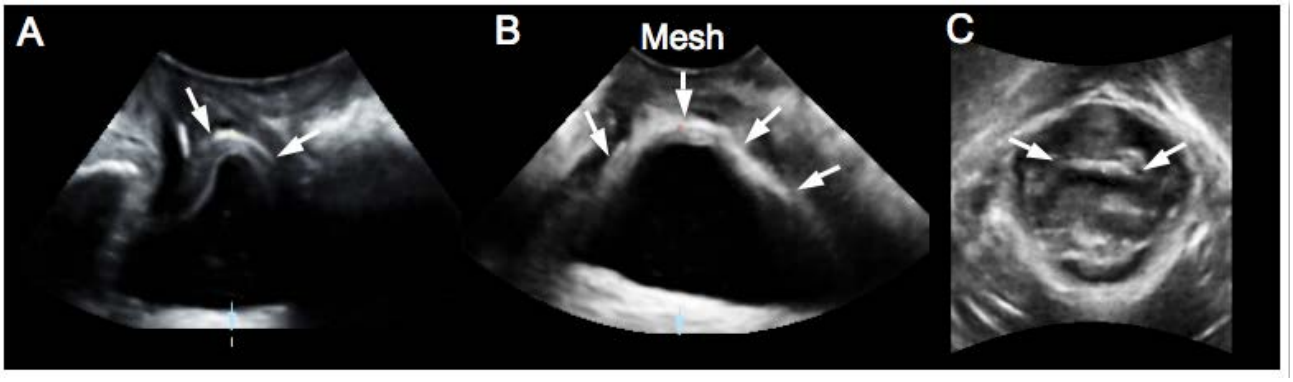

Fig 2.4: Image of the mesh in orthogonal planes; midsagittal (A), coronal (B) and axial (C) plane on maximum Valsalva. Mesh is indicated by arrows. From Wong et al. Laparoscopic sacrocolpopexy: how low does the mesh go? Ultrasound Obstet Gynecol 2017; 49: 404 – 08 with permission.

The lowest mesh position was identified in the mid-sagittal plane on maximum Valsalva, with the most caudal aspect of the mesh plotted against a reference line drawn from the infero-posterior margin of the symphysis pubis. Distal mesh mobility was assessed using the formula $\sqrt{[(X_{Valsalva} - X_{rest})^2 + (Y_{Valsalva} - Y_{rest})^2]}$ from rest to maximum Valsalva, where *X* is the horizontal distance between mesh and inferior symphyseal margin and *Y* is the vertical distance between mesh and inferior symphyseal margin (Fig 2.5). The distance from the distal mesh end to the bladder neck was also determined at rest and on maximum Valsalva. These sonographic measures were used to study correlations with prolapse recurrence.

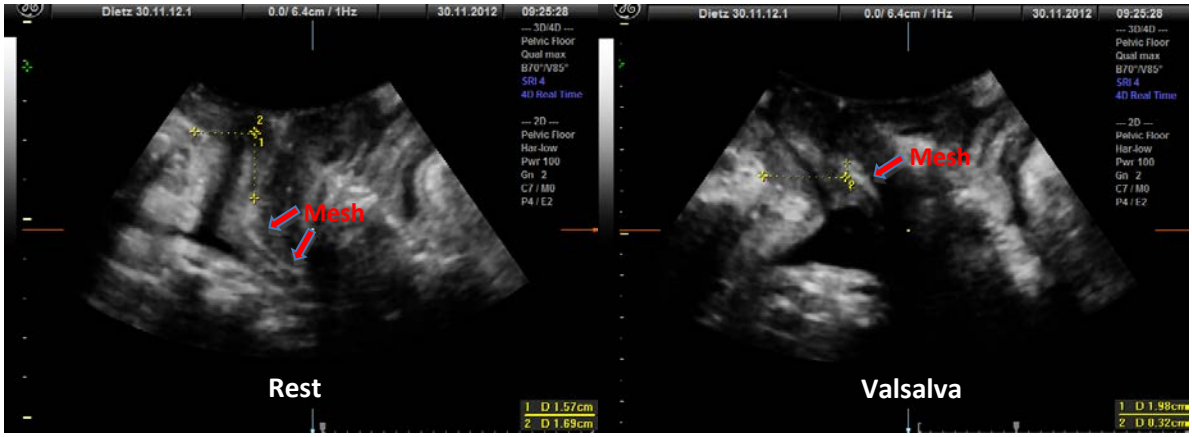

Fig 2.5: Midsagittal image of the mesh location at rest (A) and on Valsalva (B). Mesh mobility is measured using the formula $\sqrt{[(X_{Valsalva} - X_{rest})^2 + (Y_{Valsalva} - Y_{rest})^2}$.
X = horizontal distance from symphysis pubis and Y = vertical distance from symphysis pubis. Mesh as identified with arrows. From Wong et al. Laparoscopic sacrocolpopexy: how low does the mesh go? Ultrasound Obstet Gynecol 2017; 49: 404 – 08, with permission.

2.3.4 Assessment of levator hiatal area

Two methodologies have been described for the assessment of hiatal area. This can be undertaken either by using an axial sectional plane, at the plane of minimal hiatal dimensions as identified in the mid-sagittal view, or by using a rendered volume of 1-2cm thickness containing the plane of minimal hiatal dimensions (13, 27). The latter method is based on volume rendering via machine-specific software algorithms and provides a semi-transparent representation of all gray scale pixels within the 'region of interest'. As a result, it is possible to visually trace an area within a three dimensional volume, even if this does infringe the rules of Euclidean geometry (Fig 2.6). This method using rendered volumes for area measurement was used in this work as it is simpler and possibly more valid (27).

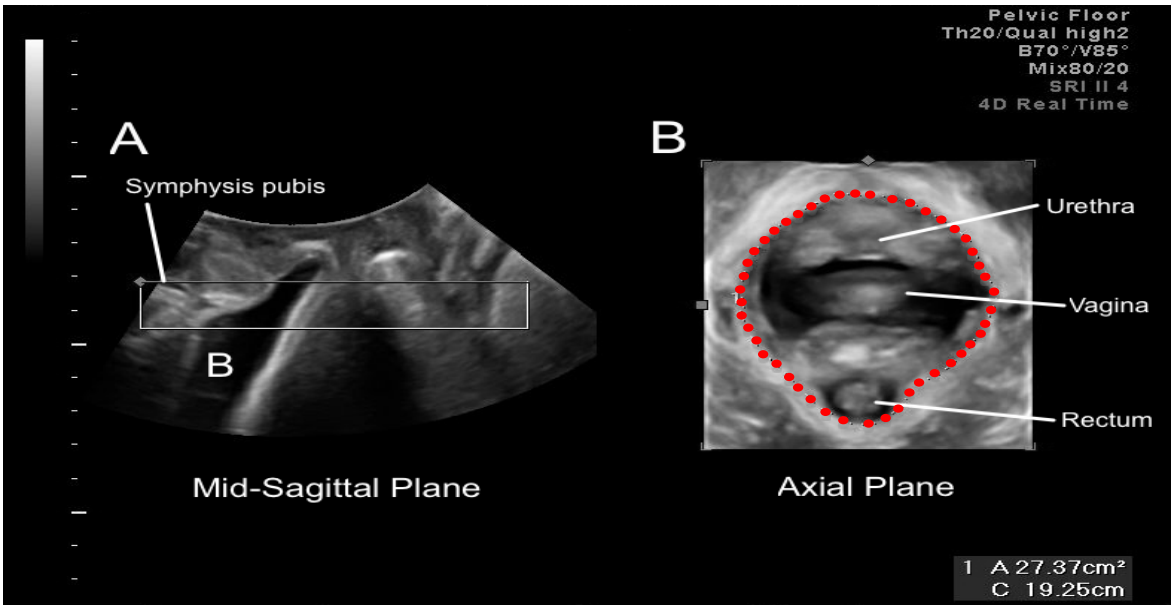

Fig 2.6: Assessment of levator hiatal area using the rendered volume method. Image A shows a mid-sagittal view on Valsalva. The plane of minimal hiatal dimensions i.e. the plane where the distance between pubic bone anteriorly and the levator ani muscle posteriorly is shortest, is identified in this mid-sagittal view. The region of interest (ROI), represented by the box in A is placed to include the plane of minimal hiatal dimensions. The corresponding rendered volume in the axial view is shown in Image B. The levator hiatus is outlined by the red dotted line in B. The area measured here is 27.37cm^2.

2.3.5 Assessment for levator avulsion

Levator integrity is assessed using tomographic ultrasound imaging or multislice ultrasound imaging as previously described (28). Tomographic ultrasound imaging was performed on volumes obtained at PFMC at 2.5mm slice intervals, from 5 mm below to 12.5 mm above the plane of minimal hiatal dimensions (Fig 2.7). Levator avulsion is diagnosed if the muscle insertion is abnormal showing a disconnection of the muscle from its bony insertion in the three central slices, i.e. slice 3, 4 and 5, such as a unilateral avulsion as seen in Fig 2.8.

In doubtful cases, we utilise the 'levator urethra gap measurement'. The muscle insertion is regarded as abnormal when the levator urethra gap is >2.5 cm (29). This method of diagnosing levator avulsion has been shown to be valid and repeatable, at least as effective as magnetic resonance imaging for diagnosing avulsion injury (30) and very unlikely to result in false positive results (31). Fig 2.7 illustrates tomographic ultrasound imaging of an intact levator and Fig 2.8, a right complete levator avulsion.

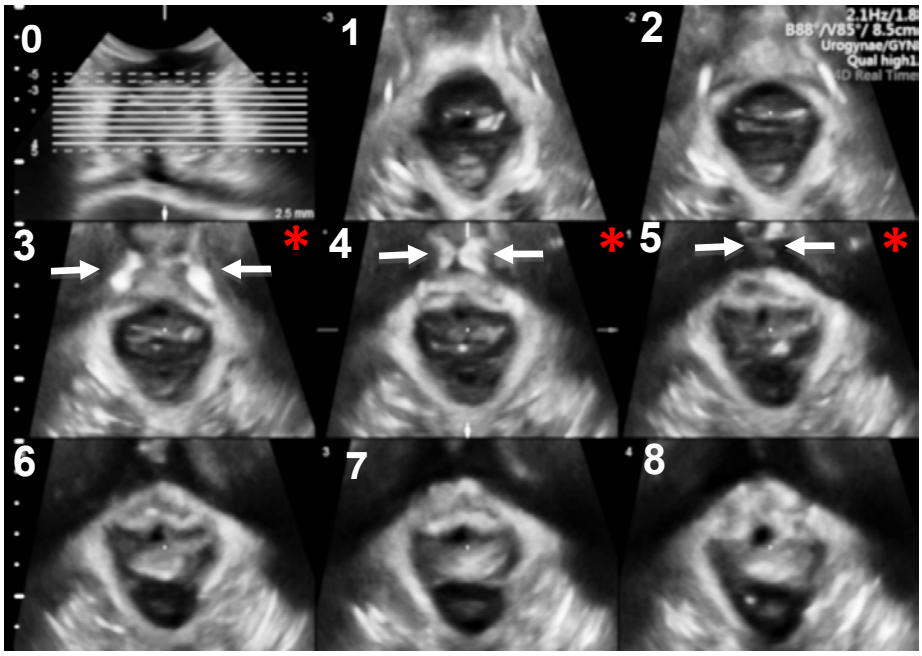

Fig 2.7: Tomographic ultrasound imaging of an intact puborectalis muscle. Eight axial plane slices are set at 2.5mm interslice intervals. The central slice (Slice 4) is placed at the plane of minimal hiatal dimensions showing 'closing' of the symphysis pubis, as identified by arrows. The slice to the left (Slice 3) is set 2.5mm caudad, showing the symphysis pubis open, the one to the right (Slice 5) is 2.5mm cranial, with the pubic rami 'closed' or invisible due to acoustic shadowing. The three central slices (Slice 3-5) as represented by the red asterisks are analysed to provide minimal criteria for the diagnosis of levator avulsion.

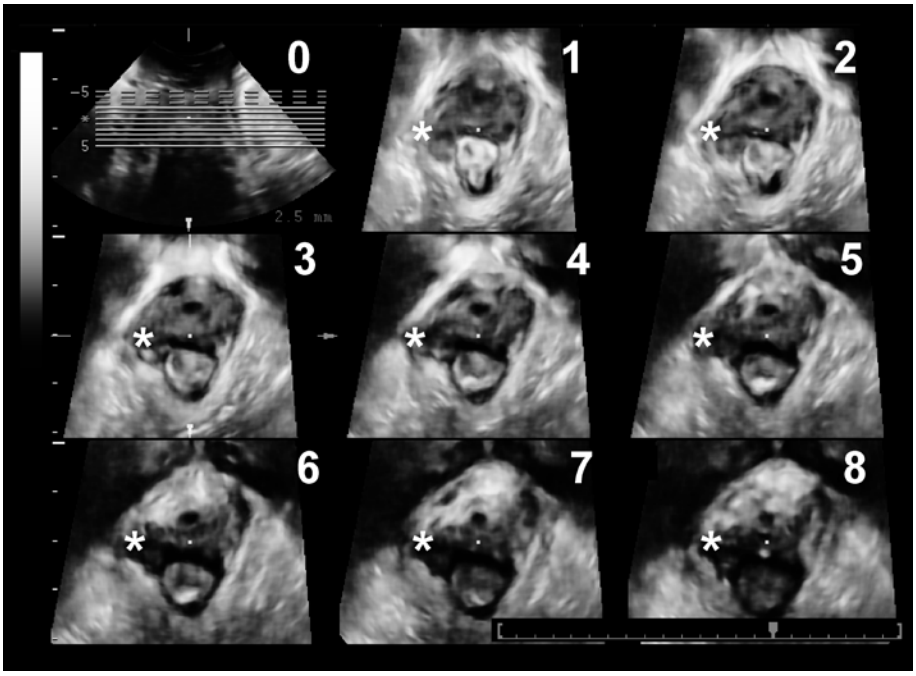

Fig 2.8: Tomographic ultrasound imaging of a right-sided (unilateral) complete levator avulsion. The asterisks identify the detachment of the puborectalis muscle from its insertion on the right inferior pubic ramus. From Dietz et al, Quantification of major morphological abnormalities of the levator ani. Ultrasound Obstet Gynecol 2007; 29: 329 – 34, with permission.

2.3.6 Statistical analysis

Paper 1: Cystocele recurrence after anterior colporrhaphy with and without mesh use.

Statistical analysis was performed with Minitab V13 (Minitab Inc, State College, PA, USA) and SAS V9.3 (Cary CR:SAS Institute Inc, USA). Between group comparisons were performed using student's *t-tests* for continuous variables and chi^2 analysis for categorical variables. A *p-value* of <0.05 was considered to be statistically significant. To compare subjective and objective outcomes between the two methods of repair, we conducted multiple regression or logistic regressing analyses, as appropriate, adjusting for significant potential confounders of prolapse recurrence such as age, BMI, previous vaginal delivery, previous vaginal repair surgery and length of follow-up.

Paper 2: Is levator avulsion a predictor of cystocele recurrence following anterior vaginal mesh placement

Statistical analysis was performed using Minitab v13 (Minitab Inc, State College, PA, USA). Student's *t-test* was performed for continuous variables and chi-square analysis for categorical variables; *p<0.05* was considered to be statistically significant.

Paper 3: A comparison of two different mesh kit systems for anterior compartment prolapse repair.

Statistical analysis was performed using Minitab v13 (Minitab Inc, state college, PA, USA) Prism v6.0b (Graph Pad Software, La Jolla, CA, USA) and SAS v9.3 (SAS Institute Inc, Cary, NC, USA). Normality was assessed using the D'Agostino & Pearson Omnibus normality test. Student *t-test* was performed for continuous variables and chi-square test analysis for categorical variables. A *p-value* of <0.05 was considered to be statistically significant. Intraclass correlation statistics (single measurement, absolute agreement definition) were used to determine the repeatability of sonographic measures of mesh location. To compare subjective and objective outcomes between the two mesh kit systems, we conducted multiple regression or logistic regression analyses, as appropriate, adjusting for significant confounders ($p<0.05$) identified following univariate analysis.

Paper 4: Laparoscopic sacrocolpopexy: how low does the mesh go?

Statistical analysis was performed with SAS v9.2 (SAS Institute, Cary, NC, USA) and SPSS Statistics v.20 (IBM Corp., Armonk, NY,USA). A two-sample *t-test* was performed for continuous variables and chi-square analysis for categorical variables. $P<0.05$ was considered to be statistically significant.

Paper 5: A pilot study on surgical reduction of the levator hiatus with a mesh sling – the Puborectalis Sling.

Statistical analysis was performed using Minitab version 13 (Minitab Inc., State College, PA, USA). Student's *t*-test was performed for continuous variables and chi^2 analysis for categorical variables. A *p*-value of <0.05 was considered to be statistically significant. Power calculations were not performed due to the pilot nature of this study, with no input data available in the literature.

2.3.7 Ethics

Paper 1:

Obtained at all three sites (SWAHS HREC 07-063, Greenslopes Private Hospital HREC ref 10-09, Townsville HREC 84/04)

Paper 2:

Obtained for all three clinical audits (SWAHS HREC 07-063, Greenslopes Private Hospital HREC ref10-09, Townsville HREC 84/04)

Paper 3:

Obtained for all three clinical audits (SWAHS HREC 07-063, Townsville HREC 84/04 and Victoria HREC No. 10310Q)

Paper 4:

Obtained from University of Sydney, Human Research Ethics Committee,

(No 15216)

Paper 5:

Nepean Blue Mountain Local Health District Human Research Ethics Committee (NBMLHD HREC 10-03).

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Chapter 3: Cystocele recurrence after anterior colporrhaphy with and without mesh use.

Publication 1

Wong V, Shek KL, Goh J, Krause H, Martin A, Dietz HP. Cystocele recurrence after anterior colporrhaphy with and without mesh use. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014;172:131-5.

3.1 Results summary

This was a retrospective study incorporating the data of two separate clinical audit projects. Three hundred and thirty two patients had undergone an anterior colporrhaphy with mesh augmentation and 242 had had an anterior colporrhaphy only, over a four-year period at three tertiary centres. One hundred and eighty three attended surgical audit follow-up at three different time points. Perigee^{TM} and Prolift^{TM} mesh kits systems had been inserted into 100 patients while 83 had had a native tissue repair only. The average follow-up was 4 years. A recurrent cystocele (≥ stage 2 POPQ) was more commonly found in the anterior colporrhaphy group compared to those who had anterior mesh reinforcement (55% vs 33%, *p=0.002)*. After adjustment for age, BMI, previous vaginal delivery, previous vaginal repair surgery and length of follow-up, the benefit of mesh on prolapse recurrence was still evident, but it was seen in women with levator avulsion only.

There was statistically significant evidence that levator avulsion status modified the effect of mesh on the risk of recurrent cystocele (Breslow-Day Chi^2 test p=0.01). The odds ratio for the effect of mesh on recurrence was 0.97 (95% CI: 0.41 – 2.30) for women with no avulsion compared to 0.15 (95% CI: 0.04 – 0.52) for women with avulsion.

Hypothesis 1: 'Mesh augmentation for anterior compartment prolapse is associated with better outcome as compared to traditional anterior colporrhaphy' was confirmed for women with levator avulsion only.

European Journal of Obstetrics & Gynecology and Reproductive Biology 172 (2014) 131–135

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Cystocele recurrence after anterior colporrhaphy with and without mesh use

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ARTICLE INFO

Article history:
Received 17 December 2012
Received in revised form 17 August 2013
Accepted 2 November 2013

Keywords:
Anterior colporrhaphy
Cystocele
Mesh
Recurrence
Levator avulsion

ABSTRACT

Objective: Mesh reinforcement in cystocele repair has become popular in recent years, with some evidence of reduced recurrence rates. In this retrospective cohort series, we aimed to assess subjective and objective outcomes, including ultrasound quantification of prolapse, following anterior colporrhaphy with and without mesh use for anterior compartment prolapse.

Study design: We assessed anatomical and functional outcomes of patients after cystocele repair in three tertiary urogynecology units. Outcome measures included either objective prolapse recurrence (defined as cystocele ≥ Stage 2 ICS POP-Q or bladder descent ≥10 mm below the symphysis pubis on ultrasound) or subjective prolapse recurrence (defined as symptoms of vaginal lump, bulge or dragging sensation post-operatively). Comparisons between mesh use and anterior colporrhaphy-only groups were undertaken, adjusting for potential confounders (age, BMI, vaginal parity, previous prolapse repair, levator avulsion and length of follow-up) using multiple linear regression and logistic regression methods.

Results: 183 patients were assessed at an average follow-up of 4 years. Eight-three patients had anterior colporrhaphy between January 2002 and December 2005, and 100 had an anterior mesh repair between March 2004 and October 2008. Forty-six (55%) patients in the anterior colporrhaphy group compared to 33 (33%) in the mesh use group were diagnosed with a recurrent cystocele (≥stage 2) ($p = 0.002$). After adjustment for age, BMI, previous vaginal delivery, previous vaginal repair surgery, and length of follow-up, the benefit of mesh on prolapse recurrence was principally experienced by women with major levator trauma.

Conclusions: At a mean of four years' follow-up, mesh augmentation was associated with reduced cystocele recurrence, but this effect was limited to patients with levator avulsion.

1. Introduction

Mesh reinforcement in cystocele repair has become popular in recent years. Until recently, anterior colporrhaphy was the standard method of repair. Due to recurrence rates of up to 50% [1], mesh kits such as PerigeeTM (American Medical Systems, Minnetonka, MN, USA) or Anterior ProliftTM (Gynecare/Ethicon, Somerville, NJ, USA) were developed to improve outcomes following pelvic organ prolapse repair. Whilst there is some evidence that mesh reinforcement can reduce recurrence rates [2,3], the use of mesh in pelvic floor reconstructive surgery has become controversial [4]. This is mainly due to associated complications such as mesh erosion, chronic pain and dyspareunia [5].

In view of the rising controversy surrounding mesh use, further evidence is required to assess the relative weight of complications of mesh use against the potential benefit of reduced recurrence rates. A number of authors have investigated risk factors for recurrence, and younger age [6], a family history of prolapse [7], a larger prolapse stage [7,8], poor pelvic floor muscle contractility [9], previous hysterectomy, body mass index (BMI), previous prolapse surgery, a larger genital hiatus [9], levator avulsion [7,10,11] and hiatal ballooning (excessive distensibility of the levator hiatus) [12] all seem to be associated with recurrence.

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http://dx.doi.org/10.1016/j.ejogrb.2013.11.001

Hence, it may be possible to identify patients that may be more likely to benefit from mesh use.

With this in mind, we aimed to evaluate the long-term subjective and objective outcomes following anterior colporrhaphy (AC) with and without mesh use. We also assessed whether the estimated effect of mesh was modified by the presence of major trauma to the levator ani muscle ('avulsion').

2. Materials and methods

This was a retrospective analysis of data obtained in external clinical audits of anterior colporrhaphy (AC) with and without mesh, performed in three tertiary urogynecology centres. All patients were seen for post-surgical audit appointments which involved a standardised interview, an International Continence Society Pelvic Organ Prolapse-Quantification (ICS POP-Q) clinical examination [13] along with a 4D transperineal ultrasound examination using Voluson 730 expert or Voluson i systems (GE Kretztechnik GmbH, Zipf, Austria) with a RAB 8–4 MHz transducer. They represent a selection of women operated at the three tertiary centres, as not every patient was able to attend for these external audits. We have no information on those who declined attendance and for those who were not contactable.

Outcome measures include either subjective prolapse recurrence (defined as symptoms of a vaginal lump, bulge or dragging sensation) or objective prolapse recurrence (defined as cystocele $\geq$ Stage 2 ICS POP-Q) or bladder descent $\geq$10 mm below the symphysis pubis as measured on ultrasound. The latter was measured on ultrasound on maximum valsalva (Fig. 1) after bladder emptying, as previously described [14]. A significant cystocele was defined as bladder descent to 10 mm or more below the symphysis pubis, a value previously determined on the basis of receiver-operator characteristic (ROC) statistics, using symptoms of prolapse as the outcome measure [15]. Ultrasound volume data sets were analysed offline on a desktop PC using proprietary software (4D View v10, GE Kretz Ultrasound, Zipf, Austria). Volumes obtained at maximum pelvic floor muscle contraction (or at rest if the patient failed to contract the pelvic floor muscles) were used to diagnose levator avulsion, using tomographic ultrasound imaging (TUI), as previously described [16,17]. The plane of minimal hiatal dimension at maximum pelvic floor muscle contraction was identified and a tomographic representation of this volume is represented in the axial plane. Using TUI, the entire puborectalis muscle is encompassed within eight slices at 2.5 mm slice intervals. Patients were regarded as avulsion positive if there was an abnormal puborectalis muscle insertion in all three central slices (i.e. the slice obtained at the level of the plane of minimal hiatal dimensions and the two immediately cranial) (Fig. 2). This method is highly repeatable and agrees well with the diagnosis of avulsion on magnetic resonance imaging [18]. Diagnosis of levator avulsion was made by the senior author, blinded against clinical data.

Patients who had undergone a traditional colporrhaphy were operated by 7 specialists and their trainees under supervision. Surgical techniques may therefore vary. Nevertheless all patients had fascial plication after reflecting the bladder off the vaginal skin, without paravaginal repair.

Perigee mesh kits were inserted according to manufacturer's (AMS, Minnetonka, MN, USA) instructions, with one of the participating surgeons involved in the development of the mesh kit system (A.R.). The Perigee mesh kit is inserted after reflecting the bladder off the vaginal skin using helical needles passing through the anteromedial and posteromedial aspects of the obturator foramen and placing the mesh in a tension-free manner. The Anterior Prolift mesh kits were also inserted according to manufacturer's (Gynecare/Ethicon, NJ) instructions with mesh arms passing through the anterior and posterior medial aspect of the obturator foramen, using specifically designed guides and cannulas.

Statistical analysis was undertaken using Minitab version 13 (Minitab Inc., State College, PA, USA) and SAS version 9.3 (Cary CR: SAS Institute Inc, USA). Between-group comparisons were performed using t-tests for continuous variables and chi^2 tests for categorical variables. A p-value of <0.05 was considered to be statistically significant. To compare subjective and objective outcomes between the two methods of repair, we conducted multiple regression or logistic regression analyses, as appropriate, adjusting for significant potential confounders of prolapse recurrence such as age, BMI, previous vaginal delivery, previous vaginal repair surgery, and length of follow-up. Ethical approval for audit projects had been obtained at all three sites (SWAHS HREC 07-063, Greenslopes Private Hospital HREC ref 10-09, Townsville HREC 84/04).

3. Results

There were 332 patients who had undergone anterior prolapse repair with mesh between March 2004 and October 2008, and 242 patients who had an anterior prolapse repair without mesh between January 2002 and December 2005. One hundred patients who had AC with mesh (51 Perigee, 49 Anterior Prolift) and 83 patients who had undergone AC without mesh attended the audit follow-up. These women had responded to an invitation to attend clinical audit appointments at the participating institutions at

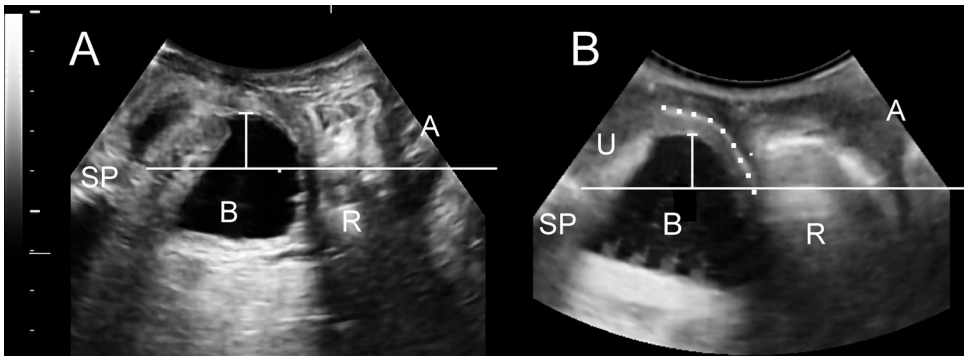

Fig. 1. Identification of bladder descent on maximal valsalva (midsagittal view). The horizontal line represents a reference line drawn against the symphysis pubis. The vertical line demonstrates the descent of the bladder caudally, below the symphysis pubis. Image on left (A) represents a recurrent cystocele following anterior colporrhaphy and image on right (B) represents recurrent cystocele following anterior colporrhaphy with mesh. The dotted lines represent an anterior compartment mesh (SP = symphysis pubis, B = bladder, R = rectum, A = anal canal).

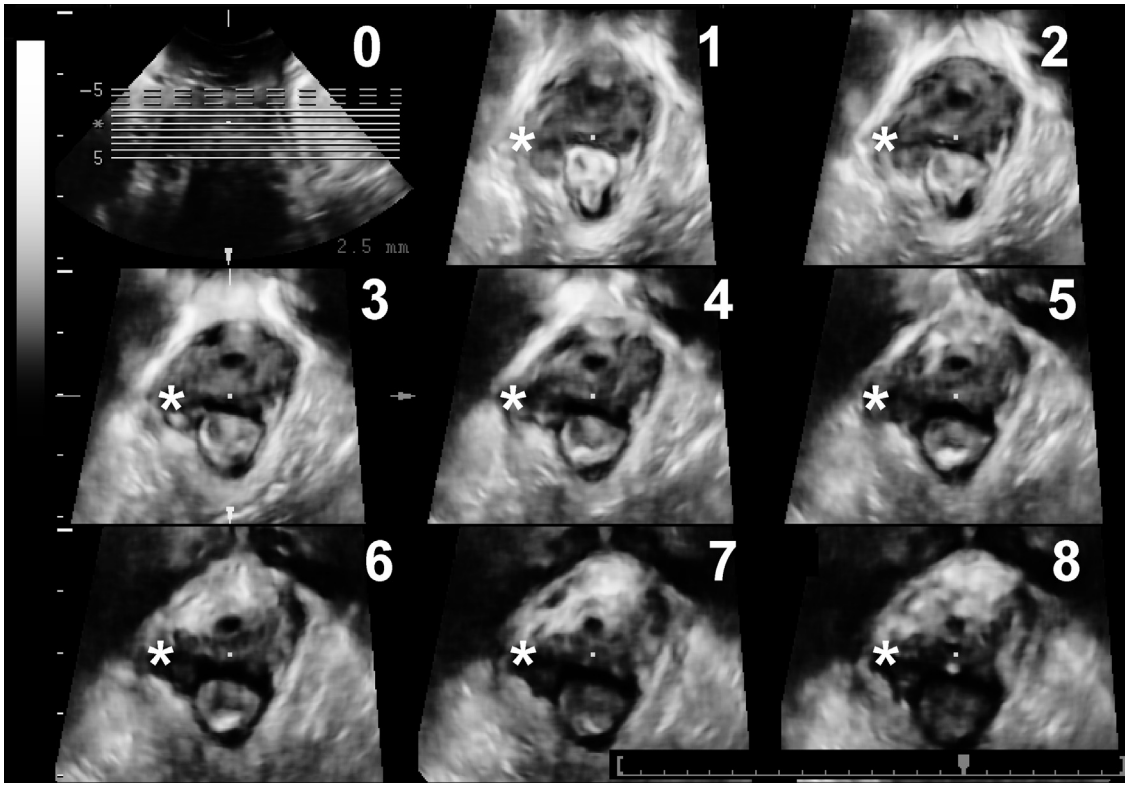

Fig. 2. Tomographic ultrasound imaging of the entire puborectalis muscle. The * demonstrates a right-sided levator avulsion. Reproduced, with permission, from Dietz [16].

Table 1
Demographic details of the patients.

Parameter	Mesh ($n = 100$)	No mesh ($n = 83$)	p-Value
Age (years)	64.9	65.3	0.807
BMI	28.56	28.36	0.814
Previous vaginal delivery	3.17 (SD 1.49)	3.20 (SD 1.56)	0.878
Previous prolapse surgery	35/100 (35%)	6/83 (7%)	<0.001
Levator avulsion	35/100 (35.0%)	29/83 (34.9%)	0.993
Follow-up period (years)	3.45 (SD 0.90)	4.47 (SD 0.95)	<0.001

three different time points. Mesh was used in 100 of these women ($N = 49$ Prolift™, $N = 51$ Perigee™). The mean duration of follow-up was significantly longer for women who underwent AC without mesh (4.47 years) compared to those in whom mesh was used (3.45 years, with $p < 0.001$ for comparison). Table 1 summarises the characteristics of each group at the time of the follow-up assessment. The mean age at assessment was 63 years, the mean BMI was 28, and the mean vaginal parity was 3. Forty-one (22.4%) women had previous vaginal repairs, 74 (40.4%) had undergone previous hysterectomy, 50 (27.3%) had concurrent vaginal hysterectomy, 20 (10.9%) had a concurrent apical suspension (13 sacrospinous fixation, 7 sacrohysteropexy), 54 (29.5%) a placement of suburethral sling, 66 (36.1%) a posterior colporraphy and 45 (24.6%) a posterior mesh insertion (9 Apogee and 36 Posterior prolift). There were 64 women (35%) with levator avulsion and of those, 37 were unilateral whilst 27 were bilateral trauma. The primary endpoint of recurrent cystocele of ≥stage 2 was observed in 33/100 (33%) in the mesh group and 46/83 (55%) in the non-mesh group ($p = 0.002$).

The rate of recurrent cystocele (≥Stage 2) for women with no avulsion in the mesh and non-mesh groups respectively was 22/65 (35%) versus 23/54 (43%), compared to recurrence rates of 11/35 (31%) versus 23/29 (79%) for the mesh and non-mesh groups among women with an avulsion ($p = 0.003$). These findings were confirmed on multivariate regression analysis, adjusting for potential predictors of prolapse including age, BMI, previous vaginal delivery, previous vaginal repair surgery, levator avulsion and length of follow-up (Table 2).

There was statistically significant evidence that levator avulsion status modified the effect of mesh on the risk of recurrent cystocele (Breslow-Day Chi^2 test $p = 0.01$). The adjusted odds ratio

Table 2
Comparison of outcomes following anterior colporrhaphy in patients with and without mesh use. All results shown are from a multivariate regression analysis († linear regression, * logistic regression) that adjusts for age, BMI, previous vaginal delivery, previous vaginal repair surgery, levator avulsion as well as length of follow-up.

Status of puborectalis muscle insertion	Anterior colporrhaphy	Mean point Ba	≥Stage 2 cystocele recurrence	Mean maximal bladder descent on valsalva[a] (mm)
Avulsion ($n = 64$)	Mesh ($n = 35$)	−1.82	31% (11/35)	−0.87
	No mesh ($n = 29$)	−0.41	76% (22/29)	−16.5
	p-Value 95% CI	0.0001† −2.12 to −0.7	0.003* 0.04 to 0.52	<0.0001† 8.92 to 22.28
No avulsion ($n = 119$)	Mesh ($n = 65$)	−1.70	38% (25/65)	−1.04
	No mesh ($n = 54$)	−1.71	38% (21/54)	−1.83
	p-Value 95% CI	0.98† −0.54 to 0.55	0.97* 0.41 to 2.39	0.76† −4.31 to 5.91

[a] Maximal bladder descent is measured against the level of symphysis pubis on valsalva, negative value represents a descent that is below the level of symphysis pubis.

for the effect of mesh on recurrence was 0.97 (95% CI: 0.41–2.30) for women with no avulsion, compared to 0.15 (95%CI: 0.04–0.52) for women with avulsion.

There was a statistically significant difference in women's overall satisfaction rate, 82% (82/100) in women with mesh compared to 65% (54/83) in women with anterior colporrhaphy only ($p = 0.04$), while there was no difference in women presenting with recurrent prolapse symptoms at 20% (20/100) compared to 29% (24/83) in the mesh and non-mesh groups respectively ($p = 0.25$).

Statistically significant evidence for avulsion status to modify the effect of mesh was also found for point Ba and maximum bladder descent on ultrasound.

4. Comment

In this study, anterior colporraphy with mesh was associated with a significantly better objective anatomical outcome both clinically and on ultrasound, at an average follow-up length of 4 years. This is consistent with a recently published randomised controlled trial by Altman et al. on short-term outcomes [3].

The presence of major levator ani muscle trauma ('avulsion') significantly modified the estimated effect of mesh on recurrence, point Ba and maximum bladder descent on ultrasound, with the benefit of mesh augmentation appearing most marked in women with levator avulsion. This study is the first in the world literature to demonstrate such an effect, which may potentially be of great value in clinical practice. Knowledge of predictors of prolapse recurrence may be important in helping clinicians identify patients who would benefit the most from mesh reinforcements at the time of anterior prolapse repair. As mesh use is likely to be associated with increased complication rates compared to traditional AC, patient selection seems of paramount importance.

There are a number of factors that can be used to identify women at higher risk of recurrence: age, prolapse stage, previous surgery, size of the genital hiatus [9], levator contraction strength [9], and levator avulsion [7,10,11]. The data presented in this study reinforce this concept. It may be reasonable to offer mesh to women who are at an increased risk of recurrence, even as a primary procedure, rather than to those who are likely to do well with conventional surgery alone. This may not be technically difficult, since all the above-quoted risk factors can be ascertained from interview and clinical examination, including the diagnosis of avulsion, which can be made on palpation [19,20].

Several potential weaknesses of this study need to be acknowledged. Firstly, this is a retrospective observational study using audit data obtained over the course of several years at several sites by several ultrasound operators. This study design is subject to a number of potential confounders, not least that of assessment bias, since the presence of mesh is evident both on clinical examination and on ultrasound imaging. Unfortunately this is true for all trials comparing conventional to mesh-augmented repair, regardless of study design. Another criticism may be that the large time span may have caused differences in assessment technique. All personnel, however, were under the direct supervision of, or trained by, the senior author, and the audit procedure had been standardised several years prior to the first data acquisition for this project. All ultrasound parameters used in the post- processing analysis have been previously shown to be valid and repeatable [10], and the post-processing methodology had also been standardised several years prior to the commencement of this study.

Unfortunately, due to the nature of an external audit and the heterogeneity of local settings, we were unable to acquire pre-operative data such as ICS POPQ staging for all patients, and we are equally unable to provide data on those women who did not present for these external audits. There may well be a degree of selection bias, although this bias may apply similarly to both AC and AC with mesh groups. In addition, the mesh arm of this series contains patients who received two different kinds of meshes, adding to the heterogeneity of our data. However, these two mesh implants (Perigee and Anterior Prolift) both use similar material and a very similar fixation method (transobturator arms) and have previously been shown to be comparable on imaging [21].

Overall, the findings from this study may be more generally applicable than a single-surgeon series examining one single mesh kit, since most of our patients were operated in public hospitals, implying the involvement of multiple trainees. In addition, patients were examined by an external clinician, and any ultrasound measures were analysed months after the patient contact, with the operator blinded against all other data.

Moreover, we cannot be sure that women who received mesh were not systematically different to those who did not, although we attempted to control this by performing adjusted analyses. Nonetheless, we acknowledge that this method of control is inferior to that achieved through random allocation in a controlled trial.

Another potential weakness is that subjective patient outcomes were not assessed with questionnaires, such as PFDI or PISQ-12. In a climate where there is an increasing drive towards research on patient-reported outcomes, recent evidence [2] has concluded that large RCTs are needed to show differences in patient-reported outcomes. Comparing surgical interventions with such instruments may be difficult since subjective recurrence is less common than objective recurrence after prolapse surgery, requiring much larger trials to achieve sufficient power. In short, questionnaires are likely to have low power in trials testing surgical interventions for female pelvic organ prolapse.

In conclusion, at an average follow-up period of 4 years, mesh augmentation of anterior colporrhaphy was associated with significantly better objective anatomical outcomes, both clinically and on sonographic imaging. This positive effect of mesh augmentation was largely limited to women diagnosed with avulsion of the puborectalis muscle. Anterior compartment mesh use in women with intact levator ani may not be beneficial whilst future surgical intervention trials assessing efficacy of prolapse mesh use should probably incorporate an assessment for major levator trauma. Levator avulsion can be used as an entry criterion for trials given the fact that it is a strong risk factor for prolapse recurrence following surgical repair. This may substantially enhance the power of such trials, as recently demonstrated by Svabik et al. [22] in a randomised controlled trial comparing outcomes following prolapse repair in women with levator avulsion.

Conflict of interest

HP Dietz has in the past acted as consultant for American Medical Systems, Continence Control Systems and Materna. He has accepted speaker's fees from GE, AMS and Astellas and has benefitted from equipment loans provided by GE, Bruel and Kjaer and Toshiba. Both HP Dietz and KL Shek have received unrestricted educational grants from GE. All other authors have no conflict of interest to declare.

Acknowledgements

We thank Prof. A. Rane, Townsville, for access to patients and other support in the context of external audit projects at his unit.

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Chapter 4: Is levator avulsion a predictor of cystocele recurrence following anterior vaginal mesh placement?

Publication 2

Wong V, Shek K, Rane A, Goh J, Krause H, Dietz H. Is levator avulsion a predictor of cystocele recurrence following anterior vaginal mesh placement? Ultrasound in Obstetrics & Gynecology. 2013;42(2):230-4.

4.1 Results summary

In this retrospective study incorporating clinical audit projects, two hundred and nine patients were evaluated at an average of 2.2 years (range 3 months – 5.6 years) after anterior vaginal mesh repair; 67 Anterior Prolift™ (Gynecare/Ethicon, Sommerville, NJ, USA) and 142 Perigee™ (American Medical Systems, Minnetonka, USA). These patients underwent a standardised interview, clinical POPQ examination and 4D transperineal ultrasound. Twenty four percent of patients had recurrent prolapse symptoms (51/209) whilst 33% (68/209) had recurrent clinical cystocele and 26% (54/209) had evidence of a recurrent cystocele on ultrasound. Mesh erosion was diagnosed in 11% (22/209) of patients at the time of evaluation. Twenty-eight out of 80 (35%) women with levator avulsion had significant sonographic cystocele recurrence (odds ratio (OR), 2.24 (95% confidence interval (CI), 1.13–4.43)).

Multivariate logistic regression analysis, adjusting for potential predictors of prolapse recurrence, such as age, BMI, vaginal parity, previous prolapse/anti-incontinence surgery and length of follow-up as well as for levator avulsion, found that women with levator avulsion were more likely to have cystocele recurrence on ultrasound than those without avulsion, 34% vs. 20% (OR 2.13, 95% CI: 1.04 – 4.39). That is, levator avulsion doubles the risk of cystocele recurrence despite mesh augmentation in anterior colporrhaphy.

Hypothesis 2: 'Levator avulsion is a risk factor for prolapse recurrence after anterior mesh repair' was confirmed.

Ultrasound Obstet Gynecol 2013; **42**: 230–234
Published online in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.12433

Is levator avulsion a predictor of cystocele recurrence following anterior vaginal mesh placement?

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KEYWORDS: anterior colporrhaphy; cystocele; levator avulsion; mesh; pelvic organ prolapse; recurrence

ABSTRACT

Objective *Levator avulsion has been shown to be a predictor of cystocele recurrence following anterior colporrhaphy. The aim of this study was to determine if levator avulsion is a risk factor for prolapse recurrence following anterior colporrhaphy with mesh.*

Methods *This was a retrospective analysis of data obtained from three surgical audits for subjective and objective outcomes following anterior colporrhaphy with mesh. Recurrence was defined as cystocele ≥ Stage 2 on the prolapse quantification system of the International Continence Society; symptoms of vaginal lump/bulge; or cystocele on ultrasound, defined as maximum bladder descent to ≥ 10 mm below the symphysis pubis. Levator avulsion was diagnosed using tomographic ultrasound imaging.*

Results *Two hundred and nine patients were followed up at a mean of 2.2 years (range, 3 months to 5.6 years) after anterior vaginal mesh placement. 24% (51/209) had recurrent prolapse symptoms, 33% (68/209) clinical cystocele recurrence ≥ Stage 2, and 26% (54/209) a recurrent cystocele on ultrasound. Twenty-eight out of 80 (35%) women with levator avulsion had significant sonographic cystocele recurrence (odds ratio (OR), 2.24 (95% confidence interval (CI), 1.13–4.43)). This finding was confirmed after adjusting for potential predictors of prolapse recurrence on multivariate logistic regression (OR, 2.13 (95% CI, 1.04–4.39);* $P = 0.04$*).*

Conclusion *Levator avulsion doubles the risk of cystocele recurrence after anterior colporrhaphy with transobturator mesh.*

INTRODUCTION

Pelvic organ prolapse (POP) is a common condition, with a reported prevalence ranging from 2 to 48%, cystocele being the most frequently encountered form of prolapse[1,2]. Management is conservative or surgical, the latter in the form of an anterior colporrhaphy procedure. Success following traditional anterior colporrhaphy has been suboptimal, with recurrence rates ranging up to 50%[3]. Several potential predictors of POP recurrence have been identified including age, previous prolapse surgery, preoperative severity of prolapse[4], size of genital hiatus[5], levator contraction strength[5] and levator avulsion[6–9].

Levator avulsion is a form of injury afflicting 15–30% of women following vaginal delivery, defined by detachment of the puborectalis muscle from the inferior pubic ramus[10–12]. It has been shown to be associated with weaker pelvic floor muscle function and ballooning, i.e. abnormal distensibility of the levator hiatus, the largest potential hernial portal in the human body[13–15]. It is a risk factor for prolapse development, especially in the anterior and central compartments[15,16]. Women with levator avulsion have been shown to have a two- to four-fold increased risk of recurrence after anterior colporrhaphy[6–8].

Over the last 8 years, mesh kits have become popular in POP repair[17]. The use of mesh anchored by transobturator arms is likely to improve both subjective and objective outcome measures following prolapse repair, especially in the anterior compartment[18–20]. However, it is not clear whether the use of anterior compartment mesh fully compensates for the recurrence risk conveyed by levator avulsion[18]. We therefore undertook this study to determine whether levator avulsion is a risk factor for cystocele recurrence following anterior compartment transobturator mesh placement.

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Accepted: 1 February 2013

METHODS

This was a retrospective analysis of data obtained through clinical audits on anterior transobturator mesh procedures (Perigee™ system, American Medical Systems, Minnetonka, MN, USA and Anterior Prolift™ system, Gynecare/Ethicon, Somerville, NJ, USA) performed at three tertiary urogynecology centers. All patients had undergone a standardized clinical interview (non-validated, local), a clinical assessment using the prolapse quantification system of the International Continence Society (ICS POP-Q) and a four-dimensional transperineal ultrasound examination using Voluson 730 Expert or Voluson i systems (GE Medical Systems, Zipf, Austria) with RAB 8–4-MHz transducers. Outcome measures were either subjective prolapse recurrence (defined as symptomatic of a vaginal lump, bulge or dragging sensation) or objective prolapse recurrence (defined as either clinical cystocele $\geq$ Stage 2/ICS POP-Q or sonographic recurrence if bladder descent was ≥ 10 mm below the symphysis pubis on ultrasound).

The ultrasound examination was performed by (or under the immediate supervision of) staff trained by the senior author for a minimum of 6 months, with the patient in the supine position after bladder emptying, as described previously[21]. Ultrasound volumes were acquired at rest, on maximum Valsalva maneuver and on pelvic floor muscle contraction. Post-processing analysis was performed on a desktop computer using proprietary software (4D View v10, GE Medical Systems). The assessment for sonographic cystocele was undertaken by V.W. (after a minimum of 3 months' training in pelvic floor ultrasound), while the assessment for levator avulsion was undertaken by the senior author (H.P.D.). Both were blinded to each other's findings as well as to all clinical data. The volume on maximum Valsalva showing the largest pelvic organ descent was used for analysis of this parameter. Cystocele recurrence on ultrasound was rated positive if the most dependent part of the bladder descended to ≥ 10 mm below the inferoposterior margin of the pubic bone, as described previously[21]. This cut-off value was determined on the basis of a receiver–operating characteristics curve, using symptoms of prolapse as the outcome measure[22].

To assess for levator avulsion, tomographic ultrasound imaging (TUI) was performed on volumes obtained at pelvic floor muscle contraction, or at rest if a patient was unable to contract the pelvic floor muscles. Using TUI, a set of eight slices was obtained at 2.5-mm intervals, from 5 mm below to 12.5 mm above the plane of minimal hiatal dimensions, as described previously[23]. This method has been shown to be valid and repeatable, at least as effective as magnetic resonance imaging for diagnosing avulsion injury[24], and very unlikely to result in false-positive results[25]. Levator avulsion was rated as present if the plane of minimal dimensions as well as the two slices cephalad to that plane showed abnormal insertions of puborectalis muscles to the os pubis (Figure 1).

Ethics approval was obtained for all three clinical audits (SWAHS HREC 07-063, Greenslopes Private Hospital HREC ref 10-09, Townsville HREC 84/04). Statistical analysis was performed using Minitab version 13 (Minitab Inc., State College, PA, USA). Student's *t*-test was performed for continuous variables and chi-square analysis for categorical variables; $P < 0.05$ was considered to be statistically significant.

RESULTS

Three hundred and thirty-two anterior compartment mesh procedures were performed at the participating units between 2004 and 2008. Two hundred and nine of the patients were seen at an average of 2.2 years (range, 3 months to 5.6 years) after anterior vaginal mesh placement (67 Anterior Prolift™, 142 Perigee™). They represent only a selection of women operated on at the three tertiary centers, as not every patient was able to

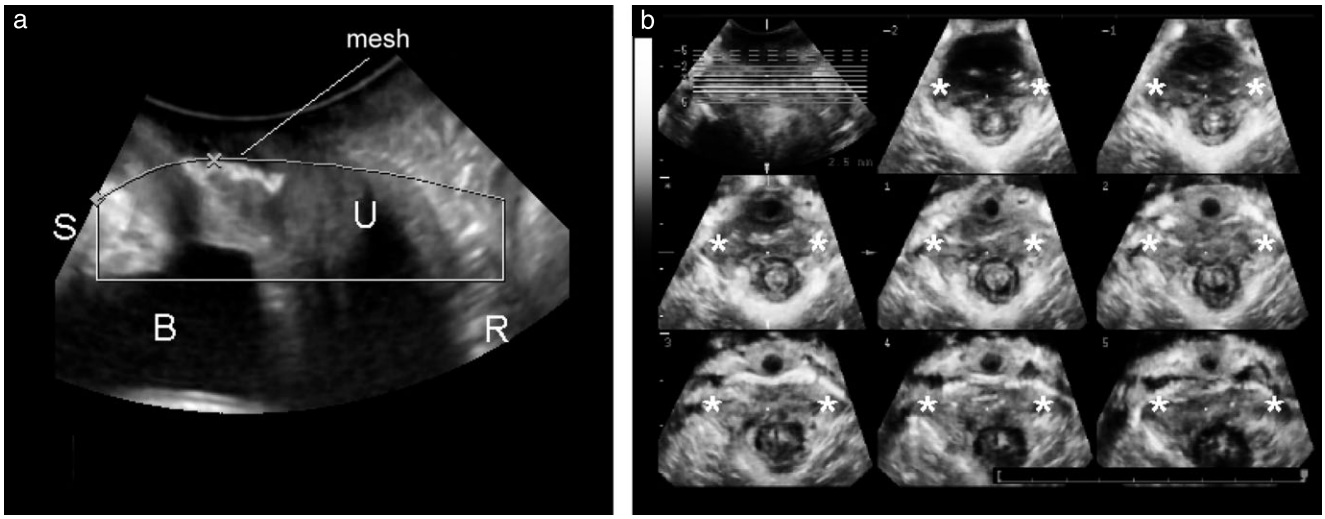

Figure 1 Pelvic floor ultrasound images showing successful cystocele reduction after anterior mesh placement, seen in midsagittal plane (a), in a patient with bilateral avulsion (*) visible on tomographic imaging (b). B, bladder; R, rectal ampulla; S, symphysis pubis; U, uterus.

attend for these external audits, which were conducted between 2006 and 2010. Mean age at follow-up was 65 (range, 32–90) years, median vaginal parity was 3 (range, 0–10) and mean body mass index (BMI) was 28.2 (range, 18.0–48.7) kg/m^2. One hundred and four patients (50%) had had a previous hysterectomy and 69 (33%) a previous vaginal repair. Twenty-eight women (13%) had undergone a concomitant hysterectomy at the time of mesh surgery, 26 (12%) a sacrospinous fixation, seven (3%) a sacrospinous hysteropexy, 67 (32%) a suburethral sling, 63 (30%) a posterior vaginal repair and 25 (12%) a posterior compartment mesh placement.

One hundred and seventy-one of the 209 patients (82%) were satisfied with the outcome of their prolapse repair. Fifty-one (24%) reported symptoms of recurrence, i.e. the sensation of a vaginal lump or a dragging sensation. On clinical examination, mean POP-Q point Ba (the most distal position on the anterior vaginal wall, with respect to the hymen) was −1.8 (range, −3 to 3) cm, with 68 patients (33%) having a clinical recurrence of ≥ Stage 2. Mesh erosion was noted in 22 patients (11%) at the time of follow-up.

Mean maximum bladder descent was 2.1 mm below the symphysis pubis (range, 21 mm above to 38 mm below). Fifty-four (26%) women had a cystocele recurrence on ultrasound, that is, a bladder descent of ≥ 10 mm below the inferoposterior margin of the pubic bone. Eighty patients (38%) were diagnosed with levator avulsion on TUI (bilateral in 41; unilateral in 39 with 25 right-sided, 14 left-sided). In women with levator avulsion, 35% (28/80) had a recurrent cystocele on ultrasound compared with 19% (25/129) of women without levator avulsion ($P = 0.012$; odds ratio (OR), 2.24 (95% confidence interval (CI), 1.13–4.43)).

All subjective and objective outcome measures favored the non-avulsion group on univariate analysis. However, there was no statistically significant difference in women with levator avulsion compared to those without in respect to recurrent symptoms (28 *vs* 21%, $P = 0.276$), clinical recurrence (39 *vs* 29%, $P = 0.131$) or mean bladder descent on ultrasound measurement (−3.8 *vs* −1.0 mm, $P = 0.142$; Table 1). These results were further confirmed on multivariate logistic regression analysis after adjusting for potential predictors of prolapse recurrence, such as age, BMI, vaginal parity, previous prolapse/anti-incontinence surgery and length of follow-up as well as for levator avulsion. Women with levator avulsion remained more likely to have a cystocele recurrence on ultrasound than women without avulsion (27/80 (34%) *vs* 26/129 (20%), $P = 0.04$, OR 2.13 (95% CI, 1.04–4.39)).

We also undertook subgroup analysis for patients after Perigee and Prolift insertion; there was no statistically significant evidence that the association between levator avulsion status and outcome was modified by mesh type.

DISCUSSION

In this follow-up study of 209 patients seen at an average of 2.2 years after Perigee or Anterior Prolift mesh implantation, we found levator avulsion to be a significant predictor of cystocele recurrence on ultrasonography. This confirms data obtained after anterior colporrhaphy, which implies that levator avulsion is a major risk factor for prolapse recurrence[6,7,26]. It appears that anterior compartment mesh implantation does not completely compensate for the increased recurrence risk associated with avulsion, although the ORs obtained by us are lower than those reported for avulsion in traditional anterior colporrhaphy[6,7,26]. While it is likely that mesh reduces recurrence rates, even (or especially) in patients with avulsion, the prevalence of recurrence symptoms and signs of prolapse in women with major levator trauma can still occur in approximately one in three patients[18,20]. This is entirely plausible given that avulsion results in marked distortion of pelvic floor anatomy[27,28].

As a result of an increase in hiatal dimensions, the forces generated by increased intra-abdominal pressure on anterior compartment fascial supports and, by inference, also on iatrogenic support structures such as mesh implants, can be much higher than in women with a normal pelvic floor[15]. Since pressure = force/area, i.e. force per unit area, a given pressure may well generate twice the force perpendicular to the surface of the hiatus in someone in whom hiatal area is double that of another person. In some instances, clinical and ultrasonic recurrence is associated with findings that can only be explained by dislodgment of transobturator anchoring arms (Figure 2). The superior anchoring arms of both Perigee and Anterior Prolift implants seem particularly vulnerable in women with avulsion and ballooning of the hiatus[29]. Future work in this area should focus on improving mesh anchoring as well as on means

Table 1 Subjective and objective outcomes after mesh implantation in women with and without levator avulsion ($n = 209$), at a mean follow-up of 2.2 years

Characteristic	*Avulsion* (n = *80)*	*No avulsion* (n = *129)*	P
Recurrent symptoms	22 (28)	27 (21)	0.276
Mean point Ba (cm)	−1.58	−1.91	0.092
≥ Stage 2 cystocele	31 (39)	37 (29)	0.131
Mean bladder descent on ultrasound (mm)*	−3.8	−1.0	0.142
Significant cystocele on ultrasound	28 (35)	25 (19)	0.012†

Data given as *n* (%) except where indicated. *The lower the value, the further the cystocele is below the pubic bone. †Odds ratio 2.24 (95% CI, 1.13–4.43). Ba, Most distal position on anterior vaginal wall, with respect to the hymen.

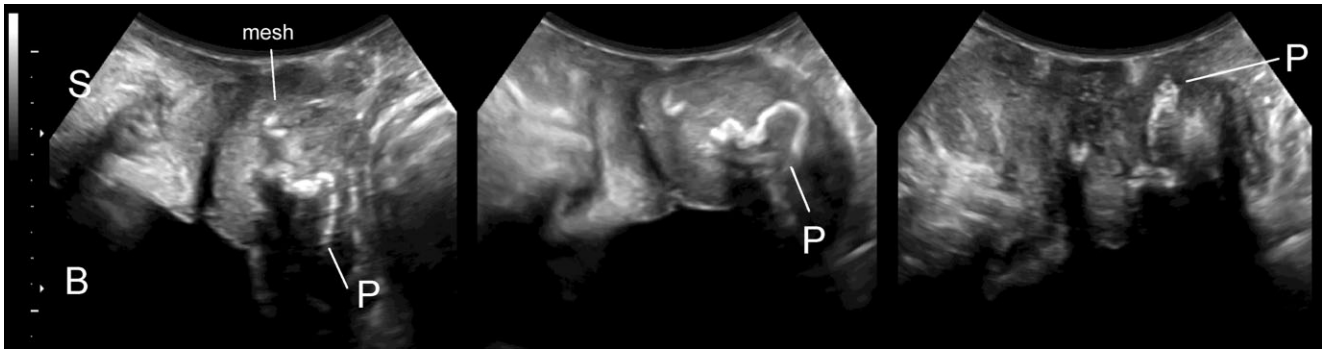

Figure 2 Ultrasound images of recurrent cystocele after anterior compartment mesh placement, caused by dislodgment of superior transobturator arms. The left image shows appearance at rest, the middle one on submaximal Valsalva and the right on maximal Valsalva. Cranial aspect of mesh (P) is no longer supported and moves freely on Valsalva maneuver. B, bladder; S, symphysis pubis.

to normalize levator morphobiometry to reduce the occurrence of mesh failure.

Several limitations of this study need to be acknowledged. First, our data were obtained in the context of three surgical audit projects, reporting the results of four subspecialist surgeons, and many patients would have been operated on by trainees. Some may regard this as a limitation, since operator experience and skills may have varied widely. However, we regard it as a strength of our study, as the results should be more generally applicable. Furthermore, the recurrence rates observed by us are very similar to those recently reported in a randomized controlled trial by Altman *et al.*[20] and likely to be realistic.

Second, we were unable to see all patients operated on during the inclusion period, implying that some form of selection bias may have operated in this study. However, it seems unlikely that any such bias would influence the relationship between levator avulsion and recurrence, analysis of which was the main objective of the study.

Third, only sonographic cystocele recurrence was a significant finding in women with levator avulsion, while there was no significant difference in symptoms of recurrence or clinical cystocele recurrence between women with and without levator avulsion. Some may consider subjective and clinical findings to be more valid than sonographic outcome measures. However, recent studies have shown that among objective measures of prolapse recurrence, ultrasound findings of significant cystocele (that is, bladder descent of ≥ 10 mm below the symphysis pubis) are likely to be the most valid[30], and symptoms are commonly poor outcome measures in surgical trials, as shown in the study of Altman *et al.*[20]. The findings of non-significance in symptomatology or clinical assessment may well be due to a lack of power/type II error. At present, we are conducting a prospective observational study to validate both ultrasound imaging of pelvic organ prolapse and clinical prolapse assessment in parallel against symptoms of prolapse and prolapse bother to investigate whether ultrasound is indeed better at identifying prolapse than is clinical ICS POP-Q assessment.

In conclusion, avulsion of the puborectalis muscle, as diagnosed by TUI, is associated with an increased risk of cystocele recurrence following transobturator anterior compartment mesh repair. At an average of 2.2 years follow-up, the OR for sonographically diagnosed cystocele recurrence in women with levator avulsion is > 2. This implies that transobturator mesh implantation in such patients does not fully compensate for the effect of levator trauma on recurrence risk. Future work should focus on developing more sophisticated models for the estimation of recurrence risk in the individual patient, and on reducing recurrence rates in high-risk patients through surgical innovation.

ACKNOWLEDGMENT

We would like to acknowledge Andrew Martin, Biostatistician, University of Sydney, for assistance with statistical analysis.

DISCLOSURES

HP Dietz has received honoraria as a speaker for GE Medical Systems, Astellas and AMS and has in the past acted as consultant for CCS, AMS and Materna Inc. He has also received equipment loans from GE, Toshiba and Bruel and Kjaer, and an unrestricted educational grant from GE. A Rane is a consultant and preceptor for AMS. The other authors have no financial disclaimers or conflicts of interest to declare.

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Chapter 5: A comparison of two different mesh kit systems for anterior compartment prolapse repair.

Publication 3

Wong V, Shek K, Rane A, Lee J, Rosamilia A, Dietz H. A comparison of two different mesh kit systems for anterior compartment prolapse repair. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2014;54(3):212 - 7.

5.1 Results summary

This was a retrospective study utilising two clinical audit projects to evaluate two different mesh kit systems; the Perigee™ and the Anterior Elevate™. Two hundred and twenty nine patients with either Perigee™ (n=138) or Anterior Elevate™ (n=91) were seen at a median follow-up of 1.09 years (IQR 0.65 – 2.01). Twenty four percent (55/229) were symptomatic of prolapse at time of follow-up, 46% (106/229) had clinical prolapse recurrence (POPQ ≥ Stage 2) and 41% (95/229) had evidence of a recurrent cystocele on imaging. All objective results favoured Perigee™ mesh, and this remained highly significantly superior after multivariate analysis (p<0.0001).

This study showed that apical anchoring with tissue fixation, such as the Anterior Elevate™ mesh kit system, did not confer an advantage over the transobturator mesh arm fixation method, such as Perigee™, in reducing cystocele recurrence.

Hypothesis 3: 'Vaginal mesh with apical anchoring to the sacrospinous ligaments is associated with improved outcomes compared to mesh implants with sidewall fixation' could not be confirmed.

Original Article

A comparison of two different mesh kit systems for anterior compartment prolapse repair

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Background and Aim: Mesh reinforcement is considered an effective method for anterior compartment prolapse repair. Two common methods of mesh reinforcement involve either transobturator fixation (eg Perigee™) or lateral and apical anchoring (eg Anterior Elevate™). The aim of this study was to assess subjective and objective outcomes after Anterior Elevate and Perigee mesh kit surgery.

Materials and Methods: This was a surgical audit of patients after anterior colporrhaphy (AC) with mesh reinforcement, undertaken at three tertiary urogynaecological centres. All patients were assessed for prolapse recurrence, which was defined as either (i) symptoms of prolapse (vaginal lump/dragging), (ii) ICS POPQ ≥ Stage 2, or (iii) bladder descent ≥10 mm below the symphysis pubis on transperineal ultrasound. Mesh co-ordinates and organ descent on Valsalva were determined relative to the inferior symphyseal margin.

Results: Two hundred and twenty-nine patients with anterior compartment mesh (138 Perigee, 91 Elevate) were assessed at a median follow-up of 1.09 years (IQR 0.65–2.01). On assessment, 24% (n = 55) had symptoms of prolapse recurrence, 46% (n = 106) had a clinical recurrence, and 41% (n = 95) a recurrent cystocele sonographically. All objective results favoured the Perigee group. The superiority of the Perigee kit remained highly significant ($P < 0.0001$ for all clinical and ultrasound measures of prolapse recurrence) on multivariate analysis.

Conclusions: This retrospective analysis suggests that apical anchoring such as Anterior Elevate mesh system does not necessarily confer an advantage over the original transobturator mesh fixation technique for anterior compartment reconstruction.

Key words: 3D ultrasound, anterior colporrhaphy, cystocele, mesh, pelvic organ prolapse, recurrence.

Introduction

Pelvic organ prolapse (POP) is a debilitating condition afflicting a substantial proportion of the female population[1] and accounts for approximately 1/3 of gynaecological consults in USA in women over the age of 50.[2] In Western Australia, the estimated lifetime risk of a patient requiring reconstructive surgery is as high as 19%.[3] Amongst the different types of POP, cystocele is the most common[4] and the most challenging to repair, with recurrence rates of about 30–50% following traditional native tissue reconstruction.[5,6]

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Received 4 December 2013; accepted 22 January 2014.

In the last nine years, anterior compartment mesh kits have become popular due to a higher anatomical success rate, when compared with native tissue repair.[7] Mesh kits such as the Perigee™ system (American Medical Systems, Minnetonka, MN, USA) use a polypropylene mesh that is anchored to the pelvic sidewall with strip-like mesh arms that perforate through the obturator foramen. Safety and efficacy of the Perigee™ system have been documented with recent five-year data.[8] However, failure (that is, pull-through) of those anchoring arms is not uncommon.[9]

Due to increasing emphasis on the importance of apical support for the anterior compartment,[10] mesh kit systems such as the Anterior Elevate™ (American Medical Systems) were introduced. In order to provide sacrospinous ligament (SSL) anchorage and to avoid blind transobturator trocar needle passes, the Anterior Elevate™ mesh kit system utilises tissue anchors to the arcus tendineus fascia pelvis (ATFP) and the SSL rather than the transobturator arms. It has been shown to be safe and

effective in treating anterior compartment prolapse in the medium term.[11]

The purpose of our study was to assess subjective and objective anatomical outcomes between the apically anchored Anterior Elevate and the transobturator Perigee mesh kit systems.

Materials and Methods

This is an observational study using data obtained in one internal and two external surgical audits of anterior compartment mesh conducted at three tertiary urogynaecological centres. The external audit follow-up assessments were conducted by a team of investigators from a unit not involved in the index surgery or ongoing patient care, over a one-week period. Women who had a Perigee or Anterior Elevate mesh repair were invited to attend an audit appointment at least three months after the procedure. All participants underwent a standardised interview, inquiring on urinary, bowel and sexual function. Women were also asked whether they were 'satisfied with outcome of surgery' and whether they felt 'cured, improved, same or worse'. The participants also underwent an ICS Pelvic Organ Prolapse quantification (POP-Q)[12] clinical assessment and a 4D transperineal ultrasound imaging using GE Kretz Voluson 730 expert or Voluson-I systems with RAB 4-8 MHz transducer (GE Medical Systems, Zipf, Austria).

Ultrasound volumes were acquired supine after bladder emptying, as previously described.[13] Volume acquisition was performed at rest, on maximal Valsalva and on pelvic floor muscle contraction (PFMC). Postprocessing analysis of these datasets was undertaken, several months after data collection, with proprietary software 4D view (version 7.0, 10.0; GE Kretz Ultrasound, Zipf, Austria), blinded against all clinical data.

The status of the puborectalis muscle was assessed using volume acquired on PFMC or at rest if the woman could not contract the pelvic floor. Using tomographic ultrasound imaging (TUI), the entire puborectalis muscle complex is imaged at 2.5-mm slice intervals. The plane of minimal hiatal dimensions, ie, an axial plane incorporating the shortest distance between posterior symphyseal margin and anterior border of the puborectalis muscle, is selected as reference plane. A woman was rated as positive for levator avulsion if the plane of minimal hiatal dimensions, as well as slices 2.5- and 5-mm cranial to that plane, all showed an abnormal insertion.[14]

Levator hiatal area was measured using rendered images as previously described.[15] Anterior compartment mesh was visualised as a hyperechoic linear structure in the mid-sagittal plane. Lowest mesh position was ascertained on maximal Valsalva with the most caudal aspect of the mesh plotted against a reference line drawn from the inferior margin of the symphysis pubis, as seen following an Anterior Elevate mesh (Fig. 1) and a Perigee mesh (Fig. 2). Due to poor visualisation of the cranial end of the mesh in most cases, cranial mesh co-ordinate measurements were not performed. A test–retest series ($n = 50$) on mesh position was performed by VW and KLS.

Women were evaluated for subjective (ie symptoms of vaginal bulge/lump) and objective prolapse recurrence. The latter was defined either clinically (point Ba ≥ -1) or sonographically (most dependent part of the bladder $\geq$10 mm below the inferoposterior margin of the symphysis pubis) as previously described.[16] The definition of significant cystocele on ultrasound was previously determined on the basis of receiver operator characteristic curve, using symptoms of prolapse as outcome measure.[17]

Statistical analysis was undertaken using Minitab version 13 (Minitab Inc., State College, PA, USA), Prism v6.0b (GraphPad Software, La Jolla, CA, USA) and SAS version 9.3 (SAS Institute Inc., Cary, NC, USA). Normality was assessed using the D'Agostino & Pearson Omnibus normality test. Student's *t*-test was performed for continuous variables and chi-square test analysis for categorical variables. A *P*-value of <0.05 was considered to be statistically significant. Intraclass correlation statistics (single measurement, absolute agreement definition) were used to determine the repeatability of sonographic measures of mesh location. To compare subjective and

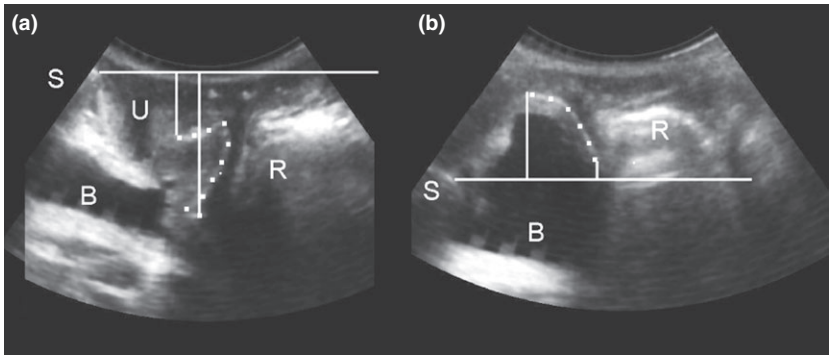

Figure 1 Mesh imaging on translabial ultrasound at rest (a) and on Valsalva (b). The Anterior Elevate mesh is identified by the dotted line. Mesh position is measured against the reference of the inferoposterior symphyseal margin. The vertical lines show the postions of cranial and caudal mesh aspects. B, bladder; R, rectum; S, symphysis pubis; U, urethra.

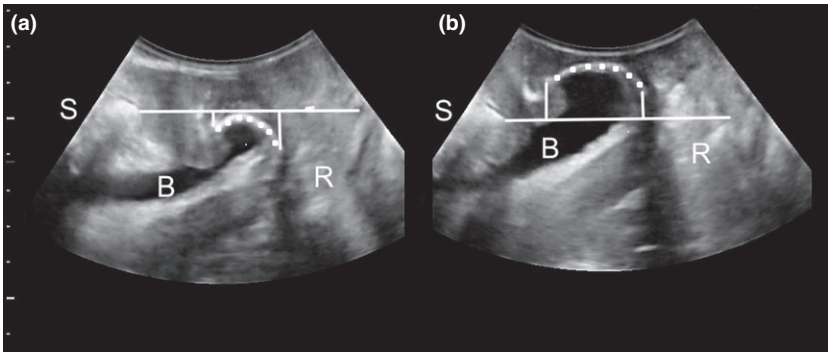

Figure 2 Mesh imaging on translabial ultrasound at rest (a) and on Valsalva (b). The Perigee mesh is identified by the dotted line. A hyperechoic mid-urethral sling can also be seen in this image. B, bladder; R, rectum; S, symphysis pubis. Reproduced with permission from Shek[9].

objective outcomes between the two mesh kit systems, we conducted multiple regression or logistic regression analyses, as appropriate, adjusting for significant confounders ($P < 0.05$) identified following univariate analysis. Ethics approval had been obtained for all three clinical audits (SWAHS HREC 07-063, Townsville HREC 84/04 and Victoria HREC No. 10310Q).

Results

Three hundred and thirty-eight women had an anterior compartment mesh between September 2004 to August 2011 (202 Perigee mesh between September 2004–February 2011, 136 Anterior Elevate mesh between July 2009–August 2011) at participating units and were invited to participate. Of these, 229 women (138 Perigee and 91 Anterior Elevate) attended (68% of Perigees, 67% of Anterior Elevate cases). The median follow-up was 1.09 years (IQR 0.65–2.01), median age was 66 years (IQR 60–72), median BMI was 27.4 (IQR 24.3–30.1) and median vaginal parity was 3 (IQR 2–4). Demographic data and concomitant procedures of the two groups are shown in Tables 1 and 2.

All women had at least a Stage 2 anterior vaginal prolapse (point Ba ≥ -1) prior to surgery; however, due to the retrospective design of the study, we were only able to retrieve pre-operative POPQ data in 158 women. Of these 158 women, 110 had POP Stage 3 or 4 (83 anterior compartment, 14 apical compartment and 13 posterior compartment). The mean point Ba pre-operatively was +1 and mean point C was −4.

One hundred and eighty-nine women (83%) were satisfied with their procedure (82% in Perigee, 84% in Anterior Elevate groups), and 85 (37%; 50 (36%) in Perigee, and 35 (38%) in Anterior Elevate groups) considered themselves cured. Fifty-five women (24%) were symptomatic of prolapse recurrence (37 in Perigee, and 18 in Anterior Elevate groups). On assessment, 46% ($n = 106$) had a clinical recurrence (ICS POPQ $\geq$ Stage 2) and 41% ($n = 95$) a recurrent cystocele on USA. Mean point Ba was −1.5, and mean bladder descent on USA was 7 mm below the symphysis pubis (SD 13). Levator avulsion was found in 99 women (43%); 46 unilateral and 53 bilateral. The mean hiatal area was 34.1 cm^2 (SD 8.8), which is defined as moderate hiatal ballooning.[18]

Table 3 shows a comparison of the subjective and objective outcomes of the two groups. On multivariate analysis of mesh type adjusting for potential confounders of prolapse recurrence, including follow-up time, concomitant sacrospinous fixation and posterior mesh surgery, the difference in outcomes between Anterior Elevate and Perigee remained highly significant ($P < 0.0001$ for clinical and ultrasound measures of prolapse recurrence). Anterior Elevate meshes seemed to descend to a substantially lower position on Valsalva. However, there was no significant difference between the groups in recurrent prolapse symptoms.

A subanalysis of women for whom pre-operative Ba and C measurements were available ($n = 158$) failed to show any predictive value of pre-operative prolapse staging and no confounding effect on groupwise comparisons.

There were 19/229 women (8%) with mesh exposure at the time of the surgical audit assessments, with 12 seen in the Perigee and seven in the Anterior Elevate groups ($P = 0.845$). Seventeen out of two hundred and twenty-nine women (7.4%) complained of pelvic pain and 20/158 who were sexually active experienced dyspareunia (12.7%). There were no differences in complaints of chronic pelvic pain between Anterior Elevate and Perigee groups ($P = 0.38$).

Discussion

Female POP is a common condition, and surgical correction remains a major challenge especially in the anterior compartment. Over the last ten years, there has been substantial change in available surgical techniques, largely due to the development of modern prolapse mesh kits. Mesh use in anterior compartment repair has been shown to be superior to traditional repair in normalising anatomy;[7] however, there are substantial disadvantages due to novel and sometimes major complications.[19]

Table 1 Demographics and pre-operative data amongst the Perigee and the Anterior Elevate women

Parameters	Perigee (N = 138)	Anterior Elevate (N = 91)	P-value
Follow-up (years) (median, (IQR))	1.38 (0.86–3.17)	0.77 (0.45–1.21)	<0.0001⋆
Age (years) (median, (IQR))	65.6 (56.1–72.7)	66.3 (62.1–71.2)	0.243⋆
BMI (kg/m2) (median, (IQR))	27.6 (24.8–30.4)	27.0 (23.8–30.0)	0.386⋆
Vaginal parity (median, (IQR))	3 (2–4)	3 (2–3)	0.305⋆
Previous vaginal prolapse repair	53	41	0.317†
Previous hysterectomy	69	47	0.807†
Previous incontinence procedure	6	5	0.691†
Pre-operative POP-Q			
Ba (mean, SD)	+1.4 (1.9)	+1.6 (1.1)	0.576‡
C (mean, SD)	−3.2 (4.1)	−3.9 (3.6)	0.289‡
Levator hiatal area (mean, SD)	34.6 cm^2 (9.15)	33.3 cm^2 (8.21)	0.269‡
Levator avulsion	59	40	0.857†

⋆Mann–Whitney U-test.
†Chi-suare test analysis.
‡Student's t-test.
POP-Q, Pelvic Organ Prolapse quantification.

Table 2 Concomitant procedures performed between the Perigee and Anterior Elevate groups

Concomitant procedures	Perigee (N = 138)	Anterior Elevate (N = 91)	P value
Hysterectomy	19	7	0.156⋆
Sacrospinous fixation	20	1	0.001⋆
Sacrohysteropexy	4	0	0.101⋆
Posterior repair	50	40	0.242⋆
Posterior mesh repair (Apogee/Posterior elevate)	24	7	0.001⋆
Mid-urethral sling	32	26	0.359⋆

⋆Chi-square test analysis.

In this current study, we tested two commonly used mesh products employing different methods of fixation. We audited subjective and objective outcomes in 229 women at a mean follow-up of over one year. Due to the timing of the respective audits, Perigee cases may be considered a 'historical control' group.

The majority of women (83%) were satisfied with the outcome of their procedure. However, objective anatomical results were less optimal, with over 40% of women showing signs of significant cystocele recurrence. The Anterior Elevate mesh procedure appears to be inferior in achieving successful anatomical reconstruction, with all comparisons of objective outcomes favouring the Perigee group. This is surprising and may be considered counter-intuitive, given that apical support has been assumed to be a crucial contributor to anterior compartment failure.[10,20] Due to this perception, there has been a gradual move towards the incorporation of sacrospinous suspension at the time of cystocele repair. However, as shown in the Anterior Elevate group of this study, superior apical support does not necessarily translate to superior anterior compartment support. Only 24 women in the Perigee group had a concurrent apical suspension compared with all in the Anterior Elevate group, but it seems that Perigee provided better mid-vaginal or 'Level II' support. This was despite longer average follow-up in the Perigee group.

The inferior performance of Anterior Elevate may plausibly be explained by the mechanical integrity of the different anchoring structures, or it may be due to the inadvertent placement of anchors to structures other than the obturator internus or sacrospinous ligament. Furthermore, it is plausible that the self-fixating anchors of Anterior Elevate may not provide sufficient load-bearing capability and Level II support compared with the transobturator arms of Perigee mesh kits which employ a 'velcro-like' effect along the entire path of mesh arm implantation. However, the transobturator anchoring employed by the Perigee system is by no means perfect as shown again in this series, with 1/3 of women having objective evidence of recurrence.

To our knowledge, this is the first comparative study of outcomes between two modalities of anterior compartment mesh anchoring. However, several limitations of our study need to be acknowledged. Firstly, the study involved analysis of data obtained in two external audit projects that were performed by a visiting team within one working week in each series. Whilst we attempted to control for potential confounders using multivariate analysis, there may be other unknown variables we have not adjusted for, which would have been controlled for in a randomised controlled trial. Secondly, due to the vast geographical distances that some women had to travel, many were unable to return for follow-up during the audit weeks, implying potential selection bias. However, we were able to assess almost 70% of women operated on during the inclusion period.

As this study was an audit of three subspecialist urogynaecology teaching centres, results are likely to be

Table 3 Comparisons of subjective and objective outcome measures between groups

Mesh types	Symptoms of prolapse	Mean point Ba	ICS POPQ ≥ Stage 2	Mean bladder descent on USA⋆ (mm)	Mean lowest mesh position on USA⋆ (mm)
Perigee (n = 138)	37/138 (26.8%)	−1.8 (SD 1.3)	46/138 (33.3%)	−3.5 (SD 12.5)	−7.8 (SD 9.0)
Elevate (n = 91)	18/91 (19.8%)	−0.9 (SD 1.1)	60/88 (68.2%)	−12.0 (SD 11.9)	−14.8 (SD 7.7)
P value	0.22	<0.0001	<0.0001	<0.0001	<0.0001
Adjusted P-value†	0.27	<0.0001	<0.0001	<0.0001	<0.0001

⋆A negative value signifies position below the pubic symphysis on maximum Valsalva.
†Performed using multiple logistic regressions or multiple regression adjusting for all confounders that reached significance on univariate analysis that is posterior mesh repair, vaginal vault suspension and length of follow-up.

representative of a wide range of skill levels and surgical techniques amongst the participating clinicians/surgeons. Mesh tension adjustment and technique of placement may vary amongst surgeons and over time, and it is impossible to assess the impact of individual technique in this data set. Some may consider the likely variations in technique a disadvantage. We would argue that our results are likely to be more representative of general gynaecological practice. Furthermore, we may have inadvertently compared older polypropylene mesh quality with newer mesh qualities and performance. However, any potential change in mesh quality would not seem to be of advantage, given the results of this study.

Thirdly, we did not utilise validated questionnaires to assess patient reported outcomes. However, questionnaires are notoriously insensitive to change after prolapse surgery, and the symptom of the 'feeling of a vaginal lump/bulge' has been shown to strongly correlate with anatomical prolapse.[21]

In this study, anatomical cure rates are inferior to those previously reported for both mesh systems[11,22,23] suggesting that perhaps our definition of anatomical success may be too strict. It has recently been proposed that cystocele recurrence should be defined as Ba ≥ 0.[24] Own data[25] suggest that point Ba = −1 and Ba = 0 are equally valid in defining 'significant prolapse' as Ba = −0.5 performs best when analysed as a predictor of prolapse symptoms with receiver operator characteristics statistics. At any rate, any re-definition of anatomical success would have no bearing on the main finding of this study, ie, the superiority of anterior compartment anatomical outcomes after Perigee mesh.

As mentioned above, our results appear to contradict other series published as regards anatomical efficacy of mesh kits, and this is true for both mesh systems. Moore *et al.*[11] have shown an objective cystocele cure rate of over 90% (≤stage 1) at a mean follow-up of 13.4 months, and Gauruder-Burmester *et al.*[26] found similar success rates after Perigee mesh kit systems. However, internal audit data invariably produce higher success rates than RCTs or external audits, and absolute numbers are of limited relevance for the main aim of our study which was to compare subjective and objective anatomical outcomes of the two techniques.

Anatomical success is of course not the only factor to consider in comparing surgical techniques. Some proponents of the single-incision mesh kits believe that avoiding lateral graft penetration of the pelvic side wall may result in less chronic postoperative pain; however, in our study, the incidence of chronic pain after mesh insertion did not appear to be significantly different between the groups.

In conclusion, in this retrospective analysis of data obtained in audit projects at three tertiary urogynaecological centres, the apical anchoring of the Anterior Elevate mesh system did not confer any advantage over the transobturator mesh fixation technique for anterior compartment reconstruction employed by the Perigee system. This study will facilitate the planning of future randomised controlled trials by allowing power calculations for both subjective and objective outcome measures.

Acknowledgement

We would like to acknowledge Andrew Martin and Kristy Mann, Biostatisticians, University of Sydney, for their help with statistical analysis.

Conflict of Interest

HP Dietz and KL Shek have received unrestricted educational grants from GE Medical Ultrasound. A Rane is a consultant and preceptor for AMS. Drs J Lee, and A Rosamilia have received external research grants from American Medical Systems and Boston Scientific. V Wong has no conflict of interest to declare.

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Chapter 6: Laparoscopic sacrocolpopexy: how low does the mesh go?

Publication 4

Wong V, Guzman Rojas R, Shek K, Chou D, Moore KH, Dietz HP. Laparoscopic sacrocolpopexy: how low does the mesh go? Ultrasound in Obstetrics & Gynecology. 2017;49(3):404-8.

6.1 Results summary

A surgical audit of 97 patients at a mean follow-up of 3.01 years (range 0.13 – 6.87yrs) after laparoscopic sacrocolpopexy found clinical prolapse recurrence in 62% (60/97) in the anterior compartment and 44% (43/97) in the posterior compartment. The apical compartment remained very well elevated with no clinical recurrence. Mesh could be visualised on ultrasound in 62% (60/97) patients in the anterior compartment. Using the formula $\sqrt{}$ ([Xvalsalva-Xrest]^2 + [Yvalsalva – Yrest]^2), mesh mobility was measured at rest and on Valsalva. Both the mesh position and mobility on Valsalva were significantly associated with recurrent cystocele on clinical and on ultrasound assessment (all p<0.01).

This study found that cystocele recurrence was not uncommon after laparoscopic sacrocolpopexy. Support of the mid-vagina appears to be crucial. For every mm that the mesh was located further from the bladder neck on Valsalva, the likelihood of cystocele recurrence increased by 6 – 7%.

Hypothesis 4: 'Abdominally placed mesh for apical or uterine prolapse is effective for anterior compartment support' could not be confirmed.

Ultrasound Obstet Gynecol 2017; **49**: 404–408
Published online 7 February 2017 in Wiley Online Library (wileyonlinelibrary.com). **DOI:** 10.1002/uog.15882

Laparoscopic sacrocolpopexy: how low does the mesh go?

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KEYWORDS: 4D ultrasound; imaging; laparoscopic sacrocolpopexy; mesh; pelvic floor; pelvic organ prolapse

ABSTRACT

Objective *Laparoscopic sacrocolpopexy is becoming an increasingly popular surgical approach for repair of apical vaginal prolapse. The aim of this study was to document the postoperative anterior mesh position after laparoscopic sacrocolpopexy and to investigate the relationship between mesh location and anterior compartment support.*

Methods *This was an external audit of patients who underwent laparoscopic sacrocolpopexy for apical prolapse ≥ Stage 2 or advanced prolapse ≥ Stage 3, between January 2005 and June 2012. All patients were assessed with a standardized interview, clinical assessment using the International Continence Society Pelvic Organ Prolapse quantification and four-dimensional transperineal ultrasound to evaluate pelvic organ support and mesh location. Mesh position was assessed with respect to the symphysis pubis whilst distal mesh mobility was assessed using the formula* $\sqrt{[(X_{Valsalva} - X_{rest})^2 + (Y_{Valsalva} - Y_{rest})^2]}$*, where* X *is the horizontal distance and* Y *is the vertical distance between the mesh and the inferior symphyseal margin, measured at rest and on Valsalva.*

Results *Ninety-seven women were assessed at a mean follow-up of 3.01 (range, 0.13–6.87) years after laparoscopic sacrocolpopexy, 88% (85/97) of whom considered themselves to be cured or improved, and none had required reoperation. On clinical examination, prolapse recurrence in the apical compartment was not diagnosed in any patient; however, 60 (62%) had recurrence in the anterior compartment and 43 (44%) in the posterior compartment. On ultrasound examination, mesh was visualized in the anterior compartment in 60 patients. Both mesh position and mobility on Valsalva were significantly associated with recurrent cystocele on clinical and on ultrasound assessment (all* $P < 0.01$*). For every mm that the mesh was located further from the bladder neck on Valsalva, the likelihood of cystocele recurrence increased by 6–7%.*

Conclusion *At an average follow-up of 3 years, laparoscopic sacrocolpopexy was highly effective for apical support; however, cystocele recurrence was common despite an emphasis on anterior mesh extension. Prolapse recurrence seemed to be related to mesh position and mobility, suggesting that the lower the mesh is from the bladder neck, the lower the likelihood of anterior compartment prolapse recurrence.*

INTRODUCTION

Laparoscopic sacrocolpopexy has become accepted widely as an alternative to abdominal sacrocolpopexy for treatment of prolapse, and surgical outcomes seem to be comparable[1–3]. Recent evidence has shown that laparoscopic sacrocolpopexy is associated with a shorter length of hospital stay and a quicker return to normal activity, with less morbidity[4]. Given the recent controversies over using mesh in vaginal prolapse repair, there is a palpable shift in practice away from inserting mesh in the vagina to placing it abdominally instead. Mesh placed abdominally appears to give fewer incidences of mesh erosions, dyspareunia and chronic pelvic pain[5].

The primary goal with sacrocolpopexy is to provide apical support for women with a predominantly vault or uterine prolapse. During the procedure, a 'Y-shaped' polypropylene mesh is attached from the anterior longitudinal ligament of the sacral promontory to the anterior and posterior vaginal vault. This provides robust prolapse repair, with high success rates of 78–100%, especially for the apical compartment. However, it is less successful for the anterior and posterior compartments[6].

Prolapse recurrence in the anterior and posterior compartments may be due to a more challenging caudad dissection during sacrocolpopexy, which is often

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Accepted: 9 February 2016

limited by poor tissue-plane separation and bleeding. Consequently, it is not surprising that the majority of failures following sacrocolpopexy occur in repair of the anterior compartment[2]. Fortuitously, mesh appears highly echogenic on ultrasound, which permits convenient assessment of its location and the functional impact it has on pelvic organ support following insertion[7]. Therefore, the aim of this study was to document the postoperative anterior mesh position after laparoscopic sacrocolpopexy and to investigate the relationship between mesh location and anterior compartment support.

METHODS

This was an external surgical audit of patients who underwent a laparoscopic sacrocolpopexy procedure by an experienced endoscopic surgeon at a tertiary center, over a 7-year period between January 2005 and June 2012. Laparoscopic sacrocolpopexy was performed in all patients who had apical prolapse ≥ Stage 2 or advanced prolapse ≥ Stage 3 in the anterior compartment.

The laparoscopic procedure was performed with dissection of the peritoneum overlying the vault and reflection of the bladder off the vagina anteriorly and the rectum posteriorly. Dissection was then continued pararectally, using a combination of blunt- and thermo-dissection towards the anterior portion of the levator ani muscle bilaterally. The peritoneum was then incised over the sacral promontory, exposing the anterior longitudinal ligament of the sacrum, and the incision was extended along the right lateral pelvic side-wall towards the vault. Once the dissection was considered satisfactory, anterior and posterior polypropylene meshes (Gynecare Gynemesh™, Ethicon US, LLC, Cincinnati, OH, USA) were introduced into the abdomen. The anterior mesh was secured onto the anterior vaginal wall using six 2.0 dissolvable polydioxanone sutures and posteriorly the mesh was placed onto the levator muscle using two 5-mm tackers (ProTack™, Tyco Healthcare, Norwalk, CT, USA) bilaterally. The meshes were then sutured together, away from the vault. At the sacral promontory, the mesh was triple-folded and anchored without tension onto the sacral promontory using the ProTack and reperitonealized. If deemed necessary, upon completion of the sacrocolpopexy, a concomitant paravaginal repair, a modified Tanagho technique[8] for colposuspension, or anterior/posterior colporrhaphy was performed.

All patients were invited to return for an audit assessment by an independent clinician who had not been involved in the index surgery or immediate postoperative care. All patients underwent a standardized interview, a clinical assessment by International Continence Society (ICS) Pelvic Organ Prolapse quantification (POP-Q)[9] and a four-dimensional (4D) transperineal ultrasound, using either a GE Voluson 730 Expert system or a Voluson S6 (RAB 8–4 transducer) system (GE Medical Systems, Zipf, Austria). Patients were evaluated subjectively (i.e. symptoms of vaginal bulge or lump) and objectively (clinical examination and ultrasound assessment) for prolapse recurrence. Patients were also evaluated for satisfaction with their surgical outcome by answering 'yes', 'no' or 'not sure' to the question 'are you satisfied with the procedure?'

Significant prolapse recurrence on clinical examination was defined as the most distal point of either the anterior, apical or posterior walls ≥ −1 cm from the hymenal remnant (i.e. ICS POP-Q ≥ Stage 2). Prolapse recurrence on ultrasound was diagnosed using previously defined cut-off values: 10 mm below the symphysis pubis for significant cystocele, 15 mm below the symphysis pubis for significant rectocele and at the level of symphysis pubis for significant uterine/vault prolapse[10].

Ultrasound volumes were acquired by V.W. and R.G.R., with the patient in the supine position after bladder emptying, using techniques described previously[11]. Volumes obtained at rest, on maximal Valsalva and on maximal pelvic floor muscle contraction (PFMC) were selected for analysis. Post-processing analysis of these datasets was undertaken with the proprietary software 4D View (versions 7.0 and 10.0; GE Medical Systems) by V.W., blinded against all clinical data.

The status of the puborectalis muscle was assessed using tomographic ultrasound imaging, as described previously[12]. Validated minimal criteria for the diagnosis of puborectalis muscle/levator avulsion[12] were used. Briefly, a patient was rated as having a levator avulsion if the plane of minimal hiatal dimensions and slices 2.5 and 5 mm cranial to that plane all showed an abnormal insertion, with a levator–urethra gap of ≥ 2.5 mm[13]. Levator hiatal dimensions (cm^2) were measured using rendered images[14].

Mesh was identified on ultrasound as a highly echogenic structure in all three orthogonal planes (mid-sagittal, coronal and axial; Figure 1), at rest and on maximum Valsalva. Lowest mesh position was identified in the mid-sagittal plane on maximum Valsalva, with the most caudal aspect of the mesh plotted against a reference line drawn from the inferoposterior margin of the symphysis pubis (Figure 2). Unfortunately, due to poor visualization of the cranial end of the mesh on Valsalva, recording of cranial mesh co-ordinate measurements was not possible. Distal mesh mobility was assessed using the formula $\sqrt{[(X_{\text{Valsalva}} - X_{\text{rest}})^2 + (Y_{\text{Valsalva}} - Y_{\text{rest}})^2]}$, from rest to maximum Valsalva, where X is the horizontal distance between mesh and inferior symphyseal margin and Y is the vertical distance between the mesh and inferior symphyseal margin. Where mesh was not visible along the anterior vaginal wall, the location of the vaginal apex was used to measure co-ordinates. The distance of the mesh from its lowest position to the bladder neck was also determined at rest and on maximum Valsalva.

Statistical analysis was performed with SAS v.9.2 (SAS Institute, Cary, NC, USA) and SPSS Statistics v.20 (IBM Corp., Armonk, NY, USA). A two-sample *t*-test was performed for continuous variables and chi-square analysis for categorical variables. $P < 0.05$ was considered to be statistically significant. This study was approved by the University of Sydney, Human Research Ethics Committee (protocol 15216).

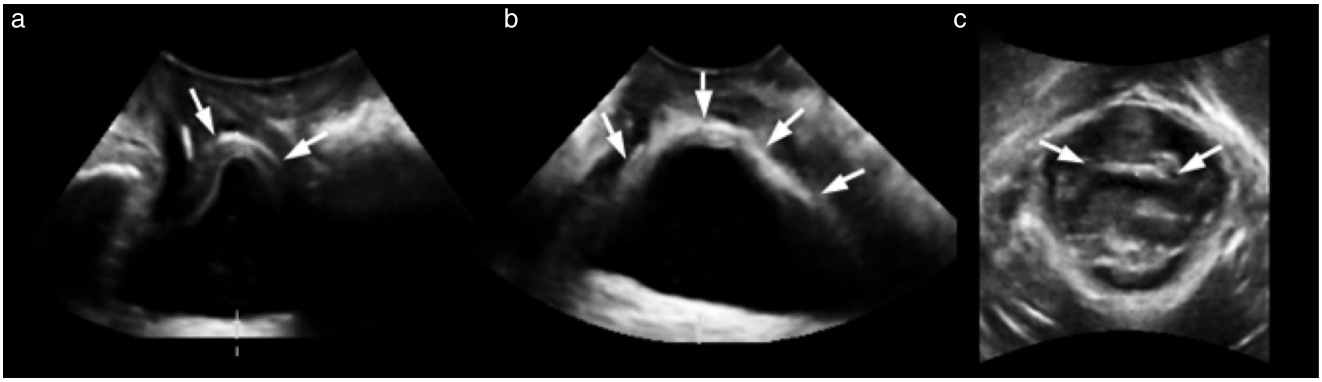

Figure 1 Mesh location (arrows) on four-dimensional transperineal ultrasound in mid-sagittal (a), coronal (b) and axial (c) planes on maximum Valsalva.

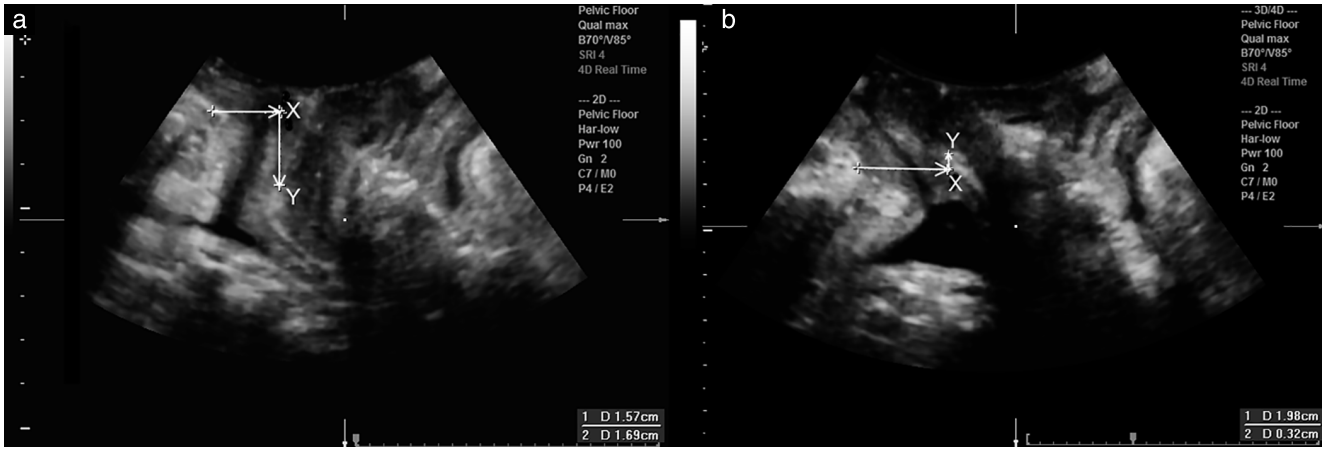

Figure 2 Measurement of mesh mobility by four-dimensional transperineal ultrasound at rest (a) and on Valsalva (b), using the formula: $\sqrt{[(X_{\text{Valsalva}} - X_{\text{rest}})^2 + (Y_{\text{Valsalva}} - Y_{\text{rest}})^2]}$, where X is horizontal distance and Y is vertical distance of mesh from symphysis pubis.

RESULTS

Between January 2005 and June 2012, 231 patients underwent laparoscopic prolapse surgery. Of all patients who were invited to return for an audit assessment, 114 (49%) were seen at a mean follow-up of 3.01 (range, 0.13–6.87) years. Three patients were excluded as they had undergone laparoscopic sacrohysteropexy. Fourteen ultrasound volumes were excluded due to a technical error with volume acquisition, leaving 97 available for analysis. All subsequent results refer to this dataset. Mean age was 61 (range, 40–77) years, mean body mass index was 26.9 (range, 18.6–39.5) kg/m^2 and mean parity was 3 (range, 0–8).

Twenty-six patients had previous vaginal hysterectomy with or without pelvic organ prolapse repair, and five had a previous anti-incontinence procedure, predominantly colposuspensions. Preoperatively, all patients who underwent surgery had prolapse ≥ Stage 2: 64 had anterior compartment prolapse ≥ Stage 3, 84 had apical compartment prolapse ≥ Stage 2 and 32 had posterior compartment prolapse ≥ Stage 3. Concurrent procedures performed were 67 total laparoscopic hysterectomies, one subtotal hysterectomy, 49 paravaginal repairs, 23 laparoscopic colposuspensions and 34 posterior colporrhaphies and perineorraphies. There were no conversions to an abdominal sacrocolpopexy, nor were there any rectal or bladder injuries.

Eighty-three patients were satisfied with their procedure and 85 (88%) considered themselves cured or improved overall. Recurrent prolapse symptoms were reported in 30 (32%) women. Clinical prolapse recurrence (ICS POP-Q ≥ Stage 2) was diagnosed in 80 patients, including 60 cases affecting the anterior compartment and 43 affecting the posterior compartment; however, recurrence in the apical compartment was not diagnosed in any patient. Nine patients had *de-novo* development of anterior compartment prolapse and 17 of posterior compartment prolapse. No patient had undergone a reoperation for prolapse in the follow-up interval. The tacks in the levator muscle were palpable in 20 patients, 16 (17%) of whom complained of tenderness upon palpation and 12 (12%) had symptomatic dyspareunia.

Ultrasound volume analysis was performed approximately 6 months after data acquisition. Eighty-one patients had sonographic prolapse recurrence: 52 in the anterior compartment, 64 in the posterior compartment and 11 in the apical compartment. Mean ± SD bladder neck descent was 24.0 ± 4.2 mm, mean cystocele descent was 10.6 (range, 18.7 to −52.3) mm below the symphysis

Table 1 Association between recurrent prolapse symptoms and recurrent cystocele on clinical and ultrasound assessment 3 years after laparoscopic sacrocolpopexy in 97 women

	Recurrent prolapse symptoms		*Recurrent cystocele on clinical assessment*		*Recurrent cystocele on ultrasound assessment*	
Mesh parameter	*OR (95% CI)*	P	*OR (95% CI)*	P	*OR (95% CI)*	P
Lowest mesh position	0.99 (0.97–1.02)	NS	0.94 (0.91–0.97)	0.001	0.93 (0.90–0.96)	0.001
Mesh mobility	1.00 (0.96–1.03)	NS	1.05 (1.01–1.09)	0.013	1.05 (1.01–1.09)	0.012

Odds ratios (OR) are per mm of mesh position or mobility. NS, not significant.

pubis, mean apical descent was 24.2 (range, −23.2 to 56.1) mm above the symphysis pubis and mean rectocele descent was 12.3 (range, −45.9 to 22.0) mm below the symphysis pubis, with a negative value representing a position below the level of the symphysis pubis. Six patients had sonographic findings of an enterocele, with mean measurements of 13.2 (range, −27.1 to 9) mm below the symphysis pubis.

In patients who had concomitant paravaginal repairs, 49 had significant preoperative cystocele on clinical examination with 45 being ≥ Stage 3, and 24 had a significant rectocele with 15 being ≥ Stage 3. At follow-up, 35 patients had recurrence in the anterior compartment with three patients having cystocele recurrence ≥ Stage 3, and 24 had recurrence in the posterior compartment with four cases of *de-novo* prolapse. Although univariate analysis of the effect of paravaginal repairs was significant for clinical prolapse recurrence ($P = 0.05$), this was no longer significant on multivariate analysis ($P = 0.276$).

Levator avulsion was diagnosed in 39 (40%) patients on tomographic ultrasound imaging; 18 were unilateral and 21 were bilateral. The mean levator hiatal area on Valsalva was 32.41 cm^2.

In 37 patients, the mesh was not visible on ultrasound. This was likely because the mesh was located too cranial for visualization. Analysis of these patients showed that 30% (11/37) were symptomatic of prolapse and 84% (31/37) had significant prolapse on POP-Q assessment: 21 in the anterior compartment, 17 in the posterior compartment and none in the apical compartment. On ultrasound, 76% (28/37) of these patients had significant prolapse, 21 in the anterior compartment, 16 in the posterior compartment and three in the apical compartment. Of those patients in whom mesh could be visualized on ultrasound, 33% (20/60) were symptomatic of prolapse at follow-up and 88% (53/60) had recurrent prolapse on POP-Q assessment: 39 in the anterior compartment, 30 in the posterior compartment and none in the apical compartment. On ultrasound, 75% (45/60) of these women had recurrent prolapse, with 29 in the anterior, 33 in the posterior and seven in the apical compartment.

In women in whom mesh was identified in the anterior compartment, the mesh was located, on average, 24 ± 11 mm dorsoventral and 38 ± 11 mm craniocaudal from the symphysis pubis at rest. The respective figures on Valsalva were 35 ± 12 mm and 24 ± 17 mm. On average, the mesh descended 20 ± 11 mm on Valsalva. The mean lowermost point of the mesh was located 26 ± 13 mm from the bladder neck at rest and 48 ± 25 mm from the bladder neck on Valsalva.

On univariate analysis, the lowest mesh position on Valsalva and mesh mobility on Valsalva were both significantly associated with recurrent cystocele on clinical as well as on ultrasound assessment (Table 1). Odds ratios were significant when correlating the risks of clinical and sonographic prolapse recurrence in the anterior compartment with the most distal position of the mesh as well as with mesh mobility. That is, for every mm the mesh was located further from the bladder neck on Valsalva, the likelihood of cystocele recurrence increased by 6–7%.

DISCUSSION

At an average of 3 years after laparoscopic sacrocolpopexy, we have demonstrated an unexpectedly high prevalence of recurrent prolapse in the anterior and posterior compartments. Sacrocolpopexy mesh can be visualized with ultrasound and appears highly echogenic in all three orthogonal views. In this study, we were able to visualize the mesh in 62% of patients and it was evident that the more distal the mesh was placed in the anterior compartment, that is the closer the mesh was placed to the bladder neck, the less likely it was for prolapse to recur in the anterior compartment. Our data suggested that for every mm that the mesh is placed closer to the bladder neck, the risk of prolapse recurrence in the anterior compartment on clinical examination was reduced by 6% and on ultrasound by 7%.

The use of transperineal ultrasound has made it much easier to assess mesh material in the pelvis as it often appears highly echogenic. To date, there is only one other study that has assessed abdominally placed mesh[15], and this methodology to assess sacrocolpopexy mesh has been shown to be feasible. This is particularly relevant given the ease of access to ultrasound machines in most institutions and with the increasing re-uptake of abdominally placed mesh. This appears advantageous especially when monitoring outcomes of patients who have undergone such a procedure.

It is interesting to note that, in this study, despite a well-supported apical compartment, on both clinical and sonographic assessment, this excellent apical support seemed to have little effect on the support of the anterior and posterior compartments. These findings

are not unprecedented, with up to 57% of patients diagnosed with recurrent rectocele following laparoscopic sacrocolpopexy in a study by Baesseler *et al.*[16]. Therefore, although apical suspension is thought to be an important factor in success of anterior compartment surgery[17], this study suggests that addressing and providing support to the mid-vaginal level is just as important in maintaining a successful anatomical outcome following prolapse repair. Hence we feel that one should aim to place the mesh as caudal along the anterior and posterior vagina as possible, in the hope of reducing recurrence at mid-vaginal level. One potential consideration may be to infiltrate with local anesthetic and adrenaline the vesico/rectovaginal space prior to commencement of the laparoscopic vault dissection for sacrocolpopexy. This might reduce intraoperative bleeding when dissecting the bladder off the vaginal vault, thus facilitating more caudal dissections.

We acknowledge several limitations of this study. First, this was a retrospective study and we were able to assess fewer than half of the patients who were operated on despite all efforts to encourage them to return for follow-up. The large geographical distances that patients had to travel precluded attendance of some at our follow-up assessments. The lower rate of return for follow-up may have accounted for some selection bias, which could have been improved by a prospective study design. Furthermore, in this study, we were not able to include validated questionnaire data to evaluate objectively functional impact and quality of life as patients did not have preoperative questionnaires for comparison. Again, this could be included when conducting a prospective study.

Second, patients included in this study were from a cohort of patients who were operated on by a single surgeon. The outcome may be operator-dependent. However, we would argue that this was an endoscopic surgeon who had performed more than 50 laparoscopic sacrocolpopexies prior to the study duration, using a consistent technique. This meant that there was little variance in surgical skills and our assessment is a true reflection of the procedural efficacy.

Unlike the study of Eisenberg *et al.*[14], we did not assess the posterior compartment mesh as this was significantly limited by the presence of echogenic stool bolus often found in the rectal ampulla. Furthermore, our aim was to assess the mesh mobility and location in relation to the anterior compartment, and hence assessing the posterior compartment was not our study focus. That being said, future attention should be placed on assessing outcomes of the mesh in the posterior compartment and the effects of different mesh anchorage techniques.

In conclusion, using 4D ultrasound for evaluation of mesh mobility and location following laparoscopic sacrocolpopexy has given us a perspective on where placement of mesh may result in failure. We found a correlation between mesh location and prolapse recurrence, particularly for the anterior compartment. Despite a higher rate of prolapse recurrence in the anterior and posterior compartments, we found excellent apical suspension outcomes with neither clinical apical recurrence nor requirement for reoperation in 97 patients over an average of 3 years.

DISCLOSURE

H.P.D. and K.L.S. have received unrestricted educational grants from GE.

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Chapter 7: A pilot study on surgical reduction of the levator hiatus with a mesh sling – the Puborectalis Sling

Publication 5

Wong V, Shek KL, Korda A, Benness C, Pardey J, Dietz HP. A pilot sutdy on surgical reduction of the levator hiatus – the Puborectals Sling, *in process of submission to International Urogynaecology Journal.*

7.1 Results summary

This was a prospective study to evaluate a novel surgical procedure designed to reduce the levator hiatal area. In this prospective multicentre surgical trial of 115 women, the novel surgical technique of placing a mesh sling in the infralevator space, lateral to and around the puborectalis muscle (the 'puborectalis sling') resulted in a significant reduction of levator hiatal area by 12cm^2, which was sustained over more than two years (p<0.0001). Despite this however, there was 30% (28/93) symptomatic prolapse recurrence, 66% (61/93) clinical prolapse recurrence and 49% (46/93) sonographic prolapse recurrence at a mean follow-up of 2.5yrs in this high-risk group of women with highly abnormal pelvic floor anatomy.

Three patients required a return to theatre with no long-term sequelae: one required implant removal due to infection, two had an examination under anaesthesia for obstructed defecation. One had a loosening of the mesh sling by division of anchoring sutures, the other did not require mesh adjustment. There were no long-term sequelae from the use of the mesh sling which appears to be a safe procedure.

This study showed 'proof of concept' of a novel surgical procedure designed to reduce hiatal distensibility. The procedure is successful in achieving hiatal area reduction with a favourable medium-term safety profile; however, prolapse recurrence rates were still high. A randomised controlled trial is currently underway to evaluate the effect of this procedure on prolapse recurrence.

Hypothesis 5: 'Surgical placement of a mesh sling around the puborectalis muscle is safe and effective in reducing hiatal area' was confirmed.

Title Page

A pilot study on surgical reduction of the levator hiatus - the Puborectalis Sling

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Financial disclaimer - HP Dietz and KL Shek have received unrestricted educational grants from GE. No other conflict of interests to declare by other authors.

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This was presented as an e-poster at IUGA 42nd ASM, Vancouver, June 2017.

Word count - 2941

7.2 Abstract

Introduction and Hypothesis:

Female pelvic organ prolapse recurrence has been shown to be associated with levator hiatal distensibility. Reducing hiatal size surgically may reduce recurrence risk. This study aims to demonstrate a novel surgical procedure, the puborectalis sling (PR Sling) designed to reduce levator hiatal area, and to assess medium-term safety and efficacy of this procedure.

Methods:

115 women undergoing prolapse repair with a pre-operative hiatal area on Valsalva of ≥ 35cm^2, were recruited into this Phase 1 prospective multicentre pilot study. All underwent a PR Sling after completion of standard repairs. They were followed up for 24 months. Primary outcome was levator hiatal area measured on ultrasound.

Results:

110 patients were evaluated at least 3 months post-operatively. Mean pre-operative hiatal area was 43.9 (35 – 63) cm^2. At 2.5 years, there was an average of 12cm^2 reduction in hiatal area. 30% (28/93) were symptomatic of prolapse, 66% (61/93) had clinical prolapse recurrence whilst 49% (46/93) had sonographic recurrence. Three patients required a return to theatre; one case of infection resulted in mesh removal, one had obstructed defecation requiring sling loosening and another had buttock pain with faecal impaction that resolved after manual disimpaction. There were no long-term sequelae.

Conclusions:

Levator hiatal area can be reduced surgically, with almost 30% reduction in area seen in this pilot study. The reduction was significant and sustained up to 2 years with no major long-term complications.

KEY WORDS

Pelvic organ prolapse, levator hiatal area, 3D-pelvic floor ultrasound, prolapse recurrence, mesh

BRIEF SUMMARY

Reduction of the levator hiatus is achievable in women at high risk of prolapse recurrence using a novel surgical technique, called the Puborectalis Sling.

7.3 Introduction

Pelvic organ prolapse (POP) is a common condition with reported prevalence rates ranging from 2 to 48%[1]. The condition accounts for a lifetime risk of 10-20% requiring surgery[2, 3]. There is a high recurrence rate following repair, with almost 1 in 3 women requiring further prolapse surgery[4]. The high rates of failure have led to the development of vaginal mesh kits. Whilst mesh reinforcements have been shown to reduce recurrence[5], their use is not innocuous. Mesh complications such as chronic pelvic pain, dyspareunia, mesh infection and erosion may occur [6].

To address the issue of prolapse recurrence, it is important to understand and modify risk factors. There is a growing body of evidence identifying excessive distensibility of the levator ani muscle and levator avulsion as important risk factors for prolapse recurrence[7-11]. The latter is a form of birth trauma sustained by 10-30% of women following their first vaginal delivery[12, 13]. These injuries most likely occur at the time of foetal head crowning[14, 15] and markedly increase the risk of POP, especially anterior and apical prolapse[14, 15]. Apart from macroscopic muscle tears, the degree of muscle stretching/lengthening during vaginal delivery may also cause permanent over-distension of the levator hiatus. In an observational study, up to 28% of primiparous women sustained enlargement of the hiatal area by more than 20% during postpartum assessment[16]. A follow up study suggested that childbirth-related changes to levator distensibility may not regress with time[17]. An enlarged levator hiatus implies greater load on any structure supporting the pelvic organs, whether the supportive structure is native tissue, suture or mesh. This may explain the

association between an enlarged hiatal area and increased incidence of prolapse recurrence.

In the US, a surgical procedure involving the placement of a mesh sling in the ischiorectal fossa, from one obturator foramen to the anococcygeal raphe and back to the contralateral side has been trialled in patients with faecal incontinence[18]. In this study by Rosenblatt, there were no significant procedure-related adverse events in a series of 29 women. Our PR sling procedure differs in that the mesh sling is secured onto the pubic rami and that the aim is to reduce hiatal area, which may result in reduction of prolapse recurrence.

In this study, we intended to demonstrate proof of concept by using a mesh as a brace around the levator hiatus to permanently reduce the distensibility of the levator ani, as well as to assess the long-term safety and efficacy of this novel surgical procedure. The study served as preparation for an ongoing randomised controlled trial designed to ascertain the effect of this procedure on prolapse recurrence.

7.4 Materials and methods

One hundred and fifteen patients were enrolled in this surgical pilot study conducted at two tertiary centres in 2010 - 2012. The primary inclusion criteria were a) patient requiring surgery for symptomatic pelvic organ prolapse and b) an enlarged hiatal area on Valsalva of ≥ 35cm^2. The latter criterion was selected in order to limit this phase I clinical trial to patients at high risk of prolapse recurrence. Patients with overt neuromuscular abnormalities, who had not completed their family and who were unable to provide informed consent were excluded. Primary outcome was hiatal area measurement on transperineal ultrasound; secondary outcomes were subjective and objective findings of pelvic organ prolapse recurrence.

Written consent was obtained from all patients. The operation was performed under general anaesthesia with full muscle relaxation. The PR sling was inserted after completion of the prolapse repair. For PR Sling placement, a groin incision was made at the level of the clitoris on both sides as for placement of a transobturator sling. Vertical perianal incisions of 2 cm in length, 3cms lateral and 3cms inferior to the anus, were made bilaterally. A tunnel was created digitally just below the anococcygeal raphe, connecting the two perianal incisions. A 3cm x 20cm strip of type 1 polypropylene mesh (Johnson & Johnson/Ethicon, Somerville NJ), was passed through this tunnel with the help of an angled clamp. A curved Stamey needle (90 degree curvature) was inserted through the obturator foramen via the groin incision, traversing the ischio-rectal fossa to exit in the ipsilateral perianal incision to retrieve one end of the mesh sling. Needle insertion was performed under digital guidance (vaginal and rectal) to ensure that the mesh sling was placed as medially

as possible, along the course of puborectalis muscle, without perforating or tethering vagina or rectum, see Figure 1.

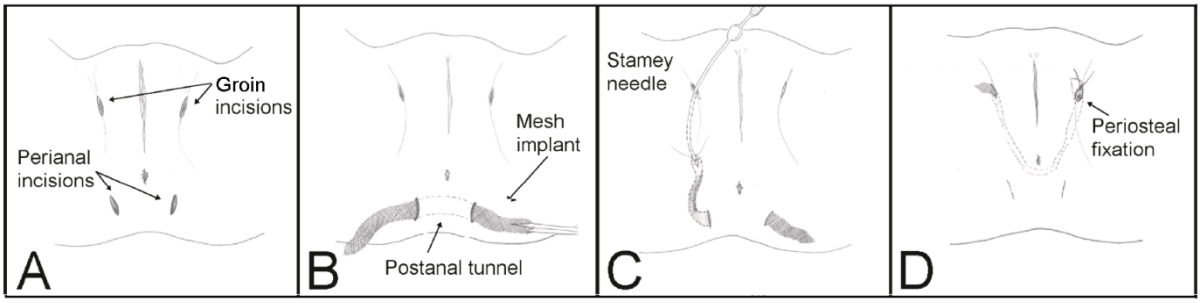

Fig. 1: Puborectalis sling procedure. A shows the incisions, B insertion of the implant, C its retrieval by curved needle, and D anchoring of the implant to the inferior pubic ramus.

The sling was tightened to obtain a genital hiatus and perineal body (Gh+Pb) measurement of approximately 7cm which is regarded as the limit of normal[19], see Figure 2.

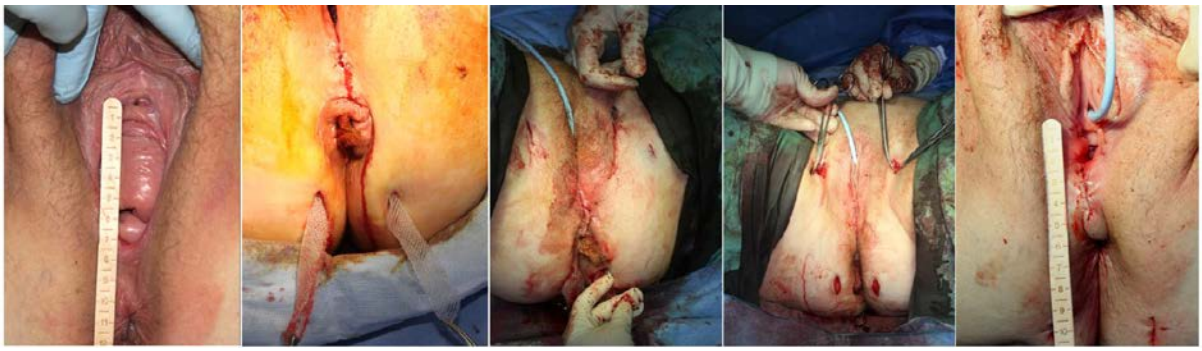

Fig 2: Puborectalis sling procedure. Image from left to right depicts measurement of Gh & Pb, insertion of the sling through the post-anal tunnel, retrieval of the mesh with the Stamey needle, securing the mesh onto the periosteum of pubic rami and the final measurement of Gh & Pb reduction at the conclusion of the surgery.

The mesh sling was then secured to the periosteum of the inferior pubic rami on both sides, using delayed absorbable sutures. All patients were given intra-operative antibiotics (Cefoxitin and Metronidazole). After the first few cases we used preoperative bowel preparation to facilitate postoperative defecation.

As part of the research protocol, post-operative follow-up visits were scheduled at 3, 6, 12 and 24 months with a standardised interview, POPQ clinical assessment and 4D transperineal ultrasound. The latter was performed in the supine position after bladder emptying using either GE Voluson 730 Expert or E8 systems (GE Medical Kretz Ultrasound, Zipf, Austria) with 8-4 MHz curved array volume transducer. The acquisition angle was set at 85° as previously described[20]. Pelvic organ descent and hiatal area were measured using volumes acquired at maximum Valsalva, according to published methodology[21]. Hiatal area on Valsalva was measured using rendered volume, where the region of interest was set at 1-2cm thickness at the plane of minimal hiatal dimension[22]. All ultrasound images were analysed using proprietary software (4D View v.10) at a later date, with the assessor blinded to all clinical data.

Subjective prolapse recurrence was defined as feeling or seeing a vaginal lump/bulge and/ or a dragging sensation. Clinical prolapse recurrence was defined as POPQ Stage 2 or higher in anterior / posterior and ≥ stage 1 in the central compartment. Sonographic recurrence was defined as either 1) a maximum bladder descent of ≥ 10 mm below the symphysis pubis, 2) the uterus at the level of the symphysis pubis or 3) the rectal ampulla descent of ≥ 15mm below the symphysis pubis.

Levator integrity was assessed using tomographic ultrasound imaging, employing a previously described methodology[23]. Levator avulsion was diagnosed if the muscle was disconnected from the sidewall at the plane of minimal hiatal dimension and two other slices at 2.5 mm interslice interval cranial to this plane. In doubtful cases, the levator-urethra gap measurement was used[24].

This study was approved by the local Human Research Ethics Committee (NBMLHD HREC 10-03). Power calculations were not performed due to the pilot nature of this study, with no input data available in the literature. Statistical analysis was performed using Minitab version 13 (Minitab Inc., State College, PA, USA). Student's *t*-test was performed for continuous variables and chi^2 analysis for categorical variables. A *p*-value of <0.05 was considered to be statistically significant.

7.5 Results

Among the 115 patients recruited and operated on, 113 (98%) returned for at least one postoperative assessment with a mean follow-up interval of 2.53 (1.72 – 5.98) years. Demographic and pre-operative clinical and sonographic findings are presented in Table 1.

Patient Characteristics	Values
Age (years), mean (range)	60 (29 – 88) years
BMI, mean (range)	29 (17 – 44) kg/m^2
Vaginal parity, mean (range)	3 (0 – 10)
Previous operative delivery	27/115 (23%)
Previous surgery	
Hysterectomy (%)	52/115 (45%)
Incontinence/Prolapse surgery (%)	38/115 (33%)
Pre-operative diagnosis of significant POP:	
Anterior compartment (%)	101/115 (88%)
Apical compartment (%)	95/115 (83%)
Posterior compartment (%)	78/115 (68%)
Pre-operative imaging	
Hiatal area on Valsalva (mean, range)	43.5 (35- 63) cm^2
Levator avulsion (%)	73/115 (63%)
Unilateral, *n*	44
Bilateral, *n*	29

Table 1: Demographic and clinical characteristics of the patient population.

All patients were symptomatic of prolapse and all patients had prolapse of ≥ stage 2 in at least one compartment. There were 69 patients with ≥ stage 3 anterior compartment descent, 83 ≥ stage 3 apical compartment descent and 67 ≥ stage 3 posterior compartment prolapse. Stress urinary incontinence was reported in 68 (59%), urge incontinence in 82 (71%), voiding difficulties in 52 (45%), obstructed defecation 40 (35%) and anal incontinence in 19 (17%). Preoperatively, mean bladder descent was 25mm (range - 65 to 66) below symphysis pubis, mean uterine/vault descent was 24mm (range - 60 to 30) below symphysis pubis, enterocele was 28mm (range - 54 to 40) below symphysis pubis and rectal ampulla was 21mm (range -45 to 18) below symphysis pubis. Mean hiatal area on Valsalva was 43.5 (range 35 – 63) cm^2 and 75/115 (65%) had severe hiatal ballooning (≥ $40cm^2$). Levator avulsion was diagnosed in 73 (63%).

A vaginal hysterectomy was performed in 47 women, a vault suspension in 66, an anterior repair in 95, a posterior repair in 80. A transobturator anchored mesh was inserted in 37, and a mid-urethral sling in 38. There were no cases of vaginal or rectal/anal perforations or major intraoperative complications with the puborectalis sling insertions. There was one case of rectal perforation during a concomitant Miya hook sacrospinous colpopexy. The suture was removed immediately with no adverse sequelae. There was one case of inadvertent cystotomy during vault dissection for sacrospinous fixation, which was recognised in theatre and repaired without any long-term consequences. There were 2 cases of infra-pubic needle passage during PR sling placement and several cases of mesh dislodgements from the needle on mesh retrieval, necessitating repeated Stamey/Pereyra needle passes. The

maximum number of needle passes on one side was 3. No procedure had to be abandoned for any reason.

In the postoperative period, one patient required removal of the PR Sling on Day 10 due to infection. Another woman had periosteal sutures cut bilaterally on Day 9 due to worsened obstructive defecation. One additional woman had an examination under anaesthesia for severe buttock pain on Day 10. She was found to have significant faecal impaction that was addressed in theatre without requiring sling adjustment. She had a fleet enema as well with good effect and resolution of pain.

There were no cases of puborectalis sling erosion. There were several cases of mesh erosions into the vagina during the follow-up period, all related to Perigee mesh (see table 4). All resolved with conservative care except two with an erosion of ≤ 5mm, who underwent mesh trimming in clinic at 12 months post-operative follow-up.

Five patients required further procedures for symptomatic prolapse during the follow-up period: one had a Perigee insertion with bilateral sacrospinous fixation, two had revision of Perigee and posterior repair with bilateral sacrospinous fixation, one had a posterior repair with bilateral sacrospinous fixation and the fifth patient had a Perigee with posterior repair and a repeat Puborectalis sling insertion eighteen months following her initial surgery. One patient required a transobturator sling for USI at 12 months' following surgery and another patient underwent a Delorme's procedure for rectal prolapse six months after the index surgery.

Subjective and objective outcomes at each follow-up time point are shown in Table 2. Table 3 showed a breakdown of significant clinical prolapse recurrence in individual compartment at follow-up. Urinary and bowel function outcomes over each follow-up time points are shown in Table 4. The reduction in hiatal area, as compared to pre-operative measurements, was highly significant at all follow-up time points and was maintained throughout the two-year follow-up period (Table 2).

Parameter	**Pre- op. status (n=115)**	**3 m postop N= 110**	**6 m postop N=106**	**12 m postop N=92**	**24 m postop N=93**
Subjective satisfaction	-	95/110 (86%)	88/106 (83%)	77/92 (84%)	73/93(78%)
Subj. improved/ cured	-	99/110 (90%)	98/106 (92%)	82/92 (89%)	81/93(87%)
Prolapse symptoms	115	18/110 (16%)	24/106 (23%)	22/92 (24%)	28/93(30%)
Clinical recurrence in any compartment	-	80/110 (73%)	77/106 (73%)	71/92 (77%)	61/93(66%)
Significant prolapse on Ultrasound*	113	50/110 (45%)	54/106 (51%)	52/92 (57%)	46/93(49%)
Hiatal area on Valsalva, mean (cm^2, SD)	43.5 (6.5)	30.5 (6.2)**	31.0 (6.9)**	32.1 (7.6)**	31.8 (7.5)**

*Table 2: Subjective and objective outcomes after prolapse repair with puborectalis sling at 3, 6, 12 and 24 months. *Cystocele ≥10mm below symphysis pubis (SP), uterus ≤15mm above SP, rectal ampulla ≥15mm below SP ; **Reductions in hiatal area all p< 0.001 at 3,6, 12 and 24 months.*

Follow-up time points	**≥ ICS POPQ Stage 2 Anterior**	**≥ ICS POPQ Stage 2 Posterior**	**≥ ICS POPQ Stage 1 Apical**
Pre-operatively	101/115 (88%)	78/115 (68%)	95/115 (83%)
3 months post-operative Mean POPQ (range)	60/110 (55%) Ba -1 (-3 to 5)	32/110 (29%) Bp -2 (-3 to 2)	20/110 (18%) C -6 (-10 to 6)
6 months post-operative Mean POPQ (range)	57/106 (54%) Ba -1 (-3 to 5)	29/106 (27%) Bp -2 (-3 to 2)	22/106 (21%) C -5 (-9 to 6)
12 months post-operative Mean POPQ (range)	58/92 (63%) Ba -1 (-3 to 5)	37/92 (40%) Bp -2 (-3 to 3)	25/92 (27%) C -5 (-9 to 7)
24 months post-operative Mean POPQ (range)	45/93 (48%) Ba -1 (-3 to 5)	33/93 (35%) Bp -2 (-3 to 5)	22/93 (24%) C -5 (-8 to 5)

Table 3: POPQ assessment preoperation and at 3, 6, 12 and 24 months post-operation.

Parameters	Pre-operative (*n=115)*	3 months post-operative (*n=110)*	6 months post-operative (*n=106)*	12 months post-operative (*n=92)*	24 months post-operative (*n=93)*
Urinary incontinence Stress Urge	 68 82	 21 41	 19 31	 16 31	 30 49
Voiding difficulty	52	19	27	35	29
Mesh erosion	-	4	3	3	2
Obstructed defecation	40	23	18	21	28
Faecal incontinence (FI)	19	12	10	10	11

Table 4: Symptomatic outcome of urinary and bowel function at each follow-up time points. All mesh erosions were secondary to Perigee™ mesh.

7.6 Discussion

In this pilot study investigating a novel surgical procedure, we have shown that levator hiatal area can be successfully reduced with a mesh sling, the Puborectalis Sling, providing proof of concept. A significant reduction in levator hiatal area was seen in one hundred and ten patients with an 81% follow-up rate at the two-year mark. On average, the levator hiatal area was reduced by 12cm^2, which equates to a reduction of almost 30%. The effect was sustained up to 2 years post-operatively with no major long-term complications related to the puborectalis sling.

Despite an anatomical recurrence of 66% at 24 months post-operative, only 30% were symptomatic of prolapse and <10% required re-operation for their prolapse. The high rate of objective prolapse recurrence is likely due to strict definitions (POPQ stage 2 anterior and posterior compartment, stage 1 central compartment) and the fact that we performed this study exclusively in patients at high risk of recurrence, resulting in an average pre-operative hiatal area of over 43cm^2 and a very high avulsion rate of 63% in this cohort.

The insertion of the puborectalis sling at the completion of prolapse surgery is a novel surgical approach based on a perception of pelvic organ prolapse as a hernia through the levator hiatus. Since this hernia portal cannot be obliterated (like in the case of umbilical hernia), or nearly obliterated (as in the case of femoral or inguinal hernia), the only option is to reduce its size permanently. While this has been

attempted by the abdominal route, this approach is highly morbid and was abandoned decades ago[25].

The Puborectalis sling is based on the TOPAS posterior anal sling[26], but it uses a wider mesh and requires anchoring to the periosteum of the inferior pubic rami. Although tunnelling post-anally towards the anococcygeal raphe may prove to be unfamiliar to gynaecologists/urogynaecologists, there were no reported intra-operative complications directly related to the anchoring and placement of the puborectalis sling. Hence the method seems to be technically feasible and accessible to any competent gynaecological surgeon.

There were three cases that required return to the operating theatre during the study period. One was in a patient with Type 2 diabetes and chronic pelvic pain. She developed persistent pain and progressive erythema at the peri-anal incision sites, unresponsive to antibiotics. Removal of her puborectalis sling on Day 10 involved re-opening of the transobturator incision sites bilaterally, dividing of the anchoring sutures and removal of the sling in total via one of the peri-anal incisions.

The second patient required a return to the operating theatre due to faecal impaction on Day 9. Her puborectalis sling was released by re-opening the groin incisions, cutting anchoring sutures bilateral and applying downward vaginal/anal traction to loosen the sling. Her symptoms resolved immediately after sling release. The third patient who also suffered from faecal impaction had an examination under

anaesthesia only with conservative treatment. All patients recovered well with no long-term sequelae.

There are several limitations of this study that need to be addressed. Firstly, we did not acquire validated questionnaires pre-operatively, therefore evaluation of subjective outcomes was dependent on the physician-directed interview. Although this may not evaluate subjective outcome comprehensively, this question was asked in an identical fashion before and after the procedure and has been found sensitive to prolapse recurrence[27]. At any rate, our primary aim was to evaluate anatomical changes following insertion of the PR Sling and not subjective outcomes.

Secondly, this was a study that was performed at two tertiary centres involving two urogynaecology subspecialist surgeons, subspecialty fellows and specialist trainees. It is possible that heterogeneity of surgical practice may have affected outcomes. However, we believe that our results are reflective of standard subspecialty practice at a public hospital, where different surgeons of varied skills are involved in patients' care and surgery. As a result, we feel that our results may be more generalisable.

The association between levator hiatal area enlargement, pelvic organ prolapse and recurrence has been comprehensively demonstrated [10, 11]. Thus, the ability to reduce levator hiatal area as shown in this pilot study is potentially an important step forward in optimising prolapse surgery outcomes. In this study, the majority of our patients had severely compromised pelvic floor muscle support. Therefore, any surgical attempt to treat prolapse in this cohort would be challenging. After proving the feasibility of hiatal reduction with an acceptable short and medium term safety profile,

we are now performing a randomised controlled trial evaluating the puborectalis sling as an adjunct to conventional prolapse surgery. Recruitment is nearly complete at the time of writing. However, it is already evident that biomechanical properties of implants play a larger role than expected, and we are continuing the search for optimal materials to be used in hiatal reduction surgery.

In conclusion, this observational trial of a novel surgical procedure has shown that the levator hiatus can be reduced safely and efficiently with a ‘puborectalis sling’. The resulting reduction in hiatal area on Valsalva is sustained to at least 2.5 years after the procedure.

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Chapter 8: The mesh debate: Transvaginal anterior anchored mesh should not be abandoned

Publication 6

Wong V, Shek KL. The mesh debate: Transvaginal anterior anchored mesh should not be abandoned. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2017;57(1):105-7.

Aust N Z J Obstet Gynaecol 2017; 57: 105–107

ANZJOG

DOI: 10.1111/ajo.12589

CURRENT CONTROVERSIES IN OBSTETRICS AND GYNAECOLOGY – OPINION

The mesh debate: Transvaginal anterior anchored mesh should not be abandoned

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Conflict of interest: Neither author has conflicts of interest.

Received: 21 November 2016;
Accepted: 8 December 2016

KEYWORDS

pelvic organ prolapse, levator ani, mesh, anterior repair, recurrence

INTRODUCTION

Einstein once said, 'In the middle of difficulty, lies opportunity'. However, in this current climate when the use of synthetic transvaginal mesh in pelvic organ prolapse (POP) surgery is associated with increasing negative publicity, there is limited opportunity for progress in this field. In fact the authors consider what happened over the last few years a retrograde development. The blanket decision to suspend all mesh use in pelvic floor reconstructive surgery in Scotland in 2014, including synthetic suburethral slings which have a proven success record reaching back about 20 years, is an obvious example. The recent removal from the market of transobturator meshes including the Perigee™ (American Medical Systems (AMS), Minnetonka, MN, USA) and Anterior Prolift™ (Ethicon, Somerville, NJ, USA) is another example of a retrograde development. While these were largely commercial decisions, it is inevitable that clinicians are now forced to revert back to procedures that have been shown to be less effective. In our opinion the discussion surrounding the use of transvaginal mesh has been dominated by emotion rather than science.

Surgical management of POP is a challenging condition for pelvic reconstructive surgeons, with approximately one-third of prolapse procedures performed for recurrence.[1] Among the different forms of POP, cystocele can be a particularly difficult condition to manage with a recurrence rate after traditional repair between 40 and 63%[2–5] and up to 90% in some women.[6] For this reason clinicians dealing with POP have been in a constant search for surgical techniques to improve outcomes. Mesh has been used in pelvic floor repair dating back to 1955, when Moore *et al.*[7] first used tantalum mesh for anterior compartment prolapse repair. However, transvaginal mesh implants did not become popular until after the worldwide success of midurethral slings introduced in the early 1990s, triggering the development of anterior vaginal meshes anchored via the transobturator route (Anterior Prolift™ Ethicon, Somerville, NJ, USA and Perigee™ AMS, Minetonka, MN, USA) in 2003–2004. Anterior anchored mesh kits were intended to provide better load resistance than native tissues in a minimally invasive approach, aiming to improve anatomical success rates. The introduction of these kits was followed by rapid and widespread adoption of polypropylene mesh in spite of limited data on safety and efficacy. In the USA, the use of vaginal mesh for prolapse repair increased from 8.1% in 2005 to 22.8% in 2010.[8]

Over the last decade, a growing body of data in this field has improved our understanding of mesh efficacy and safety. Accumulated evidence now suggests that synthetic mesh augmentation is superior to traditional repair for anterior compartment prolapse.[9,10] In a recent systemic review[11] including 13 randomised controlled trials (RCTs) and seven cohort studies, the use of synthetic nonabsorbable anterior compartment mesh was shown to result in superior anatomical success and relief of subjective prolapse symptoms, as well as lower re-operation rates for prolapse compared to native tissue repair. However, transvaginal mesh was not found to improve success in posterior and apical prolapse repair.

The marked rise in vaginal mesh procedures has seen a dramatic increase in mesh-related complications. Some of these are

serious and novel.[12] Complications such as mesh erosion, pelvic pain, dyspareunia and bowel or urinary tract injuries can be challenging to manage.[10,13] This has led to a growing concern regarding mesh use and an onslaught of negative media publicity along with litigation. In a systematic review,[11] mesh erosion rates were found to range from 1.4 to 19% at the anterior vaginal wall and reoperation rates were 3–8%. In another review no differences in the rates of *de novo* dyspareunia were found between anterior colporrhaphy and anterior mesh.[10] In regard to chronic pelvic pain following mesh use, some authors have suggested that mesh shrinkage is a contributory factor;[14] however, to date, the majority of studies on mesh shrinkage, retraction or contraction were performed with an assessment at a single time point.[15,16] Studies that evaluated mesh characteristics *in vivo* over multiple time-points have shown that mesh shrinkage was limited to the phase of physiological scar formation, that is, the first three postoperative months. These studies suggest that the greatest reduction in mesh size is likely due to a folding effect related to surgical technique or mesh design.[17,18]

We should not forget the basic fact that any surgical procedure carries risks. This is also true for prolapse surgery, whether with or without mesh. The decision for or against surgery requires a balancing of risks and benefits in the individual case. There is no doubt that serious mesh complications do occur and that such can be a major problem for women and clinicians alike. However, we hold that in some women at high risk of POP recurrence after conventional surgery, a rational assessment of the balance of risks and benefits will favour the use of mesh. The probability of recurrence after cystocele repair seems to vary enormously from one person to the other, from 10 to 90%.[6] Hence, the balance between risks and benefits of transvaginal mesh repair versus conventional surgery will differ from patient to patient. It is prudent therefore to assess individual recurrence risk whenever mesh implantation is contemplated.

A number of risk factors for prolapse recurrence have been identified in the literature, including younger age,[19,20] advanced stage of prolapse,[19–22] family history of prolapse,[21] previous prolapse surgery, a larger genital hiatus, poor pelvic floor muscle contractility,[23] higher body mass index[19] and previous sacrospinous fixation.[21] More recently, levator avulsion[3,21,24,25] and hiatal ballooning,[6] that is, an abnormally distensible levator hiatus, were found to be important risk factors for POP recurrence. Levator avulsion is a form of maternal birth injury where the most ventromedial aspect of the levator ani muscle is detached from the inferior ramus of the os pubis. It is associated with hiatal ballooning, reduced pelvic floor muscle contractility and increased muscle distensibility.[26] These mechanisms may underlie the association between levator avulsion and POP recurrence. Studies on recurrence risk have shown an odds ratio (OR) ranging 2-3 in women with avulsion.[3,21,24,25,27] The impact of major levator defects has also been demonstrated on magnetic resonance imaging. In a series of 83 women, Morgan *et al.*[28] reported poorer anterior vaginal support in patients with major levator defects six weeks after primary surgery for prolapse. In an ultrasound study comprising 334 women assessed at a mean of 2.5 years after cystocele repair, levator avulsion was associated with an OR of 2.95 for recurrence, and hiatal area on Valsalva conveyed an additional 7% per cm^2 for recurrent risk. The likelihood of recurrence may vary from 10 to 90% in a patient with a given degree of cystocele, depending on the pelvic floor status, that is, integrity of the levator ani muscle and hiatal area on Valsalva.[6] Both factors in combination may effectively identify patients in whom conventional surgery is likely to fail, and this effect seems to explain most other described predictors of recurrence, such as younger age, enlarged genital hiatus and poor levator contractility. It has become evident that pelvic floor assessment should be part of the assessment in women with POP.

In the modelling study by Rodrigo *et al.*, the authors showed that anterior anchored mesh can partially compensate the effect of levator avulsion and significantly reduce the risk of POP recurrence in women with avulsion. A woman with avulsion and a hiatal area of 40 cm^2 on Valsalva was estimated to have a recurrence risk of around 80% with traditional surgery and 45% with anterior mesh repair.[6] Testing this claim in a randomised controlled trial, Svabik *et al.*[29] compared native tissue repair to mesh kit surgery for vaginal vault prolapse in patients with levator avulsion. The authors showed significantly less prolapse recurrence in the latter group. In this study of 72 patients, 3% had anatomical recurrence at one year after Prolift Total™ (Gynecare, Ethicon, Sommerville, NJ, USA) compared to 65% after sacrospinous fixation. Abdominally placed mesh, an alternative surgical option to transvaginal mesh in this situation, is rather unlikely to show comparable surgical outcomes. A study of almost 100 women after laparoscopic sacrocolpopexy by an experienced laparoscopic surgeon showed anterior compartment recurrence in 62% of the study population at a mean follow-up of three years.[30] The study highlighted the need to extend abdominal mesh implants as caudally as possible in order to provide adequate support to the mid-vaginal level. However, this may be challenging, even in the hands of experienced surgeons because of intraoperative bleeding during deep anterior dissection under the trigone.

Unfortunately, most mesh kit products entered the market with little information on safety and efficacy. Since then we have become much better at understanding risks and benefits: there now is ample evidence supporting mesh use in certain women with increased risk of prolapse recurrence. Regrettably, it appears that this knowledge is coming too late. We are witnessing the demise of mesh kits due to negative publicity as a result of indiscriminate marketing, suboptimal implant design, inadequate surgical techniques and poor patient selection. While there are mesh kits still available in Australia and New Zealand, there is little data on long-term efficacy of these newer kits and furthermore, they differ fundamentally in that they are not anchored or insufficiently anchored to the pelvic sidewall as compared to the kits that have previously been studied. It is depressing to see the demise of a surgical option precisely at a time when we are finally starting to

understand the risks and benefits of that option in individual patients. It is equally depressing to counsel prolapse patients with levator avulsion and an enlarged levator hiatus who want and deserve surgery with the best chance of success, and to confess that we are unable to provide optimal surgical intervention as a result of regulatory and medicolegal interference.

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Chapter 9: Discussion and Conclusion

Female pelvic organ prolapse is a highly prevalent condition that can significantly impair quality of life. Women suffering from POP are more likely to report poorer sexual wellbeing as well as urinary and bowel dysfunction (1). Furthermore, urinary and bowel symptoms including incontinence are not uncommon in women with POP (2, 3). With ageing populations in developed countries, the absolute number of patients requiring treatment for POP will increase significantly in the coming years (4). Therefore, it is evident that research in this area should be a high priority. Such research should include efforts to improve our understanding of the pathophysiology of POP as well as the investigation of novel surgical techniques to improve surgical outcomes. This thesis was designed with these aims in mind.

At the outset of this work, a set of hypotheses were posited:

1. **Mesh augmentation for anterior compartment prolapse is associated with better outcome as compared to traditional anterior colporrhaphy.**
2. **Levator avulsion is a risk factor for prolapse recurrence after anterior mesh repair.**
3. **Vaginal mesh with apical anchoring to the sacrospinous ligaments are associated with improved outcomes compared to mesh implants with sidewall fixation.**
4. **Abdominally placed mesh for apical or uterine prolapse is effective for anterior compartment support.**

5. **Surgical placement of a mesh sling around the puborectalis muscle is safe and effective in reducing hiatal area.**

Finally, I attempted to answer the question:

6. **Should mesh continue to be available for the pelvic reconstructive surgeon?**

We were able to test all hypotheses posited above, with largely conclusive results. The final question I attempted to answer was: should mesh continue to be available for pelvic reconstructive surgeon? In this opinion piece, we claimed that a blanket withdrawal of vaginal mesh for prolapse repair would be a disservice to our patients, especially those with recurrent and severe prolapse. Such regulatory intervention would create an even bigger dilemma for the management of women with abnormal pelvic floor anatomy, failed multiple vaginal native tissue repairs, and in those at high risk of complications with abdominal surgery. For these patients and especially those presenting for the first time diagnosed with levator avulsion, the use of transvaginal mesh may be the safest and most effective surgical option.

9.1 Conclusions:

With approximately one-third of prolapse surgeries performed for recurrence (5), clinicians dealing with POP are in constant search for surgical techniques to improve outcomes. Among the different forms of POP, cystocele is particularly challenging to manage and for this reason, clinicians have constantly modified repair techniques over the years in hope of reducing failure rates. The concept of introducing a foreign material to provide better organ support derived from data on abdominal hernia repairs (6, 7), and indeed pelvic organ prolapse is a hernia through the largest potential hernial portal in the human body, the levator hiatus. The efficacy of mesh augmentation in prolapse repair has been shown in several large randomised controlled trials (8, 9), even in unselected populations. In the RCT by Altman et al, trocar-guided mesh kits provided higher success rates using composite outcome assessment. In this study of 389 women, those who had mesh kit repair had less objective and subjective failures at 1 year after the index surgery (8). Unfortunately, no attempts were made to identify those patients best suited for transvaginal mesh augmentation.

The widespread non-selective use of transvaginal mesh since 2004 has resulted in a dramatic increase in women presenting with mesh-related complications. Unfortunately, due to injudicious use of the new technology, patients who did not require mesh insertion, or those who were likely to gain minimal benefit, were exposed to these additional risks. Some of these complications were serious and novel (10). Concerns fuelled by mesh-affected patients and medicolegal actions have led to numerous clinical debates on vaginal mesh utilisation (11-15). Concerns about

mesh safety and negative publicity have seen the removal of some transvaginal mesh products for prolapse in Australasia (16), a suspension of their use in Scotland (17) and the United Kingdom and numerous cases of litigation, including class action law suits against manufacturers in the US and Australia (18).

Opponents of mesh use overlook the fundamental principle that any surgical procedure carries risks (19). These risks apply to prolapse surgery, whether with or without mesh use. The decision for or against a certain surgical procedure requires balancing of risks and benefits in the individual case. Lack of efficacy and safety data of transvaginal mesh and an absence of information on risk factors for recurrence have precluded a rational assessment of the balance of risks and benefits until recently. One of the aims of this work was therefore to identify patients who are more likely to benefit from mesh repair and to provide a better understanding of mesh augmentation in prolapse repair.

Levator avulsion, which affects 10-30% of women following vaginal childbirth (20), is associated with weaker pelvic floor muscle support and an abnormally distensible hiatus (21). It is a strong risk factor for POP and is likely to be the missing link between childbirth and POP (22). Several studies have also identified levator avulsion as a risk factor for POP recurrence (23-25), as confirmed in a recent meta-analysis (26). During the course of this thesis, a modelling study on 334 women following cystocele repair demonstrated that levator avulsion and hiatal area on Valsalva were independent risk factors for prolapse recurrence. Levator avulsion was shown to be associated with an odds ratio of 2.94 for sonographic cystocele

recurrence and for each cm^2 enlargement of the hiatal area on Valsalva, the risk of prolapse recurrence increased by 7%. The use of anterior anchored mesh was associated with a reduced risk of recurrence with an OR 0.4. This risk reduction was limited to patients with levator avulsion (27), concurring with the findings in Chapter 3. The findings from this study have filled our knowledge gap in regards to patient selection for mesh use: clearly, avulsion may be considered an indication for mesh use.

While randomised controlled studies have found a higher objective cure rate after transobturator mesh repair compared to anterior colporrhaphy (9, 28) in unselected patients; recurrent cystocele even after mesh is not uncommon (29). There is however limited data on risk factors for mesh failure. In the study on women with anterior mesh repair in Chapter 4, women diagnosed with levator avulsion were shown to have a higher recurrence rate, highlighting the importance of the condition in pelvic floor medicine. Developing measures to compensate for the effect of levator avulsion may be an option to reduce recurrence after surgery.

Prolapse of the bladder or cystocele seems to be associated with apical prolapse (30) which has led some authors to suggest that effective apical support should lead to better cystocele cure rates. This line of reasoning resulted in the introduction of the Anterior Elevate™ mesh kit (American Medical Systems, Minnetonka, USA) in 2008. However, there is limited data in the literature on anatomical outcomes after Anterior Elevate™, which involved tissue anchor placements into the obturator foramen and sacrospinous ligament, compared to mesh systems involving anchoring via mesh

arms placed through the obturator fossa, such as the Perigee™ (American Medical Systems, Minnetonka, USA). The superiority of the Perigee™ mesh kit system was demonstrated in Publication 3, both on clinical examination and on ultrasound assessment, almost one year after prolapse repair (31). This study showed that not all mesh kits are the same. The discrepancy in performance is likely related to anchoring. It is plausible that mesh fixation with transobturator mesh arms provides better anchoring and load-bearing ability than tissue anchors placed in the obturator fascia.

Laparoscopic sacrocolpopexy, a surgical procedure for vault or uterine prolapse, has been shown to be highly effective in apical compartment prolapse (32). However, this does not necessarily translate to satisfactory anterior and posterior compartment support (33). This has also led to the question of whether surgical outcome, especially with mesh placed abdominally, depends on how distal the mesh is placed along the anterior vaginal wall.

In Publication 4, a study of 100 patients after laparoscopic sacrocolpopexy performed by an experienced surgeon, we found the rate of anterior compartment recurrence to be over 60%, whilst no recurrence was noted for the apical compartment at a mean follow-up of three years. These findings concur with a study by Higgs et al who reported that failures in the anterior and posterior compartment were common after sacrocolpopexy (34) contradicting the notion that apical suspension is crucial to anterior compartment support (30). A correlation between mesh location and mobility with cystocele recurrence shown in Publication 4 highlights the need to extend

abdominal mesh implants as caudally as possible to provide adequate support to the mid-vagina. However, in practice this may be limited by poor visualisation and difficult dissection, especially close to the ureters.

An enlarged levator hiatus is one of the strongest independent risk factors for prolapse recurrence (35). This is because the forces acting on pelvic support structures are directly proportional to size of the hiatal area (36). Therefore, it seems plausible that measures aiming at reducing the hiatal area may decrease prolapse recurrence by reducing the load on pelvic organ support. This has led to the development of a novel surgical technique, the 'Puborectalis Sling'. In an attempt to evaluate its safety and efficacy, a pilot study was conducted. In Publication 5, a multicentre surgical trial on 117 women revealed a significant reduction of levator hiatal area by 12cm^2 that was sustained for well over two years. However, normal hiatal dimensions of <25 cm2 were achieved in only a minority of women. This may largely be due to sub-optimal biomechanical properties of the polypropylene mesh used for this purpose. In a study by Li et al., the authors showed that mesh material available in reconstructive surgery was suboptimal (37) for the purpose of permanent load-bearing in that the implants underwent significant ongoing permanent deformation ('creep') with elongation when placed under tension. This is largely due to slippage of monofilament fibres within a woven mesh. Hence, any hiatal reduction achieved at the time of surgery is unlikely to be sustained. Our unit is involved in ongoing efforts to design and use stiffer mesh that displays less permanent deformation.

9.2 Directions for future research

The findings of this thesis have led to several research questions:

Can reduction of hiatal area with the puborectalis sling reduce prolapse recurrence in women with an abnormally distensible hiatus?

The pilot study in Publication 5 has confirmed the feasibility of a new surgical procedure which involved placing a mesh strip in the infralevator space of the ischiorectal fossa, lateral and posterior to the puborectalis muscle. The Puborectalis Sling procedure was shown to be safe and effective in achieving significant reduction of the hiatal area. Moving forward, the next step is to evaluate its effectiveness in reducing prolapse recurrence compared to traditional prolapse repair only in women with levator hiatal ballooning. The author is currently involved in an ongoing multicentre randomised controlled trial with this aim.

Can concomitant levator repair during prolapse surgery improve surgical success?

In a pilot study on 17 patients, Dietz et al reported disappointing results after surgical reattachment of the puborectalis muscle stump to the inferior pubic ramus using a piece of mesh (38). Five patients had prolapse recurrence beyond the hymen and the mean hiatal area on Valsalva was reduced from 36.84cm^2 to 30.71cm^2. This

remained above the normal cut-off value (25cm^2) of hiatal area enlargement. While this early result was disappointing, it remains a worthwhile approach to explore in the future, perhaps with different graft/mesh material or perhaps by selecting patients with levator avulsion only but without major degrees of hiatal area enlargement. Such a project is currently ongoing.

Can surgical outcome of laparoscopic sacrocolpopexy be improved with robotic surgery?

Technical limitations in extending abdominal mesh implants as caudally as possible during laparoscopic sacrocolpopexy may explain high recurrence rates in the anterior and posterior compartments. Further work needs to be done to evaluate whether robotic surgery can improve surgical outcomes as a result of improved arm articulation and better visualisation of tissue planes.

Is it possible to prevent levator avulsion and de novo hiatal ballooning after vaginal childbirth?

Levator avulsion and hiatal ballooning are risk factors for prolapse development. Women with levator avulsion suffering from symptomatic POP are more likely to fail surgical treatment. Whilst more work needs to be done to improve the surgical

treatment of POP in women with levator trauma, it is evident that preventative strategies should be implemented to prevent such trauma in the first place.

Amongst antepartum and intrapartum risk factors of levator trauma such as maternal age, BMI, forceps, length of 2nd stage and head circumference (39-41), forceps remains the most obvious modifiable risk factor (20, 42, 43). Within Australia, the rate of forceps delivery ranges between 2 to 15% (44, 45) and the risk of avulsion associated with forceps delivery ranges between 30 – 65% internationally (20, 43, 44, 46, 47). Hence, it seems reasonable to suggest that forceps delivery should be abandoned to prevent levator trauma that may lead to subsequent development of POP. Other measures that could be useful and need to be studied in the future include methods to condition the pelvic floor muscles for delivery e.g. intrapartum stretching of the pelvic floor muscle or use of muscle relaxants such as epidurals or pudendal nerve blocks during the second stage of labour.

Recurrence after pelvic reconstructive surgery is a major clinical issue, leading to the quest to reduce recurrence, and the design of this thesis. The rapid development of pelvic floor medicine over the last fifteen years has seen an enthusiastic uptake of transvaginal mesh kits, followed by their swift demise in some jurisdictions. While none of the transvaginal mesh products studied in this thesis remain available in Australasia, this work has shown the role of mesh in selected patients and has highlighted the importance of proper patient selection in pelvic organ prolapse management. It has also highlighted the importance of ‘proof of concept’ studies in surgery, and the need to evaluate efficacy and safety of treatment before its

widespread use in clinical practice. Our pilot study on the ‘Puborectalis Sling’ is an example of such ‘proof of concept’ in the development of new surgical procedures. A randomised controlled trial, the next step in the evaluation of surgical techniques, is ongoing. Regardless of the outcome of this particular trial, the problem of prolapse recurrence after reconstructive surgery is likely to posit challenges to clinicians and researchers alike for many years to come.

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Appendix:

Datasheet used for data collection in this thesis

DATASHEET

Name/Address/MRN/DOB

Site: _____

Date | | | |

History: Parity: _____ Height:_____ Weight_____ preop SI _____ Preop UI _____
Procedure: _____ When:_____
Any surgery since: _____
Previous surgery: _____ _____
Satisfied with the procedure: Yes / No / Not Sure
Overall cure: Cured / Improved / Same / Worse / NA

Symptoms:

SI	m	w	d	+	Cured/improved/same/worse/NA
UI	m	w	d	+	Cured/improved/same/worse/NA
F	8-12	13-17	more	N	2 3-4 more
VC	Hesitancy, poor stream, stop-start, strain, inc. empty, UTI's _____				
Prol:	Lump, drag, pain, dyspar, bleed, discharge				
Bowel:	Constip, freq strain, in empty, digit, incont, pain				

Comments: _____
_____

Clinical Exam….. **CST pos neg**

Speculum: ……

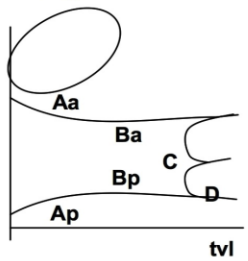
Vaginal examination: ……

Clinical Prolapse Grading:

Cystocele	1	2	3	
Uterine prolapse	1	2	3	4
Enterocele/Vault prolapse	1	2	3	4
Rectocele	1	2	3	

Levator: Left Oxford Right Oxford Resting Tone Defects

ICS Prolapse Grading:



Aa	Ba	C
		tvl
Ap	Bp	D

Comments: _____
_____