

The surgical management of uterine prolapse and the role of mesh

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Declaration

I, Matthew Izett-Kay confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Background

Uterine prolapse is a common condition that impairs quality of life. Vaginal hysterectomy with apical suspension is the standard treatment, yet associated with a high risk of recurrent prolapse. Laparoscopic sacrohysteropexy offers an alternative approach, resuspending the uterus utilising non-absorbable mesh. However, supporting evidence is low quality and mesh use is controversial. Predicting postoperative bladder function remains challenging, and patients' postoperative health concerns remains unexplored within academic literature.

Aim

Determine the safety and efficacy of laparoscopic sacrohysteropexy. Understand the role of urodynamic studies for bladder dysfunction. Explore women's health concerns following the procedure.

Methods

Cross-sectional study to determine the incidence of mesh associated complications. Randomised controlled trial comparing vaginal hysterectomy to laparoscopic sacrohysteropexy. Retrospective cohort study to compare preoperative urodynamic diagnoses to postoperative bladder symptoms. Thematic analysis exploring health concerns in women following laparoscopic sacrohysteropexy.

Results

Following laparoscopic sacrohysteropexy, the incidence of reoperation for mesh associated complications is 0.4% of from a cohort of 1,121 women at an average four years postoperatively. The randomised controlled trial with 101 participants showed a non-significant trend towards a lower rate of apical reoperation following sacrohysteropexy as compared to vaginal hysterectomy (6.1% versus 17.2% $p = 0.17$) at seven years. Only a preoperative urodynamic diagnosis of voiding dysfunction is significantly associated with

such symptoms postoperatively. The principal focus for women following the procedure are their pelvic floor symptoms and associated quality of life.

Conclusion

Laparoscopic sacrohysteropexy appears to be associated with a low risk of mesh associated complications requiring reoperation. It may confer anatomical and recurrent prolapse associated benefits as compared to vaginal hysterectomy. Preoperative urodynamic diagnoses appear to correlate poorly with postoperative bladder function, yet diagnosing stress incontinence may alter surgical management. Despite ongoing media coverage and debate about mesh, this is not the focus of women who have had mesh augmented surgery.

Impact statement

Pelvic organ prolapse is found in over 40% of postmenopausal women and for many it is associated with an adverse impact on quality of life. Following failed conservative therapies, one in ten women will undergo surgery in their lifetime to alleviate prolapse symptoms. The most common surgical treatment for this in the UK is vaginal hysterectomy with apical suspension, despite the fact that many women would prefer to keep their womb and an appreciable risk of the procedure failing over time. Laparoscopic sacrohysteropexy provides an alternative surgical option, utilising keyhole surgery and a mesh implant to restore normal pelvic anatomy. It allows for uterine preservation as well as possibly conferring other benefits.

Despite being an option for over ten years and approved by NICE, gaps remain in our understanding of the safety and efficacy of laparoscopic sacrohysteropexy. This is particularly pertinent given concerns and controversies that have evolved more recently over the use of non-absorbable mesh. In terms of investigations, we do not know whether preoperative bladder tests help surgical planning and predict postoperative bladder symptoms for both asymptomatic women, and those troubled by bladder problems associated with their prolapse. Central to all of this remains the patient perspective; despite much research in the field of prolapse generally, women's voices and their health concerns remain almost undocumented within the medical literature.

This research has utilised a number of different research methodologies to answer some of these gaps in knowledge. A large study with over 1,121 women confirmed that when it comes to complications associated with mesh, they appear infrequently and less than 1 in 200 women require surgical removal of mesh, considerably lower than other mesh augmented operations. A randomised controlled trial with long term follow-up appears to suggest the procedure is at least as affective as vaginal hysterectomy and may confer advantages such as better maintaining normal pelvic anatomy. Studying preoperative bladder tests, known as urodynamics, has shown they appear to

have little utility in predicting women's postoperative bladder function. A large study of over 700 women's comments has explored in depth their concerns about their health following mesh augmented prolapse surgery and highlighted their ongoing concerns surrounding their pelvic floor symptoms.

These studies appear to suggest that laparoscopic sacrohysteropexy is safe, yet further work is needed on a larger scale involving risk registries and population data. There is a need for more randomised studies to better understand the merits of the procedure compared to the alternatives. It would appear that preoperative bladder testing need not be routine, although this requires further scrutiny. Finally, health concerns amongst women have been explored and documented in a way never before undertaken for women who have undergone mesh augmented surgery. This will hopefully encourage similar research in the future and ensure alignment with the World Health Organisation and wider calls to place patients at the centre of healthcare systems, ensuring that the field of prolapse surgery is guided by the women it aims to help.

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List of abbreviations

AE – Adverse event

ATFP – Arcus tendinous fascia pelvis

BSUG – British Society of Urogynaecology

CARE - Colpopexy and Urinary Reduction Efforts trial

CI – Confidence interval

DO – Detrusor overactivity

EBL – Estimated blood loss

FBR - Foreign body response

FDA - US Food and Drug Agency

HES – Hospital episodes statistics

HRA - Health Research Authority

ICI – International Consultation on Incontinence

ICIQ-VS – International Consultation on Incontinence Questionnaire Vaginal Symptoms

ICIQ-FLUTS - International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms.

ICS – International Continence Society

IUGA – International Urogynecological Association

LAM – Levator ani muscles

LSH – Laparoscopic sacrohysteropexy

LUTS – Lower urinary tract symptoms

MRI – Magnetic resonance imaging

MUI – Mixed urinary incontinence

MUS - Mid-urethral sling

NHS – National Health Service

NICE – National Institute for Health and Care Excellence
NIHR - National Institute for Health Research
OAB – Overactive bladder
ODS – Obstructed defecation syndrome
OPCS - Operating procedure codes
OR – Odds ratio
PFDI – Pelvic Floor Distress Inventory
PFMT – Pelvic floor muscle therapy
PGI-I – Patient Global Impression of Improvement
PHVP – Post hysterectomy vault prolapse
PIL – Patient information leaflet
PISQ-12 - Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire
- 12
POP- Pelvic organ prolapse
POP-Q – Pelvic Organ Prolapse Quantification
POP-SS - Pelvic Organ Prolapse Symptom Score
PROM – Patient reported outcome measure
PROSPECT - PROlapse Surgery: Pragmatic Evaluation and randomised
Controlled Trials
QoL – Quality of life
RCOG - Royal College of Obstetrics and Gynaecology
RCT - Randomised controlled trial
REC - Research ethics committee
RR – Relative risk
SAE – Serious adverse event
SAID - Systemic Autoimmune Inflammatory Disorders
SCP – Sacrocolpopexy
SF-36 – Short Form 36 questionnaire
SNP - Single nucleotide polymorphisms
SUI – Stress urinary incontinence
TVL – Total vaginal length
TVT - Tension-free Vaginal Tape
UDS – Urodynamic studies

UK – United Kingdom

USI – Urodynamic stress incontinence

UUI – Urinary urge incontinence

µm – Micrometre

VD – Voiding dysfunction

VH – Vaginal hysterectomy

VUE - Vault or Uterine prolapse surgery Evaluation study

WHI – Women’s Health Initiative

WHO – World Health Organisation

1. Background and literature review

1.1 Introduction

Pelvic organ prolapse (POP) is a highly prevalent condition reported to affect 40% of women over the age of 45 [1]. The term refers to the downward displacement of the pelvic organs, namely the uterus, bladder, and/or bowels into the vagina [2]. Uterine prolapse specifically is reportedly found in over 14% of postmenopausal women on clinical examination [3]. Following failed conservative measures such as pelvic muscle floor therapy (PFMT) and the use of vaginal pessaries, some women will undergo surgery for which there is a reported lifetime risk of between 11% and 19% [4].

In the United Kingdom (UK), as elsewhere, the preferred surgical intervention for uterine prolapse is vaginal hysterectomy (VH) with a concurrent apical suspension procedure such as McCall's culdoplasty [5]. However, the majority of women would prefer uterine sparing alternatives if given the option and some studies suggest that up to 60% of women have such a preference [6, 7]. An additional shortcoming of VH is that it is associated with a high risk of recurrent vault prolapse, known as post hysterectomy vault prolapse (PHVP), rates of reoperation for this are between 4.6% and 18% [8, 9]. More generally, such 'native tissue repairs' have been reported to be associated with reoperation rates as high as 30%, due to the use of suboptimal tissue and fascia that contributed to the prolapse in the first place [10].

Such limitations with native tissue repairs and hysterectomy has led to increasing rates of uterine sparing procedures in the UK according to the latest published Hospital Episodes Statistics (HES) data [11]. One such procedure is mesh augmented laparoscopic sacrohysteropexy (LSH). This procedure utilises a polypropylene mesh to suspend the uterus to the sacrum, restoring the uterovaginal axis, returning the uterus to its normal position in the pelvis, and reducing the vaginal prolapse. Subject to a recent meta-analysis it may confer advantages such as higher apical suspension, longer vaginal length,

lower blood loss and quicker recovery when compared to VH as well as the theoretical advantage of reduced risk of recurrence [12].

However, evidence for the use of LSH has some significant shortcomings. The meta-analysis highlighted that most data come from single centre studies with short term follow-up [12]. Additionally, the use of mesh in surgery and in pelvic floor reconstructive surgery particularly, has been subject to significant scrutiny on a global scale due to adverse events (AEs) associated with some applications of mesh [13]. This has led to several national and international reports into its use and safety [14-17]. Therefore, as with all mesh augmented pelvic floor procedures, there is a need to re-evaluate the safety and efficacy of mesh augmented LSH to provide reassurance to patients, clinicians and regulatory bodies. With any assessment of medical interventions and healthcare systems, the focus should remain on patients, with the patient voice being at the heart of future regulatory and clinical decision making., Such a patient centred approach is advocated by multiple organisations, including the World Health Organisation (WHO) [18, 19].

In order to assess the safety and efficacy of LSH, there is a need for high quality research to address specific questions within these domains. The available evidence for LSH has been reviewed in Chapter 1.6.2. With respect to safety, to date there are no published studies designed to investigate the incidence of mesh associated complications following LSH. This information is critical in order to provide reassurance to both patients who have had the operation previously as well as for those women considering such a procedure, in order to allow for quality preoperative counselling. With respect to efficacy, the available data for reoperation rates for recurrent prolapse is predominantly derived from single-centre studies with short-term follow up. The published literature does not allow for adequate comparison between LSH and VH, which is the standard surgical intervention in the UK for uterine prolapse. Such a comparison is critical for patients when they are undertaking surgical decision-making and considering various options.

For the many women troubled by lower urinary tract symptoms (LUTS) in addition to their prolapse, the role of urodynamic studies (UDS) to assess bladder function prior to LSH remains unexplored within the literature. This sits in contrast to other forms of prolapse surgery and is important to allow for surgical planning and accurate counselling with respect to outcomes.

Finally, and most importantly, the patient voice remains almost absent from research into mesh and pelvic floor reconstructive surgery. There is a need to understand the sorts of health concerns faced by women who have had the operation in light of the controversies surrounding mesh, so that clinicians and regulators can make balanced, pragmatic, and evidence-based decisions about the future role of mesh in pelvic floor reconstructive surgery for women with uterine prolapse.

It is these four key areas of the safety and efficacy of LSH, the role of UDS prior to the procedure, and the patient perspective of having a laparoscopic mesh augmented uterine-sparing that need further study and are addressed by the research presented in this thesis.

1.2 Thesis aims

These studies aim to better understand the role of laparoscopic mesh sacrohysteropexy for the treatment of uterine prolapse, with a particular focus on safety in light of recent controversies surrounding the use of synthetic non-absorbable mesh in pelvic floor reconstructive surgery. In order to do this, the chapters enclosed in the thesis have the following specific aims:

- Chapter 2: Determine the safety and efficacy of laparoscopic mesh sacrohysteropexy with a focus on mesh associated complications.
- Chapter 3: To compare the efficacy of vaginal hysterectomy and laparoscopic sacrohysteropexy for the treatment of uterine prolapse.

- Chapter 4: Explore whether preoperative urodynamic studies can predict postoperative bladder symptoms for women undergoing laparoscopic mesh sacrohysteropexy.
- Chapter 5: To understand health related issues in women who have had mesh augmented prolapse surgery.

1.3 Pelvic organ prolapse

1.3.1 Definition

The organs of interest pertaining to POP that are located within the female pelvis include the bladder, genital tract (uterus and vagina), rectum as well as small and large bowel. Prolapse is loosely defined in medical terms as the slipping forward or down of an anatomical structure in relation to its normal position. In the specific case of POP, it is defined by the International Urogynecological Association (IUGA) in the terminology guidance as “The descent of one or more of the anterior vaginal wall, posterior vaginal wall, the uterus (cervix) or the apex of the vagina (vaginal vault or cuff scar after hysterectomy)” [2]. While urethral and rectal prolapse are also strictly forms of POP, clinical vernacular and the IUGA terminology document associate the term specifically to vaginal prolapse, and therefore within this thesis the term pelvic organ prolapse should be taken as reference to vaginal prolapse unless specified otherwise.

Key to considering the presence of anatomical POP in women, is that it should be correlated with the presence of symptoms, a point noted within the terminology document. Prolapse symptoms are varied but are defined by IUGA as “the departure from normal sensation, structure or function, experienced by the woman in reference to the position of her pelvic organs” [2]. Commonly these symptoms include the feeling of a vaginal bulge (or alternatively ‘lump’ or the sensation of ‘something coming down’ or ‘falling out’), pelvic pressure, backache as well as a host of vaginal, lower urinary tract

and anorectal symptoms associated with vaginal prolapse, as discussed in Chapter 1.3.5. When defining prolapse with respect to clinical examination, a variety of classification systems may be used, and these are discussed in Chapter 1.4.1.

1.3.2 Anatomy

There are a number of structures, familiarisation with which are essential prior to discussing POP in more detail. The main organs involved include the urethra and bladder, uterus and cervix, small bowel and rectum, and the vagina as shown in sagittal cross-section in

Figure 1.1. With reference to vaginal prolapse, there are three compartments that are considered, the anterior, apical and posterior compartments. Anterior wall prolapse is also referred to as a cystocele as the bladder sits adjacent to the anterior wall. Prolapse of the middle compartment is referred to as apical prolapse which encompasses uterine prolapse, or for women without a uterus, vault prolapse. The posterior vaginal wall is adjacent to the rectum in the distal two thirds and therefore POP here is termed a rectocele. The proximal or cranial most third of the vagina, when prolapsed, is referred to as an enterocele as the rectovaginal fascia is not present at this site and therefore it is commonly small bowel on the peritoneal side of the vaginal wall.

There are two principal mechanisms that maintain the normal anatomical position of the pelvic organs with reference to the vagina, and these are the endopelvic fascia (with associated ligaments) and the levator ani muscle (LAM) complex. Compromise of these two mechanisms from a host of risk factors leads to POP, although there is debate as to which of these is most critical in the role of providing this support. Support of the vagina with respect to the pelvic organs may be divided into what is commonly referred to as the three 'levels' of support, first proposed following cadaveric studies by John DeLancey in 1992 [20]:

Level I – The cervix and upper third of the vagina are attached to the pelvic sidewalls by the uterosacral ligaments and cardinal ligaments.

Level II – The middle third of the vagina is attached laterally by the arcus tendinous fascia pelvis (ATFP), part of the endopelvic fascia, with a similar structure at the posterior vagina as part of the rectovaginal fascia.

Level III – The distal third of the vagina is fused to adjacent structures including the LAM complex and perineal body.

Magnetic resonance imaging (MRI) studies have shown alterations in length and axis of cardinal ligaments and in the axis of uterosacral ligaments in women with prolapse, supporting the hypothesis of level I support [21]. Cadaveric studies have clearly defined the structure of the ATFP that forms level II support, a condensed fascia formed from the endopelvic fascia of the pubococcygeus and iliococcygeus muscles [22]. The anterior most proximal third attaches to the pubic bone and the anterior vagina wall, the middle third to the anterolateral vagina as well as fascia of the LAM and rectovaginal septum, with the posterior segment attached at the ischial spine, and commonly found to be detached in parous women [22]. There is clear evidence from MRI studies illustrating the concept of level II support, these have shown defects in the ATFP to be associated with prolapse [23].

The role of the LAM complex that forms level III support has been recognised with respect to injury and POP since 1907 [24]. Pubococcygeus, iliococcygeus and puborectalis sit as a ‘hammock’ within the bony pelvis, forming the LAM and supporting the pelvic organs that sit cranial to these muscles. It is through this hammock that the urethra and vagina pass, in what is known as the urogenital hiatus, shown in

Figure 1.2. Defects in the LAM, specifically puborectalis, have shown to be associated with POP particularly of the anterior and apical compartments [25]. This has been very well studied through the use of 3D and 4D ultrasound, corroborating earlier cadaveric and MRI studies [26].

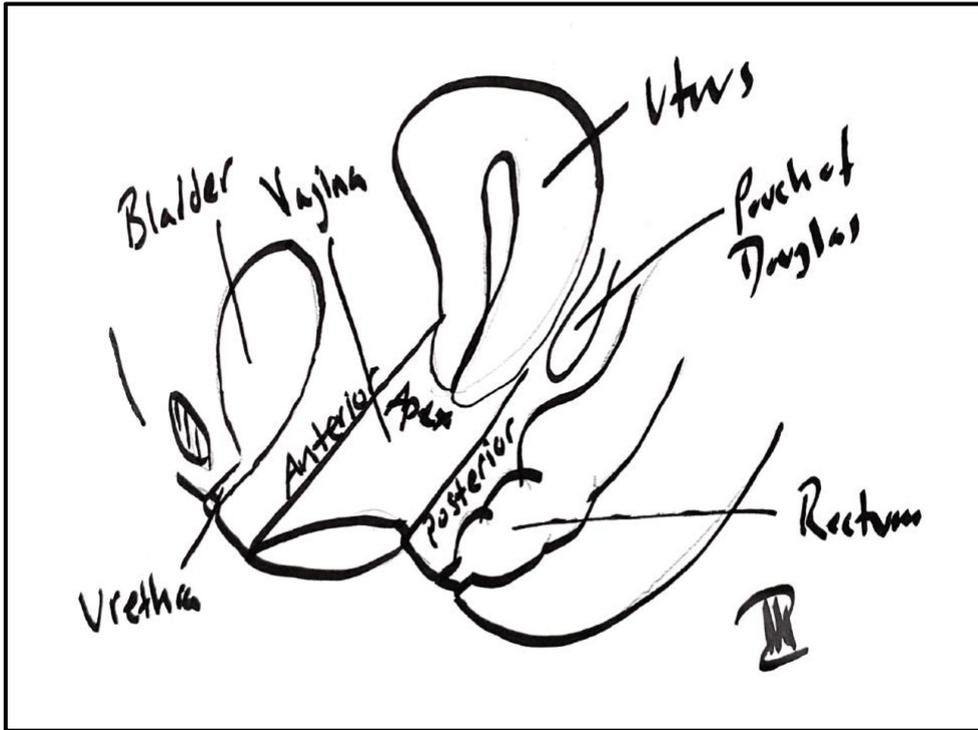


Figure 1.1 Sagittal cross-section of female pelvis

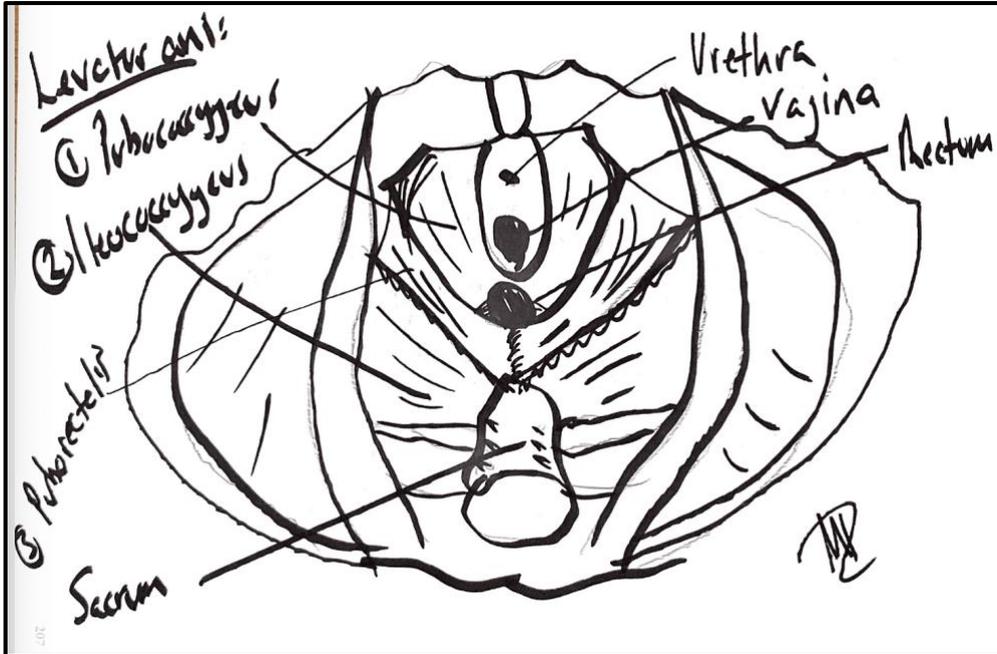


Figure 1.2 Levator ani muscle complex

1.3.3 Aetiology

The risk factors for POP are principally any that disrupt the two vaginal support mechanisms outlined within Chapter 0. These can be divided into genetic and environmental determinants. From the genetic perspective, a family history of POP is an independent risk factor for the development of prolapse, with an eight times higher risk as compared to those women without such a family history [27]. Using studies comparing nulliparous and parous sisters, Buchsbaum et al. have further supported the link of a familial predisposition towards the development of POP [28]. Twin studies have compared monozygotic and dizygotic twins to provide population data supporting a genetic link, and more recently, genome wide studies have identified both chromosomal loci and polymorphisms associated with the development of POP [29-31]. Such genetic risk factors have been implicated in abnormal extracellular matrix remodelling and impaired elastic fibre formation, compromising the biophysical properties of the tissue structures responsible for supporting the pelvic organs [32, 33]. Chief among the components of the extracellular matrix is collagen, which comprises 70-80% of structures such as the cardinal ligaments (Level 1 support) and this is thought to be the main determinant of biomechanical strength [34]. Studies have repeatedly shown that for those women with prolapse, there are alterations to total collagen volume and proportions of various collagen sub-types as compared to non-prolapse controls, genetic variation in collagen metabolism may therefore explain the familial aggregation seen with prolapse [35, 36].

At least six single nucleotide polymorphisms (SNPs) have been identified as being associated with POP, located within the genes ZFAT and COL18A1, both of which have a role in soft tissue development and maintenance [30]. ZFAT has a regulatory role in immune regulation and apoptosis, potentially affecting muscle and connective tissue development within the pelvic floor. The COL18A1 gene is a precursor of collagen XVIII and is likely to play a role in structural formation of the basement membrane, the key component of the extracellular matrix, a structure that provides the framework for tissues such as those supporting the pelvic organs [30]. Other implicated genes include

the LOXL1 and fibulin-5 genes, mutations of which in mice are associated with altered assembly of the elastic tissue fibres known to be associated with the development of POP, and HOXA11, which in mice has been identified as being involved in development of the uterosacral ligament, an integral structure providing level I support [32, 37, 38].

A 2014 systematic review identified some 21 studies looking at the genetic epidemiology of POP which involved 10 candidate genes Collagen type 1 alpha 1 (COL1A1), collagen type 3 alpha 1 (COL3A1), laminin gamma-1 (LAMC1), matrix metalloproteinase 9 (MMP9), matrix metalloproteinases 1 and 3 (MMP1 and 3), lysyl oxidase-like 1 (LOXL1), estrogen receptor alpha (ER α), estrogen receptor beta (ER β), and progesterone receptor (PGR) [39]. The paper undertook a meta-analysis that identified COL3A1 rs1800255 genotype AA as being associated with POP (odds ratio, 4.79; 95% confidence interval, 1.91–11.98; $P = .001$) as compared to the reference genotype. Individual studies also found an association with POP. estrogen receptor alpha (*ER- α*) rs2228480 GA, *COL3A1* exon 31, chromosome 9q21 (heterogeneity logarithm of the odds score 3.41).

Chief among the environmental risk factors is pregnancy and childbirth, linked by high-quality epidemiological studies assessing both the presence of symptoms and risk of prolapse surgery [40-44]. Compared to nulliparous women, population studies have shown that those who have delivered one child are four times more likely to develop POP requiring hospital admission and this rises to over eight times after having two children [45]. Increasing birthweight, instrumental delivery, foetal malposition and length of labour have all been identified in these studies as further risk factors. It must be noted however, that POP is observed in nulliparous women as well as those delivering by caesarean section only, and therefore other risk factors do need consideration [46, 47].

The pathophysiology of POP related to pregnancy is due to compromise of the previously outlined support mechanisms, as a result of either tissue changes occurring in pregnancy or direct trauma. Hormonally mediated tissue changes are essential for the musculoskeletal and pelvic floor adaptations of the state of pregnancy and to allow for vaginal delivery. Progesterone and relaxin have both been implicated in these physiological changes [48, 49]. Histological studies in pregnancy have clearly illustrated a reduction in collagen and alteration in collagen structure, affecting the resistance of tissues to compressive forces and reducing elastic recoil, biomechanical pressures that are integral to the normal function of the pelvic floor [50]. For some women, following the stretching involved with delivery, such changes may not revert after pregnancy [51]. These tissue changes are likely to affect level I and II support, i.e. fascia and ligaments, although the link between pregnancy and compromise of level I and II support specifically are not clearly illustrated by evidence, and this area deserves further study albeit beyond the scope of this thesis.

Compromise of level III support, the musculature of the pelvic floor, during delivery is probably the most well studied. To allow for passage of the foetal head, the levator hiatus distends between 25% and 245% [52]. For many women the hiatus remains enlarged postpartum, which has been shown to be associated with increasing risk and severity of POP [53]. Some of this distension is the result of muscle and fascial trauma rather than simple stretching. Ultrasound studies have consistently illustrated postpartum avulsion of the LAM in 30-40% of women delivering vaginally for the first time [54, 55]. The presence and magnitude of LAM injury has been shown to correlate with existence and severity of clinically detected POP [56, 57]. A study by Rostaminia et al. found that in women with stage III prolapse, that is the prolapse more than 1cm beyond the hymen, all participants had some form of LAM defect [56]. Second degree perineal lacerations at delivery which are those involving the transverse perineal and bulbocavernosus muscles, occur in over a third of women delivering for the first time [58]. Whether repaired or left to heal by secondary intention, such trauma is likely to impair their function

in maintaining perineal support for the vagina and pelvic organs. A link between intrapartum trauma at vaginal delivery leading to denervation of the pelvic floor muscles is also well established [59-61]. However, reinnervation does occur and the exact correlation with POP remains unclear.

Outside of pregnancy, alterations in the tissues that form the structures integral to type I and II support have been investigated. Specifically, reduced total collagen, altered collagen sub-type ratios and changes in elastin metabolism have all been linked with the presence of POP [62, 63]. This is further corroborated by the strong link between Marfan and Ehlers-Danlos syndromes, joint hypermobility, and an increased risk of developing prolapse [64, 65]. It may be that some women have an inherent tissue morphology that predisposes them to POP, yet remains subclinical with respect to other manifestations of connective tissues disorders.

The role of hormones with respect to developing POP remains unclear. Several studies have failed to find a significant correlation between systemic hormonal status and prolapse [45, 66]. Some evidence suggests that in fact it may be changes in hormone receptor expression that are more to blame [66, 67]. Yet both the prevalence and incidence of POP increases with advancing age, particularly highest in the fifth and sixth decade of life [3]. This could be the result of the cumulative effect of multiple risk factors in addition to those already outlined, including obesity, constipation, chronic pelvic floor stress (such as a physically intensive job), and pelvic surgery, coupled with the progressive tissue degeneration that occurs with ageing [3, 45, 66, 68-70].

1.3.4 Epidemiology

Determining the true prevalence of POP is confounded by the wide range of diagnostic criteria. Studies may use a subjective diagnosis on the basis of symptoms, however this requires the use of a validated measure and raises the question as to which symptom most accurately predicts the anatomical presence of POP. Objective diagnosis by examination may include

asymptomatic women and those with a variant of normal laxity; a range of cut-offs and methods for classification exist, as outlined in Chapter 1.4.1. Regardless, POP is a very common condition with 40% of women over the age of 45 reporting having had symptoms of prolapse [1]. In the largest study involving an objective diagnosis of POP by clinical examination, the Women's Health Initiative (WHI) Hormone Replacement Therapy Clinical Trial with 27,342 women aged 50-79, found some form of prolapse in 40% of the study participants [3]. Cystocele was the most common and found in 34% of women, with uterine prolapse the condition studied within this thesis, found in over 14%. Another study utilising clinical examination and undertaken in Sweden, found a lower rate of uterine prolapse at 5%, however the overall prevalence of POP was also lower at 31% [71].

The impact of POP has been shown to be associated with decreased body image and quality of life (QoL) [72]. In addition to removing the symptoms of prolapse, improvement in QoL remains one of the principal aims of surgery for POP [73]. The lifetime risk of such surgery is likely to be between 11% and 19% [4]. A study based on Scottish database figures found a 12.2% risk of surgery by the age of 80, with 19% of these women requiring reoperation for prolapse [74]. A study using UK HES data has estimated that 25% of hysterectomies are for POP, and the annual rate of admission for POP procedures is 1.13 per 1000 women at a cost of €81,028,828 (2005) in England alone [75]. This rate of surgical intervention places the UK very close to the median value found in a study of 15 Organization for Economic Co-operation and Development (OECD) countries analysed in 2012 (median rate 1.38/1000), although the range in this study was 0.51 - 2.55/1000 [76]. This suggests wide variations in surgical practice between the countries studied. Despite already large numbers of procedures, with an ageing population rates of surgery for prolapse are likely to increase significantly over the coming decades, justifying the scrutiny of the surgical interventions such as LSH that are likely to be undertaken in higher numbers [77].

Corroborating the case for genetic predisposition towards prolapse are data from large studies that have shown ethnic variations in the incidence of POP. Whilst studied, the role of ethnicity remains relatively poorly understood. Studies are confounded by socio-economic, cultural, and healthcare system factors that make differentiation between the incidence of anatomical prolapse, bother by prolapse, and healthcare seeking attitudes for prolapse difficult and full exploration of these are beyond the scope of this thesis. From an anatomical perspective, White Caucasian and Hispanic women appear to be at higher risk as compared to those of African and Caribbean descent [3, 78, 79]. Caucasians appear to be more prone to posterior compartment prolapse as compared to east Asian women who more commonly have uterine prolapse [80]. From a symptom bother point of view, it appears Hispanic and Native American women are more bothered by stage 2 prolapse as compared to non-hispanic white women [81]. As with anatomical prolapse studies, women of both White and Latin background appear much more likely to have symptomatic prolapse than those of African-American ethnicity [47, 82]. A study comparing white, black, and Hispanic American women found that Hispanic ethnicity, and younger age, were associated with treatment-seeking behaviour for prolapse, whilst socioeconomic status does not appear to be [83].

1.3.5 Symptoms

The symptoms of POP are defined by IUGA as 'A departure from normal sensation, structure or function, experienced by the women in reference to the position of her pelvic organs' [2]. They clarify that 'Symptoms are generally worse in situations when gravity might make the prolapse worse (e.g. after long period of standing or exercise) and better when gravity is not a factor.'. Table 1. 1 illustrates the definitions of the various symptoms reported by women with vaginal prolapse based on the IUGA terminology document by Haylen et al [2]. Several studies have shown these symptoms to negatively affect body image, QoL and a woman's ability to perform day to day activities [72, 84, 85].

The International Consultation on Incontinence Questionnaire Vaginal Symptoms module (ICIQ-VS) is a patient reported outcome measure (PROM) symptom questionnaire for use in assessing symptom of POP, with a Grade A recommendation from the International Consultation on Incontinence (ICI) [86]. Validation studies of this questionnaire have shown that the most common reported symptoms of POP include a 'dropping down feeling' and a 'lump felt inside' [87]. These symptoms have been used by other researchers to constitute the subjective patient reported presence of prolapse [88]. Another study, using a questionnaire without Grade A recommendation has shown that 'visualisation of a bulge' and 'impairment of sex life' most closely correlated with increasing severity of POP, while 'lower abdominal pressure; and 'pelvic discomfort when standing' are most frequently reported in the urogynaecology cohort [89]. While it is important to recognise that women with POP often have a range of pelvic floor symptoms, generally the primary aim of intervention for prolapse should be to correct the complaints detailed above.

Prolapse associated symptoms include bladder, bowel and sexual dysfunction. A 2016 terminology document published jointly between IUGA and International Continence Society (ICS) recognises that POP is often associated with these non-prolapse symptoms, as a result of anatomical distortion of adjacent organs, and these are detailed further in Table 1. 2 [2]. Bladder symptoms are particularly common in the cohort of women with prolapse. A large study of women with POP using the validated Pelvic Floor Distress Inventory (PFDI) PROM found that 96% of women with POP had some complaint of LUTS [90]. From a cohort of 336 women, 72% (n=242) had mixed urinary incontinence (MUI), 24% (n=80) had urinary urgency only and <1% (n=1) had stress-only symptoms. Of the 242 women with MUI, 57% (n=137) reported stress predominant MUI and 43% (n=105) reported urge-predominant MUI. These findings have been corroborated by a large cross sectional study of over 905 women undergoing treatment for POP [91]. The relationship between POP and bowel and sexual dysfunction while common, are beyond the scope of this thesis.

When considering surgery, patients and clinicians will reflect on the role of prolapse surgery not just on prolapse and prolapse symptoms, but also with respect to concurrent symptoms such as LUTS, and the potential implications of POP surgery on these symptoms. So-called 'occult' or new onset stress urinary incontinence (SUI) following prolapse surgery is one example of this. The phenomenon is attributed to correction of any anatomical urethral kinking (which may have been preventing the presence of urinary leakage due to a weakened sphincter mechanism) associated with prolapse, and has an incidence of between 11% and 20% [92-94]. A large body of work has looked at preventing this through the use of concurrent incontinence procedures at the time of surgery for POP [95-98]. The Colpopexy and Urinary Reduction Efforts (CARE) trial, the largest and longest study using a concomitant colposuspension to prevent SUI at the time of treatment of vault prolapse, showed that continence is maintained in the long-term with lower rates of SUI at seven years as compared to those who undergo an isolated vault procedure (probability of failure 0.62 after urethropexy versus 0.77 after colpopexy alone, treatment difference -0.153; 95% CI -0.268 to -0.030) [96]. The implication of POP surgery on LUTS is discussed and explored in more depth in Chapter 4.

Table 1. 1 Symptoms of POP based on IUGA terminology [2]

Symptom	Definition
Vaginal bulging	Complaint of a “bulge”, lump or “something coming down” or “falling out” through the vaginal introitus. The woman may state she can either feel the bulge by direct palpation or see it, perhaps aided with a mirror.
Pelvic pressure	Complaint of increased heaviness or dragging (pain or discomfort) in the suprapubic area and/or pelvis
Bleeding, discharge, infection	Complaint of abnormal vaginal bleeding, discharge or infection which may be related to ulceration of the prolapse.
Splinting / digitation	Complaint of the need to digitally replace the prolapse or to otherwise apply manual pressure, e.g. to the vagina, perineum or perianal area (splinting), or rectally (digitation) to assist voiding or defecation.
Low backache	Complaint of low, sacral (or “menstrual-like”) backache associated temporally with vaginal POP and relieved when prolapse is reduced.

Table 1. 2 Symptoms associated with POP based on IUGA terminology [2].

System	Symptom
Potential prolapse-related symptoms	
Vaginal prolapse	Bulge, visualisation, pelvic pressure, sacral backache
Urinary tract	Frequency, recurrent UTI, incomplete emptying/retention, slow stream
Ano-rectal	Incomplete defaecation, digitation/splinting, rectal urgency, post-defaecatory soiling
Sexual	Dyspareunia, vaginal laxity
Other possible associated symptoms	
Urinary incontinence	Stress, urge, postural, nocturnal, coital
Bladder storage	Urgency, nocturia

1.4 Investigation of pelvic organ prolapse

1.4.1 Examination

History and clinical examination remains the cornerstone of assessment for POP. This may be done in the dorsal lithotomy or Sims (left lateral) position. Following visualisation of the external genitalia, the labia are parted and visualisation of the introitus, with and without Valsalva are undertaken, assessing for prolapse. Manual examination, often facilitated with the use of a Sims speculum is then undertaken. This enables the clinician to assess the three compartments outlined in Chapter 1.3.2. Traditionally, prolapse of the three compartments was subjectively categorised as ‘mild’, ‘moderate’ or ‘severe’, presenting great difficulty in standardising classification and with significant inter-observer variability. This led to the development of two classification systems in routine use. The Baden-Walker system was developed in 1972, followed by the advent of the comprehensive and research oriented Pelvic Organ Prolapse Quantification (POP-Q) tool developed by the ICS [99, 100]. The pelvic floor muscles should also be digitally assessed by vaginal examination to determine tone, as a marker of functional capacity as first described by Kegel in 1948 [101]. The strength can then be quantified using the Modified Oxford Grading System, although the reliability and reproducibility of this mode of assessment has been challenged [102, 103].

For the Baden-Walker system, the hymen provides a landmark as outlined in Table 1.3, with classification of prolapse within each of the three compartments from Stage 0 – IV. The POP-Q system has been widely adopted and has been validated showing good inter- and intra-observer reliability [104, 105]. It allows a more meaningful, quantified and objective assessment of not just the various vaginal compartments, but also the genital hiatus and perineal body, as well as vaginal length. Using the hymen as a reference point, various landmarks are identified within the vagina, with their lowest position to the nearest 0.5 centimetres on Valsalva documented. Those above the hymen are demarcated by a ‘-‘ and those beyond the hymen with a

'+'. Figure 1.3 illustrates the measurements taken during a POP-Q assessment, and how they are recorded.

Table 1.3 Baden-Walker classification of POP [99].

Grade	Definition
0	Normal
I	Descent to half way to hymen
II	Progression to hymen
III	Progression halfway through the hymen
IV	Maximal progression through hymen

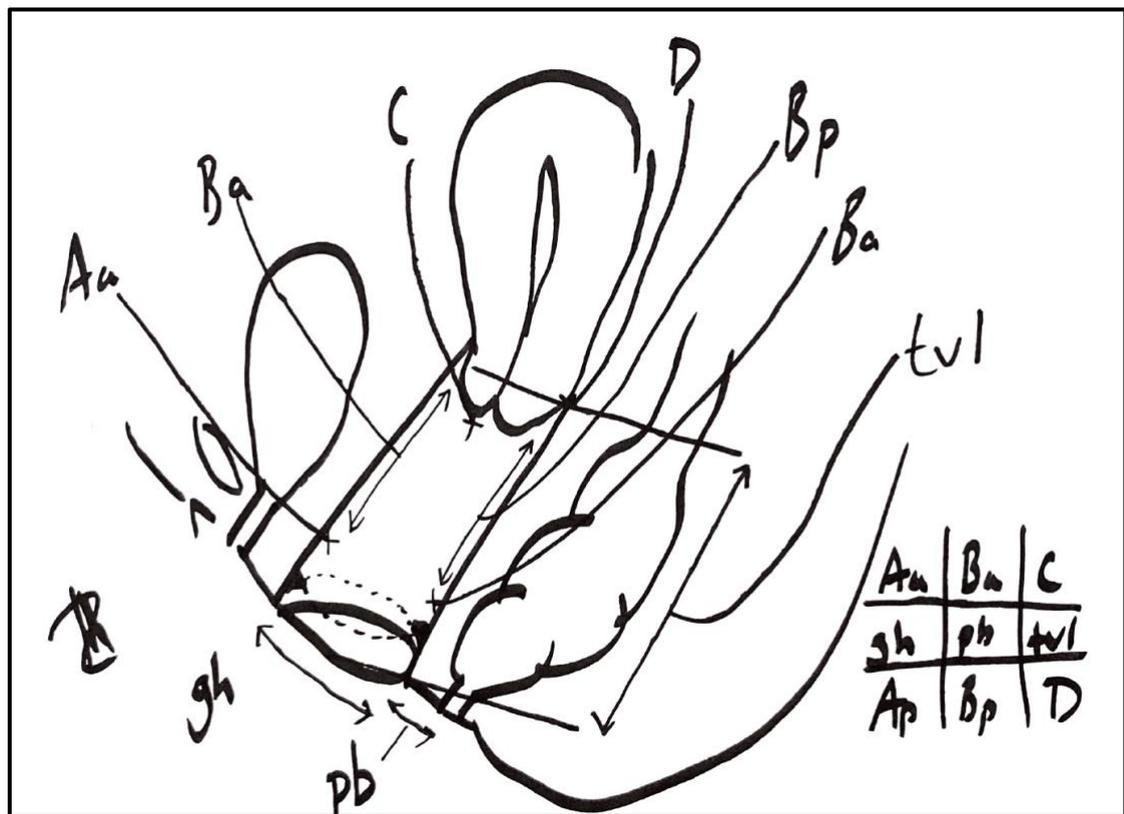


Figure 1.3 Schematic representation of POP-Q .

1.4.2 Patient reported outcome measures

Patient reported outcome measures (PROMs) are questionnaire-based tools that enable a more objective assessment of symptom status, among other measures [106]. They are defined as ‘a series of questions that patients are asked in order to gauge their views on their own health’ [107]. They may be generic such as the EQ-5D™ or system specific such as the ICIQ-VS, and their utility varies. They may be used by healthcare systems to measure efficiency, quality of care and cost efficacy, by researchers to measure efficacy of an intervention both in terms of QoL and symptom status, and finally on an individual patient basis to help target consultations, identify and quantify symptoms by screening or to measure changes in health related QoL and symptoms following an intervention [107]. Another way of framing these distinctions within the field of PROMs are economical, clinical and humanistic driven measures [108].

With respect to the assessment of POP, particularly in the research setting, the PROMs available have been appraised by ICI, with a number of such questionnaires being supported by Grade A evidence, shown in Table 1.4 [86]. The rationale for the choice of PROMs utilised within some of the studies contained within this thesis are explained within the individual methodology sections (Chapters 2.3.2, 3.3.2, 4.3.2, and 5.3.2). It must be noted, that for some studies, the use of a validated PROM is not always possible. In such situations some form of validation study is helpful, although not always feasible, particularly in the case of rare outcomes, such as those detailed within Chapter 2.3.2.

Patient Global Impression in Improvement (PGI-I) is another PROM that has been utilised to assess outcomes after pelvic floor surgery. Rather than focussing on specific symptoms and their quantification of various component parts, such global indices offer a simpler and easier measure that is transferable across different conditions and research settings [109]. A shortcoming of such a measure is that it is difficult to ascertain which component of patients symptom and health complex leads to a specific score

[110]. Yet they have been shown to have good repeatability in individuals and offer a unique measure of patient perception of outcome [110, 111]. The PGI-I measure has been used for incontinence, as well as having been validated for women with prolapse [109, 112]. Srikrishna et al. undertook this by assessing construct validity against other validated measures such as POP-Q and validated QoL scores (prolapse quality of life - pQoL) [112].

Table 1.4 Evidence base for PROMS used for POP [86].

Grade of supporting evidence	Patient reported outcome measure
A	Pelvic Floor Distress Inventory (PFDI)
	Pelvic Floor Impact Questionnaire (PFIQ)
	Prolapse Quality of Life Questionnaire (P-QoL)
	Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire
	Pelvic Organ Prolapse Urinary Incontinence Sexual Questionnaire –IUGA Revised (PISQ-IR)
	ICIQ vaginal symptoms questionnaire (ICIQ-VS)
B	The Austrian Pelvic Floor Questionnaire (AFPQ)
	Pelvic Floor Symptom Bother Questionnaire (PFBQ)
	Electronic Personal Assessment Questionnaire-Pelvic Floor (ePAQ-PF)
C	Pelvic Floor Dysfunction Questionnaire
	Danish Prolapse Questionnaire

1.4.3 Other diagnostic tests

With respect to the assessment of POP, there a range of imaging modalities exist to augment clinical examination, yet it must be noted that vaginal prolapse remains a clinical diagnosis. The use of ultrasound assessment to quantify POP and assess the pelvic floor muscles has been relatively well studied [113]. However, there is no consensus on the standardisation of assessment, and a paucity of data to illustrate an advantages over and above clinical assessment. On this basis, the latest recommendations from the ICS advise against the routine use of ultrasound for the assessment of POP [86].

Magnetic resonance imaging has also entered into relatively routine clinical practice, predominantly for those with recurrent POP, those complaining of POP in the absence of positive clinical findings, and in women with concurrent defaecatory dysfunction [114]. It has also been used along with computer modelling to further the understanding of mechanisms that underpin the anatomical and functional support of the pelvic organs, as well as failure of these mechanisms and pathology related to POP [115-117]. As with ultrasound, the evidence to support more widespread use of MRI is lacking, leading to a relatively recent recommendation against routine use [86].

In addition to diagnostic tests for POP, there may be a role for investigation of common concurrent symptoms of bladder and bowel dysfunction, or pelvic floor muscle tone and neurological function. For example, it is well recognised that more than 50% of women with POP have symptoms of obstructive defaecation syndrome (ODS) such as a feeling of straining and incomplete emptying [118, 119]. Imaging of these symptoms in the form of dynamic proctography, along with vaginal, bladder, and intestinal contrast medium, has been recommended by a recent consensus statement from the European Society of Coloproctology [120]. Traditionally such patients would be assessed through the use of fluoroscopic defaecography, utilising plain film ionising radiation in conjunction with a radio-opaque enema, to study ano-rectal physiology during defaecation. However this involves radiation, global pelvic floor assessment is limited, and detailed soft tissue imaging as well as that of

other pelvic organs is limited by the nature of the test, there are also recognised issues with over-diagnosis in health volunteers and significant inter-observer variability [121, 122]. The use of MRI has been the next evolution in pelvic floor assessment, particularly in those with ODS. It allows higher anatomical detail, the ability to more easily assess other compartments and surrounding structures in a dynamic fashion, and the ability to identify enterocele and levator ani herniation in a superior fashion to fluoroscopic imaging [123, 124]. MRI proctography has been shown to have utility in determining the underlying pathology behind such symptoms, potentially guiding conservative therapies and informing the surgical approach to pelvic floor reconstruction [125, 126]. More recent comparative data suggest both modalities have specific advantages and that ultrasonographic techniques may confer patient acceptability advantages to both approaches [127].

As outlined in Section 1.3.5, there is a high rate of concurrent LUTS in patients with POP. To guide the assessment and preoperative decision making of these symptoms, there has been an attempt to understand bladder function more objectively and various authors have explored the role of invasive preoperative UDS [128-130]. This involves the placement of catheters and transducers into the bladder and/or other body cavity (commonly the rectum) to allow a direct assessment of lower urinary tract function by assessment of physiological parameters, namely pressure changes within the bladder and patient symptoms [131]. The practicalities of urodynamic testing and parameters measured are discussed in more detail as part of the methodology discussion within Chapter 4.3.1.

Analysis of data from the CARE trial found wide variation in the prognostic value of office as well as invasive bladder function testing in patients undergoing prolapse surgery [132]. Reflecting concerns about the utility of such preoperative UDS, for women undergoing surgery for POP and reporting SUI, the last decade has seen their routine use amongst UK urogynaecologists fall from 70% to 9% [5]. Yet there remains wide variation in practice, the same survey study showed that 36% of special interest

urogynaecologists would perform routine preoperative urodynamics for any women with uterovaginal prolapse, versus 13% amongst subspecialists and 9% amongst generalist gynaecologists. The latest guidance from NICE manifests the lack of evidence to support a consensus in practice, suggesting there is a role for such investigations [133]:

‘Consider investigating the following symptoms in women with pelvic organ prolapse:

- Urinary symptoms that are bothersome and for which surgical intervention is an option.’

To date, no studies have been undertaken to determine the role UDS may have in predicting postoperative bladder function for those undergoing LSH.

1.5 Management of pelvic organ prolapse

The management of POP is generally considered to utilise an escalating step-wise approach from the least to most invasive interventions. These are therefore presented and discussed in this order. For ease of comparison of these interventions, Table 1. 5 presents the features of the key studies referenced within this thesis, with the exception of laparoscopic mesh sacrohysteropexy, for which the primary studies are presented in Table 1. 7.

1.5.1 Non-surgical interventions for pelvic organ prolapse

The first line intervention for the treatment of POP is PFMT, a form of physical therapy which is more broadly defined as ‘the exposure to training load or a work stress, of appropriate intensity to produce a noticeable or measurable training effect’ [134]. Such exercises target increased muscle volume and structural support, as well as preventing organ descent on straining [135]. While there is significant heterogeneity amongst included studies with respect to the specific nature of the PFMT regimens used, the protocol from the large POPPY study by Hagen et al. best illustrates the specifics of a PFMT regimen in the context of UK physiotherapy practice [136]. The study involved a one

to one physiotherapy programme with appointments at 0, 2, 6, 11, and 16 weeks, with individualised modifications of the home regimen according to patient needs. The ultimate aim was for women to achieve ten times ten-second pelvic floor muscles holds and up to 50 fast contractions, three times per day, augmented by the use of a diary. The study found that after 12 months, 76% of participants required no further treatment and 57% of women reported their prolapse symptoms to be better, although 70% still reported the feeling of something coming down in the previous 4 weeks. A randomised study by Wiergersma et al. similarly found that at three months, 57% of patients undergoing PFMT reported improvement in symptoms [137].

The routine and first line use of PFMT is supported in the UK by recommendations from the National Institute for Health and Care excellence (NICE) [133]. A large systematic review and meta-analysis of 13 studies with 2,340 women found that PFMT was associated with subjective improvement in prolapse symptoms as well as objective improvements in severity of POP [138]. These findings were similar to an older Cochrane review that concluded PFMT may improve prolapse stage and muscle function [139]. Both papers also reported that exercises were associated with improvements in concurrent bladder dysfunction.

A variety of other physical therapy interventions have been subject to varying degrees of academic study. These include biofeedback, vaginal manometry and electrical stimulation. There is limited consensus on how these interventions may be used, and therefore more extensive discussion of these conservative modalities is beyond the scope of this thesis.

For women who are unable or unwilling to undertake PFMT, or for whom it has failed, vaginal pessaries offer an additional non-surgical alternative. They are 'devices inserted into the vagina to provide structural support to one or more of the descending vaginal compartments' [2]. There are numerous types of pessaries in use which either support the vagina, or act as a space-filling device. Ring pessaries are widely used as first line due to ease of use, a wide

range of sizes and generally lower procurement costs [140]. With a few adverse events and widely available, 87% of urogynaecologists in the UK routinely use pessaries to manage POP [141]. It is normal UK practice for women to attend on a biannual basis for review and change of pessary. The rationale for this is to provide the opportunity for vaginal examination to exclude vaginal erosion, however the practice is without evidence base and utilises significant healthcare resources. Self-management in the UK population appears viable, in keeping with practice in other countries [142]. The TOPSY trial is a large randomised trial currently recruiting to investigate the feasibility, acceptability, and efficacy of self-management in British women [143].

While the use of pessaries for POP forms part of IUGA and NICE guidance, there is limited evidence supporting their efficacy and a 2013 Cochrane review found only one randomised trial looking at their efficacy, reporting a success rate in the region of 60% [144, 145]. Data from a number of large observational studies illustrate similar efficacy of between 41% and 68%, up to a maximum of 12 months [84, 146, 147]. This appears to drop to as low as 28% over time, based on a study with five year follow-up [148]. With a significant proportion of women reporting ongoing symptoms following either PFMT or pessary use, progression to surgical intervention is therefore relatively common.

1.5.2 Surgical interventions for pelvic organ prolapse

There are three predominant, compartment-dependent classifications of POP. This thesis focuses on uterine prolapse; that is descent of the middle compartment in women with a uterus, and therefore the surgical options discussed are limited to those applicable to this form of POP. The choice of surgical procedure undertaken generally tends to depend on the training and preferences of the operating surgeon, in combination with the woman's specific desires. Approaches may involve hysterectomy or uterine conservation, an abdominal or vaginal approach, and either native tissue or mesh augmented surgery. As the procedure subject to investigation within

this thesis, LSH is discussed in more detail separately from the other procedures, in Chapter 1.6.

Vaginal hysterectomy remains the preferred surgical procedure in UK practice for the treatment of uterine prolapse, favoured by 75% of respondents to a recent British Society of Urogynaecology (BSUG) survey [5]. The majority of clinicians undertake a concurrent fixation of the vault to the uterosacral ligaments, followed by a McCall culdoplasty and then sacrospinous ligament fixation, in an attempt to reduce the risk of PHVP. This is a practice recommended in the UK by the Royal College of Obstetrics and Gynaecology (RCOG) [149]. Sacrohysteropexy remains the second most commonly preferred procedure (10%), followed by sacrospinous hysteropexy (8%), then subtotal hysterectomy with sacrocervicopexy (4%), and finally a Manchester repair (2%) [5]. Similar surgical practices have been noted amongst clinicians in the Antipodes [150]. Colpocleisis or vaginal obliterative equivalents also exist, for those unable to undergo invasive surgery and with no intention of ever having penetrative vaginal intercourse.

Vaginal Hysterectomy and apical suspension

Despite being a longstanding procedure at the disposal of gynaecologists, the efficacy of VH in treating POP is difficult to determine. There are few randomised studies of the procedure, significant heterogeneity amongst outcome measures, and many cohort studies have not used validated PROMs. This is compounded by the range of practices with respect to vault suspension. The latest guidance from NICE quotes that at one year following VH; 35% of women remain symptomatic for POP and there is a 1-10% risk of recurrent POP [151]. However, the evidence to support these estimated failure rates is of low quality.

The largest randomised study involving VH and apical suspension was the OPTIMAL trial with outcome data at five years, however it also included women with vault prolapse, randomising women with apical prolapse undergoing vaginal repair to either uterosacral ligament suspension (ULS) or

sacrospinous ligament fixation (SSLF) [8]. At five-years the failure rates in both arms were high, 11.9% of women after ULS and 8.1% of women after SSLF had undergone retreatment for POP. The 'surgical failure' rate based the study's primary outcome which was defined as the patient reporting reoperation for POP, recurrent symptoms of POP or being found to have moderate prolapse of any of the three compartments, was 61.5% after ULS and 70.3% after SSLF. Unfortunately, subgroup analysis was not undertaken of those who underwent VH versus those who had a procedure for PHVP.

More recently, the Vault or Uterine prolapse surgery Evaluation (VUE) study has reported its initial 12 month follow-up, and one arm within this study looked at the management of uterine prolapse [152]. The comparative data from this study is discussed in detail in Chapter 3. In this large multicentre RCT with 563 women in the uterine prolapse arm, 238 women underwent a VH with an apical suspension procedure and follow up data at 12 months was reported. The primary outcome was based on symptoms of prolapse from the Pelvic Organ Prolapse Symptom Score (POP-SS) PROM, and following VH 79% of women continue to have some form of prolapse symptom, of which 28.9% reported an ongoing feeling of 'something coming down'. This would equate to a cure rate of just 21% with respect to any prolapse symptoms as a marker of surgical success. On clinical examination, 34.1% of women continued to have stage 2b prolapse (leading edge at or 1cm beyond the hymen) or more, and 4.5% of women underwent subsequent surgery within one year of which 1.2% underwent a subsequent apical procedure.

A large observational cohort study of 94 women with follow-up eight years after VH found that 90% (n=84) remained asymptomatic for POP, 90% (n=85) required no subsequent apical support procedure and 95% (n=67) of the 70 women who were examined had no significant prolapse (Grade 1 or lower) [153]. Patients were simply asked about the presence of 'prolapse' symptoms for this study, as opposed to using a validated symptom questionnaire, which may explain the high rates of symptom relief as compared to more rigorously designed studies. A Finnish study reported that 83% (n=105) of women were

asymptomatic for symptoms of a bulge at 12 months using a non-validated questionnaire, authors also reported significant improvements in validated generic measures of health associated QoL [154]. A large study from Sweden found that 81% (n=620) of women remained asymptomatic for prolapse at six months postoperatively, however a non-validated PROM was used and 'symptoms of heaviness or pressure' was used as a marker for symptomatic POP [155].

A randomised controlled trial (RCT) comparing vaginal and abdominal hysterectomy for prolapse, with 41 women in the VH arm, found that at one-year postoperatively, only 12% of patients visited a doctor with symptoms of prolapse [156]. This would suggest that 88% of patients were cured of prolapse. The same group published eight year follow up, reporting that 87% of patients reported improved prolapse symptoms compared to before primary surgery, although this was only published in the form of a conference abstract, and therefore should be interpreted with caution [157]. Finally, a recent large registry study from Denmark published data for 4045 women at a median follow up period of 34 months (range 1 to 90 months) [158]. Following VH, the risk of reoperation for prolapse at five years was 11%, corroborating the 85-90% efficacy rates based on reoperation reported within the other studies that have been highlighted.

Further discussion of comparative studies between LSH and VH are presented in Chapter 1.6.2. To summarise the data for VH alone, there are few randomised studies, with significant heterogeneity of outcome measures for those that do exist. Higher quality studies appear to suggest significant rates of ongoing symptoms of POP following surgery and many data are derived from single cohort studies, often retrospective in nature. This evidence would appear to suggest while VH with apical suspension remains in clinical practice the 'gold standard', it may be associated with failure rates of at least 30% when this is defined as recurrent symptoms or anatomical prolapse. Generally, short-term reoperation rates are at least 10%, although the quality of evidence underpinning this remains low. This points to a need for further research of

VH, but also justifies the consideration of alternative surgical procedures for uterine prolapse, such as LSH, as a valid and worthy area in need of clinical research.

Sacrospinous hysteropexy

Another procedure used to treat uterine prolapse is sacrospinous hysteropexy, which in contrast to hysterectomy involves conservation of the uterus. This involves uterine suspension to the sacrospinous ligaments, usually through a vaginal approach utilising the right sided ligament and was first described in a case series of five patients in 1989 [159]. The largest procedure specific randomised study by Detollenaere et al. had over 103 women in the hysteropexy arm [160]. They reported the procedure was noninferior to VH, finding that at 12 months none of the women had symptomatic apical POP. A meta-analysis by Kapoor et al. has also compared the two procedures [161]. They reported no significant difference in either the primary outcome of apical failure (six studies, 651 women, 25/293 vs 17/358, odds ratio (OR) 2.08; 95% confidence interval (CI) 0.76–5.68), nor in the risk of repeat surgery for prolapse (five studies, 581 women, 10/251 vs 12/330, OR 0.99; 95% CI 0.41–2.37). Various laparoscopic approaches have also been described and one cohort study with a median 12 month follow up reported an 80% cure rate in 43 women [162].

An observational study of 99 women who underwent a mesh augmented variant of sacrospinous hysteropexy, using a branded device inserted vaginally (Uphold®; Boston Scientific Corporation), reported a one year cure rate of 96% using a composite outcome of anatomical POP and the presence of symptoms [163]. However as detailed in Chapter 1.7, the availability of such transvaginal mesh augmented approaches for POP are now relatively limited.

In contrast to the positive findings outlined in previous studies, the recent large Danish registry by Husby et al. reported the failure rate of sacrospinous hysteropexy at a median of 43 months (range 1-90) in 416 women to be 30%,

comparing poorly with reoperation rates of 7% and 11% after Manchester procedures and VH respectively [158]. There are other limitations and considerations when using sacrospinous hysteropexy including issues with buttock pain, vaginal length, risk of further endometrial pathology, and the implications of uterine volume [161].

Abdominal hysterectomy and vault suspension

A further surgical alternative for uterine prolapse is abdominal hysterectomy, either laparoscopic or open, with concurrent mesh cervicopexy or sacrocolpopexy (SCP), which both involve suspension of the residual vaginal apex to the sacral promontory using mesh. The predominant issue with this intervention is the high rate of mesh erosion into the vagina. A systematic review by Jia et al. reported the overall risk of such a mesh associated complication of between 4.3% and 10.5% following hysterectomy and concurrent SCP [164]. In that review, authors considered four studies with a total of 311 women. All were low quality; Braun et al. reported an RCT in abstract form only, with 23 women undergoing hysterectomy and SCP versus 24 who underwent VH [165]. While no patients had POP at 33 months after hysterectomy and SCP, which compared favourably to the 4.2% (n=1) incidence of POP in the VH group, 4.3% (n=1) were found to have a mesh erosion. This same group have subsequently published an RCT with 12 month follow-up following randomisation to either SCP or high uterosacral vault suspension as a vaginal alternative [166]. This study recruited both hysterectomised and non-hysterectomised women, and in the SCP arm 21.4% (n=12) underwent only SCP, and 78.5% (n=44) underwent subtotal hysterectomy and SCP. The only two mesh erosions were in previously hysterectomised women, rather than those that underwent the procedure concurrently. The risk of intraoperative complications was similar between the two groups (1.9% vs. 3.6%, p=0.58). The risk of reoperation for POP was much lower in the SCP group as compared to the hysterectomy and vault suspension group (5.6% vs 17%, p=0.04). The authors did not undertake subgroup analysis to compare those with or without concurrent hysterectomy.

Another study in the Jia et al. systematic review was by Constantini et al, comparing hysterectomy with SCP to abdominal sacrohysteropexy, and therefore this paper is discussed in Chapter 1.6.2 [167]. These authors reported no failures at 51 months in this non-randomised comparative study with 39 women in the SCP arm. A further included paper was a large case series of 101 women by Wu et al. with 15 months follow-up [168]. Again, the focus of this study was mesh erosions, reporting a 6.9% risk presenting at an average of 8 months postoperatively. Other case series have reported mesh erosion rates of 0%-6.5% and success rates of 92% to 100%, however many have focused on mesh associated complications rather than efficacy with respect to POP [169-171].

Finally, the systematic review included a paper by Griffis et al. that was a retrospective study focused on mesh associated complications [172]. They reported overall erosion rates of 8.2%; 10.5% for those undergoing total hysterectomy and concurrent SCP compared to 3.6% following subtotal hysterectomy and cervicopexy. This suggests preservation of the cervix may confer a benefit with respect to safety, however there were only 88 women in this study, 28 of whom were in the cervicopexy group and the average follow up was only 13 months. A study by Crane et al. of robotic assisted sacrocolpopexy also explored a possible advantage to utilising a subtotal hysterectomy technique [173]. They reported a mesh erosion rate of 3.8% (3/79) following total hysterectomy and SCP, and 0% (0/33) following subtotal hysterectomy and cervicopexy. However, this was a single centre retrospective study with follow-up limited to six weeks. On the basis of these studies, the safety advantages of the subtotal approach should be interpreted with caution.

Manchester-Fothergill procedure

A further vaginal approach to managing uterine prolapse surgically is the Manchester-Fothergill procedure, first described in 1888 and then modified in

1915 [174]. It involves amputation of the cervix, with plication of the uterosacral ligaments and fixation to the remaining cervico-uterine body. The procedure was commonly used for many years; however, it fell out of routine use over the last two decades. This has resulted in there being limited available efficacy data, and the ICS to deem the procedure as having a limited role in contemporary practice [86]. A retrospective case series of 203 women, with case note review at a median 3.6 years postoperatively reported the risk of recurrent uterine prolapse to be as low as 3.9% [175]. Another retrospective study comparing the procedure to VH found that in the fifty patients who had follow up at one year, none had recurrent prolapse on clinical examination of the middle compartment [176]. However, 58% of the women had stage 2 prolapse of one other compartment, and there was no mention of the number of women symptomatic for POP.

With concerns about mesh use, and increasing trends towards a desire for uterine sparing approaches, there is renewed clinical interest in the procedure. The previously mentioned large Danish registry study by Husby et al compared the procedure to sacrospinous hysteropexy and VH, concluding that it had comparatively low reoperation rates and the authors called for further study [158]. At one year, 3% of the 2,786 women who underwent a Manchester Fothergill procedure had undergone a subsequent operation for prolapse which was comparable to the reoperation rate following VH. However, at 5 years this rate was 7%, considerably lower than the 11% reoperation rate found following VH at the same length of follow-up.

Colpocleisis

Colpocleisis, meaning 'vaginal closure', is an obliterative procedure generally reserved for elderly women who have been deemed unfit for major surgery due to anaesthetic risks and comorbidity. Sexual intercourse is not possible following the procedure, restricting the appropriateness of the procedure to a specific patient group. Multiple cohort studies have shown high rates of satisfaction and improved QoL, with low rates of surgical regret [177, 178]. A large multicentre study with 153 women at one-year follow up reported that

95% of patients reported being 'satisfied' or 'very satisfied'[179]. A prospective cohort study with unmatched controls undergoing vaginal reconstructive surgery found no difference between the groups with respect to bladder, bowel and prolapse symptoms, and improved QoL in both groups using the validated Short Form – 36 (SF-36) PROM [180]. A review article from 2006 summarised the available published literature and reported that colpocleisis was associated with a near 100% success rate, albeit from a group of historical studies with highly heterogeneous definitions of success [181]. The authors concluded that the procedure was associated with a 4% risk of major complications attributable directly to the surgery, such as pyelonephritis and haemorrhage, and a 1% risk of death. However, this cohort would tend to be high risk due to patient selection and therefore the AE profile must be interpreted with caution and needs further prospective study.

Vaginal mesh kits

Following the success of mesh kits for the treatment of SUI, there was a proliferation of branded devices that utilised mesh to augment apical suspension and colporrhaphy procedures. However, many of these devices have been subsequently withdrawn from the market and in UK practice they are not available. The data to support these devices was scanty and the shortcomings of the FDA regulatory process that led to their approval is discussed in Chapter 1.7.1, as well as having been discussed in a systematic database review by Heneghan et al. [182].

Maher et al. performed a systematic review for the Cochrane collaborative and identified six randomised controlled trials have been undertaken comparing native tissue versus mesh augmented devices for the treatment of apical prolapse [183]. Four of these studies looked at the Prolift™ device (Ethicon Inc., Somerville, NJ, USA), a monofilament polypropylene weave product. The randomised studies of these devices are small with between 32 and 94 patients in the mesh augmented arms [184, 185]. Most only had twelve months follow-up and the systematic review concluded there was no advantage over native tissue with respect to either objective anatomical

outcomes, reoperation or validated symptom scores [183]. However, mesh erosion rates averaged at 18%, with reoperation rates for mesh erosion at 9.5%.

Table 1. 5 Summary of evidence for key studies of interventions for uterine prolapse.

Study	Intervention	Design	Number of participants	Definition of prolapse	Primary outcome measure	Efficacy rates (outcome measure)
Hagen et al. 2014. [136]	Individualised PFMT vs advice leaflet and no training	RCT	447	Stage I-III and 'prolapse' as presenting complaint	Prolapse symptoms (POP-SS) at 12/12	70% vs 74% ('something coming down')
Wiegersma et al. 2014. [137]	Face to face individualised PFMT vs watchful waiting	RCT	287	Stage I-II POPQ and a range of prolapse symptoms	Bladder, bowel and pelvic symptoms (PFDI-20)	57% vs 13% ('improvement in symptoms')
Cundiff et al. 2007. [145]	Ring vs Gellhorn pessary	Randomised crossover	134	Stage II or greater POPQ	Bladder, bowel and pelvic symptoms (PFDI)	Not reported, no difference in scores between groups
Jones et al. 2008. [84]	Pessary (various)	Observational cohort	90	Stage I-II POPQ and a range of prolapse symptoms	Change in genital hiatus (GH)	47% (continued at three months)
Brazell et al. 2014. [146]	Pessary (various)	Observational cohort	104 (43 analysed)	Not defined	Bowel symptoms (CRADI sub-score of PFDI)	Not reported, significant improvement in bowel symptoms scores.

Abdool et al. 2011. [147]	Pessary (various) vs surgery	Cohort study (retrospective)	181	Not defined	Pelvic floors symptoms (SPS-Q)	65% vs 69% ('awareness of a lump')
Lone et al. 2015. [148]	Same cohort as Abdool et al. 2011.					
Jelovsek et al. 2018. [8]	USL vs SSF (with or without VH)	RCT	244	Stage II or greater POPQ	Failure was any of 1)POPQ C descent >1/3 TVL, 2)prolapse beyond the hymen, 3)prolapse symptoms or 4)further intervention for prolapse	38.5% vs 29.7% (as per primary outcome measure)
Hemming et al. 2020. [152]	VH vs uterine sparing (various)	RCT	563	'required surgery'	POPSS	21% vs 22.6% ('Any prolapse symptoms')
Prodigalidad et al. 2012. [153]	VH	Cohort study (retrospective)	94	Not defined	Not defined	89.4% ('sensation of prolapse')
Humalajarvi et al. 2014. [154]	Hysterectomy (various) for those with and without POP	Cohort study	322 (102 with POP)	Stage II or greater POPQ	Non-validated questionnaire	83.3% ('sense of bulging')
Pakbaz et al. 2009. [155]	VH	Population cross-sectional study	682	Not defined	Perioperative outcomes and	81.3% ('sensation of vaginal heaviness of pressure')

					non-validated questionnaire	
Roovers et al. 2003. [156]	VH vs open sacrocolpohysteropexy	RCT	82	Not defined	UDI	95% vs 95% (apical prolapse \leq Stage II)
Husby et al. 2019. [158]	VH vs vaginal hysteropexy vs MFP	Population cross-sectional study	7247	Not defined	Reoperation for apical prolapse	11% vs 30% vs 7% (apical re-operation)
Detollenaere et al. 2015. [160]	Sacrospinous hysteropexy vs VH	RCT	208	Stage II or greater POPQ	Stage II or greater POPQ point c (apex)	100% vs 96% ('symptom of bulge' or reoperation)
Maher et al. 2001. [162]	Laparoscopic suture hysteropexy	Cohort study	43	'symptomatic uterine prolapse'	'symptoms of prolapse'	81% (primary outcome measure)
Jirschele et al. 2015. [163]	Mesh augmented vaginal hysteropexy	Cohort study	99	Stage II or greater POPQ	Composite POPQ Ba and C and 'feeling of bulge in vaginal area'	97% (primary outcome measure)
Rondini et al. 2015. [166]	Vaginal high uterosacral vault suspension vs SCP with or without hysterectomy	RCT	110	Stage II or greater POPQ	Stage II or greater POPQ point c (apex)	82% vs 100% (apical prolapse \leq Stage II POPQ)
Marinkovic. 2008. [169]	TAH with concomitant SCP	Cohort study (retrospective)	64	Stage II or greater POPQ	Mesh erosion	95% (any Stage II or greater POPQ)
Karaman et al. 2015. [175]	MFP	Cohort study (retrospective)	24	Stage I-III uterine prolapse	Not defined	96% (any Stage II or greater POPQ)

De Boer et al. 2009. [176]	MFP vs VH	Cohort study (retrospective)	98	Not defined	Not defined	100% vs 96% (recurrent apical prolapse)
Hullfish et al. 2007. [177]	Colpocleisis	Cohort study	40	Not defined	Goal attainment (non-validated)	95% ('satisfied' / 'very satisfied')
Vij et al. 2014. [178]	Colpocleisis	Cohort study (retrospective)	34	Not defined	P-QoL	92% (recurrent clinical prolapse)
Fitzgerald et al. 2008. [179]	Colpocleisis	Cohort study	132	Stage III or greater POPQ	Not defined	73% (any Stage II or greater POPQ)
Sokol et al. 2012. [184]	Mesh augmented colpopexy device vs anterior colporrhaphy	RCT	65	Stage II or greater POPQ	Stage II or greater POPQ	37.5% vs 30.3% (primary outcome measure)
Silveira et al. 2015. [185]	Mesh augmented colpopexy device vs colporrhaphy	RCT	184	Stage III or greater POPQ	Stage II or greater POPQ	92.1% vs 80.3% (primary outcome measure)

1.6 Mesh sacrohysteropexy

This procedure preserves the uterus. The reasons for women electing for uterine conservation to treat uterine prolapse are varied; it may be because of a patient desire for uterine conservation, other personal reasons or a wish to maintain the potential for further pregnancies. That being said, women are generally encouraged to defer surgery until their family is complete due to the additional adverse defects of a pregnancy on the pelvic floor and compromised of surgical repair. Alternatively, it may be the surgeon's preferred procedure due to potential advantages such as anatomical outcomes outlined in Chapter 1.6.2. Regardless, in the UK patients are routinely offered a number of surgical choices with varying levels of supportive evidence with respect to safety and efficacy, in keeping with best practice and the latest guidance from NICE [133]. Contraindications to sacrohysteropexy include uterine or endometrial pathology such as cervical dysplasia, abnormal uterine bleeding, large uterine fibroids or fibroids located where peritoneal dissection occurs, and certain uterine anomalies.

1.6.1 Technique

While techniques continue to evolve, there are broadly two approaches to LSH. Some authors advocate the use of a sheet of mesh, which following dissection of the rectovaginal fascia is attached to the posterior vaginal wall and posterior cervix [186]. However, one of the principal advantages of an abdominal approach is the opportunity to avoid the placement of mesh in close proximity to, or on, the vaginal wall. Such an approach is known to be associated with a risk of vaginal erosion as described in further detail in Chapter 1.7.3. Therefore, the technique studied within this thesis is known as the 'wrap round' hysteropexy, the details of which are explored further below. The theoretical advantage of the 'wrap round' approach is a reduced or negligible risk of vaginal mesh erosion due to the site of its placement. The distinction between these approaches is important, and therefore this is highlighted when discussing outcome data below.

The contemporary LSH is the result of evolution over the last 150 years, illustrated in Table 1.6. Howard A. Kelly first described a number of cases of uterine suspension in 1887 in a procedure termed hysterorrhaphy, whereby the uterus was fixed to the anterior abdominal wall utilising peritoneum [187]. The earliest sacral fixation was described by Arthure and Savage in 1956, using an abdominal approach and fixing the uterus by the posterior uterine corpus or fundus [188]. In 1979, SK Chaudhuri described the use of the external oblique muscle to fashion a sling for the uterus and in 1993, Andrew Farkas published results of the first use of a synthetic material as a fixation device, utilising Goretex™ mesh to secure the uterus to the sacrum [189, 190]. The closest precursor to the technique studied within this thesis was that described by Cutner et al. in 2007, where a mersilene tape was used as the synthetic material for uterine suspension [191]. However, there was then a move away from heavy mesh materials due to high rates of AEs, towards lighter macroporous materials such as Prolene [14]. The approach utilised by centres involved in the studies described within this thesis is the laparoscopic 'wrap round' mesh sacrohysteropexy. The technique was formally described by Price et al. in 2010 [192].

Laparoscopic sacrohysteropexy is performed with the patient supine in lithotomy, with standard skin preparation, surgical draping, catheterisation and insertion of laparoscopic ports in accordance with recommendations from the RCOG [193]. Generally, this involves 11mm umbilical and suprapubic ports, with two 5-mm lateral ports. The peritoneum over the sacral promontory is opened, facilitated by graspers and scissors or an energy device. This incision is extended in a caudal direction into the pelvis, toward the rectum, following careful identification of the ureters bilaterally. This peritoneal relaxing incision runs medial to the right ureter, allowing it to retract further medially and away from the operative site. The peritoneum is also mobilised at the level of the uterosacral ligaments. At the level of the cervico-uterine junction the broad ligament is opened bilaterally through an avascular space, using diathermy and scissor dissection to create windows within the ligament to allow for mesh

suspension. The vesico-uterine peritoneum is then incised to allow for 2-3 cm of bladder dissection caudally away from, and off the uterine corpus.

A sheet of 'type 1' monofilament macroporous non-absorbable mesh is cut to provide a bifurcated implant. The two arms are passed through the broad ligament windows bilaterally and secured to the anterior cervix with approximately five non-dissolvable polyester 2-0 sutures. The uterus is elevated via the long arm of the mesh with moderate tension aiming to achieve adequate elevation to lift the uterus to approximately 8 cm above the introitus. The mesh is secured to the anterior longitudinal ligaments over the sacral promontory, with 5mm helical fasteners. To prevent bowel adhesions to the mesh, the peritoneal edges are then re-opposed using either interrupted or continuous sutures, at both the vesico-uterine dissection site as well as the incision from the sacral promontory to the Pouch of Douglas. A vaginal examination is then undertaken to assess the need for concurrent anterior or posterior colporrhaphy in those patients who have been consented for such an approach.

Table 1. 6 Evolution of uterine sparing prolapse surgery.

Year	Surgeon / Technique	Description
1886	Howard Kelly 'Abdominal Ventrosuspension'	Open abdominal approach. Uterus sutured to anterior abdominal wall at the level of the cervix using peritoneum.
1891	Donald and Shaw 'Manchester Repair'	Vaginal approach. Anterior and posterior colporrhaphy with amputation of cervix [194].
1956	Arthure and Savage 'Suture sacral hysteropexy'	Open abdominal approach. Uterine fundus or posterior uterine corpus sutured to ligamentous tissue of sacral promontory [188].
1979	SK Chaudhuri 'Abdominal autologous fascial uterine sling'	Fascial sling from external oblique brought through transversalis fascia and sutured to anterior aspect of cervix [189].
1993	Andrew Farkas 'Mesh hysteropexy'	Open abdominal approach. Goretex mesh used to fix uterus to sacrum [190].
2010	Price and Jackson 'Laparoscopic hysteropexy'	Laparoscopic approach. Bifurcated polypropylene mesh wrapped round the uterus through broad ligament and suspended to sacral promontory [192].

1.6.2 Review of evidence

There is relatively limited high-quality data underpinning the use of LSH, particularly in the long term. Table 1.7 provides a summary of the peer-reviewed and published RCTs and cohort studies available that have assessed the outcomes following this type of surgery. These studies have been summarised in a number of systematic reviews, with a recent meta-analysis undertaken in 2018 by Meriwether et al [164, 183, 195, 196]. To date only one procedure specific randomised study of LSH has been published, reported by Rahmanou et al. in 2015 [197]. The recent VUE study compared VH to uterine sparing procedures including LSH, however over half of women underwent a vaginal hysteropexy and therefore this study is appraised in more detail within Chapter 3.1[152]. Due to the procedure specificity of this thesis, studies of uterine sparing prolapse procedures that do not involve mesh and suspension to the sacral promontory have not been included.

Table 1. 7 Summary of evidence for sacrohysteropexy augmented by synthetic implant

Study	Design	Number of participants	Follow-up (months)	Findings	Comments
Daniels S et al. 2019. (laparoscopic) [198]	Case series	138	1.5 (55% attended 12/12 FU)	Subjective cure: 84% Objective cure: 98% (1.5/12) and 80% (12/12) Eight women reported mesh erosions, however authors state this was attributable to ‘vaginally placed mesh’.	Subjective cure – heterogenous follow up time. Non-validated measure. Objective cure – patients with stage 0 POP. 24/134 underwent concurrent anterior vaginal mesh placement, 16/34 underwent concurrent posterior vaginal mesh placement.
Lone F et al. 2018 (laparoscopic) [199]	Parallel cohort study	125 (44 LSH, 81 VH)	12 months (50% further 24 months)	Subjective cure: Not reported No difference in ICIQ-VS scores between two groups. Objective cure: Not reported. No difference in point C at 3/12. Reoperation rate (24/12): 3.6% after VH and 0% after LSH. No mesh complications.	Subjective cure: ICIQ VS and ICIQ UI. Objective cure: POP-Q at 3/12 and reoperation rates.
Pandeva et al. 2017. (laparoscopic – sheet.) [186]	Case series.	144 (159 notes reviewed)	48	Subjective cure: 81% for PGI-I and 76% for P-QoL. Objective cure: 95% Reoperation rate 8%. No mesh complications.	Subjective cure - PGI-I ‘very much better’ or ‘much better’ or P-QoL ‘not at all’. Objective cure - POP-Q point C =/< 0.

Jefferis et al. 2017. (laparoscopic) [200]	Case series	507 (3/12 FU for 441 patients)	3	SH Subjective cure: 94% SH Objective cure: N/A, only change in point C. Reoperation for apical prolapse: 2.8%. 0.7% risk bowel adhesions to unperitonised mesh. No mesh erosions. No mesh erosions.	Subjective cure – PGI-I ‘very much better’ or ‘much better’. Objective cure - POP-Q. Surgical technique altered through series to prevent bowel adhesions to mesh.
Kupelian et al. 2016. (laparoscopic) [201]	Retrospective cohort	110	31	Subjective cure: 3/12 - 94% (PGI-I) 31/12 – 81% (asymptomatic at telephone interview) and 96% (PGI-I) Objective cure: 3/12 - 98% 31/12 - 95% (5% reoperation rate for POP) No mesh associated complications.	Subjective cure – PGI-I, non validated telephone questioning. Objective cure – POP-Q 81 women only at the 31/12 telephone follow up. Telephone followed standardised questioning based on validated PROM.
Grimminck et al. 2016. (robotic) [202]	Case series	100	50 women = 60 months 50 women = 12 months)	60/12 SH Subjective cure: N/A% 60/12 SH Objective cure: 81% 12/12 SH Subjective cure: 92% (1.5/12 only) 12/12 SH Objective cure: 98% Mesh erosions: 4%	Subjective cure at 6 weeks - the absence of ‘feeling a ball’ according to UDI. Objective cure - POP-Q >2.

Gutman et al. 2016. (laparoscopic) [203]	Parallel cohort study	150 (74 lap SH vs 75 VH)	12	SH Subjective cure: 100% SH Objective cure: 90% Primary outcome composite cure rate for SH was 72%. No difference in primary outcome, PFDI or PGI-I data between the two groups. Mesh exposure: 2.7%	Primary outcome was 'surgical success' = Objective cure - No anterior or posterior wall POP beyond hymen and point C above mid vagina (TVL/2), all according to POP-Q, AND Subjective cure - Negative answer to PFDI-20, being the absence of a bulge.
Paek et al. 2016. (robotic, laparoscopic and open) [204]	Non-randomised comparative study. Retrospective.	111 (11 robotic SH, 43 lap SH and 57 open SH)	30	Lap SH Subjective cure: 93% Lap SH Objective cure: 95% (versus 100% for robotic and 91% subj. and 98% obj. for open) 4.7% risk of reoperation for POP after LSH. No mesh erosions.	Subjective cure - non-validated questionnaire. Objective cure - POP-Q C >2.
Gracia et al. 2015. (laparoscopic) [205]	Non-randomised comparative study.	45 (SH = 15, STH – 30)	12	SH Subjective cure: 100% SH Objective cure: 53% 100% patients reported PGI-I improved / cured. No mesh associated complications.	Subjective cure - absence of prolapse symptoms according to question 35 of EPIQ. Objective cure - POP-Q C <2.
Rahmanou et al. 2015. (Laparoscopic) [197]	RCT (Lap SH vs VH)	101 (Lap SH = 50, VH = 50, one VH aborted intra-	12	SH Subjective cure: 82% SH Objective cure: 94% Apical reoperation, cervical elevation and TVL all	Subjective cure - PGI-I prolapse 'very much better or much better'. Objective cure 'not requiring further apical reoperation'.

		op due to anatomy).		favoured SH, with no difference in ICIQ-VS or PGI-I scores when comparing SH and VH. No mesh associated complications.	
Api et al. 2014. (laparoscopic) [206]	Case series	33	6	Subjective cure: 96.9% Objective cure: 93.9% Mesh complications not reported.	Subjective cure - non-validated measure. Objective cure – non-validated.
Rahmanou et al. 2014. (laparoscopic) [207]	Case series	140	24	Subjective cure: 89% Objective cure: Not reported. 9% risk of reoperation for prolapse. 2% risk bowel adhesions to unperitonised mesh. No mesh erosions.	Subjective cure - PGI-I prolapse ‘very much better or much better’
Lee et al. 2013. (robotic) [208]	Case series	15	11	Subjective cure: 80% Objective cure: 93% No mesh associated complications.	Subjective cure - non-validated Objective cure - Grade 0 Baden-Walker.
Khursheed et al. 2013. (open) [209]	Case series	33	6	Subjective cure: Not reported. Objective: No recurrences reported.	Authors did not state method of pre and postoperative assessment of POP and symptoms status.

				Mesh complications not reported.	
Cvach et al. 2012. (open) [210]	Case series with unmatched controls (hysterectomy with sacropexy).	20	17	Subjective cure: 89% Objective cure: 100% (uterine prolapse), 39% if all compartments considered. No mesh associated complications in SH group.	Subjective cure -PGI-I Objective cure - POP-Q
Mourik et al. 2012. (165) 1 122-127. (robotic) [211]	Case series	50	16	Subjective cure: 88% Objective cure: 98% No mesh associated complications.	Subjective cure - non-validated Objective cure - < Grade 2 Baden-Walker.
Bojahr et al. 2012. Jul;16(3):428. (laparoscopic) [212]	Case series	19	9.3	Subjective cure: Not reported Objective cure – 90%, reoperation rate 6.7% Mesh complications not reported	Objective cure – unspecified presence of uterine POP. Retrospective series comparing these women to SCP cohort.
Costantini et al. 2011. (mixed open and laparoscopic) [213]	Case series.	55	63.8	Subjective cure: Not reported Objective cure: 100% (uterine prolapse). 7.7% had \geq stage 2 cystocele and 5.7% had \geq stage 2 rectocele. No reoperations for POP. Mesh erosion 3.6%	Prolapse symptoms were not reported. Objective cure – Cervix >6 cm above hymenal plane and $<$ grade 2 POP in other compartments.
Moiety et al. 2010. (open) [214]	Case series	33	6	Subjective cure: 81.8% Objective cure: 94%	Subjective cure - non-validated Objective cure - presence of POP-Q $>$ Stage 1.

				Mesh complications not reported.	
Price et al. 2010 (laparoscopic) [192]	Case series	51	2.5	Subjective cure: Not reported. Objective cure: 98% Mean reduction ICIQ VS -39. Mesh associated complications: 3.9% (bowel adhesions on to exposed mesh)	Assessment of subjective symptoms- ICIQ VS scores. Objective cure - POP-Q C <-2
Jeon et al. 2008. (route unspecified) [215]	Retrospective cohort with unmatched comparison to hysterectomy with mesh sacrocolpopexy and hysterectomy with mesh uterosacrocervical colpopexy	35	36	Subjective cure: Not reported. Objective cure: 100% Mesh complications not reported.	Did not report on prolapse symptoms. Objective cure – POP-Q
Demirci et al. 2006. (open) [216]	Case series	20	25	Subjective cure: Not reported. Objective cure: 95% Mesh complications not reported.	Subjective cure - validated PROMs to report reduced POP symptoms, but no comparator group. Objective cure – not specified.
Bai et al. 2005. (route unspecified, appears open) [217]	Retrospective cohort	10	12	Subjective cure: Not reported Objective cure: 100% No mesh associated complications.	Subjective cure with respect to prolapse symptoms not reported. Baden walker for objective cure.

				30% patients underwent postoperative transfusion.	
Costantini et al 2005. (open) [167]	Prospective cohort with unmatched controls (hysterectomy with sacropexy).	34	51	Subjective cure: 85% Objective cure: 91%. No mesh associated complications.	Non-validated measure of subjective cure. POP-Q for objective cure.
Roovers et al. 2004. (open) [156]	RCT (Open SH vs VH)	82 (Open SH = 39, VH = 41)	12	SH Subjective cure: Not reported. No difference in prolapse domain of UDI scores between groups. SH Objective cure: 95%. Reoperation rates: SH – 22% VH – 2.4% No mesh associated complications.	Subjective cure - UDI. Objective cure - POP-Q. SH group more likely to visit a doctor with prolapse symptoms.
Barranger et al. 2003. (open) [218]	Case series	30	Subjective 94.6 Objective 44.5	Subjective cure: 96.7% Objective cure: 96.7% Mesh erosion: 3.3%	Subjective cure – non-validated. Objective cure – Baden walker All patients underwent concomitant incontinence procedures
Leron et al. 2001. (open) [219]	Case series	13	16	Subjective cure: 77% Objective cure: 93% Mesh complications not reported.	Subjective cure - non-validated Objective cure - cervix >1cm above hymenal ring.
Banu et al. 1997. (Open) [220]	Case series	19	36-60	No recurrences.	Nature of follow-up not detailed.

				Mesh complications not reported.	
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Safety data

With respect to safety, there needs to be consideration of both mesh associated and non-mesh associated AEs. Much of the safety data for the 'wrap round' approach to LSH come from the group in Oxford, UK. In an initial small series of 51 women, two patients underwent subsequent laparoscopy for abdominal pain and were noted to have adhesions between exposed mesh and bowel, sigmoid colon in one and small bowel in another [192]. This led to the subsequent adoption of routine re-peritonisation of all mesh. There were no major intraoperative complications in this study, however follow-up was limited to a maximum of six months. The group has published one of the few RCTs, comparing VH and LSH by Rahmanou et al. in 2015. At one year follow-up they reported no major intraoperative complications amongst the 50 women randomised to LSH, no vaginal mesh erosions, and no difference in AEs between the two groups [197]. However, LSH was associated with significant lower blood loss, fewer nights in hospital, and lower 24-hour postoperative pain scores and time to return to normal activity.

Subsequently, the same group published a large single-centre cohort study, undertaken in 2017 by Jefferis et al. involving a case note review of 507 women who had been operated on over a decade, most of whom had three month routine follow-up [200]. It is worth noting that the unit is the only urogynaecology centre in the region and therefore the likelihood of patients having received care elsewhere is low. In this series there was one intraoperative bladder injury, three incidences of haemorrhage and three of bowel adhesions requiring re-laparoscopy. The latter three patients were managed with adhesiolysis and re-peritonisation, and the surgical approach was adapted early in the series to involve routine mesh re-peritonisation. There were no vaginal mesh erosions and the overall incidence of complications is shown in Table 1. 8. Two patients underwent subsequent hysterectomy for menstrual dysfunction and three patients were diagnosed with gynaecological cancers (two with early endometrial cancer at 2 and 18 months postoperatively and a third with cervical cancer at two years postoperatively). Seventeen

patients had their LSH abandoned due to anatomical variants, with most undergoing VH, for which they were consented preoperatively.

Table 1. 8 Summary of LSH complications from Jefferis et al (507 women). [200].

Complications	Incidence , % (n)
Major complications	
Haemorrhage	0.6 (3)
Adhesions to mesh	0.6 (3)
Pulmonary embolus	0.4 (2)
Bladder injury	0.2 (1)
Mesh extrusion	0 (0)
Minor complications	
Perineal infection (concomitant posterior repair)	3.2 (16)
Voiding difficulty post-surgery	2.2 (11)
Urinary tract infection	1.2 (6)

The other RCT was published by Roovers et al, and looked at open sacrohysteropexy [156]. They reported a 2% risk of intraoperative complications (1 patient required blood transfusion due to haemorrhage) and a 24% (14 women) risk of perioperative complications. However, these were routine complications of abdominal surgery including LUTS (eight women), fever (three women) and vault abscess (2 women). Two women (4.8%) developed infections of the mesh implant requiring hospital admission. Importantly, there was no difference in the rate of complication between these women and those who underwent VH. The VUE RCT comparing variable routes of hysteropexy, including vaginal, to VH found the risk at 12 months of

a mesh erosion to be 0.4%, they did not specify whether this was an abdominal or vaginal approach to hysteropexy [152].

The remaining safety data come from case series. Daniel et al. reports a relatively modest complication profile with a 2.2% risk of wound infections, 2.9% risk of vaginal infection, 2.9% risk of pain and 0.7% risk of bleeding [198]. However, follow-up was limited and non-validated as shown in Table 1.7. Authors also undertook concurrent vaginal placement of mesh and reported that eight women (5.8%) developed vaginal mesh erosions. Lone et al. have undertaken a parallel cohort study with 125 patients (44 LSH and 81 VH) [199]. There was no difference in the rate of AEs in the two study arms. Following LSH there were two readmissions, one for a haematoma (2.3%) and one for a UTI (2.3%) and two intraoperative bowel serosal injuries (4.6%). Importantly, there were no mesh associated AEs at two years follow-up. Another recent and large series by Pandova et al. reviewed the notes of 159 patients of whom 101 (64%) had at least two years follow-up [186]. They reported two cases of bowel obstruction that required repeat surgery giving a risk of 1.3%. However, it is not clear how they screened for the risk of complications and no comprehensive review of case notes and direct questioning appears to have been undertaken.

In a slightly smaller series utilising the 'wrap round' approach by Kupelian et al., authors systematically reviewed case notes and contacted patients [201]. This study reports two serious adverse events (SAEs) including a thermal bowel injury that was repaired intraoperatively and a small bowel obstruction due to an exposed suture, repaired laparoscopically giving an overall risk of SAE of 0.9%. Both patients had prolonged inpatient stays but no long-term disability. There were no cases of vaginal mesh erosions. Nightingale et al. undertook a similar cross-sectional study, inviting patients who had undergone either LSH or laparoscopic SCP to attend follow-up at a median of 6 years (range 1-9 years) [221]. Of the 112 patients included, 88 women (79%) had a SCP for vault prolapse, which involves vaginal wall placement of mesh, and 22% of women undergoing both procedures had a concurrent ventral mesh rectopexy, thus making comparison with aforementioned studies of LSH

difficult. Authors reported one case of small bowel obstruction related to a LSH, no cases of vaginal mesh extrusion, and three patient reported abdominal pain but it was not clear if these were following SCP or LSH.

In summary, for the 'wrap round' approach to hysteropexy, there does not appear to be a risk of vaginal mesh erosions from the data that are available [197, 200, 201]. However, failing to re-peritonise appears to carry a risk of small bowel adhesions and associated complications. Alternative approaches appear to carry a 0-4% risk of vaginal mesh erosion, with several case series reporting the incidence to be between 2% and 4% as illustrated in Table 1.7 [186, 202, 203, 213].

Efficacy data

The UK's NICE guidance conclude that there is adequate efficacy data supporting mesh hysteropexy, provided adequate clinical governance and audit procedures [222]. As previously noted, supporting data are limited, and the meta-analysis by Meriwether et al. and a systematic review by Nair et al. both report difficulties with formal statistical analysis owing to the heterogeneity of outcome measures and surgical techniques [195, 223]. Nonetheless, the reviews demonstrate high rates of objective and subjective success, associated with excellent patient satisfaction rates, exceeding 90%.

To date there is one non-randomised prospective controlled study and one RCT comparing VH, the current 'gold standard' intervention, to 'wrap round' LSH. In both of these studies, by Lone et al. and Rahmanou et al. respectively, the data demonstrated no difference in patient-reported prolapse symptoms at one and two years after surgery when comparing LSH to VH [197, 199]. However, Rahmanou et al reported LSH was associated with a higher apical suspension of point C (-5.4 vs -4.3, $p < 0.001$) and a longer total vaginal length (TVL) (8.35 vs 6.5, $p < 0.001$), a findings supported by a recent meta-analysis [195]. The implications of this with respect to long-term objective and subjective outcomes remain uncertain. The risk of reoperation for apical prolapse was lower in the LSH group (4% vs 8%), although this was not

statistically significant and the objective cure rate of the LSH arm was 90% at one-year, on the basis of reoperation for POP [197]. Eighty-two percent of women rated their symptoms as 'much better' or 'very much better' after LSH, there was no difference between the PGI-I and ICIQ-VS between the two groups.

In the large cohort study by Jefferis et al., the objective cure rate based on reoperation for POP was 87.7% with a mean elevation of POP-Q point C of 7.9 cm [200]. Fourteen women (2.8%) underwent a subsequent apical procedure and for ten of these women, this was simply a laparoscopic plication of the in-situ hysteropexy mesh. A further 36 women (7.1%) underwent colporrhaphy following LSH. With respect to PGI-I data, available for 404 patients, 93.8% (n=367) described their prolapse as 'much better' or 'very much better'. Findings within this study should be interpreted with caution, follow-up was non-blinded, limited to routine short-term three month follow-up, and the retrospective cohort study design presents inherent limitations with respect to interpretation.

Kupelian et al. reported outcomes at three months and then by telephone follow-up at variable timeframes with a median of 2.6 years [201]. The rate of concurrent vaginal repair in this cohort was 11% (n=12), which is significantly lower than the 54% (n=276) reported in the paper Jefferis et al. [200]. Overall, the objective cure rate based on reoperation for POP over the study period was 95%. At the three-month clinical review with clinical assessment of prolapse, the median point C was -7 and 98% of patients had an apical compartment prolapse stage 1 or less. However, many women had ongoing prolapse of either the anterior wall prolapse (41% stage 2 or higher) or the posterior wall (25% stage 2 or higher). Of the 81 women with telephone follow-up, 96% were satisfied with the surgery, reporting their prolapse as 'much better' or 'very much better' and 81% were asymptomatic for POP based on a screening question from the ICIQ-VS. Limitations of this study include short term follow-up, the absence of pre-stated outcome measures, and non-blinded outcome assessors meaning efficacy should be interpreted with caution.

The most recent case series of 138 women reported by Daniels et al. reported a subjective cure of 84%, although no validated measure was used, and an objective cure rate of 80% at twelve months[198]. In the parallel cohort study by Lone et al., while the subjective and objective cure rates were not reported, none of the LSH patients had undergone reoperation for POP at two years, comparing favourably to the 3.6% risk of reoperation for POP in the VH arm [199]. It must be noted that there was significant baseline and demographic heterogeneity between the two study arms which makes meaningful comparison of efficacy between LSH and VH very difficult. Pandeva et al. reported a subjective cure rate of 81% based on PGI-I and objective cure rate of 95% based on POP-Q point C, however 8% of patients underwent reoperation for POP over the four years [186]. This study was a retrospective cohort study limiting its ability to be used for comparison to prospectively designed studies of other interventions. A long term study looking at robotic LSH reported 81% objective cure at five years in 50 women [202]. Small number, non-blinded follow-up, and the lack of a comparator group for this study provide challenges for its utility.

In summary, for the 'wrap round' approach to LSH there appears to be a subjective cure rate in the medium term of between 82% and 96% [197, 200, 201]. These three principal studies show objective cure rates of between 87% and 96% based on reoperation for POP. Alternative surgical approaches to LSH appear to carry an 81-84% subjective cure rates when followed up beyond the immediate postoperative visit using validated measures, although one paper by Gutman et al. reported 100% cure, with no patients reporting a symptomatic bulge or lump on a validated PROM [186, 198, 202, 203]. Objective cure rates from these same papers varies between 80 and 97%, with Pandeva et al. reporting no reoperations for POP [186].

1.7 Gynaecological mesh

1.7.1 Development and uses

The term 'mesh' applies to a range of materials and devices and is defined by IUGA and ICS as 'a (prosthetic) network fabric or structure; open spaces or interstices between the strands of the net' [224]. It is important that a distinction is made from the term graft, which typically refers to a product derived from biological tissue. The evolution of surgical mesh was born out of a need to augment the repair of abdominal hernias. As materials sciences developed a range of synthetic products, a number of materials were used before the advent of plastics. Most mesh materials are now based on the plastic polypropylene, which was first used to repair inguinal hernias in the 1960s [225]. The mesh augmentation of native tissue hernia repair appeared to translate well into the field of pelvic floor reconstructive surgery, which shared the aetiological basis of weak tissues and trauma, and high rates of recurrence. Many of the subsequent mesh augmented pelvic floor procedures were an evolution of established techniques that utilised suture or native tissues.

The preliminary application of mesh to pelvic floor reconstruction was for the treatment of SUI. This was based on a technique first described in 1907 by Von Giordino who is credited with undertaking the earliest pubovaginal incontinence sling, utilising gracilis muscle grafted around the urethra [226]. The first use of a synthetic material to do this was published in 1965, and following further evolution the US Food and Drug Agency (FDA) approved the ProteGen™ sling to treat SUI in 1996 [182, 227]. Concurrently, work by Petros and Ulmsten in the 1980's on what was later termed the integral theory, led to the development of what became the most popular mid-urethral sling (MUS), the Tension-free Vaginal Tape (TVT) [228]. The basis for the integral theory is that pelvic floor disorders result from a laxity of the vagina and/or the supporting ligaments resulting from connective tissue weakness [229]. The initial work on a synthetic MUS to treat urethral laxity leading to SUI involved mersilene, however this was found to be associated with a 14% risk of mesh

erosion. The technique was subsequently refined and the use of polypropylene adopted and this led to approval by the FDA in 1998 [230]. Subsequent to approval, several large studies built a substantial body of evidence showing equivalent efficacy to colposuspension whilst avoiding laparotomy, and this led to the MUS becoming the 'gold standard' treatment for SUI [231, 232].

The evolution of mesh use in LSH has been highlighted Chapter 1.6.1. Other applications of mesh for the surgical treatment of POP include abdominal mesh placement for post hysterectomy vault prolapse in the form of SCP, a procedure that has been well studied with over 25 years of published data and supported by high quality evidence and national guidelines in the UK [133, 183]. Mesh has also been utilised through a transvaginal application, either as a custom cut mesh inlay cut from a standard mesh sheet by the operating surgeon or through commercially available mesh devices. Large numbers of these devices were approved by the FDA, often via the 501k process, a regulatory system subsequently subject to considerable criticism [13, 182]. While some data do suggest superior anatomical outcomes from transvaginal placement as compared to native tissue, more recent studies have shown higher than acceptable rates of mesh associated adverse events, a finding highlighted in a Cochrane review [233, 234]. This has led to a temporary suspension of vaginal mesh in the UK, and loss of approval or severe restrictions in other locations such as the United States and Australia [17, 235, 236].

1.7.2 Biocompatibility and biophysical profile of mesh

In contemporary gynaecological surgery, the most commonly used material is polypropylene due to it being inert, economical, and easily tailored [237, 238]. As with all implants, the material's biocompatibility and biophysical profile determine clinical utility, patient outcomes and the risk of complications. Biocompatibility is defined as 'the ability of a material to perform with an appropriate host response in a specific application' and this is mediated by host immunological response and the degree of tissue integration [237, 239].

The foreign body response (FBR) is the term used to refer to the interplay between these processes, and varies according to the composition of the implant and individual immunogenic response [240].

The pathophysiology of mesh erosion or extrusion remains unclear but is likely to be multifactorial. There are some data from animal studies to suggest there is a local implant mediated immune response that leads to either subclinical or indeed overt infection before evolving on to erosion or extrusion [241]. Mesh materials are categorised according pore size using the Amid classification [242]. The pore size has been shown to influence the interaction between small pathogens and host immunological cells. For example, leucocytes average between 9–15 micrometre (μm) whilst a typical bacterium is 2 μm [242]. Small pore size may therefore inhibit clearance of pathogens within the mesh due to reduced permeability for immune cells [243]. Finally, the heavyweight mesh materials have been found to be less biocompatible and it is therefore lightweight and macroporous meshes that are favoured for implants [14].

Aside from local immune response to the implant, there is also the impact that mesh may have on surrounding tissues and structures. Studies in animal models have shown the presence of mesh results in reduced biomechanical tissue compliance leading to stiffness, which may translate clinically into symptoms such as dyspareunia [244]. Fibroblast deposition and granuloma formation associated with the FBR will result in reduced tissue elasticity and alter the tissue adaptation to physical forces. In the case of transvaginal mesh, histological studies have shown that mesh leads to alterations in the structure and function of vaginal smooth muscle which may be implicated in the development of some of the adverse events attributed to mesh [245]. The process of excess fibroblast deposition and adaptation to the extracellular matrix may also result in a process known as 'stress shielding' where the forces exerted on tissue are altered [246]. Tissues are then shielded from dynamic forces, leading to thinning and atrophy and potentially in the case of mesh causing an erosion or extrusion [247].

In addition to the material composition itself, it is likely that there are intraoperative variables that also alter the biological response. The technique of mesh placement and its anatomical location influences the likelihood of erosion. Ovine models have demonstrated there to be a greater risk of mesh erosion associated with the placement of transvaginal mesh as compared to that placed abdominally [248]. Histological examination of the mesh explants used in these studies demonstrate the FBR to be more pronounced after vaginal placement, perhaps explaining clinical findings in human studies of higher rates of mesh erosion seen with vaginal rather than abdominal placement. The volume of implanted mesh also affects the risk of mesh erosion, with both animal models and human studies showing smaller mesh volumes reduce the risk of erosion [249, 250].

There have been concerns raised over the potential for mesh to induce malignant changes in tissues. However, a comprehensive review of five decades worth of data during which millions of implanted polypropylene mesh devices have been used, did not demonstrate a link to carcinogenesis [251].

1.7.3 Mesh complications

When considering mesh-specific complications, it is important to do so within the context of AEs associated with native tissue surgery, or indeed no treatment at all. And whilst the presence of mesh outside its intended anatomical location is a clearly defined complication, the evidence linking mesh implants to some of the other adverse events is less clear. Recognised complications associated with mesh-augmented surgery include vaginal mesh erosion (or exposure), extrusion, pain (affecting the abdomen, pelvis, groins, vulva or vagina, and lower limbs), dyspareunia, hispareunia (pain for the partner during sexual intercourse), infection, urinary voiding dysfunction, functional bladder and bowel symptoms, and treatment failure or recurrence [252-254]. Further associated complications include reports of neuromuscular problems, vaginal scarring and implant shrinkage. Psychological sequelae as a result of these physical problems are also common.

The incidence of mesh associated AEs following pelvic floor reconstructive surgery varies according to the type of mesh, volume of mesh and location of insertion amongst a variety of other variables. The highest risk use appears to be transvaginal mesh for POP, estimated to carry a 12% risk of vaginal mesh erosion and 8% risk of reoperation for mesh AEs, according to a systematic review [234]. Such rates are corroborated by the largest randomised study of transvaginal mesh for POP, the PROLapse Surgery: Pragmatic Evaluation and randomised Controlled Trials (PROSPECT) which was published in 2017 [233]. In this study by Glazener et al., it was reported that the risk of non-mesh associated AEs was 7%, and of any mesh complication it was 7%, as compared to <1% for those who have a standard native tissue prolapse repair. Twenty-three women (5%) required surgical removal and eight women (2%) were managed conservatively.

For procedures still undertaken in the UK, SCP for the treatment of PHVP has been shown to carry a 7.1% risk of mesh erosion and a 4.7% risk of reoperation for such complications according to one of the largest trials, the CARE study [96]. However, this study was undertaken a number of years ago and participants underwent implantation of a variety of mesh materials including those that are now recognised to be associated with high rates of erosion. Despite being a high-quality study with good follow-up it could be argued that such complication rates should not be translated as the incidence associated with lighter polypropylene meshes now in use. More recently, a systematic review looking at SCP suggested the risk of mesh exposure was in the order of 3% and this is the incidence quoted in much of the literature available to clinicians and patients [183]. While not advocated by NICE, hysterectomy and concurrent SCP or cervicopexy is undertaken in many countries and a Cochrane review quotes the mesh exposure rate is between 4.3% and 10.5% [164].

Transvaginal mesh for SUI remains subject to a pause in the UK, but was included in the most recent NICE guidance published in 2019 [133]. A large study of hospital coding statistics in the UK with an eight-year follow-up found

the risk of readmission for removal or repair of such mid urethral slings to be 3.4%, in a population of over 68,000 women [255]. The Cochrane review of MUS for SUI reported a 2% incidence of vaginal mesh erosion, it is worth noting that the authors acknowledged the lack of long term follow-up studies contributing to this figure [256]. The risk of mesh associated AEs following LSH is discussed in Chapter 1.6.2.

A coding system has been developed by IUGA for the classification of mesh complications to standardise the reporting of adverse events associated with mesh surgery [224]. The organisation has also standardised terminology as shown in Table 1. 9.

Table 1. 9 Mesh complication terminology according to IUGA [224].

Contraction:	Shrinkage or reduction in size.
Prominence:	Parts that protrude beyond the surface (e.g. due to wrinkling or folding with no epithelial separation).
Separation:	Physically disconnected, for example, vaginal epithelium.
Exposure:	A condition of displaying, revealing, exhibiting, or making accessible (e.g., vaginal mesh visualized through separated vaginal epithelium)
Extrusion:	Passage gradually out of a body structure or tissue (e.g., a loop of tape protruding into the vaginal cavity)
Compromise:	Bring into danger.
Perforation:	Abnormal opening into a hollow organ or viscus.
Dehiscence:	A bursting open, splitting, or gaping along natural or sutured lines.
Sinus tract formation:	(Localized) formation of a fistulous tract towards vagina or skin, where there is no visible implant material in the vaginal lumen or overlying skin.

One of the most common symptoms that appears to be experienced by those reporting a mesh complication is pain. Amongst patients reporting adverse events to the FDA, 38% of complaints reported pain or dyspareunia, and 89% of women reporting complications to the Scottish review reported pain [15, 254]. However, it is important to note that few studies of gynaecological mesh have used validated pain measures pre- and postoperatively. It is therefore difficult to confidently determine the incidence of new-onset pain and more difficult still to attribute this pain to the mesh itself. From the data that is available, it would appear that the incidence of new postoperative pain in following a procedure using gynaecological mesh is between 0% and 15% [257, 258]. The underlying aetiology of the pain is also difficult to ascertain. It may be that pain is generated as a result of contraction of the mesh over time, causing tethering of fascia and muscles [259]. Pelvic floor hypertonia has also been reported in association with the transvaginal placement of mesh [260]. It is likely that chronic pain symptoms are multifactorial in origin, potentially driven by peripheral nervous system stimulation from the implant at initial insertion. This may then lead to the evolution of chronic pelvic pain after surgery involving peripheral and central nervous system 'centralisation', with central changes implicated in the development of regional somatic and visceral pain symptoms. Referred pain believed to be a result of afferent neurons from various anatomic sites converging together, with higher centres being unable to distinguish between these distinct inputs, has also been reported following the insertion of mesh [261].

An additional complication is extrusion or exposure of mesh and this may be asymptomatic or conversely lead to discomfort, discharge and/or pain. The aetiology of pain remains poorly understood particularly in the absence of erosion. For those patients with chronic pain who are affected by mesh erosion or extrusion there is emerging evidence supporting the role of excisional surgery [262, 263]. In the absence of such exposure or extrusion, there is a paucity of evidence to direct the management of pain that is attributed to the presence of mesh. Until enough data are available to formulate clear evidence-based pathways, multidisciplinary decision-making

with particular close involvement of pain specialists and careful counselling are advocated [15, 16]. More recently a systematic review has attempted to provide a management framework for mesh complications affecting patients and this is discussed in further detail below [262].

There have been anecdotal cases published to support an association between the presence of Systemic Autoimmune Inflammatory Disorders (SAID) [264]. These include conditions such as fibromyalgia, rheumatoid arthritis and lupus, amongst many other conditions. It is important to note that the background incidence of SAID in the female population undergoing mesh procedures is high. A large study that utilised a state-wide registry in the United States by Chughtai et al, estimated that 41% of women undergoing mesh-augmented surgery had an pre-existing diagnosis of an SAID at the time of their surgical procedure [265]. The authors found that at six-years follow up, there was no difference in rates of SAID amongst 2000 patients who had undergone mesh augmented gynaecological procedures when compared to matched cohorts who underwent screening colposcopy or VH without mesh. Another recent study that compared 30,000 patients with hernia mesh to 70,000 control subjects also failed to illustrate an increased incidence of SAID in the mesh group [266]. These high-quality data provide some reassurance that mesh is not associated with SAID in the medium term, however ongoing epidemiological data are worthy of scrutiny particular with longer term study of any potential causation.

1.7.4 Managing adverse events attributed to mesh

The management of AEs that are related to the use of gynaecological mesh continues to be considered on a case by case basis, often guided by a local multidisciplinary team. As an attempt to achieve high-quality care, 24 units in the UK identified themselves as having the necessary expertise to assess and manage mesh complications. All centres have a multidisciplinary team comprising of a gynaecologist, pain management specialist, urologist and colorectal surgeon, in addition to clinical nurse specialists and pelvic floor

physiotherapists. However, there remains a lack guidance as to who should be referred to specialist centres. In the primary or secondary care setting, patients with signs or symptoms of erosion or extrusion should be referred to a specialist unit, as well as those not alleviated by conservative interventions. Further management is dictated by the route of mesh insertion, mesh type, and the nature of the complication. More recently the National Health Service (NHS) has commenced further centralisation of mesh services through specialised commissioning, the provision of a tariff, and clear criteria that are likely to continue to enhance the care provided for these women in need.

With respect to an evidence base, Cundiff et al. have systematically appraised the published evidence with respect to the management of AEs attributed to gynaecological mesh, in an attempt to develop an evidence-based algorithm for the treatment such complications [262]. It is important to note that at present there is a lack of high-quality evidence to guide clinicians as to whether to pursue expectant or conservative management or whether to offer partial and/or complete mesh excision. There is a particular difficulty in cases where there is an absence of convincing evidence of extrusion into or injury of adjacent organs, for example in the context of pain. From a surgical perspective, mesh excision is technically demanding and therefore it is important that patients are aware of a paucity of supportive evidence before embarking on surgery. There is some limited evidence to suggest that for pain attributed to adhesions between bowel and exposed mesh, adhesiolysis and endoscopic re-peritonealisation may be successful [200]. For exposed vaginal mesh, authors have advocated expectant and office management with positive short-term results [203]. The management of adverse events associated with the use of mesh during sacrohysteropexy was not reviewed by Cundiff et al. The lack of evidence to support decision making for mesh complications following sacrohysteropexy makes the need to establish the safety of the procedure all the more important, justifying one of the principal aims of this thesis as outlined in Chapter 1.2.

1.8 The patient voice

A theme found to recur in both the UK Mesh Oversight Group Report and the Scottish Report was the repeated failure of clinicians and regulators to recognise the existence of AEs due to mesh. Many women reported feeling as if their problems were dismissed or not taken seriously. To combat this issue, the Scottish Report has outlined the need for multi-disciplinary working, patient-centred care, the collection of long-term safety and efficacy data, and the development of care pathways [267]. But perhaps the concept of patient-centred care should be taken one step further. These report findings resonate even more strongly when one considers the wider move to encourage more routine integration of a 'patient voice' into healthcare systems, a concept promoted by health organisations internationally including the WHO [18, 19, 268]. Indeed, within academic research there have been calls to involve women more in women's health research [269]. One could consider whether more routine involvement of a patient voice into every component of the healthcare system, from bench research to study design or protocol writing to product development, would have lessened the issues that have developed from the use of gynaecological mesh?

The 'patient voice' is not a clearly defined concept, but has been described by the Association of Medical Research Charities as 'All activities that seek the views of patients and their families in the diagnosis, management and treatment of diseases and long-term conditions. This also encapsulates the views of care givers, the wider public and healthcare professionals' [270]. Given the size and complexity of healthcare systems, there are numerous stages at which identifying a patient voice is important. The importance of developing this voice and putting patients at the centre of healthcare systems is noted by the WHO, such that empowering and engaging people is their primary strategic goal as part of developing patient-centred healthcare systems [18]. Central to this is the role of patient satisfaction and the routine use of PROMs as a measure of healthcare quality. Moving from healthcare systems more broadly to health and medical research, the UK's National Institute for Health Research (NIHR) produces standards for public

involvement to improve health and social care research [271]. Indeed, most funding bodies for medical research now require active patient and public involvement (PPI) in research design.

So what role has the patient voice had with respect to controversies surrounding gynaecological mesh? As outlined, patients were active participants in both of the UK governmental reviews into mesh [15, 16]. The English Mesh Working Group contained associate members sourced from patient groups for women who reported complications associated with the use of mesh, however, the report did not include data from these or any other women. In contrast, the Scottish Independent Review makes some attempt to capture the experiences of patients affected by mesh. However, the authors highlight the fact that there is a predominance of those who have had complications, and a mesh complications patient group was closely involved with the generation of the report and submitted the bulk of the patient experiences that were detailed. It is worth noting that the Scottish report makes mention of a complete absence of qualitative research exploring women's experiences, providing compelling justification for the aims of this thesis and the study detailed in Chapter 5. Finally, there is the independent review by Baroness Cumberledge, published in 2018 [236]. It set out to make recommendations on improving the ability of UK healthcare systems to respond to safety concerns about clinical interventions. The review aimed to 'listen to those who have suffered harm', adding 'their voices, their experiences and views will be at the heart of our Review.' This approach raises issues further outlined in Chapter 5.1.

It also worth noting that the report raised a number of governance issues to be addressed. These include the need for high vigilance scrutiny of mesh augmented procedures, that is, strict governance controls, audit, informed consent, patient awareness of mesh issues and limited data, shared decision making, non-mesh alternatives and the need for a medical device registry. While many of these conditions have been met, there is yet to be an approved device registry within UK urogynaecological practice.

1.9 Summary of thesis questions

To summarise, uterine prolapse is a common condition for which mesh augmented LSH is a recognised surgical intervention. Yet evidence to support the procedure is sparse and generally of low-quality. Several key questions remain unanswered, particularly in light of the controversies surrounding the use of mesh. First among these, is to establish the incidence of mesh associated complications following LSH and this is addressed through the use of a large cross-sectional study in Chapter 2. Once safety of the procedure is assessed, consideration of its efficacy in comparison to VH, the current UK ‘gold standard’ needs undertaking. The results of a long-term RCT are therefore presented in Chapter 3. Given the high incidence of co-existing LUTS, the thesis then tries to address whether preoperative UDS confer any prognostic benefit for women considering surgery, using a cohort study as presented in Chapter 4. To conclude, in an attempt to address the unanswered issue of the patient perspective within the context of surgical management of POP and the mesh controversy, Chapter 5 utilises qualitative research methodologies to try and give a ‘patient voice’ from a large cohort of women who have previously undergone mesh augmented LSH.

2. A cross-sectional study of the safety and efficacy of laparoscopic mesh sacrohysteropexy

2.1 Introduction

As outlined, mesh augmented LSH offers a uterine sparing alternative to VH. The 'wrap round' technique investigated within this doctoral studies has previously been described within the literature, and explicitly detailed in Chapter 1.6.1 of this thesis [272]. Published studies of the technique have reported high satisfaction, and low rates of reoperation and complications in both the short and mid-term [200, 201]. An RCT with short term follow-up found this approach confers advantages as compared to VH with respect to higher apical suspension and longer TVL, as well as lower blood loss, hospital stay, pain scores, and return to normal activity [197]. A systematic review by Meriwether et al., has shown that a uterine-preserving abdominal approach confers benefit in terms of reduced blood loss and operating time as compared to vaginal approaches [12]. More detailed discussion of the available evidence with respect to LSH has been presented in Chapter 1.6.2 of this thesis.

The fact that most evidence comes from single-centre studies with short term follow-up, as highlighted by Meriwether et al., is particularly pertinent given the concerns regarding mesh associated complications as discussed in Chapter 1.7.3. However, uterine preservation may confer the benefit of a lower risk of mesh erosion than that seen in other abdominal approaches to prolapse. For example, following subtotal hysterectomy and cervicopexy, the reported mesh exposure rate is between 4.3% and 10.5% [164]. Given these controversies surrounding mesh use, there is a need for higher-quality data to support patient's and clinician's decision making, as well as regulators and care commissioners. Specifically, there is a need for longer term follow-up studies of mesh associated complications and rates of reoperation to determine the safety and efficacy of the procedure. To date, no study has been designed with the intention of determining the incidence of mesh associated complications following LSH.

The aim of this study is to determine the safety and efficacy mesh augmented LSH, with a focus on mesh associated complications through the use of patient reported data.

2.2 Objectives

The primary objective was to assess the safety of LSH by determining the incidence of patient reported mesh associated complications requiring reoperation.

Secondary objectives included assessment of the:

- Timing of mesh associated complication requiring reoperation.
- Symptoms leading to diagnosis of mesh associated complication requiring reoperation.
- Incidence of reoperation rates for recurrent POP.
- Incidence of reoperation rates for new onset SUI.
- Incidence of newly diagnosed SAID.
- Incidence of chronic pain service usage for pain attributed to mesh associated complication.
- Patient satisfaction with LSH.
- Improvement in POP symptoms following LSH.

2.3 Methodology

2.3.1 Study design

This was a multicentre, cross-sectional study of women who underwent mesh augmented LSH. Potential participants were identified from the surgical databases of five consultant surgeons based at two tertiary urogynaecology centres with an expertise in laparoscopic urogynaecology, with specific recruitment details outlined in Chapter 2.3.3. The two centres were University College London Hospitals in London, UK

and The John Radcliffe Hospital, Oxford University Hospitals, Oxford UK. The study adhered to the following inclusion and exclusion criteria, so as to ensure that only those with mesh complications or treatment failures attributable to the LSH were identified.

Inclusion criteria:

We included all women with adequate spoken English over the age of 18, who underwent LSH at one of our participating centres.

Exclusion criteria:

We did not contact or include any patients who were identified as deceased on our hospital databases and also excluded any patient who was identified as ever having undergone a trans-vaginal mesh augmented prolapse operation, or concurrent mesh rectopexy.

Potential participants were sent a questionnaire designed to appropriately capture the outcomes outlined in Chapter 2.3.2. The questionnaire is contained within Appendix 1. Patient Questionnaire for study in Chapter 2. Due to the rare incidence of many of the study's main outcomes, it was not possible to validate the questionnaire prior to commencing this study. The questionnaire items were assessed among the study team for face validity, before piloting at one site. We designed the questionnaire to attempt to capture the outcome measures that have been outlined below. We were not able to test for reliability due to the rarity of the outcome measure. Following consensus development by the senior authors, we then piloted the questionnaire on the Urogynecological post-operative population. This involved completion by women who met out inclusion criteria who then provided verbal or written feedback regarding comprehensibility that led to editing and the development of the final version used within the study.

Response options for participants included postal response with a prepaid envelope or to request a telephone questionnaire. Telephone interviews for the questionnaire were carried out according to a telephone script

following verbal consent. Alternatively, they could submit responses using the REDCap electronic data capture tools hosted University College London [273, 274]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources. Potential participants who had not responded to the first postal contact within eight weeks were sent a second questionnaire in order to increase our response rate. Participants were also asked for consent for the study team to contact clinicians who managed any mesh complications, to obtain further details for analysis.

2.3.2 Outcome measures

The outcome measures were chosen by the study authors to represent objective measures of mesh associated complications, reoperation rates, satisfaction and efficacy related to LSH. To answer our study objective, the following patient reported outcome measures were chosen:

Primary Outcome

- Mesh associated complication requiring removal of the hysteropexy mesh.

Secondary Outcomes

Mesh associated complications:

- The categorisation of complication in accordance with the IUGA classification system for graft complications, including [224]:
 - Categorisation of site.
 - Type of pain associated with complication.
 - Timing of onset of symptoms associated with complication.
- A new diagnosis of SAID condition subsequent to LSH.

- Being under the care or previously under the care of chronic pain services subsequent to LSH.

Non-mesh associated outcomes:

- Occurrence of further prolapse surgery.
- Type of further prolapse surgery.
- Occurrence of subsequent continence procedure.
- Type of subsequent continence procedure.
- PGI-I of prolapse symptoms.
- Friends and family test.

Tertiary outcomes

For those patients who reported a mesh complication requiring removal of the hysteropexy mesh, the following were obtained from a review of the patient case notes: past medical history, surgical history, body mass index (BMI), type of mesh implant, grade of operator (for primary sacrohysteropexy), intraoperative findings (for primary sacrohysteropexy), investigations prior to mesh removal surgery, management prior to mesh removal surgery, indication for mesh removal surgery, intraoperative findings (at time of mesh removal surgery) and clinical outcomes following mesh removal surgery.

The primary outcome measure was chosen as it was determined by the study collaborators to be the most objective measure of associated complication. While other complications such as pain, discharge and mesh erosion are important, as outlined within Chapter 1.7.3, we felt that the subjective nature of these would make analysis of patient reported data unreliable.

The secondary outcomes were divided into those addressing mesh associated complications and therefore safety of LSH, and then those that focused more on efficacy. Collecting specific data on location of the complication, type of pain, and timing of symptoms allowed for

classification in accordance with IUGA, allowing for comparison the data on mesh complications reported in the literature. As outlined, autoimmune disease has been associated with the use of synthetic mesh and allowing patients to select condition they had diagnosed subsequent to the operation appeared a feasible method for addressing this outcome. Pain is a highly subjective symptom and it was felt the use of chronic pain services was the only meaningful marker of chronic pain as validated pain scores had not been collected preoperatively.

The principle measure of efficacy of LSH chosen was reoperation for subsequent prolapse, as a lack of preoperative data and an inability to clinically assess participants precluded any other objective measure. We also included the specific operation to determine the classification of recurrent POP. The friends and family test, which asks 'Would you recommend keyhole prolapse surgery to a friend?' is widely used as a measure of success for QoL interventions and was therefore selected [275]. The PGI-I in prolapse symptoms has been validated specifically for determining the efficacy of surgical intervention for POP and was therefore also included [112]. Finally, the presence of subsequent surgery for SUI, and type of surgery was felt an important outcome to guide the counselling of future patients considering the procedure and therefore also included.

2.3.3 Recruitment

Potential participants were identified from the surgical databases of five consultant urogynaecologists. Database searches utilised operating procedure codes (OPCS) Y75.2 (laparoscopic approach to abdominal cavity) or T43.9 (unspecified diagnostic endoscopic examination of peritoneum) in combination with Q54.1 (suspension of uterus NEC), Q54.4 (suspension of uterus using mesh) or Q54.5 (sacrohysteropexy). Following implementation of the inclusion and exclusion criteria, all potential participants were then allocated a unique research identification number (research ID). They were contacted via post and provided with an invitation letter (Appendix 4. PIS for study in Chapter 2) with a link to the

secure online questionnaire platform, as well as email, telephone and postal contact details should they prefer a telephone consultation. Additionally, they were sent a patient information leaflet (PIL) (Appendix 5. Patient information sheet for study in Chapter 2), and a paper questionnaire (Appendix 1. Patient Questionnaire for study in Chapter 2) and a pre-paid return envelope. With respect to consent, all participants responding by post were assumed to have given implied consent. Those responding online or via a telephone questionnaire underwent completion of a formal consent form prior to completing the study questionnaire.

Potential participants who did not respond within 8 weeks of the first postal questionnaire received one further postal contact with all of the documents outlined previously. Those who have not responded after 8 weeks following the second postal contact were not contacted again. The study schedule is outlined in Table 2.1.

Table 2.1 Study schedule

<p><i>0-8 weeks</i> Enrolled sites</p>	<ul style="list-style-type: none"> - Identify patients who have undergone wrap round LSH - Potential participants provided by post with a secure online questionnaire option, pre-addressed envelope and paper questionnaire or option of a telephone call back.
<p><i>8-16 weeks</i> All sites</p>	<ul style="list-style-type: none"> - Responders unique ID passed to enrolled sites from primary site. - Non-responders identified by enrolled sites and contacted by telephone by clinical care team to complete questionnaire via telephone.
<p><i>16-18 weeks</i> Primary Site</p>	<ul style="list-style-type: none"> - Data collated on central secure database by primary study site.
<p><i>18-22 weeks</i> Quality Control</p>	<ul style="list-style-type: none"> - Contact with any clinical care teams outside of the enrolled centres who have diagnosed or managed mesh related complications to cross-check participants responses.

2.3.4 Data collection

All postal responses were returned to the thesis author (MI), and with the help of an MSc student (Dana Aldabeeb) these were transferred on to the REDcap® database. Data were entered using only the allocated research ID, therefore allowing for the handling and analysis of anonymised data. The paper copies were kept in accordance with the research protocol and ethical approval requirements for this study. Online responses were generated automatically and those requesting telephone questionnaires were called and underwent the scripted telephone questionnaires with responses entered into REDcap® directly by MI.

For those participants that reported a mesh associated complications requiring mesh removal surgery and consented to the collection of further data, their hospital notes were requested from their recruitment site, or alternatively from the clinician identified as having managed the complication. All of the details outlined in the tertiary outcome measures listed in Chapter 2.3.2 were then collected and stored as anonymised data within an excel spreadsheet under the participants research ID.

2.3.5 Power and statistical analysis

Due to the paucity of previous research into the primary outcome measure, it was not possible to power this analysis as part of the study protocol. Available data were analysed using descriptive statistic with frequencies expressed as percentages. Survival analyses for mesh excision and reoperation for POP as the failure variables were undertaken using the Kaplan-Meier method. These analyses were performed using Stata/SE 15® (StataCorp LLC., Texas, USA).

2.3.6 Ethical approval

This study was sponsored by University College London. The study protocol received a favourable research ethics committee (REC) opinion from the London - City & East REC on 11/05/2018 (reference 18/LO/0637) and was registered with the UK's Health Research Authority (HRA) and),

receiving favourable HRA approval on the same date. Letters from the REC and HRA are contained within Appendix 2. Favourable REC letter and Appendix 3. HRA approval letter

2.4 Results

Database searches identified 1779 women who had undergone laparoscopic mesh sacrohysteropexy. Thirteen women were identified as deceased, leaving 1766 potential study participants. Following two rounds of postal questionnaires, eight weeks apart, we received 1121 responses giving a response proportion of 63.5%. A further twenty questionnaires were returned but not included within the analysis as 16 of these potential participants had moved, three had died and seven declined participation. A flow chart of our study recruitment is shown in Figure 2.1. The average age of the study participants at the time of surgery was 58 years (range 24-86 years). The median length of follow up from the primary hysteropexy to response was 46 months (range 2-141 months), as showing in Figure 2.2.

2.4.1 Mesh complications requiring reoperation

For our primary outcome, which was 'patient reported mesh complication requiring removal of hysteropexy mesh', the incidence was 0.4% (4/1121) over this study period. We undertook a Kaplan-Meier survival analysis, with this primary outcome as the failure variable to allow for graphical representation of the development of this event over our study period and this is shown in Figure 2.3. For comparison with the published literature, we calculated that this was equivalent to 0.86 mesh removal operations per 1000-person years of follow up. All women underwent a reoperation for a mesh complications within four years of the sacrohysteropexy.

All women who responded to our questionnaire and reported reoperation for excision of mesh consented to the use of their medical notes to ascertain further details. This led to the exclusion of two women from the analysis of the primary outcome as both women in fact had their hysteropexy mesh left in situ

as this was not the aetiology of their complication. One patient who reported the removal of the sacrohysteropexy mesh had undergone a concurrent insertion of a synthetic mid urethral sling for SUI at the time of the sacrohysteropexy. Approximately 18 months postoperatively she presented to one of the participating centres with vaginal pain and dyspareunia. On clinical examination she was found to have a small exposure of sub-urethral mesh from the mid-urethral sling. Following failed conservative and then outpatient management, she underwent a partial excision of the sub-urethral portion of the tape from a vaginal approach and the hysteropexy mesh was left in situ. She underwent routine follow up for three months postoperatively and was subsequently discharged as asymptomatic.

A second study participant developed abdominal pain within four weeks of her prolapse surgery. Following failed expectant management, she underwent both pelvic ultrasound and MRI and was found to have hematometra. She opted to undergo a laparoscopic subtotal hysterectomy. The mesh that was placed during the hysteropexy was left in situ and used to undertake a stump cervicopexy. She was subsequently discharged from follow-up. Participants reporting mesh excision surgery all consented to review of their medical notes, allowing a more detailed understanding of mesh attributed complications and these are shown in Table 2.2.

Participants who reported undergoing mesh removal surgery for a mesh associated complication were then asked to report what the symptoms they had noticed prior to diagnosis. The full details of this are shown in Table 2.3. This included two participants who reported pain and a further two who reported bladder symptoms. Three women reported the symptoms associated with the mesh complication as having commenced within 12 months of the LSH.

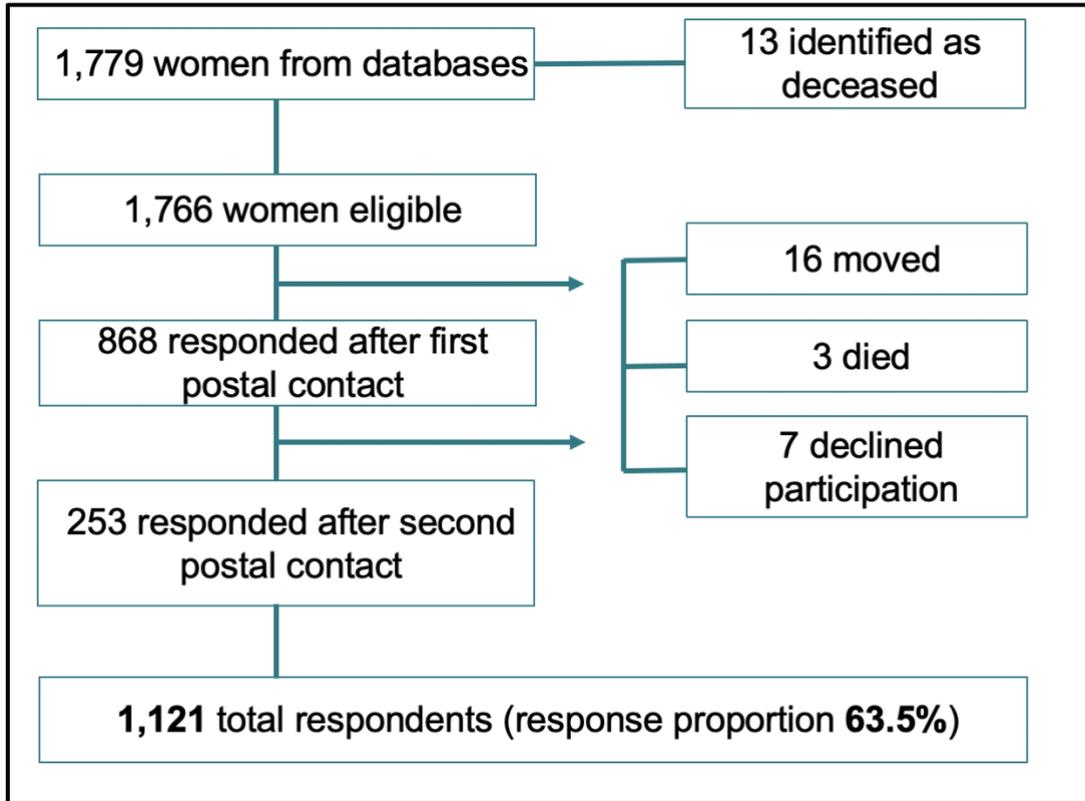


Figure 2.1 Flow chart of participant recruitment.

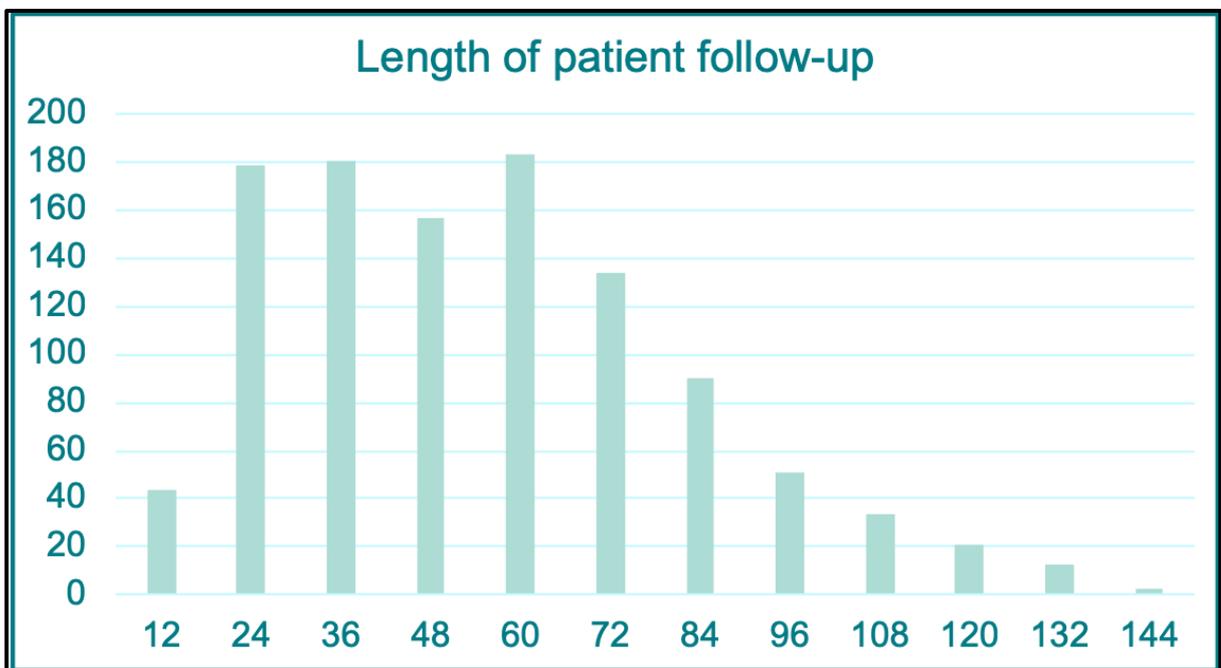


Figure 2.2 Length of follow-up (months)

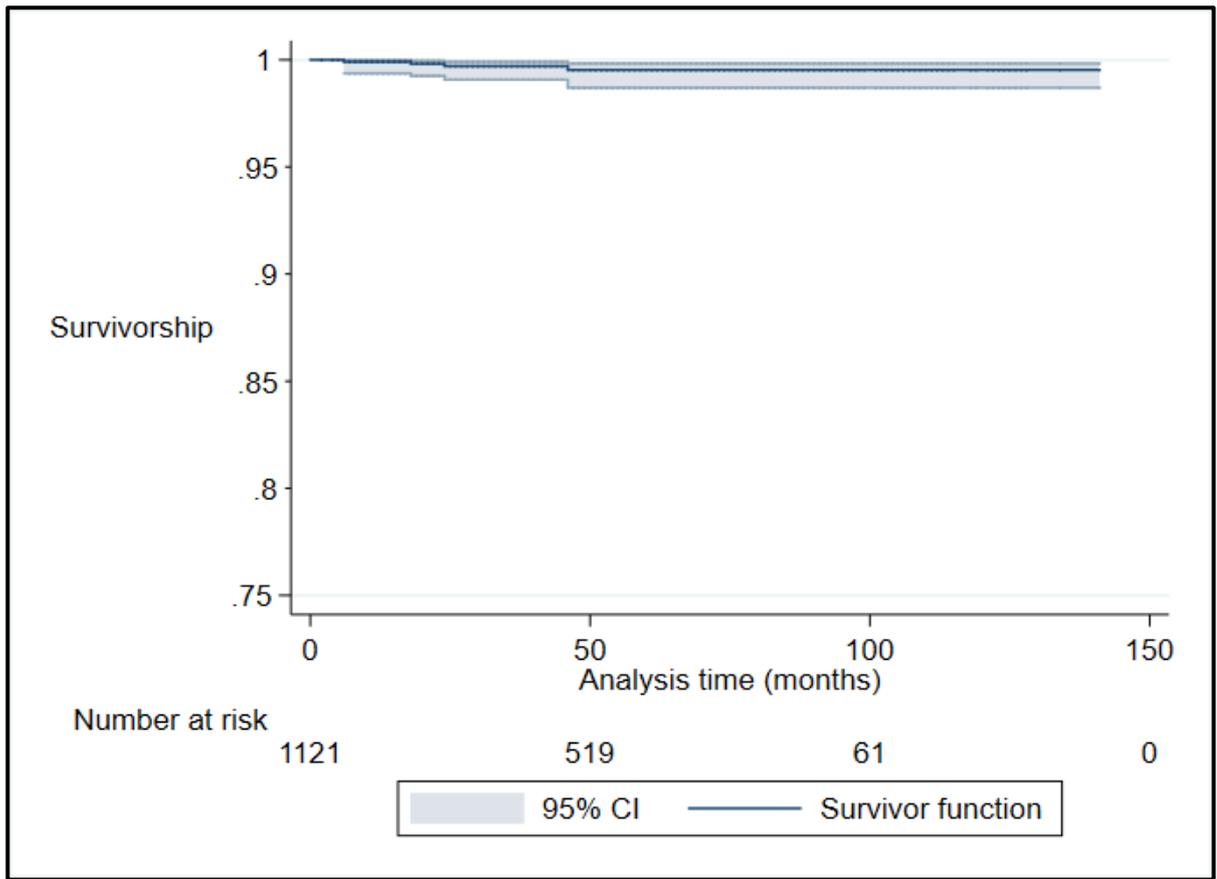


Figure 2.3 Kaplan-Meier survival analysis with mesh removal surgery as failure variable.

Table 2.2 Case details of patient reported mesh complications.

	Age at surgery	Time from sacrohysteropexy to mesh removal surgery (months)	Case details
1	54	-	Year of surgery: 2008. No hospital notes available for further analysis.
2	68	46	Year of surgery: 2013. Implant: Unknown. Grade of surgeon: Consultant. Sacrohysteropexy details: Unremarkable. Indication for mesh removal: Acute small bowel obstruction. Preoperative imaging: CT – small bowel obstruction. Conservative management: N/A. Operation and approach: Midline laparotomy, partial small bowel resection, partial excision of hysteropexy mesh with re-peritonealisation. Intraoperative findings: Suspected SBO due to mesh, small 1-2cm exposure of mesh at broad ligament – excised, and mesh end peritonealised, Additional non-tensioned peritonealised mesh at sacral aspect of implant was excised and peritonealised. Recovery. Chronic abdominal pain, noted adhesions – managed conservatively, ventral hernia repaired with mesh. Clavien-Dindo: IIIb
3	64	18	Year of surgery: 2014. Implant: Prolite Mesh, Atrium Medical, 5cm x 30.5cm. Grade of Surgeon: SST. Sacrohysteropexy details: Diverticular disease noted. Indication for mesh removal: Lower abdominal and back pain, recurrent prolapse. Preoperative imaging: None. Conservative Management: Plication of mesh. Mesh removal surgery: Laparoscopic complete resection of mesh and ProTack, laparoscopically assisted vaginal hysterectomy, anterior colporrhaphy. Mesh removal surgery findings: Elongated cervix at -1, cystocele +2. Recovery: Uncomplicated, seen at 3/12 and discharged with no issues. Clavien-Dindo: IIIb
4	40	24	Year of surgery: 2016. Implant: Prolene, Ethicon, 15cm x 15cm. Grade of surgeon: Subspecialty trainee. Sacrohysteropexy details: Unremarkable. Indication for mesh removal: Abdominal and vaginal pain, dyspareunia. Preoperative imaging: MRI and laparoscopy with EUA, both normal. Conservative management: PFMT, Paracetamol, Amitriptyline. Operation and approach: Total laparoscopic hysterectomy with complete removal of mesh and ProTack. Intraoperative findings: Unremarkable. Recovery. Ongoing vaginal ‘soreness’, discharged at three months. Clavien-Dindo: IIIb

Table 2.3 Patient reported events leading to mesh complication.

Reason for mesh removal	
Asymptomatic	-
Pain on examination	-
Pain during sex	-
Pain during physical/daily activities, % (n)	25 (1)
Pain unrelated to above, % (n)	25 (1)
Vaginal discharge	-
Bladder symptoms, % (n)	50 (2)
Bowel symptoms	-
Timeframe from operation to symptoms of mesh complication	
< 48 hours	-
49 hours to 2 months, % (n)	25 (1)
3 months to 12 months, % (n)	50 (2)
> 12 months, % (n)	25 (1)

2.4.2 Mesh associated complications

With respect to the other patient reported mesh associated complications, 5.8% (65/1121) of the study participants reported a new diagnosis of a SAID condition subsequent to their LSH. 1.8% (20/1121) of the study participants reported that they had previously been or were awaiting referral to chronic pain services for pain specifically attributed to the mesh.

2.4.3 Reoperation for POP and SUI

The risk of a subsequent reoperation for recurrent POP was 13.6% (152/1121). Of these, it is noteworthy that 3.7% (41/1121) reported a repeat apical procedure for prolapse. 2.3% (26/1121) of respondents underwent further surgery for SUI and the details of reoperation for both POP and SUI are shown in Table 2.4.

2.4.4 Further results

The majority of patients reported their symptoms as 'very much better' or 'much better' accounting for 81.4% (912/1121) of the study participants. A similarly large proportion, 82.2% (921/1121), would recommend the procedure to a friend with the same condition.

Table 2.4 Subsequent procedures for POP and SUI.

Subsequent POP procedure (n=152)	
Apical procedure, % (n)	3.7 (41)
Hysterectomy, % (n)	0.8 (9)
Colporrhaphy, % (n)	9.1 (102)
Subsequent SUI procedure (n=26)	
Synthetic mid urethral sling, % (n)	1.2 (13)
Mid urethral fascial sling, % (n)	0.1 (1)
Periurethral bulking, % (n)	0.4 (3)
Colposuspension, % (n)	0.5 (5)
Unspecified, % (n)	0.4 (4)

2.5 Discussion

Principal findings

The principal finding from this study is the low rate of reoperation for mesh associated complications. At a median follow-up of nearly four years, the incidence was 0.4% of from a large cohort of 1,121 participants who underwent laparoscopic mesh sacrohysteropexy. The risk of other mesh associated complications that were looked at within this study, namely chronic pain and SAID were also low, as was the reoperation rate for POP or SUI. It would appear most women continued, at nearly four years, to report ongoing improved prolapse symptoms with the majority recommending the procedure to a friend.

Research in context

It is of course essential to consider these findings of this study within the context of the available evidence, outlined in more detail in Chapter 1.6.2. In this study we report the largest reported cohort of women who have undergone mesh augmented uterine preserving prolapse surgery, and arguably the largest and longest cohort study of any mesh augmented surgery to date. Comparing our results with the data reported in the literature with respect to reoperation for mesh associated complications is difficult due to the heterogeneity of reporting such events. There are some longer term data from cohort studies that have reported mesh erosion rates as high as 4% following robotic assisted sacrohysteropexy, and 5% following open sacrohysteropexy [202, 204]. Both studies describe an alternative placement of the mesh than that used within our study, involving pelvic dissection down to the vagina, therefore potentially explaining the higher mesh complication rate than that seen in our results. Also of note was that neither of these studies reported whether or not these erosions were managed operatively versus conservatively and therefore these are not analogous enough outcomes to allow for meaningful comparison.

The most comprehensive investigation of LSH available is the systematic review by Meriwether et al., and this did not report any cases of mesh erosion or reoperation following abdominal mesh sacrohysteropexy [12]. In the analysis comparing LSH to hysterectomy with SCP, six studies reported mesh complications as an outcome [167, 205, 210, 212, 217, 276]. In only three of these studies did this outcome actually occur and they were all seen in the hysterectomy with concurrent SCP groups, where the risk of reoperation for a mesh complication was between 2-3% [205, 212, 276]. Another analysis within this review compared LSH to VH reported on two studies. One, by Roovers et al. published data as an abstract only, and did not report on mesh complications [277]. The other by Rahmanou et al. reported one year data of an RCT and no mesh erosions or reoperations for mesh associated complications occurred in either group [197]. The VUE study reported one case of mesh erosion after hysteropexy, but did not specify whether it was a vaginal or abdominal approach, nor whether a concurrent mesh continence procedure was performed [152].

The incidence of reoperation for a mesh associated complication in our cohort compares very favourably with that found in the literature for other mesh augmented pelvic floor procedures. Following SCP for PHVP, this figure is in the region of 5% at a median of seven years postoperatively [96]. After subtotal hysterectomy and cervicopexy, the reported mesh exposure rate is between 4.3% and 10.5% [164]. For the synthetic MUS, the most commonly performed mesh augmented pelvic floor procedure, the largest available database study has estimated the risk of reoperation for a mesh associated complications to be in the region of 2.4% at eight years [255].

With respect to the other mesh associated complications it would appear that the risk of utilising chronic pain services in our cohort appears relatively low. While pain is exceptionally understudied within the literature on pelvic floor surgery generally, after VH for example, the risk of chronic pain is in the order of 25% [278]. Recent data suggest that chronic pain and so called central sensitivity syndromes predispose patient to report poorer outcomes after prolapse surgery and such syndromes appear to be prevalent in the

urogynaecological population [279]. When looking at newly diagnosed SAID conditions, the 5.8% risk subsequent to surgery appears relatively high. A study by Chughtai et al. has reported the largest and most methodologically robust available data that looked at the association between gynaecological mesh and autoimmune disease [265]. They reported the risk of developing such a condition to be 2.8%, and there was no difference between women who underwent mesh augmented procedures and those in a matched cohort undergoing non-mesh augmented gynaecological procedures. Most importantly, over 40% of women undergoing mesh augmented POP surgery in this matched cohort study had pre-existing diagnoses of SAID conditions. They noted the extensive literature that supports the high risk of developing any SAID condition following a pre-existing diagnosis. On this basis they excluded women with pre-existing SAID, which we were not able to do due to limitations within our methodology. One would therefore argue that our findings should be interpreted with caution.

The risk of undergoing an apical prolapse operation for PHVP is in the order of 6% to 8% following VH [280]. Our findings of a 3.7% risk of undergoing such a procedure for recurrent POP therefore compares favourably. One could argue that this supports a role for mesh augmentation in pelvic floor surgery for POP. More specifically that for apical prolapse, mesh offers some superiority over native tissue repair. The overall 13.6% risk of reoperation for any form of POP in our cohort is equivalent to that reported in a recent large registry study from Denmark that reported a reoperation rate of 11% at five years [158]. Other studies have reported the risk of reoperation to be as high as 30% after native tissue surgery generally [10]. The Danish study reported a risk of reoperation for POP following suture hysteropexy of 30%, again corroborating the conclusion that mesh confers an advantage over native tissues and the use of suture.

The 9% risk of subsequent colporrhaphy for our study participants may reflect the surgical practice seen within our participating centres. As a general rule, concurrent anterior and posterior colporrhaphy for prolapse above the hymenal ring is avoided. This is because there is evidence to suggest that

such prolapse is less likely to be symptomatic, and may be considered a normal finding [88]. Furthermore, vaginal surgery may lead to scar tissue and nerve disruption resulting in issues such as dyspareunia [281, 282]. There is therefore an acceptance of the potential for reoperation due to anterior or posterior wall prolapse. Reoperation for SUI is a well-recognised risk following surgery for POP and the incidence of this in our study is comparable to the 2% risk found in large national studies [283]. The PGI-I prolapse has been validated as a measure for POP surgery, and we report high rates of improvement in prolapse symptoms [112].

Strengths and limitations

There are three principal strengths of this study including the high number of study participants, long-term follow up and patient reported nature of our data. The value of outcomes that are patient reported cannot be understated given the current climate with respect to synthetic mesh and pelvic floor surgery. Both anecdotally and within the literature concerns have been raised about the potential breakdown in trust between patients and their clinicians following these recent controversies [284]. The fact that study participants were operated on by five surgeons based at two centres also reduces the risk of reporting bias seen with single centre single surgeon cohort studies. While large national database studies and hospital coding data are often considered to be of high-quality, one must also consider that these data are often prone to coding errors and highly dependent on clinicians and non-clinicians alike to provide comprehensive and accurate data. This provides further support of our methodology of reporting patient generated outcomes as opposed to other such data.

There are some key methodological limitations inherent within our study design. Given the rare nature of our primary outcome measure we were not able to use a validated patient reported outcome measure questionnaire, nor undertake validation testing ourselves. Furthermore, to date there are no consensus agreed outcome measures for use within studies of mesh

associated complications, despite ongoing work within the field of women's health as part of the CROWN initiative [285]. We therefore settled for a discrete primary outcome that was measurable, rather than one based on evidence of consensus agreement. The data in its presented format poses a risk of omitted variable bias due to the lack of covariate analysis. This was due to the sparsity of baseline data held about the included participants, so as to make analysis about multiple variables futile. Therefore, analysis without cox model adjustment is potentially mis-leading but was felt a pragmatic compromise given the available data [286].

It must be noted that our participants underwent their procedures in centres with specific expertise in laparoscopic pelvic floor surgery and undertaken by tertiary level urogynaecologists. Therefore, the research setting and findings may not be applicable to a more generalist setting and secondary care centres. As with all forms of questionnaire studies, there is the potential for recall bias of participants. Individual may not recall undergoing a subsequent surgical procedure or the nature of such surgery. This also applies to the use of chronic pain services, and subsequent SAID diagnoses. The sensitivity of our questionnaire for these outcomes is not validated which may make comparison with other published literature of limited value. Finally, interpretation of our results requires consideration of the potential for response bias. We have no way to determine whether the responders are representative of the whole cohort of potential participants, or whether those greatly troubled by mesh complications potentially opted not to participate or conversely were most keen to respond. It is also not possible to account for the potential adverse influence from women's concerns about mesh and recent media coverage. This may have impacted our subjective outcomes of PGI-I prolapse and the 'friends and family' test.

Clinical implications

The findings from our study have potentially important clinical implications given our large cohort, the long-term follow up and arguably most importantly,

the patient reported nature of our data. Most notable, is the fact that the majority of patients would recommend laparoscopic mesh sacrohysteropexy to friends or family, and this is even despite the well-publicised controversies surrounding the use of mesh in urogynaecology. Combining this with the low risk of reoperation for mesh complications and low rates of chronic pain service use, the data should provide reassurance to both clinician, patients and regulatory bodies as to both the safety and efficacy of LSH. It could therefore be proposed that the procedure should continue to be offered as a choice to women for the surgical treatment of uterine prolapse.

Research implications

There is however, a need for ongoing clinical research looking at the role of mesh augmented prolapse surgery, and specifically sacrohysteropexy. While the hierarchy of evidence-based medicine tends to favour large, prospective, multicentre studies, when it comes to surgical interventions these are notoriously difficult for undertake. Controversies surrounding mesh use in pelvic floor reconstructive surgery are likely to make such an undertaking very difficult in the future. Large database studies are helpful, yet their quality is highly dependent on accurate data from clinicians or hospital coders, as well as engagement. Therefore, studies such as that presented within this chapter provide a pragmatic and valuable evidence base for those involved in surgical correction of pelvic floor disorders

Conclusions

The data presented provide a pragmatic insight into the safety and efficacy of laparoscopic mesh sacrohysteropexy. The large, patient reported dataset must be considered within the wider context of other forms of available evidence. We report a low incidence of mesh complications requiring removal of hysteropexy mesh of 0.4% at nearly four years. This provides adequate reassurance that laparoscopic mesh sacrohysteropexy should continue to be offered with the appropriate clinician training, decision-making processes, consent, audit and governance.

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3. Vaginal hysterectomy versus laparoscopic sacrohysteropexy for the treatment of uterine prolapse: a randomised controlled trial.

3.1 Introduction

In UK practice, VH remains the preferred surgical option for urogynaecologists treating uterine prolapse, with 75% of respondents to a BSUG survey indicating that this was their favoured procedure [5]. Half of these survey respondents offer LSH, the second most preferred procedure, and this is supported by NICE guidance [133]. Yet the important question of LSH efficacy as compared to VH remains unanswered. Whilst for women with uterine prolapse and a strong desire for uterine preservation, the clinical decision-making process is relatively straightforward; surgical options include either a mesh LSH or Manchester-Fothergill procedure. Suture hysteropexy is not supported by larger population studies due to the high risk of recurrence [158]. For the many women who have no preference regarding uterine preservation, there is a dilemma; should they opt for VH or mesh LSH, and what are the relative merits of both with respect to outcomes and safety?

The reason for consideration of mesh LSH lies with the several disadvantages associated with VH. Firstly, removal of the uterus does not address the pathophysiological factors that have led to uterovaginal prolapse, principally the deficiencies in level one support provided by the uterosacral and cardinal ligaments [20]. It is therefore unsurprising that the risk of PHVP is relatively common, with some studies reporting that it affects up to 40% of women after hysterectomy for POP [288, 289]. In accordance with guidance from the RCOG it is routine practice to undertake a concurrent apical suspension procedure at the time of VH [149]. However, the risk of vault prolapse remains, with reoperation rates of between 4.6% and 18% [8, 9]. Other data suggest that this figure is at least 8%, and following native tissue repair of prolapse more generally, the risk of reoperation for POP may be as high as 30% [10, 290]. Secondly, is the potential for new onset symptoms associated with surgical disruption of tissues. There is some evidence hysterectomy is

associated with pelvic neuropathy that in combination with trauma to adjacent structures can lead to urinary incontinence, bladder dysfunction and changes in sexual function [291-294]. Another consideration is morbidity associated with more invasive surgery, a Cochrane review has suggested subtotal hysterectomy may offer advantages over total hysterectomy such as a lower risk of postoperative pyrexia and voiding dysfunction, and in theory this may follow for hysterectomy versus hysteropexy [295]. Indeed the systematic review by Meriwether et al. that compared VH to hysteropexy pointed to shorter hospital stays, lower blood loss, quicker return to activity and lower pain scores in patients that underwent hysteropexy [195]. It must be noted however that only two RCTs contributed to this analysis and one of them utilised an open abdominal approach to hysteropexy.

More recently the VUE trial tried to answer the question of uterine preservation versus VH [152]. A previously discussed this was a multicentre RCT with 563 participants and authors reported no difference between the two intervention groups with respect to validated symptoms scores, the primary outcome, nor with rates of SAEs or overall stage of prolapse. They did find that more women would recommend VH. Yet uterine preservation was undertaken utilising various techniques including vaginal sacrospinous fixation, colpocleisis, and both open and laparoscopic approaches to abdominal suture hysteropexy and abdominal mesh hysteropexy. Many of those having uterine preservation procedures failed to receive the benefits of LSH, namely a minimally invasive approach, good access to the pelvis allowing for higher uterine suspension and the potential longevity associated with mesh use.

The evidence presented in Chapter 1.6.2 suggests LSH has a comparable adverse event profile to other routinely used mesh augmented procedures such as SCP and therefore should be deemed appropriately safe. Given current prolapse surgery trends surgery, ageing populations, changing patient desires, and the high failure rate associated with VH, the merits of abdominal hysteropexy deserve further scrutiny. In this study, we aim to compare outcomes between VH with apical suspension versus LSH, reporting the long-

term outcomes at seven years in participants of the study previously reported by Rahmanou et al. [197].

3.2 Objectives

The primary objective of this study was to compare the efficacy of VH and mesh augmented LSH by determining the risk of reoperation for apical prolapse between the two groups.

Secondary objectives included comparing the two groups through the assessment of:

- The overall risk of reoperation for any type of POP.
- The incidence of mesh associated complications such as mesh exposure, mesh removal or chronic pain.
- Patient impression of the improvement in POP symptoms.
- The anatomical presence of POP.
- The presence of vaginal symptoms including POP symptoms.
- The presence of LUTS.
- Sexual function.

3.3 Methodology

3.3.1 Study design

This study was a single-centre RCT of VH versus mesh augmented LSH for the treatment of uterine prolapse undertaken at the John Radcliffe Hospital, Oxford, UK from May 2009 to September 2012. Potential participants were identified from the urogynaecology unit as women requesting surgical treatment for grade 2-4 uterine prolapse. The study adhered to the following inclusion and exclusion criteria.

Inclusion criteria:

Women diagnosed with symptomatic uterine prolapse (grade 2-4 uterine descent according to the Baden-Walker system) aged 18 years or above. They had to have completed their family with no desire for future childbearing and if of reproductive age had to be willing to ensure that she or her partner would use effective contraception during the study and for 3 months thereafter.

Exclusion criteria:

Included the following:

- Desire to maintain fertility, pregnant, lactating or planning pregnancy during the course of the study.
- Having significant renal or hepatic impairment.
- Having participated in another research study involving an investigational product in the previous 12 weeks.
- Having abnormal cervical cytology, abnormal uterine bleeding or evidence of uterine disease.
- Having any other significant comorbidity which in the opinion of the operating surgeon, may either put the participant at risk of another surgical intervention, or may influence the result of the study, or the participant's ability to participate in the study.

With respect to our surgical intervention, both LSH and VH were combined with anterior and/or posterior repair on the basis of intraoperative assessment and judgment at the time of surgery by the senior operating surgeon. Generally anterior or posterior wall prolapse above the hymen was left, unless explicitly planned preoperatively following patient wishes. For LSH, the technique utilised is described in detail within Chapter 1.6.1. Briefly this involves the use of a bifurcated polypropylene mesh (PRO-Lite™, Atrium Medical Corporation, Hudson, NH, USA) wrapped around the cervix through broad ligament windows and secured anteriorly with non-absorbable sutures (Ethibond Excel™; Ethicon) that is then secured to the sacral promontory with a helical fastener (Protack™; United States Surgical, Tyco Healthcare, Norwalk, CT,

USA). For VH, the uterosacral ligaments were reattached to the vaginal vault following hysterectomy with re-absorbable sutures (Vicryl 1; Ethicon, Somerville, NJ, USA). This is referred to as a modified McCall's culdoplasty and was undertaken as it is the most common technique employed in the UK [5]. For those participants with procidentia, additional vault support was undertaken by employing a sacrospinous fixation. This utilised re-absorbable sutures (PDS II 0; Ethicon), again mirroring common UK practice and complying with RCOG recommendations [149].

3.3.2 Outcome measures

The outcome measures were based on objective patient reported data, clinical examination and the results from ICS Grade A PROMS ICIQ-VS, ICIQ-FLUTS and PISQ-IR which are contained in Appendix 8. To answer our study objective, the following outcomes were selected:

Primary outcome:

- Subsequent operation for apical prolapse within the study period.

Secondary outcomes:

Objective measures:

- Reoperation for any form of POP.
- Presence of POP according to the POP-Q.
- Mesh associated complications including patient reported removal of mesh, mesh erosion or chronic pain attributed to the use of mesh.

Subjective measures:

- Satisfaction with surgery according to PGI-I in prolapse symptoms.
- Prolapse symptoms measured by Question 5 of the ICIS-VS.
- Vaginal symptoms measured by ICIQ-VS
- Sexual function measured by ICIQ VS sexual matters and Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire – 12 (PISQ-12.)
- Vaginal symptom related QoL measure by ICIQ VS quality of life

- LUTS measured by International Consultation on Incontinence Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS)

Tertiary outcomes:

- Blood loss (millilitres)
- Operating time (minutes)
- Postoperative complications
- Hospital stay (days)

3.3.3 Recruitment

Potential participants were women who were referred to the Urogynaecology department of the John Radcliffe Hospital, Oxford University with symptoms of prolapse. They were seen as part of the routine clinical care pathway and underwent a clinical history, vaginal examination and assessment of prolapse using POP-Q followed by a discussion about the conservative and surgical management of prolapse. Those potential participants who met the inclusion and exclusion criteria set out in Chapter 3.3.1 were then given a PIL (Appendix 7) the study and offered the opportunity to participate. Those women who agreed were then consented for participation at a later date on re-attendance to the outpatient clinic or at the time of surgical consent taking.

Randomisation was conducted in the urogynaecology clinic at the John Radcliffe Hospital. Sealed randomisation envelopes were kept secure and unopened by the investigators. Each subject was assigned a study number and then randomised through the use of sealed envelopes placing participants into groups A or B (group A = laparoscopic sacrohysteropexy, group B = VH). Randomisation occurred sequentially as each subject entered the study.

The data presented within this thesis comes from the seven-year follow-up of participants of this study. This was not part of the original study protocol and was carried out after approval for a substantial amendment as detailed in Chapter 3.3.6. All study participants were contacted by telephone and invited

for a study visit in clinic as detailed below and those who attended completed written consent. Telephone verbal consent was obtained for those who were happy to undertake a telephone history and send postal questionnaires. Following two attempts at telephone contact all study participants were contacted by post with a PIL, questionnaires for PGI-I, ICIQ-VS, ICIQ-FLUTS, PISQ-12, and a study questionnaire asking about subsequent operation or mesh associated complications. These questionnaires were chosen as they all have Grade A evidence to support their use [86]. Return of these questionnaires was taken as implied consent and a case note review of these participants was undertaken.

3.3.4 Data collection

There were three principle data collection points, as outlined in the study schedule shown in Table . The following visits were undertaken as part of the study plan, with relevant data collection as highlighted.

1st visit (baseline assessment):

Potential participants attending urogynaecology clinic at John Radcliffe Hospital as part of routine clinical care pathway.

- Demographic data
- Clinical history, abdominopelvic examination including POP-Q
- Completion of ICIQ-VS
- Checked against inclusion and exclusion criteria
- Given PIL

2nd visit:

- Surgical consent.
- Study consent.
- Randomisation.

3rd visit:

Admission to hospital for surgery

- Intraoperative data
- Short-term complications

4th visit:

Eight-week postoperative visit as part of routine clinical care

5th visit:

Twelve months postoperative in urogynaecology outpatient clinic.

- Routine clinical history covering postoperative recovery, vaginal, urinary, bowel and sexual symptoms, any subsequent prolapse operations and review of case notes.
- PGI-I prolapse symptoms.
- ICIQ-VS
- POP-Q

6th visit:

Not part of original study protocol and subject to a substantial amendment. At a minimum of seven years postoperatively, study participants were contacted by telephone and offered the following:

Attendance in clinic

- Routine clinical history covering postoperative recovery, vagina, urinary, bowel and sexual symptoms, any subsequent prolapse operations and complications related to mesh including removal of mesh, mesh erosions or pain attributed to the mesh and review of case notes.
- PGI-I prolapse symptoms.
- ICIQ-VS
- ICIQ-FLUTS
- PISQ-12
- POP-Q

Those patients declining a clinical review were offered a telephone or postal consultation with one of the clinical care team to undertake:

- Routine clinical history covering postoperative recovery, vagina, urinary, bowel and sexual symptoms, any subsequent prolapse operations and complications related to mesh including removal of mesh, mesh erosions or pain attributed to the mesh and review of case notes.
- PGI-I prolapse symptoms.
- ICIQ-VS
- ICIQ-FLUTS
- PISQ-12

Following two attempts to contact participants by telephone (voice messages were not left), a single postal contact was made using the cover letter to allow for postal completion of questionnaires. Contact details of the clinical care team were enclosed within the postal contact to allow participants to request a follow-up appointment if this was their preference. Those participants that responded underwent:

- Review of case notes.
- PGI-I prolapse symptoms.
- ICIQ-VS
- ICIQ-FLUTS
- PISQ-12

Table 3. 1 Study flow chart

Intervention or procedure	Time	Details
Participant identification in gynae clinic: clinical assessment, Questionnaire assessment, recruitment and randomisation. (potential participants will be given up to three months to think).	20-40 min	Mr SR Jackson and his team of co-investigators will conduct interviews and procedures that will take place at the John Radcliffe Hospital Oxford and Pembury Hospital Tunbridge Wells.
Admission for the prolapse operation, operation itself and postoperative recovery.	2-5 days	Mr SR Jackson and his team of co-investigators will conduct interviews and procedures that will take place at the John Radcliffe Hospital Oxford and Pembury Hospital Tunbridge Wells.
Follow up at 8 weeks, post operation for clinical assessment in gynaecology clinic. (this is the follow-up procedure that all our patients (patients not participating in any trial) normally receive).	20 min	Mr SR Jackson and his team of co-investigators will conduct interviews and procedures that will take place at the John Radcliffe Hospital Oxford and Pembury Hospital Tunbridge Wells.
Postal follow up at 6 months post operation for Questionnaire assessment. (this is the follow-up procedure that all our patients (patients not participating in any trial) normally receive).	20 min	Mr SR Jackson and his team of co-investigators will conduct interviews and procedures that will take place at the John Radcliffe Hospital Oxford and Pembury Hospital Tunbridge Wells.
Follow up at 12 months post operation for clinical assessment in gynaecology clinic. (this is the follow-up procedure that all our patients (patients not participating in any trial) normally receive).	20 min	Mr SR Jackson and his team of co-investigators will conduct interviews and procedures that will take place at the John Radcliffe Hospital Oxford and Pembury Hospital Tunbridge Wells.
Follow up at 72 months post operation for clinical assessment in gynaecology clinic. (this is follow-up as part of the study)	20 min	Mr SR Jackson and his team of co-investigators will conduct interviews and procedures that will take place at the John Radcliffe Hospital Oxford and Pembury Hospital Tunbridge Wells.

3.3.5 Power and statistical analysis

This RCT was originally conducted as a pilot study and therefore a power calculation was not undertaken. A sample size could be calculated assuming an 85% cure rate following LSH, based on previously discussed literature utilising an anatomical outcome, with a 5% difference in cure rate being deemed as clinically significant. To detect this level of difference with 80% power would require 62 patients in each arm of the trial. Therefore, for adequate power the total study sample size would have been 124 women. This power calculation did not account for loss to follow-up and its secondary use as part of this study would not be considered to be statistically robust. It was not used to calculate a sample size for seven-year follow-up.

Data for the whole study population were subject to descriptive statistics. For the primary outcome of a dichotomous variable of either having had reoperation for apical prolapse or not, a chi-squared test was used. This was used for all other dichotomous variables, parametric data were subject to a student t-test and non-parametric data such as PROM scores were subject to a Mann-Whitney U test, all requiring a significance level set at $p < 0.05$. These were all analysed on an intention to treat basis. Kaplan Meier survival analyses were also undertaken using the primary outcome as a failure variable. Statistical analysis was undertaken with Stata/SE 15® (StataCorp LLC., Texas, USA).

3.3.6 Ethical approval

This study was originally approved by the National Research Ethics Committee (reference number: 09/H0606/28). In order to undertake the seven-year follow-up that was not part of the original protocol a substantial amendment was made. This was approved along with Health Research Agency approval on 08/01/2019 by the South Central – Oxford C REC, as detailed in Appendix 9.

3.4 Results

Over the recruitment period 481 women were seen with stage 2-4 symptomatic uterine prolapse and invited to participate. Many declined participation due to a particular preference for one of the surgical options. One hundred and thirty-two women were recruited, however 31 of these women later withdrew due to a desire for a specific surgical procedure. A further patient randomised to LSH had an intraoperative conversion to VH due to a low bifurcation of the aorta precluding safe access to the sacral promontory for access. The one-year follow-up of 79 study participants has previously been reported, with no significant difference in the primary outcome of reoperation for apical surgery [197].

A summary of the demographics between the LSH and VH groups at recruitment and for those with seven-year follow-up is shown in Table . Following telephone and postal contact, 62 women (62%) provided long-term outcome data. Comparison of baseline demographics and characteristics between those that attended for long-term follow-up and those lost to follow-up, is shown in Table 3.3 C. It is notable that those who did not attend the long-term follow-up had worse preoperative ICIQ-VS scores than those who did participate (37 vs. 32, $p = 0.04$). The enrolment, allocation, follow-up and analysis of patient is outlined within **Error! Reference source not found..** With a minimum of seven years, the mean length of follow-up was 100 months (range 84-119 months).

3.4.1 Rate of apical reoperation

For the primary outcome of reoperation for apical prolapse, 6.1% of participants underwent such a procedure following LSH and 17.2% following VH, however the difference was not statistically significant (relative risk (RR) 0.34, 95% CI 0.07 – 1.68, $p = 0.17$). A Kaplan-Meier survival analysis graph comparing the two groups based on the primary outcome is shown in Figure 3.2. The nature of the surgical procedures undertaken for all forms of recurrent

POP are shown in Table 3 and the results from case notes review of the entire cohort are shown in Table 3.5 Reoperation rates from case note review for all women enrolled in study.

3.4.2 Subjective measures

There was a statistically significant difference in the postoperative composite ICIQ-VS scores when comparing those women who had VH and LSH, in favour of VH (6 and 9 respectively, $p = 0.04$). However, given the difference in preoperative ICIQ-VS scores between those that attended 7-year follow-up and those that did not, this should be interpreted with caution. Comparison of the mean change in ICIQ-VS scores between those undergoing VH versus those undergoing LSH were not statistically significant, illustrated in Table 3.6 . Data presented in this table also illustrate that there was no difference between the two groups with respect to the other PROM scores including the seven-year postoperative ICIQ-VS SM and QoL subscales, the composite ICIQ-FLUTS score as well as filling, voiding and incontinence subscales, and the PISQ-12. Likewise, when analysing the likelihood of 'awareness of a lump of bulge coming down in the vagina' (Q5 ICIQ-VS), a symptom determined by consensus to be an accepted marker of symptomatic prolapse, there was no difference between the two groups (31% following VH and 45.5% following LSH; RR 0.68, 95% CI 0.35 to 1.32, $p = 0.24$) [2]. The likelihood of patients reporting their prolapse symptoms as 'very much better' or 'much better' was 86% after VH and 76% after LSH ($p = 0.29$).

3.4.3 Objective measures

There were no reported cases of mesh removal surgery, mesh erosion or chronic pain attributed to the mesh in the LSH group. With respect to POP-Q parameters as shown in Table 3.6 , data would appear to support LSH with statistically significant higher apical suspension (POP-Q point C -5 vs -4.25, $p = 0.02$) and longer TVL (9cm vs 6cm, $p = <0.001$). If POP-Q point C ≤ -2 is used as an anatomical discriminator of surgical success, there is no difference between the two groups (84.6% after VH, 81.2% after LSH, $p = 0.73$), likewise if a more generous cut-off C ≤ 0 is used as a discriminator (92.3% after VH,

90.1% after LS, $p=0.82$). As reported in the one-year follow-up study there were no major intraoperative complications in either group. It appeared that total operating time was shorted in those having VH by a mean difference of 11.4 minutes ($p < 0.001$). However estimated blood loss (EBL), length of hospital stay, pain scores and time returning to normal activity all favoured LSH.

Table 3.2 Baseline demographic data at initial recruitment and for those with 7-year follow-up.

Baseline characteristics	LSH	VH	p value
	n = 51	n = 50	
Mean age, years (range)	63.9 (44–83)	65.5 (36–80)	0.136
Mean BMI, kg/m ² (range)	25.9 (20–36)	27.5 (19–37)	0.068
Median parity (range)	2 (1–5)	2 (1–6)	0.165
Stages of prolapse before surgery			
Uterine descent stage 2–4,	51(100)	50 (100)	1
Anterior prolapse (Ba)			
Stage 0–1	3 (6)	14 (7)	0.185
Stage 2–4	47 (94)	43 (86)	0.185
Posterior prolapse (Bp)			
Stage 0–1	13 (26)	6 (12)	0.076
Stage 2–4	37 (74)	44 (88)	0.076
Concomitant urogynaecology procedures			
Posterior colpoperineorrhaphy,	33 (66)	45 (90)	0.004
Anterior colporrhaphy	18 (36)	38 (76)	<0.001
Any pelvic floor repair	41 (82)	49 (98)	0.008
Tension-free vaginal tape	2 (4)	4 (8)	0.402
Sacrospinous fixation	0	3 (6)	0.08
For those with 7-year follow up			
	n = 33	n = 29	
Mean age, years (range)	64.1 (51-83)	66.2 (49-81)	0.20
Mean BMI, kg/m ² (range)	25.9 (20-36)	26.9 (19-35)	0.24
Median parity (range)	2 (1-5)	2 (1-4)	0.42
Preoperative ICIQ VS	31.58 +/- 12.61	32 +/- 12.15	0.92
Preoperative ICIQ VS SM	28.63 +/- 15.16	25.27 +/- 20.52	0.49
Preoperative ICIQ VS QOL	6.58 +/- 2.54	7.74 +/- 2.30	0.08
Length follow-up, months (range)	99 (84-119)	95 (86-114)	0.39*
POP-Q parameters			
Ba	1 +/- 2.20	1 +/- 2.51	0.61
C	1 +/- 2.65	1 +/- 3.45	0.21
Bp	0 +/- 2.60	0 +/- 2.45	0.51
GH	5 +/- 0.72	5 +/- 0.86	0.002
TVL	8 +/- 0.80	8 +/- 1.24	0.95

Continuous data are listed as mean +/- SD (Mann Whitney U test), except parity which is median and interquartile range or n (percentage). Mann-Whitney use for test of significance with the exception of *, which was calculated with student t-test.

Table 3.3 Comparison demographics between those who attended 7-year follow-up and those who did not

	No 7-year follow-up n = 39	7-year follow-up n = 62	p value
Age, years	63.95 +/- 9.81	65.11 +/- 6.69	0.88
BMI, kg/m ²	27.24 +/- 4.21	26.39 +/- 19.4	0.29
Parity	2 (1)	2 (1)	0.95
Preoperative ICIQ VS	37.11 +/- 10.12	31.77 +/- 12.31	0.04
Preoperative ICIQ VS SM	29.42 +/- 17.02	27.52 +/- 16.89	0.67
Preoperative ICIQ VS QoL	7.81 +/- 1.51	7.05 +/- 2.49	0.19
POP-Q parameters			
Ba	1 +/- 2.42	1 +/- 2.32	0.62
C	2 +/- 2.55	2 +/- 3.02	0.79
Bp	0 +/- 2.36	0 +/- 2.53	0.36
GH	5 +/- 0.75	5 +/- 0.84	0.85
TVL	8 +/- 0.65	8 +/- 1.01	0.80

Continuous data are listed as mean +/- SD (Mann Whitney U test), except parity which is median and interquartile range.

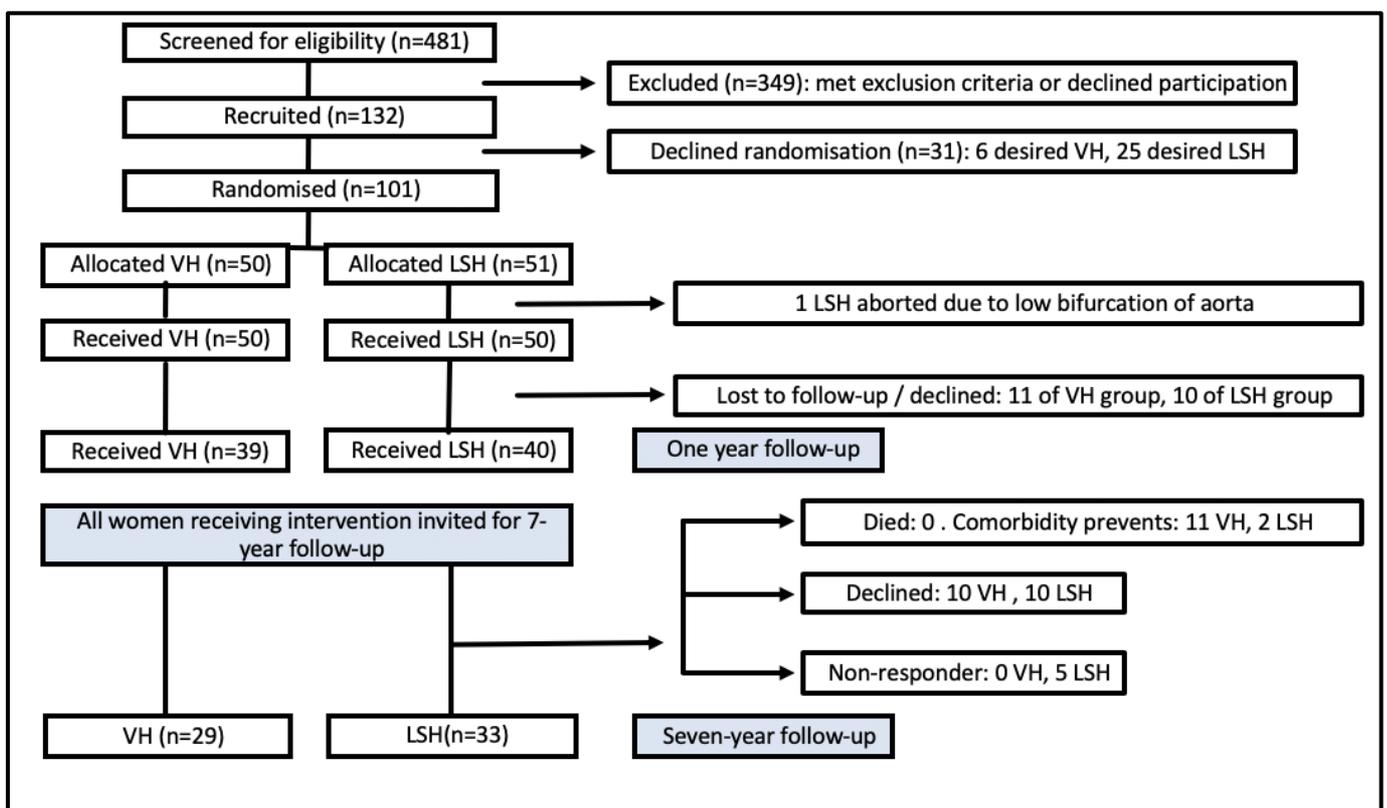


Figure 3.1 CONSORT diagram

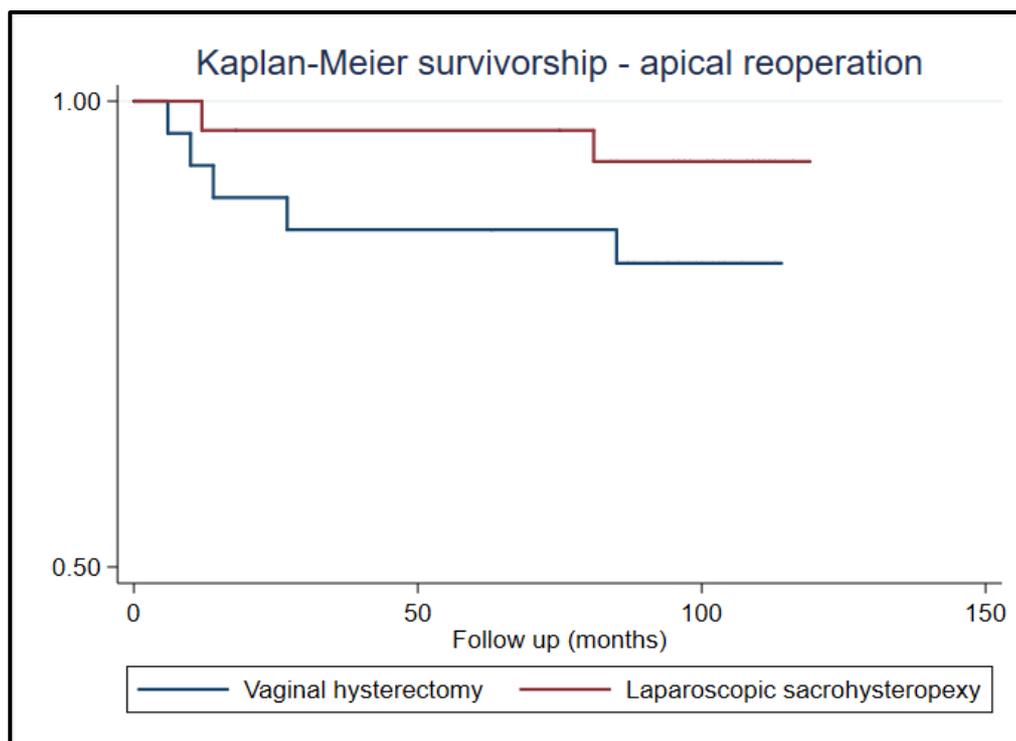


Figure 3.2 Kaplan-Meier survivorship using primary outcome as failure variable

Table 3.4 Re-treatment for POP at seven years

Follow-up data	LSH (n=33)	VH (n=29)	p value
Subsequent treatment for POP, %	9 (27.3)	7 (24.1)	0.78
Recurrent apical POP (reoperated apex or C>/-1), %	2 (6.1)	5 (17.2)	0.17
Subsequent surgery for POP, %	6 (18.2)	6 (20.7)	0.80
Apical			
LSH, %	2 (6.1)	-	0.17
SCP, %	-	5 (17.2)	
Colporrhaphy			
Anterior colporrhaphy, %	2 (6.1)	-	-
Anterior and posterior colporrhaphy, %	2 (6.1)	-	-
Posterior colporrhaphy, %	-	1 (3.4)	-
PFMT, %	2 (6.1)	1 (3.4)	0.63
Pessary, %	1 (3)	-	0.34

Categorical data are listed as n (percentage) with chi-square testing.

Table 3.5 Reoperation rates from case note review for all women enrolled in study.

Follow-up data	LSH (n=51)	VH (n=50)	p value
Subsequent treatment for POP, %	14 (27.5)	11 (22)	0.53
Subsequent surgery for POP, %	9 (17.6)	10 (20)	0.76
Apical			
LSH, %	3 (5.8)	9 (1.8)	0.13
SCP, %			
VH, %	1 (2)		
Colporrhaphy, %	5 (9.8)	1 (2)	
PFMT, %	3 (0.6)	1 (2)	0.31
Pessary, %	2 (3.9)	-	0.15

Categorical data are listed as n (percentage) with chi-square testing.

Table 3.6 Outcome data

	LSH (n=33)	VH (n=29)	p value
Change in ICIQ VS, mean	-22.39 +/- 13.06	-24.91 +/- 14.05	0.59
Postoperative ICIQ VS SM, mean	7.42 +/- 13.15	1.28 +/- 3.40	0.42
Postoperative ICIQ VS QOL, mean	1.42 +/- 1.98	1.03 +/- 1.72	0.43
Positive response to ICIQ VS Q5, %	15 (45.5)	9 (31)	0.24*
POP-Q			
Ba (cm)	-1 +/- 1.69	-0.5 +/- 1.70	0.99
C (cm)	-5 +/- 2.58	-4.25 +/- 2.92	0.02
Bp (cm)	-2 +/- 1.68	-2 +/- 0.54	-
GH (cm)	3 +/- 0.88	3 +/- 0.88	0.97
TVL (cm)	9 +/- 3.0	6 +/- 1.20	<0.01
PGI-I (1-2), %	25 (75.8)	25 (86.2)	0.30*
ICIQ FLUTS , mean	9.42 +/- 5.95	9.53 +/- 5.97	0.97
ICIQ FLUTS_F , mean	3.39 +/- 1.97	3.86 +/- 2.08	0.46
ICIQ FLUTS_V , mean	1.70 +/- 1.94	1.76 +/- 1.57	0.53
ICIQ FLUTS_I , mean	4.33 +/- 4.26	3.89 +/- 3.42	0.88
PISQ-IR, mean	16.67 +/- 3.67	13.75 +/- 5.72	0.28
Change in ICIQ VS, mean	-22.39 +/- 13.06	-24.91 +/- 14.05	0.59

All values are mean +/- standard deviation with Mann-Whitney use for test of significance with the exception of POPQ with median values. * = dichotomous outcome of either positive or negative response to ICIQ VS Question 5 and yes or no to PGI-I 1 and 2, where chi-square test was used.

3.5 Discussion

Principle findings

Our data show that for the primary outcome, there appears to be a trend towards a lower rate of apical reoperation following LSH as compared to VH, although this was not statistically significant. This may represent the fact that this study is underpowered as discussed in Chapter 3.3.5. This outcome is important as apical reoperation in the form of LSC and SSF are relatively higher morbidity interventions than simple colporrhaphy [86]. The data suggest that at over 7 years, the objective success rate based on apical reoperation would be 83% after VH and 94% after LSH. It is also noteworthy that the POP-Q parameters of TVL and point C also significantly favour LSH, as increased vaginal length and apical support are both features of normal vaginal anatomy and therefore markers of optimal surgical correction. The perioperative data would also seem to favour LSH. However, prolapse is widely considered to be a QoL condition patient reported outcomes may be considered the gold standard marker of surgical efficacy [296]. There was no difference between the intervention arms in any of the validated PROM outcomes with the exception of composite ICIQ-VS scores, which is confounded by significant differences in preoperative ICIQ-VS scores between those lost to follow-up and those attending.

Research in context

These data must be considered within the context of previously reported randomised and observational cohort studies, although this is difficult due to the heterogeneity of reported outcome measures and current lack of consensus for core outcome measures when studying pelvic floor disorders [285]. The most recent meta-analysis to compare the same two interventions investigated within this chapter is that by Meriwether et al. [195]. It must be noted only two studies contributed to this part of the review and one of these was the data from the 12-month pilot study by Rahmanou et al, with the same participants presented within this thesis [197]. Additionally, the two studies were not subject to a meta-analysis. Roovers et al. reported that QoL questionnaires, LUTS, mobility and postoperative pain favoured VH, with no

significant advantages to sacrohysteropexy, although this was done with an open approach [156, 277]. The findings by Rahmanou et al. unsurprisingly largely mirror our own, with no difference in the apical reoperation rate principally; elevation of POP-Q point C, TVL, EBL, and hospital length of stay favouring LSH, while theatre time and rate of concurrent colporrhaphy favoured VH.

More recently the results of a long anticipated high-level multicentre RCT trial, the VUE study have been reported, with 12 month follow-up for women randomised to either VH or hysteropexy in the uterine prolapse arm [152]. In total 563 women were randomised to either uterine sparing surgery or VH, with 238 women undergoing VH with an apical suspension procedure providing data at 12 months, and 230 women undergoing uterine preservation. It must be noted that most of the uterine preservation procedures were undertaken with a vaginal approach, and only 69 women (24.7%) underwent an abdominal approach, of which 66 (23.6%) were LSH; data for the individual procedures was not provided and therefore direct comparison with our own study is difficult. There was no significant difference in the primary outcome, prolapse symptoms based on POP-SS at twelve months between the two groups (POP-SS scores 4.2 following VH, versus 4.2 following uterine preservation mean difference (MD) 0.05, CI 0.91 to 0.81, $p=0.91$); nor in prolapse associated QoL. Many patients in both groups had an ongoing feeling of something coming down (30.7% and 28.9% respectively), comparing favourably to our own longer-term symptom status results. Significantly more women would recommend VH to a friend as compared to uterine preservation (95% vs 88.3%, odds ratio (OR) 0.39, CI 0.18 – 0.83, $p 0.01$). Finally, there was no significant difference between reoperation rates for prolapse (3.3% following VH, 6.1% following uterine preservation, OR 2.01 CI 0.81 to 4.95, $p = 0.120$), and while lower than our own rates, these are twelve-month data so comparison is not possible. There was no difference in rates of SAEs; with one mesh exposure in the uterine preservation group, no details are provided as the nature of this and it may be related to vaginally placed mesh or a synthetic MUS which were both undertaken as concurrent procedures within

the study. There are some significant shortcomings to the VUE study; the group failed to reach their recruitment target to meet their power calculation, there were a large number of recruitment centres and many of these would not be high volume centres for LSH procedures, and 50% of their hysteropexy procedures were undertaken with a vaginal approach which fails to make use of a principle advantage of abdominal hysteropexy, which is access to the upper pelvis to allow for higher uterine suspension.

The non-randomised prospective comparative study comparing LSH and VH by Lone et al. found no difference in reoperation rates between the two groups, POP-Q point C, or in subjective outcomes [199]. There were differences in POP-Q parameters Ba, Bp and GH favouring LSH, however small numbers at follow-up and significant differences between the baseline characteristics of the two cohorts make meaningful comparison difficult.

It would appear that our findings at 7 years mirror the short term RCT and observational study findings previously reported by our group [197, 207]. If the primary outcome is used as the definition of objective failure, our long-term cure rate of 94% is similar to the findings from the largest, medium-term cohort studies by Pandeva et al. and Kupelian et al., who reported rates of 95% at 48 months and 98% at 3 months respectively [186, 201]. Pandeva et al used POP-Q point C of $= / < 0$ as a cut off for objective success and Kupelian et al. used POP-Q point C of $= / < -2$, an evidence-based discriminator for symptomatic prolapse based on work by Dietz et al. [88]. As outlined in our results, sub-analyses of our data show comparable success rates using these same outcome measures, with no significant difference between the two intervention arms. Daniels et al. reported an 80% cure rate based on POP-Q point C of $= / < 0$ in 138 women at 12 months, against which our 93% cure rate using this outcome measure for the LSH cohort compares favourably [198].

A recent RCT reported an apical reoperation rate of 3.9% following VH and <1% following sacrospinous hysteropexy at five years, although there was no difference between these two groups with reference to anatomical outcomes

[297]. Although the reoperation rates in this RCT are lower than those within our own study, the risk of recurrent apical prolapse appears to be similar. The RCT by Roovers et al. found a 22% reoperation rate at 12 months following LSH, to which the findings in this thesis compare favourably [156]. The latest Cochrane review reported a reoperation rate for POP following vaginal surgery for apical prolapse of 9.3%, albeit with a heterogeneous group of procedure within the meta-analysis [183]. A recent large population study of 7,247 patients at a median of five years reported reoperation rates of 30%, 7% and 11% after sacrospinous hysteropexy, Manchester repair and VH respectively [158]. The largest series reporting on PHPV would suggest a reoperation rate of between 6% and 11.6%, again suggesting the interventions in both treatment arms are at least comparable [280, 290].

Assessing the rate of symptomatic cure in our study with that reported in the literature is also confounded by the heterogeneity of outcome measures, failure to report subjective data or the use of unvalidated measures. Subjective cure rates after LSH in large cohort studies with mid-term follow-up are reportedly between 80% and 84% [186, 198, 201]. Some of these studies have also used PGI-I and therefore report a more favourable subjective cure rate than that we have presented, however our data are longer term which may lead to increasing rates of prolapse and therefore lower reported subjective cure and it is noteworthy that there was no difference between the groups. The only other RCT comparing the same two interventions, by Roovers et al. did not report subjective cure rates. They reported no difference in the validated symptom measures, however those undergoing hysteropexy were more likely to consult a doctor with prolapse symptoms, a finding mirrored in the same group's five-year data that was presented as an abstract only and therefore not subject full peer-review [156, 277]. The Cochrane meta-analysis reported 'awareness of prolapse' based on validated questionnaires and provided a risk of 13.7% at two years following vaginal surgery, however as stated this group included a number of procedures some of which utilising mesh, making it difficult to compare to our figure of 45.5%

and 31% (after LSH and VH respectively) based on a positive response to ICIQ-VS Question 5 [183].

Strengths and limitations

The principal strengths of our study include the use of randomisation with comparable baseline demographics in both intervention arms, adherence to a pre-stated primary outcome, and long-term follow-up. Additionally, much of the data is patient reported and gathered through the use of validated measures. This will allow for future inclusion in meta-analyses. This is important as this study was not adequately powered for the primary outcome measure. Additional shortcomings include the large loss to follow-up, common in long-term randomised studies of surgical interventions. The choice of a dichotomous outcome also poses a challenge. Emergent data has shown prolapse to be a dynamic state, both pre and post operatively, and therefore the use of such discrete outcomes may challenge the clinical utility of the findings of this study[298]. Finally, follow-up observations were undertaken by the thesis student and were not blinded to patient's primary intervention, potentially introducing bias with respect to outcomes such as POP-Q.

Clinical implications

The implications of the findings within this chapter on clinical practice should not be overstated. The lack of power and resulting inability to detect a statistically significant difference in the primary outcome may lead one to conclude that the findings should not alter future clinical practice. However, they do have utility in framing the discussions around surgical decision making for patients considering options for surgery for uterine prolapse. That is, in keeping with earlier studies and observational data that there may be some advantages to LSH as outlined. Women worried about the risk of needing another significant operation or wanting to maintain vaginal parameters as close to anatomically normal as possible may opt for LSH. However, they can be reassured as the presented data suggest it unlikely there is any large difference between the two options and their functional outcomes are likely to be good regardless of choice of intervention.

Research implications

There are two predominant issues that need addressing within the academic literature with respect to the choice of surgical intervention for uterine prolapse. Firstly, is a consensus on core outcomes for pelvic floor disorders, this is currently being addressed via the CROWN initiative [285]. The other is the need for further randomised studies to allow for meaningful comparison of surgical interventions for this form of POP. With changes in the landscape with respect to mesh use, many of the procedures that were investigated by the studies included in the Maher 2016 meta-analysis are not fit for contemporary pelvic floor surgery due to risk of mesh associated complications. With the current options on the table for patients in UK practice, this need for quality prospective data is pressing. Data from the VUE study presents its own issues as discussed [297]. Our data as well as the VUE studies and future prospective work are likely to form part of further meta-analysis.

4. Prognostic role of urodynamic studies in patients undergoing laparoscopic sacrohysteropexy.

4.1 Introduction

As outlined within Chapter 1.3.5 there is a significant correlation between the presence of POP and concurrent LUTS, and in the case of SUI the conditions may even share aetiology [299]. However, the relationship is complex and poorly understood. Surgical correction of POP is not necessarily associated with resolution of LUTS; indeed up to 20% of women who are continent preoperatively go on to develop SUI and 30% develop postoperative overactive bladder (OAB) [93, 95]. Conversely, a large study by Lensen et al. showed that 39% of women with preoperative SUI reported cure by POP surgery alone, without the use of a concurrent incontinence procedure, and 42% of those pre-existing urinary urge incontinence (UUI) reported cure [300].

There are therefore three questions that deserve consideration. Firstly, what is the likelihood that new onset LUTS develop following surgery for POP? Secondly, what is the likelihood that a patient can expect concurrent LUTS to resolve following surgery for POP? And finally, would preoperative diagnostics such as UDS facilitate the prediction of postoperative bladder function, and therefore might they have a role in counselling patients and allowing for consideration to undertaking concurrent incontinence procedures? Specifically, as part of this thesis the need to be considered within the context of the use of LSH.

The most well studied relationship between surgery for POP and LUTS has been the role of continence procedures for SUI in women undergoing surgery for prolapse. A number of studies have compared isolated POP surgery versus that with concurrent incontinence surgery in cohorts both with and without preoperative incontinence [98, 301-306]. A meta-analysis in 2014 by Van der Ploeg et al. considered outcomes for preoperatively asymptomatic women and the pooled data suggested there was an advantage to concurrent incontinence

procedures, with significantly lower rates of patient reported postoperative SUI (9% [32/373] versus 20% [81/399] in five studies, RR 0.5, 95% CI 0.2–1.4) [97]. In those with pre-existing stress incontinence, the results were conflicting; one study by Borstad et al. that found lower rates of incontinence in those who had a concurrent MUS, whereas Constantini et al. found no such difference [98, 301]. These studies were part of a pooled analysis that suggest there was no significant difference in rates of objective SUI postoperatively between those that did and did not have concurrent incontinence procedures [97]. One of the largest included studies, the CARE trial, found that while there was no significant difference in objective SUI rates between the two groups based on a positive cough stress test, all other measures of SUI were lower at two years in the group that received a concurrent Burch colposuspension [302]. Such variations highlight study heterogeneity with respect to using subjective measures such as PROMs, versus objective testing in the form of standardised office stress test or UDS, as well as a lack of consensus on the role of concurrent incontinence procedures. While the literature has utilised a range of prolapse procedures including colporrhaphy, VH, and vault suspension procedures, to date none have considered sacrohysteropexy.

For those with preoperative OAB symptoms, another LUTS complex, surgical correction of prolapse has been shown to be associated with an improvement of symptoms [129, 130]. Digesu et al. reported that 70% of patients with OAB reported resolution of urgency after anterior colporrhaphy and 60% of those with frequency had an objective reduction of daytime urinary frequency episodes to normal (≤ 8 times per day) [130]. The authors also reported that following surgery for prolapse, 50% of those with preoperative detrusor overactivity (DO), a common cause of OAB, had no such findings on repeat postoperative studies. While prolapse surgery alone may resolve such symptoms, undertaking incontinence procedures may cause or exacerbate OAB with no good evidence to support a method of predicting which patients are likely to develop such symptoms [307, 308].

Objective assessment of LUTS can be undertaken utilising UDS, a general term defined by the ICS as ‘measurements that assess the function and dysfunction of the lower urinary tract by any appropriate measure’ [131]. Within UK clinical practice the term UDS commonly refers to a combination of ICS defined cystometry ‘continuous fluid filling of the bladder via a transurethral catheter, at least with intravesical and abdominal pressure measurement and display of detrusor pressure, including cough (stress) testing’, in combination with uroflowmetry ‘a test producing .. the flow rate of the external urinary stream as .. millilitres per second’. Therefore, UDS within this thesis and as undertaken within the present study was the combination of these two investigations correlated with patient symptoms during the filling, storage and emptying phases as part of routine clinical practice. While much debate exists with respect to their clinical utility across a myriad of clinical situations, their use is recommended by NICE for those with urinary urge incontinence, voiding dysfunction, apical and anterior prolapse and following previous incontinence surgery [133].

According to the latest international consensus documents, the utility of UDS prior to prolapse surgery has not been determined [86]. A retrospective study by Jha et al. has examined the utility of UDS for women undergoing colporrhaphy with or without VH, and found that it altered surgical management in 7% of cases and overall management for 33% of patients [128]. Another small study (n=77) found that UDS offered no value over basic office evaluation for SUI in patients undergoing a vaginal repair[309]. More recently, a literature review and consensus document from the International Consultation on Incontinence Research Society (ICI-RS) with respect to SUI, did not advocate routine use of urodynamics [310]. The most recent NICE guidance in the UK, advocates ‘consideration of investigating urinary symptoms that are bothersome and for which surgical intervention is an option’ in women with prolapse, suggesting it may have a role within the context of concurrent incontinence surgery, and even potentially for those who may be candidates for intravesical botulinum [133]. It would therefore follow that the

role of UDS as a routine diagnostic test for those women considering uterine sparing surgery deserves further examination.

The aim of this study was to explore postoperative LUTS following LSH and determine whether preoperative UDS can predict postoperative bladder symptoms.

4.2 Objectives

The primary objective of this study was to determine the likelihood of resolution of LUTS symptoms associated with preoperative UDS findings, as well as the risk of de novo postoperative LUTS.

4.3 Methodology

4.3.1 Study design

This was a single-centre, retrospective cohort study of women who underwent invasive UDS prior to LSH between May 2010 at October 2018 at University College London Hospital (UCLH). Cases were identified from a search of the hospital surgical database according to the following inclusion and exclusion criteria:

Inclusion criteria:

Women who underwent LSH for the treatment of uterine prolapse, who had undergone invasive UDS prior to their operation.

Exclusion criteria:

Any patients for whom care records did not include a documented preoperative symptom status and those who did not complete at least one follow-up visit.

The electronic patient records of each case of hysteropexy identified from the surgical databases were screened against the inclusion and exclusion criteria

listed above. Those that fulfilled these criteria were then subject to a detailed electronic patient record review to collect demographic and outcome data as listed in Section 4.3.2.

Following decision to undergo surgery for prolapse, patients were referred for UDS. Urodynamics in the unit were performed by a certified professional who was either a trained urogynaecologist or urogynaecology nurse specialist, in accordance with ICS guidance [131]. Indications for preoperative urodynamics did not follow a standardised protocol and the decision to undertake the test was at the discretion of the clinician responsible for each patient, and the cohort therefore included patients asymptomatic of LUTS. For the testing of 'occult' SUI, prolapse reduction is generally undertaken with speculum upward displacement of the uterus while avoiding urethral compression. For the purpose of statistical analysis, the UDS diagnoses used were normal, DO, urodynamic stress incontinence (USI) and voiding dysfunction (VD). Where patients had more than one diagnosis, the first diagnosis listed by the clinician was used as their UDS diagnosis as this would generally correlate with their most bothersome symptom.

Laparoscopic sacrohysteropexy was undertaken in keeping with the technique described in Chapter 1.6.1. For those patients with bothersome SUI and USI on UDS a clinical discussion would have been undertaken regarding the possibility of undergoing a concurrent incontinence procedures. Choice of intervention was led by individualised counselling between patient and clinician, with patients offered a range of incontinence procedures. Historically, this would have involved stating the synthetic MUS sling as the lowest risk and most efficacious intervention, however over the study period there was a shift towards a less directed counselling in accordance with more recent national UK NICE guidance, and therefore options would more generally include a synthetic MUS, peri-urethral bulking or laparoscopic colposuspension, with patients desiring alternative procedures being referred onwards to urology colleagues [133]. Postoperative review was routinely undertaken via telephone at 6 weeks, followed by a face to face at 3 months

with the use of validated PROMs. Patient reported LUTS were determined by a positive patient reporting to routine screening questions at the time of consultation and not by any validated form of PROM.

4.3.2 Outcome measures

Primary Outcome

- Postoperative patient reported presence of normal bladder function, SUI, OAB, UUI or voiding dysfunction.

Secondary Outcomes

- Concurrent incontinence procedure at the time of prolapse operation.
- Composite postoperative ICIQ-UI scores.
- Requirement for subsequent continence procedure.
- PGI-I in bladder symptoms.
- Reported change in SUI and UUI.

4.3.3 Recruitment

As this was a retrospective cohort study, participants were not prospectively recruited.

4.3.4 Data collection

Data were collected from electronic patient records with the help of Anthony Kupelian (Consultant Urogynaecologist at UCLH) and Folakemi Oladinni (Medical Student). Urodynamic data were obtained from standardised urodynamic proformae completed by the clinician at the time of investigation. Data was stored on a secure database in accordance with NHS data protection regulations.

4.3.5 Power and statistical analysis

Available data were analysed using descriptive statistic with frequencies expressed as percentages. Wilcoxon signed-rank matched pairs test was used to compare pre and post-operative PROM scores. The Chi² test was used to compare all other dichotomous variables. Data were analysed using StataSE 15 (Stata Corp, TX, USA).

4.3.6 Ethical approval

Ethical approval was not required as determined through the use of the UK's Health Research Authority (HRA) decision tool. Local approval was obtained for this work as a service evaluation.

4.4 Results

Seventy women were identified as having undergone UDS prior to LSH from the database, with a median follow-up of nine months (range 2-79). Baseline demographic details and previous surgery are shown in Table 4.1. With respect to previous prolapse surgery, two had undergone a previous LSH with or without colporrhaphy, one a sacrospinous fixation with posterior colporrhaphy, one a posterior colporrhaphy, one an anterior and posterior colporrhaphy, and one had an unspecified history of prolapse surgery. All three of the women who reported previous continence procedures had undergone colposuspension.

The correlation between preoperative symptom status and urodynamic diagnosis is shown in Table 4.2, illustrating that OAB was the most common preoperatively reported LUTS (74.3%, n=52). However, most women with OAB had a UDS diagnosis of USI (69.2%, n=36), which was also the most common UDS diagnosis for women with preoperative symptoms of SUI and VD. Most asymptomatic women had normal UDS (75%, n=6). The table also illustrates the frequency of the various UDS diagnoses in the cohort. The most

common of these was USI found in 61% of women (n=43) of which 39% underwent a concurrent incontinence procedure.

The absolute risk of the various LUTS postoperatively are illustrated in Table 4.4, with the majority of women being asymptomatic (52.9%). The likelihood of developing specific LUTS as compared to the whole cohort for each of the individual UDS diagnoses is shown in Table 4.5. Only a diagnosis of VD on UDS was predictive of specific postoperative LUTS, with these patients having a statistically significant higher likelihood of postoperative VD compared to the group as a whole (25% versus 1%, $p = 0.01$). When compared to the entire cohort, a preoperative UDS diagnoses of normal did not predict an asymptomatic postoperative status, USI did not predict postoperative SUI, nor was DO more likely to result in women having postoperative OAB, illustrated in Table 4.5. Similarly, when compared to those with normal UDS preoperatively, USI on UDS did not result in a significantly higher likelihood of SUI (31.8% vs. 38.5%, $p = 0.65$), nor did those with DO report higher rates of postoperative OAB (22.2% vs 15.4% $p = 0.68$).

The majority of women with normal, DO or VD diagnoses on UDS reported being asymptomatic postoperatively (Table 4.4). Likewise, the majority of patients with preoperative USI (64.7%) who underwent a concurrent incontinence procedure also reported being asymptomatic. However, amongst those with USI who did not undergo a concurrent incontinence procedure, only 33.3% reported being free from LUTS postoperatively and therefore only 43.1% of the USI cohort as a whole were asymptomatic postoperatively. Undergoing a concurrent incontinence procedure with preoperative USI, was associated with a significantly lower risk of postoperative SUI compared to those who did not undergo such a procedure (11.8% vs 44.4%, $p=0.02$). Interestingly, there was also a trend towards a lower rate of OAB symptoms in the concurrent incontinence procedure group, however this was not statistically significant (23.5% vs 44.5%, $p = 0.16$).

There was a statistically significant improvement in median ICIQ-UI scores for the whole cohort (preoperative 8 vs. postoperative 4, $p = 0.006$). However, when comparison was made with pre- and postoperative scores for each of the individual UDS diagnosis (normal, USI, DO or VD) there was no statistically significant difference in average scores, although there was a clear trend towards lower postoperative scores, as shown in Table 4.3. With respect to PGI-I in incontinence symptoms, as shown in Table 4.6, only those with a preoperative diagnosis of USI who underwent concurrent incontinence procedures were more likely to report being 'very much better' or 'much better' as compared to the cohort as a whole. No other preoperative UDS diagnosis was associated with a higher likelihood of reporting such an improvement of symptoms as compared to the cohort as a whole, or compared to those with normal urodynamic studies. Only one patient underwent an incontinence procedure subsequent to their LSH. They had preoperative USI and had not undergone a concurrent incontinence procedure. Due to the small numbers no statistical analysis was possible.

Table 4.1 Baseline demographics

Demographic data (n=70)	
Mean age, years (range)	58 (20 – 75)
Mean BMI, kg/m ² (range)	27 (20 – 42)
Median parity (range)	2 (0 – 6)
Mean follow-up, months (range)	9 (2 – 79)
Previous POP surgery, n (%)	6 (8.6)
Previous SUI surgery, n (%)	3 (4.3)

Table 4.2 Preoperative symptom status and urodynamic diagnoses

Preoperative symptoms		Preoperative urodynamic diagnosis			
		Normal	USI	DO	VD
Asymptomatic	8 (11.4)	6 (75)	1 (12.5)	0	1 (12.5)
Stress urinary incontinence	44 (62.9)	4 (9.1)	33 (75)	9 (20.5)	5 (11.4)
Overactive bladder (urgency or urge incontinence)	52 (74.3)	6 (11.5)	36 (69.2)	11 (21.2)	10 (19.2)
Voiding dysfunction	24 (34.3)	4 (16.7)	15 (62.5)	6 (25)	6 (25)
Primary preoperative urodynamic diagnosis					
Normal		13 (19)			
Urodynamic stress incontinence		43 (61)			
Detrusor overactivity		9 (13)			
Voiding dysfunction		4 (7)			

All data are presented as number (percentage)

Table 4.3 ICIQ-UI scores pre and postoperatively

	Average preoperative ICIQ UI score	Average postoperative ICIQ UI score	Significance test (p)
Entire cohort	8	4	0.006
UDS diagnosis			
Normal	2	0	0.425
DO	5	3	0.109
VD	11	0	0.317
USI	11	4	0.061
USI without concomitant procedure	10	4	0.115
USI + concomitant procedure	16	5	0.317

Continuous data are listed as mean, Mann Whitney U test for significance

Table 4.4 Urodynamic diagnosis and short-term postoperative LUTS status

		Short-term postoperative LUTS status			
		<i>Asymptomatic</i>	<i>SUI</i>	<i>OAB</i>	<i>VD</i>
Entire cohort		37 (52.9)	19 (27.1)	21 (30)	1 (1.4)
Primary UDS diagnosis					
Normal (n=13)		7 (53.8)	5 (38.5)	2 (15.4)	0
Urodynamic stress incontinence (n=44)					
	All USI	19 (43.1)	14 (31.8)	16 (36.4)	1 (2.3)
	USI + concurrent incontinence procedure	11 (64.7)	2 (11.8)	4 (23.5)	0
	USI without concurrent incontinence procedure	9 (33.3)	12 (44.4)	12 (44.4)	1 (4.3)
Detrusor overactivity (n=9)		7 (77.8)	0	2 (22.2)	0
Voiding dysfunction (n=4)		75 (3 (75)	0	0	25 (1)

All data are presented as number (percentage)

Table 4.5 Comparison of UDS diagnosis versus whole cohort for short-term postoperative LUTS status

UDS diagnosis	Postoperative LUTS status				
	<i>Asymptomatic</i>	<i>SUI</i>	<i>OAB</i>	<i>VD</i>	<i>p-value</i>
Normal	7 (53.8)	-	-	-	0.95
USI	-	14 (31.8)	-	-	0.59
USI + concurrent	-	2 (11.8)	-	-	0.18
USI w/out concurrent	-	12 (44.4)	-	-	0.10
DO	-	-	2 (22.2)	-	0.62
VD	-	-	-	1 (25)	0.01

All data are presented as number (percentage), Chi² test of significance

Table 4.6 Comparison of UDS diagnosis versus whole cohort for PGI-I

	PGI-I incontinence	
	<i>PGI-I 1/2</i>	<i>p-value</i>
Entire cohort	67.4	-
UDS diagnosis		
Normal	66.1	0.65
USI	70.4	0.79
USI + concurrent	100	0.02
USI w/out concurrent	50	0.21
DO	100	0.12
VD	33.3	0.22

All data are presented as percentage, Chi² test of significance

4.5 Discussion

Principle findings

The principal finding from this study is that specific preoperative UDS diagnoses for women undergoing LSH correlate poorly with their postoperative LUTS status. Only a preoperative UDS diagnosis of VD was predictive of the

outcome, with 25% of this group reported postoperative VD. However, as only 4 women had this diagnosis, despite the statistical significance, this result should be interpreted with caution. No statistically significant association was found between any other UDS diagnosis and the associated postoperative LUTS complex.

There are however findings that provide information to support patient counselling. The majority of patients (52.9%, n=37) were asymptomatic of LUTS following LSH and the procedure significantly improves LUTS overall on the basis of the validated ICIQ UI scores. Such an improvement is particularly notable for those patients with preoperative DO and VD for whom 77% and 75% of patients respectively were asymptomatic postoperatively. For those with USI, there was a significantly lower rate of postoperative SUI in those who underwent a concurrent incontinence procedure versus those that did not (11.8% vs 44.4%). There were also superior PGI-I scores in the concurrent incontinence procedure group as compared to the cohort as a whole, a trend not seen with other groups, and this was statistically significant. These findings should be considered within the context of risks and controversies associated with such incontinence procedures, discussed below.

Research in context

The inability to find an association between preoperative urodynamic diagnosis and associated postoperative symptom status, with the exception of VD could be argued to corroborate the general findings in medical literature that have lead to recent NICE and ICIQ-RS recommendation against the routine use of UDS for women undergoing POP surgery [133, 310]. Indeed Jha et al. found that UDS altered surgical plans in less than 7% of patients undergoing surgery for POP, and altered management more generally for only a third [128].

There are two probable explanations for this poor correlation; firstly, would be that the majority of patients have resolution of their LUTS following surgery for POP. A study by Iliano et al. reported resolution of most UDS confirmed

bladder dysfunction following SCP [311]. Indeed, in our study there was a statistically significant improvement in ICIQ-UI scores for the entire cohort, mirroring the findings of other studies [300]. A small cohort study by Basu et al. investigating UDS, showed that prolapse surgery resolves OAB for the majority of patients, even if DO persists [312]. And for those with VD, symptoms are improved by the correction of urethral kinking associated with the surgical repair of POP, with Iliano et al. illustrating this with objective postoperative bladder studies following SCP [311, 313]. This same paper found that most patients with preoperative DO had resolution following apical correction. Such findings are mirrored in our own data with the majority of patients with DO and VD being asymptomatic postoperatively.

The second explanation for consideration is the onset of de-novo symptoms. At least one in ten women develop new OAB symptoms after surgery for POP according to the Cochrane review by Maher et al. [183]. A meta-analysis that included five studies of women having surgery for POP who were asymptomatic for SUI reported a 20% incidence of postoperative SUI [97]. This may explain the lack of predictive value of UDS for our USI subgroup as the entire cohort had high rates of postoperative SUI, in keeping with other observational studies [93, 314]. There is also the limitation of undertaking statistical analyses with such a small cohort.

For those with USI, one must not only consider this subgroup as a whole, but also the two distinct groups of those who did and did not undergo concurrent incontinence procedures. None of these three subgroups had significantly different rates of postoperative SUI as compared to the entire study cohort. Yes those who underwent a concurrent incontinence procedure had significantly better PGI-I scores, and when compared to directly to those who did not undergo concurrent procedures, significantly lower rates of postoperative patient reported SUI. The role of concurrent continence procedures to prevent incontinence after prolapse surgery has been studied [95-98]. The CARE trial which is the largest and longest study using a concomitant colposuspension at the time of treatment of vault prolapse

showed that continence is maintained in the long-term, with lower rates of subjective SUI at seven years as compared to those who undergo an isolated vault procedure, a finding mirrored by our own data [96]. A meta-analysis undertaken by Van der ploeg et al., also found lower rates of patient reported SUI following concurrent incontinence operations [97]. Interestingly, when looking at objective SUI testing postoperatively such a benefit was not so clear, with significant heterogeneity amongst study findings. Authors noted the counterintuitive findings in studies by Constantini et al. and Brubaker et al. which failed to find lower rates of objective SUI in those that underwent concurrent incontinence procedures as compared to those that did not [302, 303]. One must also consider the limitations of incontinence procedures. They can be associated with mesh associated complications sometimes requiring reoperation, exacerbation of OAB symptoms, voiding dysfunction and worsening of posterior wall POP [97, 255]. Our study does not account for any of these issues; although, no significant AEs were noted in the women that underwent concurrent procedures, and they were not subject to a higher risk of postoperative OAB.

Strengths and limitations

Strengths of our study include a novel study area, in which UDS were undertaken by experienced clinicians in a cohort of women with a range of preoperative LUTS and UDS diagnoses prior to LSH. This may provide helpful information, particularly with respect to counselling women specifically with regards to LSH and LUTS as this area has not been previously studied. Dichotomous UDS variables combined with validated symptom scores and routine clinical questioning lend weight to our findings. Specific limitations include our tertiary setting as well as our selected patient cohort. A well-designed study would either have integrated routine UDS for all patients undergoing surgery for POP, i.e. the study population; some in our cohort underwent UDS because of the significant LUTS from which they suffered, and it is likely that asymptomatic and less severe LUTS patients are underrepresented in our group. There was not a standardised clinical pathway on the role of UDS and therefore the study population is not reflective of the

population in which findings would be implemented. For our primary outcome, we did not use a validated questionnaire to determine symptom status which impacts the reliability of symptom reporting. Retrospective studies have inherent bias in terms of symptom reporting and most of our reported outcomes come from short-term follow-up. Our small numbers also make meaningful analysis difficult. A larger cohort would allow for comparison of the various subgroups to each other as opposed to just the entire cohort, or perhaps with an asymptomatic control cohort. A larger study population would also reduce the bias introduced by the possible over representation of SUI in our cohort.

Clinical implications

To answer the three questions raised in Chapter 4.1. Firstly, we have identified the absolute risk of postoperative LUTS following LSH as shown in Table 4.4, specifically noting that the majority of patients are asymptomatic (52.9%), while postoperative SUI and OAB remain common (27.1% and 30% respectively). This provides helpful information when counselling women who are undergoing LSH, although our cohort is unrepresentative given many had a clinical indication for UDS. Secondly, we can give further information about the likelihood of LUTS resolution following surgery for POP, more specifically that the majority of those with DO and VD are asymptomatic after LSH (77.8 and 75% respectively). However, with respect to our third and final aim to determine the predictive value of UDS for postoperative LUTS, our data have failed to show that any specific UDS diagnosis is more predictive of postoperative LUTS as compared to the cohort as a whole from a statistical perspective. While limitations are outlined above, one could not confidently estimate the likelihood of symptom resolution or de-novo symptoms from a UDS diagnosis on the basis of our study. That being said, for those with USI, our data present a strong argument for consideration of a concurrent incontinence procedure at the time of LSH and providing patients with the option to consider such an approach.

Research implications

As detailed, this study corroborates many findings within the literature. There remain two important research questions to be addressed. Most importantly is the role of concurrent incontinence procedures for women undergoing LSH, utilising such an approach appears to be supported by our study. Given the current climate with respect to the synthetic MUS, a prospective controlled study looking at both safety and efficacy of concurrent incontinence procedures such as colposuspension or periurethral bulking at the time of LSH, as well as other apical procedures, is warranted. Secondly, a prospective study utilising validated symptom PROMS in combination with routine UDS would likely provide a definitive answer to the clinical utility of UDS in predicting postoperative LUTS, this remains important for women considering surgery and our study has failed to reach a meaningful conclusion in this respect.

5. A thematic analysis of the comments of women following laparoscopic mesh sacrohysteropexy

5.1 Introduction

The significant scrutiny of mesh augmented pelvic floor surgery over the last decade has been clearly illustrated previously in this thesis, most notably within Chapter 1.7.3. There appeared to be a revolution in pelvic floor surgery following the introduction of the tension-free vaginal tape in 1996, which was succeeded by a proliferation of mesh augmented devices [182]. Subsequent to this it became apparent that some applications of synthetic mesh, principally the placement of vaginal mesh for POP, led to unacceptably high rates of adverse event associated with the implantation of the various products and devices [13]. In the UK, this has resulted in a temporary suspension of vaginal mesh for both POP as well as SUI and in some countries such as Australia, vaginal mesh for POP has been banned outright [17, 284]. This leaves women, specifically those with pelvic floor disorders, with an uncertain future with respect to the therapeutic options available to them and their role within the regulatory process moving forward.

Various factors lead to the development of mesh augmented pelvic floor procedures. The principle shortcomings of native tissue repair include high rates of recurrent prolapse after surgery for POP, and higher morbidity associated with colposuspension particularly when undertaken as an open operation compared to alternatives such as the TVT [10, 315]. Tied into discussions around surgical options for POP and SUI include the all-important patient choice. The majority of women would prefer a uterine sparing approach if given the option [6, 7]. Laparoscopic mesh sacrohysteropexy allows for uterine preservation and offers the potential for higher apical suspension, stronger fixation with promising short and mid-term data outlined within Chapter 1.6.2 [200, 201]. A recent meta-analysis has shown perioperative and anatomical advantages as compared to various vaginal approaches [12].

There were two particular issues identified in the various reports into gynaecological mesh pertaining to the development of this study [14-16, 254]. Many noted systemic delays in the recognition of mesh associated complications and there have been calls for a greater emphasis on the patient voice within healthcare systems. In the UK, Baroness Cumberledge's independent review commissioned in 2018 has made recommendations on improving UK healthcare systems' ability to respond to safety concerns about clinical interventions [236]. It aims to 'listen to those who have suffered harm', adding 'their voices, their experiences and views will be at the heart of our Review.' Yet within the academic literature, there is little research exploring the patient perspective following mesh augmented pelvic floor surgery.

Qualitative research methodologies such as thematic analysis have previously been used to study women's perspectives of other health issues subject to controversy, such as termination care, postpartum pelvic floor health, and decision making for pelvic floor disorders [316-318]. The technique allows for a rigorous and systematic exploration of narrative-type data, unrestrained by the pre-determined outcomes used in quantitative methodologies. Adopting what is known as an interpretivist approach can provide meaningful insights, rather than a focus on simply the frequent or common emerging themes [319].

Alternative forms of qualitative research methodology can also be considered when considering commentary of questionnaire free-space data. Interpretative phenomenological analysis is one such methodology, however, this tends to lend itself to interview style studies with small numbers of participants [320]. This allows for a more in-depth examination of those individuals with an idiographic focus, trying to understand how individuals process and frame their thoughts and experiences. Given the number of participants and relative superficial nature of much of the data, it was felt to be inappropriate. Grounded theory is very similar to thematic analysis and was considered as an appropriate framework to use to allow for construction of hypotheses through inductive reasoning[321]. Liaising with a qualitative researcher (Dr Belinda

Rahman, see acknowledgements) led to the consensus that given the relative inexperience of the key researchers, that thematic analysis allowed for more flexibility and a less prescriptive approach to analysis.

The aim of the present study is to understand health related issues in women who have had mesh augmented prolapse surgery, in light of the current controversies around mesh use.

5.2 Objectives

Our primary objective was to analyse the comments of women mesh augmented prolapse surgery for the treatment of uterine prolapse.

Secondary objectives included:

Establish themes describing the data.

Explore health concerns within the data provided.

5.3 Methodology

5.3.1 Study design

Data analysed within this chapter were obtained as part of the same study protocol described within Chapter 2. We undertook a multicentre cohort study of women who had previously undergone laparoscopic mesh sacrohysteropexy. In addition to the quantitative data related to mesh associated complications, the questionnaire provided an opportunity for respondents to fill in a free-text response to the following question:

“Are there any comments or further information you would like to provide to the research team about the operation, your recovery and/or current symptoms with regards to general health and prolapse?”

This provided data for qualitative study using an inductive approach to thematic analysis, described in further detail in Chapter 5.3.5. Questionnaire items were assessed for face validity among the study team and piloted at one

site prior to commencing the study. The potential participants were identified from the surgical databases of five consultant surgeons who were based at two tertiary urogynaecology centres with an expertise in laparoscopic urogynaecology. The specific recruitment details outlined in Chapter 5.3.3. The two centres were University College London Hospitals in London, UK and The John Radcliffe Hospital, Oxford University Hospitals, Oxford UK. The study adhered to the following inclusion and exclusion criteria, the rationale for which was determined by the quantitative component of the protocol as discussed in Chapter 2.

Inclusion criteria:

We included all women with adequate spoken English over the age of 18, who underwent laparoscopic mesh sacrohysteropexy at one of our participating centres.

Exclusion criteria:

We did not contact or include any patients who were identified as deceased on our hospital databases and also excluded any patient who was identified as ever having undergone a trans-vaginal mesh augmented prolapse operation, or concurrent mesh rectopexy. All potential participants were sent the questionnaire that is contained within Appendix 1. Patient Questionnaire for study in Chapter 2. Response options for participants included postal response with a prepaid envelope, online via a secure database (REDCap®) or to request a telephone questionnaire. Telephone interviews for the questionnaire were carried out according to a telephone script following verbal consent. Potential participants who had not responded to the first postal contact within eight weeks were sent a second questionnaire in order to increase our response rate.

5.3.2 Outcome measures

The principle outcome measures were the themes developed following thematic analysis.

5.3.3 Recruitment

Potential participants were identified from the surgical databases of five consultant urogynaecologists. Database searches utilised operating procedure codes (OPCS) Y75.2 (laparoscopic approach to abdominal cavity) or T43.9 (unspecified diagnostic endoscopic examination of peritoneum) in combination with Q54.1 (suspension of uterus NEC), Q54.4 (suspension of uterus using mesh) or Q54.5 (sacrohysteropexy). Following implementation of the inclusion and exclusion criteria, all potential participants were then allocated a unique research identification number (research ID). They were contacted via post and provided with an invitation letter (Appendix 4. PIS for study in Chapter 2) with a link to the secure online questionnaire platform, as well as email, telephone and postal contact details should they prefer a telephone consultation. Additionally, they were sent a PIS (Appendix 5. Patient information sheet for study in Chapter 2), a paper questionnaire (Appendix 1. Patient Questionnaire for study in Chapter 2), and a pre-paid return envelope. With respect to consent, all participants responding by post were assumed to have given implied consent. Those responding online or via a telephone questionnaire underwent completion of a formal consent form prior to completing the study questionnaire.

Potential participants who did not respond within 8 weeks of the first postal questionnaire received one further postal contact with all of the documents outlined previously. Those who had not responded after 8 weeks following the second postal contact were not contacted again.

5.3.4 Data collection

All postal responses were returned to the thesis author MI, and with the help of an BSc student, Catharine Lumb (CL) these were transcribed to a data processing software (Word Excel®). Data were entered using only the allocated research ID, therefore allowing for the handling and analysis of anonymised data. The paper copies were kept in accordance with the

research protocol and ethical approval requirements for this study. Online responses were generated automatically and those requesting telephone questionnaires were called and underwent the scripted telephone questionnaires with responses entered into a secure REDcap® directly by MI, and then transferred as anonymised data to Word Excel. These data were then transferred to Vivo® software that is designed for qualitative analysis of data.

5.3.5 Thematic analysis methodology

Qualitative research allows for the study of data that would not normally be subjected to rigorous analysis by quantitative approaches [322]. There are a large range of qualitative methodologies, with many nuances and complexities between the various techniques, highlighted by Holloway and Todres [323]. They note that a foundation skill seen with many approaches is the development of themes from data. Some qualitative approaches are highly prescriptive and based on epistemological and theoretical approaches to analysis, such as conversation analysis [324].

Other techniques such as the thematic analysis approach proposed by Braun and Clarke in 2006, offer a more generalised approach that can be implemented on a variety of data sources free from a predetermined theoretical mindset [325]. This method was chosen for our analysis because of its flexibility, as well as dynamic potential, meaning themes could be developed and adapted in accordance with findings. Using the analysis in this way developed a 'patient voice', bearing witness to women's health issues and concerns. This lived experience of one's own body is described by medical anthropologists as embodiment and counters the dualistic nature of typical western medical practices [326].

Steps of the analysis, in accordance with Braun and Clarke are shown in Figure 5.1. We utilised an inductive approach to thematic analysis, meaning we did not have any pre-existing codes or framework into which we placed our datasets, an approach advocated by Frith and Gleeson [327]. Instead we

developed the codes where the findings within the data drove the development of subsequent codes and sub-codes, with no pre-conceived intentions with respect to subsequent themes, and allowing for detailed coding. This attempts to remove researcher's theoretical interests or pre-conceptions of the topic area. Independent of each other, familiarisation with the data and transcription was undertaken by MI and CL. We then developed a broad set of codes to describe and summarise the comments, discussed in more detail within Chapter 5.4.1. Final codes and sub-codes were agreed upon, and applied to the data using N Vivo®. The codes were then mapped out and collated into a broad set of themes that summarise the comments. These themes were then reviewed, consolidated, assessed against the available codes, before being clearly defined into a set of core themes. During the process of recoding, it was possible to analyse the data and the significance of the comments in a more focused way, observing links between the various themes. These links were formally recognised and mapped out using N Vivo®. Finally, interpretation and development of the report was then undertaken as described by Braun and Clarke.

5.3.6 Ethical approval

This study protocol was registered with the Health Research Authority (HRA) in the UK and received a favourable research ethics committee (REC) opinion from the London - City & East Research Ethics Committee on 11/05/2018 (REC reference 18/LO/0637). It received favourable HRA approval on the same date (Appendix 2).

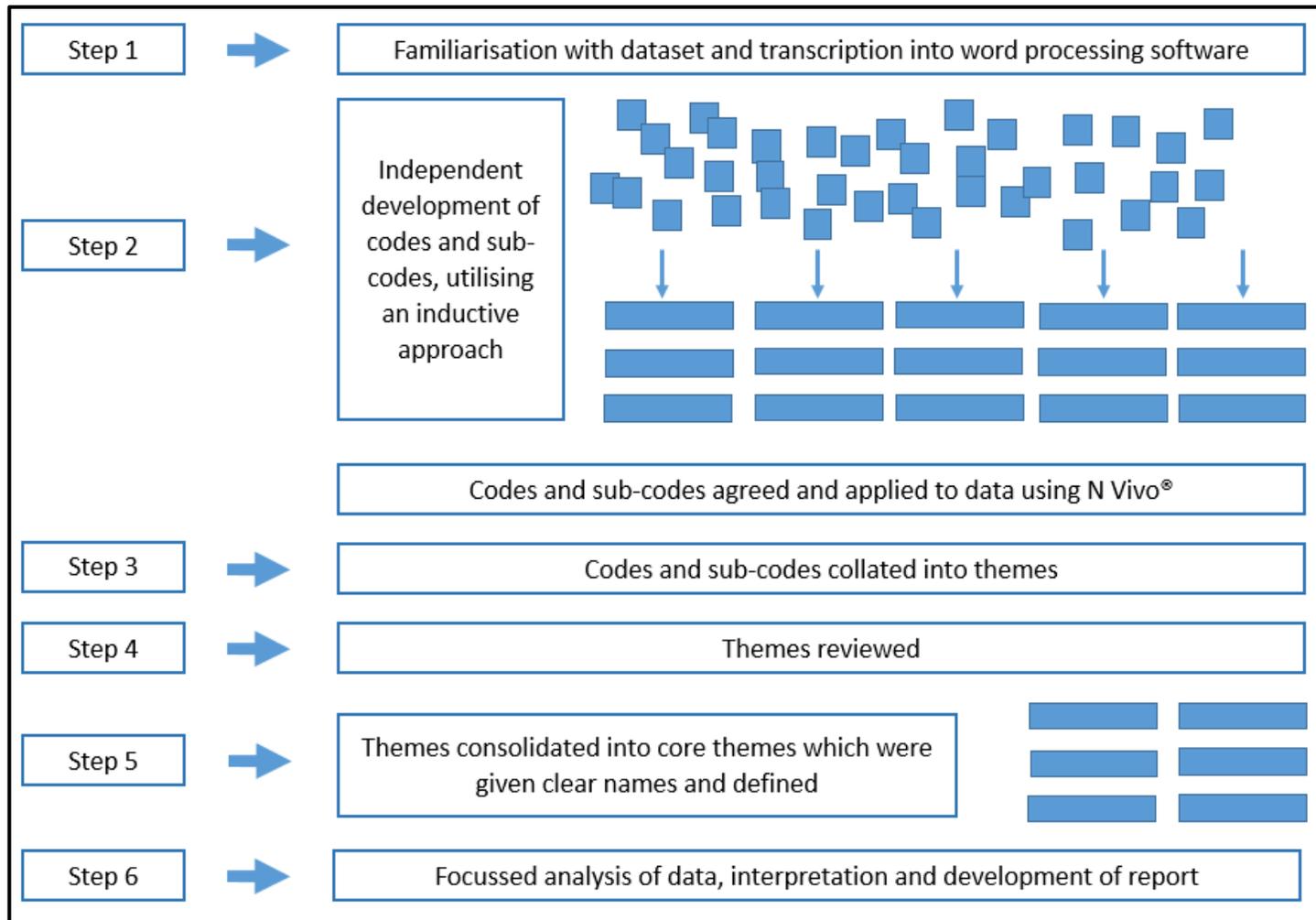


Figure 5.1 Process of inductive thematic analysis for this study

5.4 Results

We identified 1,766 potential participants and following two rounds of postal contact, 1,121 women responded (response proportion 63.5%), of whom 752 (67.1%) gave a free-text response, shown in Figure 5.1. We did note that due to the limited space provided within the paper questionnaire for respondents to write down their comments, a number of women decided to return written or typed more detailed accounts. For Step 1, MI and CL read through all of the comments as paper or REDcap® responses and uploaded them into an excel spreadsheet. This was then transferred to N Vivo®.

5.4.1 Codes and themes

For Step 2, MI and CL independently went through and coded the data in N Vivo® coding. They met twice to compare evolving codes and then re-coded the data with a total of 189 sub-codes devised to accurately described the data, it was felt that these fell within 29 separate codes. The subsequent charting stage led to Step 3 and 4, where MI and CL met to discuss themes and review and consolidate them leading to the creation of 6 core themes to encompass all codes. Codes and themes are illustrated in , with sub-codes listed in Appendix 1.

Our six core themes are outlined and defined below for Step 5, along with illustrative examples that helped shape the analysis.

Pelvic floor symptoms, health status and treatment success

The majority of comments that were left by the study participants related in some way to pelvic floor symptoms and any impact these may have had on day to day living. These comments were consistent with the current understanding of the impact of pelvic floor dysfunction on QoL and the improvements seen in this following successful surgical treatment. Following coding and analysis of these comments, three overlapping themes emerged. These were pelvic floor symptoms (263 total codes, 14.0% of the total 1877

codes), health status (461 total codes, 24.6% of the 1877 total codes) and treatment success (562 total codes, 29.9% of the 1877 codes). Many participants made mention of the resolution of symptoms and correlated these with benefits in psychological wellbeing, overall health status, as well as general and health related QoL (69 women, 9.2% of respondents). Other women simply chose to discuss the presence of current symptoms or changes in symptoms seen following surgery. They commented on how they had responded to, coped with and felt about these ongoing symptoms. While it is important not to undertake overt quantitative analysis of data when performing thematic analysis, it is helpful from a clinical perspective to recognise the frequency of the various codes pertaining to pelvic floor symptoms. This is shown in Figure 5.4 and the predominance of the codes falling within these first three themes is clearly illustrated.

A number of participants remarked that their surgery successful in resolving their prolapse symptoms (37 women, 4.9% of respondents).

“I have had absolutely no health problems following the operation. It was a total success. I had the surgery because of a prolapse that could not continue to be managed with a ring pessary. The surgery transformed my quality of life”
Study ID 163. Aged 72, 77 months since surgery.

Women frequently recognised that surgery was not a cure all and discussed changes in health status and QoL following the treatment.

“This surgery has enabled me to take up exercising again, and has very much improved my day to day life. While not 100% better, the improvement is dramatic and I am glad I did not need a hysterectomy”
Study ID 1131. Aged 39, 22 months since surgery.

Interestingly, despite ongoing pelvic floor dysfunction, many women appeared satisfied with their treatment (55 women, 7.3% of respondents).

“I've been very pleased with the outcome of my surgery. I do still have some urine leakage and take 2mg tolterodine tartrate twice a day, but it's easily managed”

Study ID 517. Aged 66, 62 months since surgery.

For those women with what appeared to be significant ongoing symptoms often voiced regret at the choice of surgical intervention (20 women, 2.7% of respondents). Associated with this, they often mentioned their thoughts surround preoperative counselling and information giving.

“I am still suffering since my laparoscopic sacrohysteropexy. I wish I had a hysterectomy”

Study ID 309. Aged 45, 93 months since surgery.

Mesh

This core theme incorporated the variety of opinions expressed by respondents regarding the use of surgical mesh, and was particularly focused on participants' concerns about the safety of mesh usage (123 total codes, 6.6% of the total 1877 codes).

A handful of women expressed concern at the fact that they had undergone a mesh augmented procedure (18 women, 2.4% of respondents). Women considered themselves fortunate that they had not experienced mesh associated complications, but expressed anxieties about future risks (31 women, 4.1% of respondents).

“I haven't had any problems after surgery but I am worried I might have problems in the future, as I have heard it has gone wrong for a lot of women”

Study ID 904. Aged 66, 38 months since surgery.

It appeared that negative comments regarding mesh tended to be broadly directed at those who had developed mesh and the regulatory process, rather than clinicians.

“What research was carried out on this vaginal mesh?”

Study ID 910. Aged 76, 37 months since surgery.

A number of women voiced the fact that they felt there was a lack of easily available information, stating they would be unsure of whom to contact and

where to seek help should a complication arise (11 women, 1.5% of respondents).

“It would really help to know what the procedure would be, should I begin to experience these painful side effects in the future”

Study ID 891. Aged 59, 36 months since surgery.

Pain

The theme of pain was defined by any reference to acute or chronic pain, regardless of the anatomical location of such pain (227 total codes, 12.0% of the total 1877 codes). Most of the comments about pain referred to the impact of these symptoms on QoL (27 women, 3.6% of respondents) and psychological wellbeing (8 women, 1.1% of respondents). It appeared that pain symptoms had a greater influence over QoL as compared to pelvic floor symptoms, with more sub-codes linking it to other themes. In contrast to the tendency to downplay the impact of ongoing pelvic floor symptoms, the presence or prospect of pain appeared to impact women's perceptions of surgical success. It was noted that in spite of these issues, the majority of women appeared to conclude they found their pain manageable (22 women, 2.9% of respondents).

“Lower back pain and heaviness in the vaginal area. I don't undertake any heavy lifting now”

Study ID 829. Aged 63, 42 months since surgery.

While some participants directly queried an association between the presence of mesh and pain (25 women, 3.3% of respondents), it often appeared linked to concerns about how the mesh had been placed (6 women, 0.8% of respondents) or the recurrence of prolapse (4 women, 0.5% of respondents).

“I am in pain every day since the operation. I feel that this is because of the mesh but visits to a doctor and consultant have not confirmed, but not diagnosed anything else”

Study ID 1253. Aged 54, 42 months since surgery.

“I have experienced intermittent back pain for short periods which gave me concerns that the problem was connected to the attachment to the spine site”

Study ID 913

Care

The theme ‘care’ incorporated comments made about participant’s perception of the care received from healthcare professionals, as well as references to aspects such as information giving and postoperative recovery (346 total codes, 18.4% of the total 1877 codes). There were widespread and regular positive comments with respect to the clinicians and multidisciplinary team involved in participants’ care. This was frequently associated with affirmation of the care pathway and counselling process.

“Pre-op, operation and post-care was excellent and made such a difference to my quality of life”

Study ID 645. Aged 71, 54 months since surgery.

Recovery time was often noted to be more painful and longer than patients’ recollection of the information given to them during the preoperative counselling, often taking many months (18 women, 2.4% of respondents).

“I experienced a great deal of pain immediately after my op and my recovery took much longer than suggested so I think expectations should be adjusted when advising women of possible”

Study ID 1688. Aged 59, 26 months since surgery.

Some women stated that they would have preferred to have had more preoperative information about alternatives and the potential adverse events associated with mesh use (17 women, 2.3% of respondents). Participants appeared to use the study as an opportunity to seek reassurance from researchers, having developed concerns about mesh from the media.

“... with all the talk in the press of painful and negative results of sacrohysteropexies, I worry sometimes. Will this apply to me one day? Will my

body reject the mesh one day? Are the little 'niggles' I have - probably due to ageing - related instead to the mesh inside me?"

Study ID 67. Aged 68, 93 months since surgery.

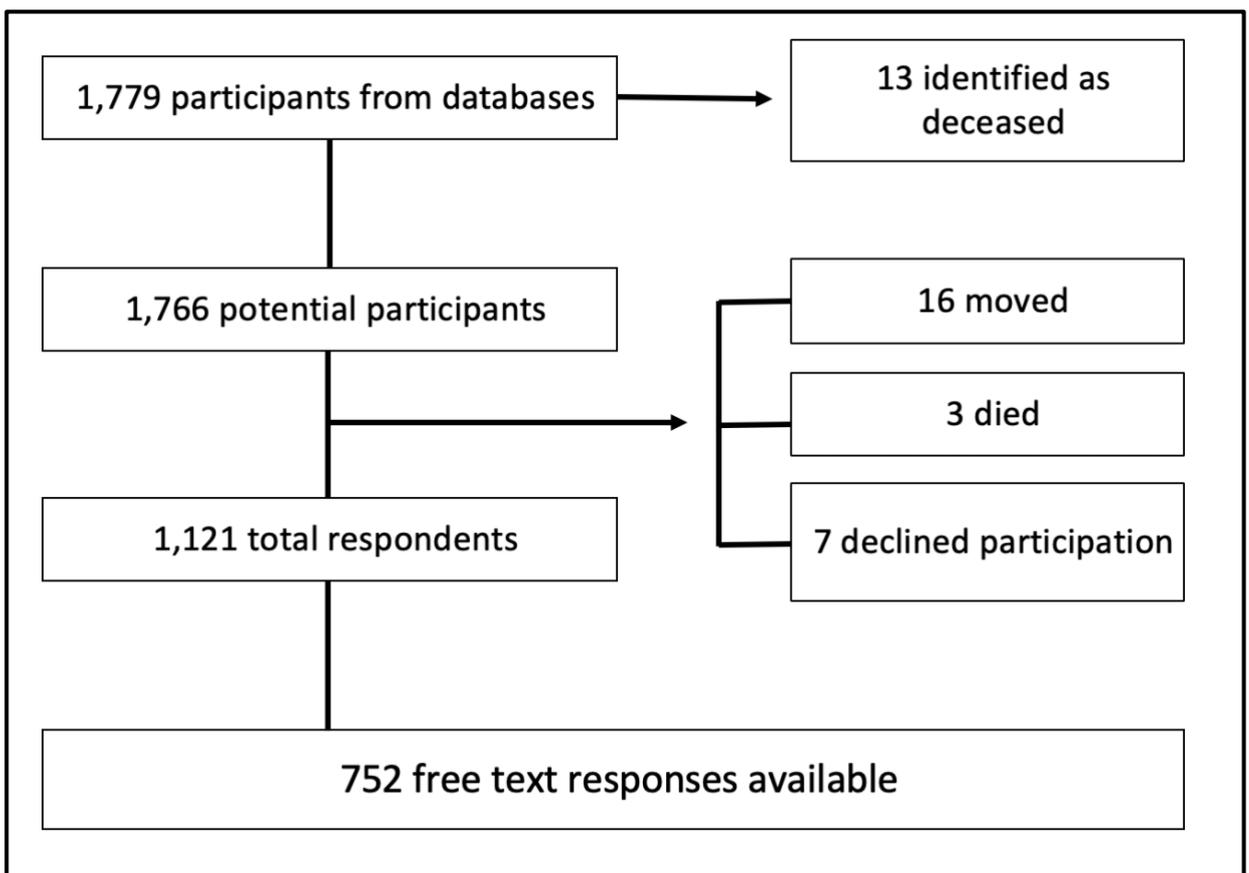


Figure 5.2 Study flow diagram.

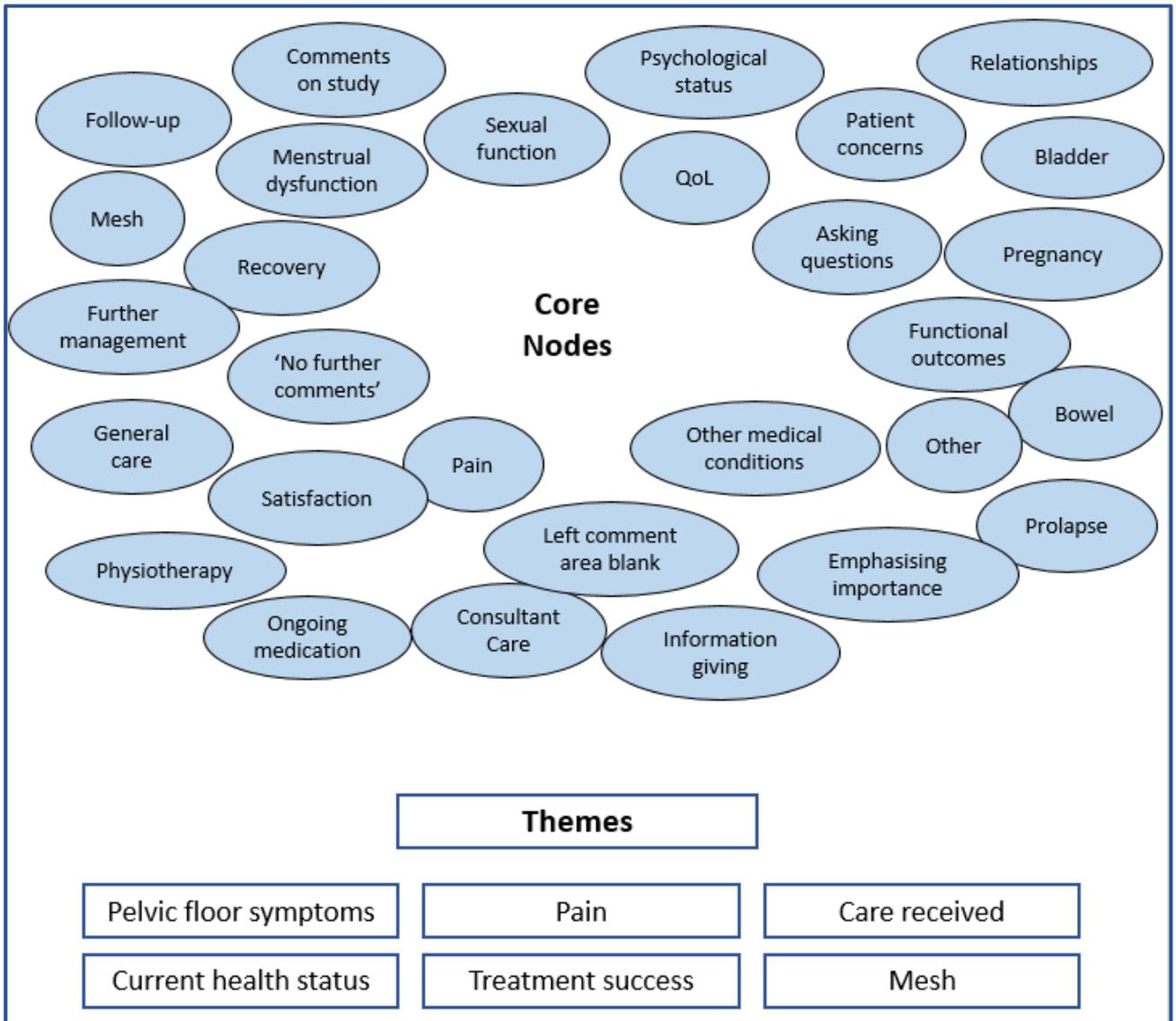


Figure 5.3 Codes and themes.

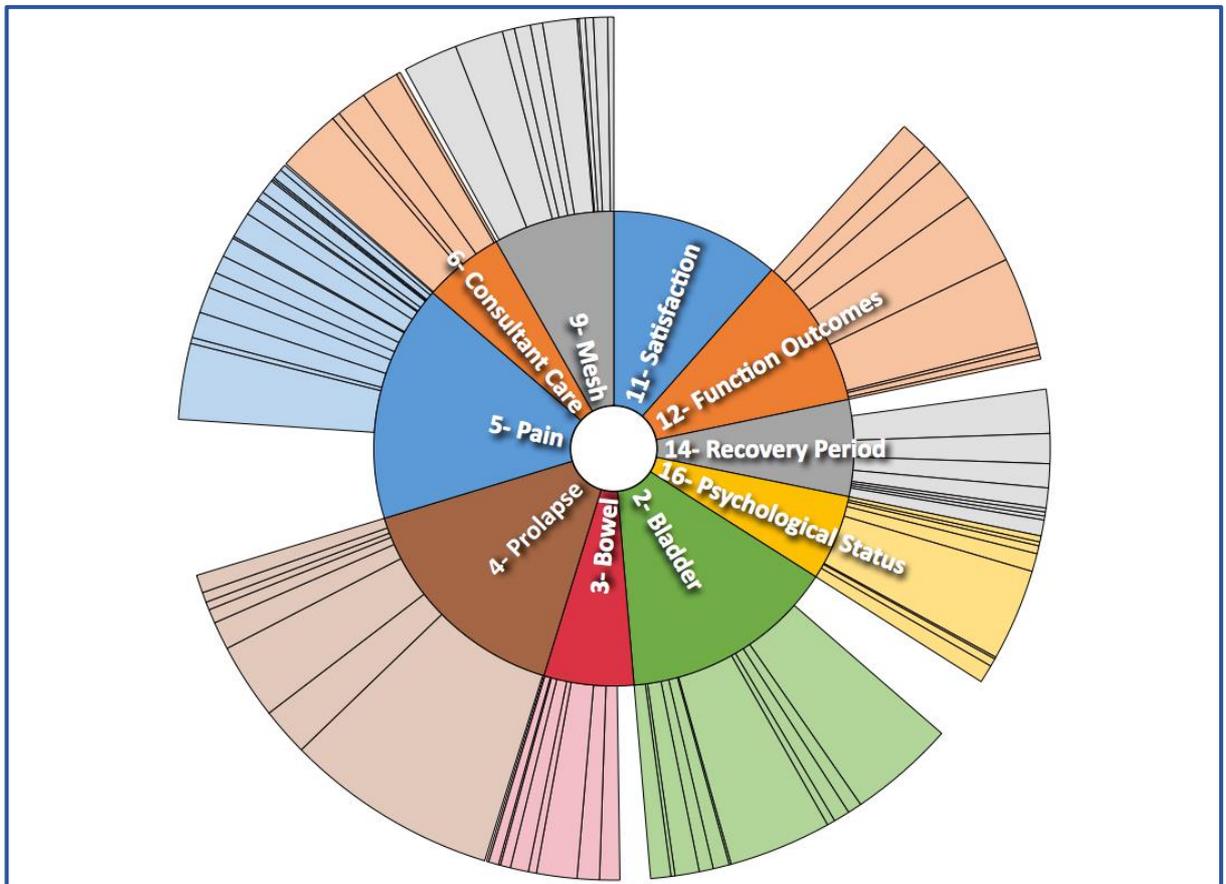


Figure 5.4 Frequency of codes

5.4.2 Key findings

Step 6 involved analysis of the themes, we found this dataset to provide a unique insight into the general comments and health-related issues experienced by women following mesh augmented prolapse surgery. It is essential to consider these within the context of the current controversies and media attention surrounding the use of surgical synthetic mesh in gynaecological surgery [13]. From the six core themes that emerges from our analysis there are three important conclusions that can be drawn. Firstly, is that despite the ongoing media coverage and public conversation surrounding mesh and mesh associated complications, the principal focus of women are their pelvic floor symptoms and associated QoL. There was a frequent crossover of sub-codes and codes between the themes pelvic floor symptoms, health status and treatment success corroborating the established relationship between prolapse and QoL in the literature [296, 328]. It appeared that women determine the success of surgery based on an improvement in their pelvic floor symptoms and any associated improvement in the ability to function in daily life, rather than by the side effects of surgery or ongoing symptoms. This illustrates the nuanced and highly considered interpretation by women of their own personal treatment success, and an understanding that surgery may not be a panacea for the many symptoms associated with pelvic floor dysfunction, a finding noted in similar studies [329].

Secondly, analysis uncovered that many women have concerns about the use of mesh following their pelvic floor surgery. It appears that these concerns often exist in the absence of symptoms attributable to mesh associated complications and in women who report a successful surgical outcome. They voiced concerns about the development and subsequent regulation of mesh devices their use in pelvic floor surgery, an issue highlighted in the medical literature [330]. Anxiety about the potential to develop mesh associated complications in the future appears to be relatively common. Women also commented on a need for high quality pre- and postoperative information resources, a subject recognised in previous qualitative studies of prolapse [329, 331].

Finally, there was regular reference to pain, either associated with other pelvic floor symptoms, attributed to surgery or the use of mesh. It is clear that chronic pain has huge implications for those women that suffer from it. It must however be recognised that has been associated with many forms of gynaecological surgery and has a multifactorial aetiology [278]. While most women clarified that they found their pain manageable, the frequent reference to pain symptoms in women who have had prolapse surgery raises questions as to the relationship between pelvic floor symptoms, reconstructive surgery and pain.

5.5 Discussion

Principal findings

The analysis and interpretation of these data provide several key considerations for women's health researchers and the wider medical community. The proportion of women that chose to respond and then also to provide free-text responses in our study illustrates that women value research participation. This highlights the importance of placing the patient voice at the centre of medical research, and routine integration into the wider healthcare infrastructure, a concept promoted by health organisations internationally including the World Health Organisation [18, 19, 268].

Clinical implications and research implications

With respect to the implications for the future, one could advocate three courses of action. Firstly, is that the controversies that have mired the use of mesh should not distract clinicians caring for women with pelvic floor dysfunction from the fact that prolapse, bladder and bowel symptoms, as well as sexual dysfunction, remain their predominant health concerns as illustrated by our first three themes. Secondly, is the recognition that coverage of these controversies has created a public health issue in the form of widespread concern. There are therefore two issues that need to be addressed. One is the provision of evidence-based and high-quality information resources to

provide reassurance for the many women who we found to be actively concerned about having had mesh augmented surgery. This means that high quality research into mesh associated complications needs to be undertaken with rapid translation into patient friendly information sources. The other factor to address is that women affected by potential mesh complications need accessible care that is delivered to a high standard. This will require coordinated and regulated centres of excellence delivering evidence-based care where with appropriate governance and care pathways. In the UK this is taking the form of specialised commissioning. Finally, there is a need for further research into the relationship between pelvic floor dysfunction, pelvic floor surgery and pain. Such a relationship has not been adequately explored in the literature to date, with many studies of mesh augmented procedures failing to collect data on pain in a validated way.

Other issues raised cover aspects such as information giving and regrets over decisions surrounding surgery. This highlights the need for routine and comprehensive patient information resources and counselling, reaffirming the latest NICE guidance that emphasise conservative management and a framework for shared decision making [133]. The final consideration is that there remains widespread appreciation for the care provided to women and a value of the patient clinician relationship. Sometimes lost amongst the more critical headlines found within the field, this could provide reassurance for clinicians. It also frames the importance of such a relationship both for individuals and on a wider national level.

Strengths and limitations

The strengths of this study include the use of an inductive approach to thematic analysis. This allowed for a wide-ranging documentation and examination of women's comments. While open to subjectivity and interpretation, this methodology does allow for a more detailed understanding of key issues that is not afforded by more prescriptive quantitative techniques. It therefore delivers an open, patient reported dataset, rather than a pre-

defined and categorised responses found with more quantitative methodologies,

The data come from one of the largest available studies of women who have undergone mesh augmented prolapse surgery and are therefore more likely to be representative of this cohort of women. This sits in stark contrast to the comments and experiences presented in the Cumberland report and in national reviews. These reports have actively solicited comments from those who report mesh associated complications, providing a sample that is likely to be unrepresentative of most women's experiences [15, 236]. Our data provide a more balanced commentary on this form of surgery, studied in a methodological and systematic process.

The key limitation of this study is the use of a questionnaire. This introduces inherent methodological biases, and it is difficult to ascertain how representative respondents are of the wider patient group, and how reflective their recollections of areas such as symptom status are of their true preoperative state. Future work could benefit from both pre and postoperative data collection with more in-depth interviews to explore some of the themes identified in this study. Despite attempts to provide as balanced analysis of comments as possible, qualitative researchers bring their own subconscious bias in how they interpret data and draw conclusions from this.

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6. Conclusion

6.1 Introduction

This thesis describes the role of LSH for the treatment of uterine prolapse. For many women this common condition leads to the need for corrective surgery, and for the majority of these patients VH is the surgical intervention of choice. Yet there remain significant disadvantages associated with this 'gold standard' procedure. Laparoscopic mesh sacrohysteropexy may offer a solution to some of these shortcomings, yet is supported by a paucity of evidence and much of that which exists is of low quality. The need for more data is particularly noteworthy given the concerns and global scrutiny of non-absorbable mesh use in gynaecological surgery. This thesis therefore set out to answer four principal aims. Firstly, to establish the safety of LSH with particular reference to mesh associated complications. Secondly, to compare LSH to the current gold standard of VH. Thirdly, to explore the role of UDS in predicting postoperative bladder function. Fourthly, and perhaps most importantly, to contextualise these three chapters by framing them with the patient perspective through the use of qualitative research methodologies assessing the health concerns of women following LSH.

6.2 Principal findings

The principal findings from the data presented within the various chapters are as follows:

Chapter 2

A low rate of reoperation for mesh associated complications following LSH. At a median follow-up of nearly four years, the incidence was 0.4% of from a large cohort of 1,121 study participants.

Chapter 3

A trend towards a lower rate of apical reoperation following LSH as compared to VH, although this was not statistically significant. At seven years, the

objective success rate based on apical reoperation was 83% after VH and 94% after LSH.

Chapter 4

While UDS diagnoses appear to correlate poorly with postoperative bladder function in women undergoing LSH, they may facilitate patient counselling with respect to risk of de-novo symptoms, resolution of LUTS, and consideration of concurrent incontinence procedures.

Chapter 5

Despite ongoing media coverage and public conversation surrounding mesh, the principal focus for women is their pelvic floor symptoms and associated QoL. There are concerns about the use of mesh following their pelvic floor surgery, and there was regular reference to pain, associated with other pelvic floor symptoms as well as attributed to the surgery and use of mesh

6.3 Summary

The data presented in Chapter 2 provide a pragmatic insight into the safety and efficacy of LSH. The large, patient reported dataset must be considered within the wider context of other forms of available evidence supporting LSH. The principle finding was a low incidence of mesh complications requiring removal of hysteropexy mesh of 0.4% at nearly four years. This provides adequate reassurance that laparoscopic mesh sacrohysteropexy should continue to be offered with the appropriate clinician training, decision-making processes, consent, audit and governance.

Findings from Chapter 3 illustrate that LSH and VH both offer safe interventions for the common condition of uterine POP. With reasonably low rates of reoperation and good symptomatic resolution across the range of pelvic floor disorders, women can be confident that neither surgery appears significantly inferior. Given a trend towards differences in apical reoperation rates and advantages with respect to TVL and POP-Q point C, some patients

may opt to choose LSH over VH, however this study does not definitively support such an advantage. Indeed, with composite IVIQ-VS scores favouring VH the choice of surgical procedure for women continues to need the support of a rigorous consent processes and the field of urogynaecology needs further action towards quality RCTs.

In Chapter 4, the clinical utility of UDS for women undergoing LSH has been appraised. The only significant correlation between UDS diagnosis and postoperative LUTS is for those with VD for whom there remains a statistically significant yet low risk of ongoing VD following surgery. For women with USI, undergoing a concurrent continence surgery is associated with a significantly lower risk of postoperative SUI and improved incontinence, supporting an argument for considering such procedures at the time of LSH. Overall, most patients are asymptomatic after surgery regardless of diagnosis, reflected by a significant reduction in validated PROM scores and an asymptomatic symptom status particularly in those with DO and VD. Translation of the findings into clinical practice is limited by retrospective data and small numbers, however further research is required to better understand the prognostic role of UDS to aid patient counselling as well as the role of concurrent continence procedures and LSH.

Finally, Chapter 5 presents the first comprehensive and systematic study of comments from women who have undergone mesh augmented surgery for prolapse. These comments must be contextualised with respect to the current media coverage that has surrounded the use of mesh in pelvic floor surgery. It is clear that the main priority for women remain their pelvic floor symptoms regardless of the treatment controversies. Clinicians who work within the field of pelvic floor medicine should remain alert to this fact and shape their care to match patient needs. There is a requirement for high quality research into mesh associated complications and further exploration of links between pain and pelvic floor symptoms and treatments. There is also a need for contemporary as well as evidence-based information resources for patients. With widespread calls for the voices of women to be put at the centre of the

regulatory process and clinical decision making, this study shows that it is possible. Furthermore, it illustrates that a truly representative patient voice gives valuable hitherto unheard insights, far beyond messages captured by the medical and mainstream media headlines.

To summarise, LSH appears to be safe from the perspective of mesh associated complications, yet large database studies that have been used to study other mesh augmented procedures are needed. These, along with high-quality RCTs with long-term follow-up designed to consider both safety and efficacy should be able to establish the relative merits of LSH, particularly in comparison to VH. It would appear that there may be advantages to LSH, but these are not proven by the RCT data presented. Given the frequent co-existence of LUTS, UDS deserve further prospective scrutiny but do not generally appear to offer significant prognostic value. Pelvic floor symptoms remain women's predominant concern, despite concerns about mesh; further qualitative studies to firmly establish patient priorities may help to shape future regulatory frameworks, commissioning, as well as the design of quantitative studies.

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8. Appendix

Appendix 1. Patient Questionnaire for study in Chapter 2

Please write in your Research ID Number (enclosed)

Confidential Patient Questionnaire

Please read the attached patient information sheet before completing. By returning this questionnaire you are consenting to participation within the study as detailed within the attached information sheet. For convenience, this form can be completed ONLINE with the link provided to you.

Please answer the following questions in reference to your keyhole prolapse operation:

Today's date (DD/MM/YY):

1. Following your keyhole prolapse surgery, have you required an operation to remove some or all of the mesh used to lift up your womb?

Yes No

if **Yes**, proceed to Question 2

if **No**, proceed to Question 6

2. Which of the following best describes the operation to remove the mesh ?
(Please only select one)

Removal of mesh from the vagina

Removal of mesh from the bowel

Removal of mesh from the bladder

Removal of mesh due to chronic pain

3. How long after your keyhole prolapse surgery did you first notice the problem caused by the mesh?

Less than 48 hrs 48 hrs – 2 months

Between 2 and 12 months more than 12 months

4. Please provide the following details about the operation you had to deal with the mesh complications (leave blank if unsure):

Name of Hospital: _____

Name of Consultant: _____

Year operation performed: _____

Continued overleaf.....

LSF FU Questionnaire Version 1 11.01.2018

Please write in your Research ID Number (enclosed)

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5. Which of the following best describes the problems caused by your mesh complication? (please only select one)

- No symptoms
- Pain on physical examination
- Pain during sexual intercourse
- Pain during physical / daily activities
- Pain that is not related to the above
- Vaginal discharge
- Bladder symptoms
- Bowel symptoms

6. Following your keyhole prolapse surgery, have you required another operation to treat further prolapse?

Yes No

if yes, select the option that best describes the operation you have had:

- Another operation to lift the up womb
- Removal of the womb, also known as hysterectomy
- An operation for prolapse of the vaginal walls

7. Following your keyhole prolapse surgery, have you required a procedure to treat NEW leaking of urine when you cough, sneeze, run and/or strain (stress incontinence)?

Yes No

if yes, please select the best description of the operation you have had (leave blank if unsure):

- A mesh sling, also known as a TVT or vaginal tape
- A fascial sling, using tissue taken from your abdomen
- The injection of a 'bulking agent' into your water pipe
- A colposuspension, using stitches to support the bladder

Continued overleaf.....

Please write in your Research ID Number (enclosed)

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8. Following your keyhole prolapse surgery, have you been newly diagnosed with any of the following medical conditions? (select all that apply)

- | | | | |
|---|--------------------------|------------------------------|--------------------------|
| Underactive/overactive thyroid | <input type="checkbox"/> | Polymyositis | <input type="checkbox"/> |
| Autoimmune/Pernicious Anaemia (B12 deficient anaemia) | <input type="checkbox"/> | Multiple Sclerosis | <input type="checkbox"/> |
| Autoimmune thrombocytopenic purpura (low platelets) | <input type="checkbox"/> | Myaesthesia Gravis | <input type="checkbox"/> |
| Guillain-Barre Syndrome | <input type="checkbox"/> | Rheumatoid Arthritis | <input type="checkbox"/> |
| Goodpasture Syndrome | <input type="checkbox"/> | Fibromyalgia | <input type="checkbox"/> |
| Vasculitis | <input type="checkbox"/> | Systemic Lupus Erythematosus | <input type="checkbox"/> |
| Celiac Disease | <input type="checkbox"/> | Motor Neurone Disease | <input type="checkbox"/> |
| Pemphigous Vulgaris | <input type="checkbox"/> | Dermatomyositis | <input type="checkbox"/> |
| | | Ankylosing Spondylitis | <input type="checkbox"/> |
| | | Sjogren's Syndrome | <input type="checkbox"/> |
| | | Systemic Sclerosis | <input type="checkbox"/> |

9. Following your keyhole prolapse surgery, have you been referred to or are you currently under the care of pain specialist due to problems because of mesh?

Yes No

10. Would you recommend keyhole prolapse surgery to a friend?

Yes No

11. Overall, which of the following best describes your PROLAPSE symptoms (specifically feeling a lump, bulge or heaviness in the vagina) now, compared with before your surgery?

- Very much better
- Much better
- A little better
- No change
- A little worse
- Much worse
- Very much worse

Continued overleaf.....

Please write in your Research ID Number (enclosed)

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12. Are there any comments of further information you would like to provide to the research team about the operation, your recovery and/or current symptoms with regards to general health and prolapse? *(There may be a delay in reviewing your response so please ensure to see your doctor if you are having any current issues)*

13. If you would like a copy of the final report, select one of the following:

Post: or, Email: _____

Thank you for taking the time to complete this questionnaire. Please return in the pre-addressed envelope.

Appendix 2. Favourable REC letter for study in Chapter 2

NHS
Health Research Authority
London - City & East Research Ethics Committee
Bristol Research Ethics Committee Centre
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

11 May 2018

Mr Arvind Vashisht
Consultant Urogynaecologist
University College Hospital
Urogynaecology and Pelvic Floor Unit
Level 2 North
250 Euston Road
NW1 2PG

Dear Mr Vashisht

Study title:	Complications after laparoscopic sacrohysteropexy with a focus on mesh, a multi-centre retrospective cohort study.
REC reference:	18/LO/0637
Protocol number:	Z6364106/2017/11/98
IRAS project ID:	235195

Thank you for your letter of 11.05.18 responding to the Proportionate Review Sub-Committee's request for changes to the documentation for the above study.

The revised documentation has been reviewed and approved by the chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Appendix 3. HRA approval letter for study in Chapter 2



Ymchwil Iechyd
a Gofal Cymru
Health and Care
Research Wales



Mr Arvind Vashisht
Consultant Urogynaecologist
University College Hospital
Urogynaecology and Pelvic Floor Unit
Level 2 North
250 Euston Road
NW1 2PG

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

11 May 2018

Dear Mr. Vashisht,

**HRA and Health and Care
Research Wales (HCRW)
Approval Letter**

Study title: Complications after laparoscopic sacrohysteropexy with a focus on mesh, a multi-centre retrospective cohort study.
IRAS project ID: 235195
Protocol number: Z6364106/2017/11/98
REC reference: 18/LO/0637
Sponsor: University College London

I am pleased to confirm that [HRA and Health and Care Research Wales \(HCRW\) Approval](#) has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?

You should now provide a copy of this letter to all participating NHS organisations in England and Wales*, as well as any documentation that has been updated as a result of the assessment.

*"In flight studies" which have already started an SSI (Site Specific Information) application for NHS organisations in Wales will continue to use this route. Until 10 June 2018, applications on either documentation will be accepted in Wales, but after this date all local information packs should be shared with NHS organisations in Wales using the Statement of Activities/Schedule of Events for non-commercial studies and template agreement/ Industry costing template for commercial studies.

Following the arranging of capacity and capability, participating NHS organisations should formally confirm their capacity and capability to undertake the study. How this will be confirmed is detailed in the "summary of assessment" section towards the end of this letter.

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Appendix 4. PIS for study in Chapter 2

LSH Cover Letter V2 23.4.18 JRO # 17/0729



University College London Hospitals 
NHS Foundation Trust


Oxford University Hospitals
NHS Foundation Trust

Dear

You have received this letter as you have previously undergone a keyhole operation for prolapse (Laparoscopic Sacrohysteropexy) that involved the use of mesh.

Before responding, please take the time to read the enclosed 'patient information leaflet'. If you are happy to proceed, please complete the secure online questionnaire as detailed below.

We want to reassure you that studies of this operation at present confirm it is a safe operation. However, you may have seen recent controversy surrounding the use of mesh in surgery. It is therefore important that further research is undertaken to support these previous studies.

We feel the involvement of women and their experiences is central to such research and are therefore conducting this study. We are contacting all patients who have had the operation to see how they are doing and if any problems have arisen. This is important research to provide future patients, doctors and regulators with as much information as possible. We feel women deserve options when undergoing surgery. Failure to show the safety of this operation may lead to it being withdrawn as an option.

Studies such as this one are often limited by a low number of people responding. We would therefore greatly appreciate you taking the time to complete to participate as outlined below.

Go to: www.laprolapse.com and enter your unique research ID:

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Alternatively, you may select **one** of the following:

1) Return the enclosed paper questionnaire in the pre-paid envelope.

2) If you would prefer a telephone questionnaire: Tick this box
And return this form in the prepaid envelope. **Alternatively**, you can email your name, date of birth and contact details to: m.izett@nhs.net. Finally, you may also telephone 07887959926 leaving your full name and contact telephone number.

3) I do not want to be contacted again for this study : Tick this box
And return this form in the prepaid envelope.

Yours Sincerely

(to be personalised by the clinical care team at each site)

Appendix 5. Patient information sheet for study in Chapter 2



Patient Information Sheet – Part 1

Short Title: Complications after laparoscopic sacrohysteropexy

Complications after laparoscopic sacrohysteropexy with a focus on mesh, a multi-centre retrospective cohort study.

We would like to invite you to complete this questionnaire for our research study. This study is being carried out by a medical doctor undertaking a post-graduate research degree. Before you decide to complete the questionnaire, it is important that you to understand why the research is being done and what it would involve for you. Talk to others about the study if you wish.

Part 1 tells you the purpose of this study and what will happen to you if you take part.

Part 2 gives you more detailed information about the conduct of the study.

Please contact us if there is anything that is not clear. Take time to decide whether or not you wish to take part.

What is the purpose of the project?

The purpose of this study is to determine the rate of complications, particularly mesh related complications for women who have undergone keyhole prolapse surgery (laparoscopic sacrohysteropexy). Prolapse is a common condition where the womb or vaginal walls drop down from their normal position.

Laparoscopic sacrohysteropexy is an operation to treat prolapse of the womb that does not require the womb to be removed. Laparoscopic sacrohysteropexy involves restoring the womb to its normal position using a sling made of mesh. Placement of the mesh in this respect is similar to that used to repair hernias, this has shown to be safe.

Mesh used in other types of women's pelvic surgery has been shown in some cases to be associated with complications. This is when the mesh is placed using a vaginal approach in contrast to the abdominal approach using for laparoscopic sacrohysteropexy. Numerous studies have shown laparoscopic sacrohysteropexy to be safe, but no one has followed women up over a long time. We are therefore trying to contact women who have had the procedure to work out if they have had complications related to the mesh.

The results will help to inform patients, doctors and healthcare regulators as to whether laparoscopic sacrohysteropexy should continue to be offered to patients.

Why have I been invited?

You have been invited as you previously underwent laparoscopic sacrohysteropexy, the key-hole operation to repair vaginal prolapse.

Do I have to take part?

No. It is up to you if you decide whether or not to take part. It is up to you to decide to respond to the questionnaire. We will describe the study in this information sheet. If you agree to take part, we will ask you to respond to the enclosed questionnaire. This will not affect the standard of care you receive should you seek medical attention in the future.

What will happen to me if I take part?

If you decide to take part in the project we ask that you kindly follow the online link provided, return the postal questionnaire or leave a message for a telephone call. If you agree to participate we will also obtain information regarding your operation details and any subsequent problems from your hospital notes. If we do not hear from you we will attempt to contact you by telephone to ensure you received the letter and offer a telephone version. Your responses will be entered into an anonymised and secure database as outlined in part 2. Should your responses need further clarification, the student researcher or a member of your clinical care team may contact you in relation to this study and your responses only. This would be within 8 weeks of receiving your response.

Other studies

Responding to our questionnaire should not impact any other studies you may be involved in.

What will I have to do?

You will have the choice of **ONE** of the following three options:

Online; Go to www.prolapse.com, insert your research ID (contained in cover letter), undertake the consent form and complete questionnaire. **Or**

Complete the postal questionnaire and return in the pre-paid envelope.

Or

Email m.izett@nhs.net or telephone 07887959926 (leaving a message) with your name, date of birth and telephone number and we will call you back and/or carry out a telephone consultation.

What are the possible disadvantages and risks of taking part?

Completing the questionnaire will take approximately five minutes. For those patients who have had a complication, they may find it challenging to fill out the questionnaire. If completing the questionnaire raises issues that you feel need further addressing, please contact the team at either UCH or OUH who undertook your surgery, alternatively you can email the research team at m.izett@nhs.net.

What are the possible benefits of taking part?

There is no direct benefit to you. However, you will enable women considering the operation in the future to have accurate information with regards to the likelihood of a mesh related complication.

What if there is a problem?

Any complaint about the way you have been dealt with during the study will be addressed. The detailed information concerning this is given in Part 2 of this information sheet. If you have any concerns or complaints you should contact your study doctor in the first instance.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

Contact Details

Your Doctor: (to be personalised by the clinical care team at each site)

Name:

Tel. Number:

Your Research Doctor:

Name Dr Matthew Izett

Tel. Number: 07887959926

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision

Participant Information Sheet – Part 2

What will happen if I don't want to carry on with the study?

If you change your mind after completing the questionnaire and would prefer not to have your response included in our study, you can contact us on the details above. Your care will not be affected and only data you have provided that does not contain personal information will be included. All other responses and data will be destroyed in accordance with NHS data protection practices.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the student researcher, Dr. Matthew Izett who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from

the Patient Advice Liaison Services (PALS) at [either UCH or OUH They can be contacted by:

UCH

Telephone: 020 3447 3042

Address: PALS, Ground Floor Atrium, University College Hospital, 235 Euston Road, London NW1 2BU

email: PALS@uclh.nhs.uk

OUH

Telephone: **01865 221473**

Address: PALS, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU

email: PALS@ouh.nhs.uk

Will my taking part in this study be kept confidential?

If you agree to participate in this study, the records obtained while you are in this study as well as related health records will remain strictly confidential at all times. The information will be held securely on paper and electronically at the hospital site managing this research under the provisions of the 1998 Data Protection Act. Your name will not be passed to anyone else outside the research team or the Sponsor (UCL), who is not involved in the trial. You will be allocated a trial number, which will be used as a code to identify you on all trial forms. In addition to your hospital site, patient information will be kept on a secure database designed to hold information of this type for research.

Your records will be available to people authorised to work on the trial but may also need to be made available to people authorised by the Sponsor, which is

the organisation responsible for ensuring that the study is carried out correctly. By responding to the questionnaire you agree to this access for the current study and any further research that may be conducted in relation to it, even if you withdraw from the current study.

If you withdraw consent from further study treatment, unless you object, your data will remain on file and will be included in the final study analysis

In line with the regulations, at the end of the study your data will be securely archived for a minimum of 20 years. Arrangements for confidential destruction will then be made.

What will happen to the results of the research?

The results of the study will be published in scientific journals so that other researchers working on improving treatments for women with prolapse will benefit from our knowledge. Additionally, it will be included in the student researchers thesis. You will not be identified of any publications but we shall provide you with a report of the results of the trial. If you would like the results, please let us know at the end of the questionnaire.

Who is organising and funding the research?

This study is organised by the Department of Urogynaecology and Pelvic Floor Unit at University College Hospital London. The study is being sponsored by University College London. Oxford University Hospital is also involved in this study.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and approved by the XXX Research Ethics Committee.

If you decide you would like to take part then please log in online and after completing the online consent, complete the questionnaire. Alternatively, return the postal questionnaire or telephone/email for a call back.

You can have more time to think this over if you are at all unsure.

Thank you for taking the time to read this information sheet and to consider this study.

Appendix 6. Telephone script for study in Chapter 2

Telephone script for clinicians contacting patients as part of IRAS study 235195

'Complications after laparoscopic sacrohysteropexy'

Please use the following scripted prompts to format your telephone contact with potential participants. Prior to telephone contact ensure you have the patients name and date of birth as well as address to confirm identity. Additionally you will be required to be logged on to the 'safe haven' database so as to allow direct data entry.

1) Clinician: 'Hello, I am Dr. _____ (*full name*)_____ from ____ (*hospital site*)_____.' 'Can I confirm I am speaking to _____ (*patient full name*)_____'

2) Following confirmation of correct potential participant

Clinician: 'Is now a convenient time to discuss a questionnaire regarding your previous prolapse surgery, it should take around fifteen minutes?'

3) If the potential participant would prefer a phone call at a more convenient time, log this within the call log and arrange to call back.

4) If the potential participant would prefer not to be contacted again

Record in the call log and document within the study database that the patient has declined participation. Patient should not be contacted again.

5) Following confirmation of convenience:

Clinician: 'Can I just take your date of birth or address to confirm I have the correct person. We are currently undertaking an important study into complications following the key-hole prolapse surgery that you had. We have sent you a questionnaire in the post and wanted to see if you would be able to complete this or would prefer to do it over the telephone'

6) If potential participant wants to complete the postal questionnaire

Clinician: 'Please take a moment to have a look at the information we have given you and feel free to contact us if you have any further questions. We would really appreciate you taking the time to complete the questionnaire on paper or through the web-link provided. This will provide important information for patients, their doctors and regulators as to what happened to patients who have had the operation. Thank you for your time'

Continued overleaf

7) If potential participant wants to complete the questionnaire over the telephone

Clinician: 'Prior to going through the questions, I have to explain a little bit about the study:

'Clinician should refer to the patient information sheet (PIS) and read to the patient the questions and answers within the PIS.'

8) Following this:

Clinician: 'Now that I have explained to you the details of the study, are you happy to be involved within the study?'

9) If potential participant declines:

Clinician: 'Are there any specific issues that I could clarify that would make you feel comfortable to participate?'

Clarify as appropriate. If unable to answer the query, record within the call log and refer to the CI.

Clinician: 'I am sorry I am unable to answer that today. I will notify the Chief Investigator of this query, would you be happy for me to contact you once I have clarified this?'

10) If potential participant does not want to participate:

Clinician: 'Thank you for taking the time to talk to me today. Please understand that not participating will not influence any care you have in the future.'

Record in the call log and document within the study database that the patient has declined participation. Patient should not be contacted again.

11) If potential participant does want to participate:

Clinician: 'Please can you confirm that you have understood the study as I have explained from our information leaflet?'

Patient must answer yes/no

'Also that you are happy for your details and responses to be stored within our

secure research database?

Patient must answer yes/no

'Additionally that we may need to contact any named clinicians who have dealt with complications as a result of your operation?

Patient must answer yes/no

Continued overleaf

12) If the potential participant does not consent:

Clinician: 'Thank you for taking the time to talk to me today. Please understand that not participating will not influence any care you have in the future.'

Record in the call log and document within the study database that the patient has declined participation. Patient should not be contacted again.

13) If potential participant consents to participation, record this on the safe haven and proceed

Clinician: 'I am going to go through a questionnaire with you. Please feel free to ask me to repeat or clarify any questions that you do not understand'

'Clinician should refer to questionnaire and read to the patient the questions. Responses should be entered directly into the safe haven.'

14) Following completion of questionnaire

Clinician: 'Thank you for taking the time to talk to me today. Should you have any further questions, please feel free to contact us on the details provided within the postal pack. We appreciate you taking the time to help with this project.'

Appendix 7. PIS for study in Chapter 3.



Mr. Simon Jackson
John Radcliffe
Hospital/Gynaecology
Women's Centre
Headley Way, Headington
Oxford,
OX3 9DU
Switchboard: 0300
3047777
01865
221626
8am-6pm Monday -
Friday

Participant Information Sheet – Additional Follow Up

‘Laparoscopic hysteropexy versus vaginal hysterectomy for prolapse’

You have been invited to attend for an additional study visit as you have participated in the above research study. This additional study visit is a change to the study pathway that you originally agreed to. Before you decide, it is important that you understand why the research is being done and what it would involve for you. Please take time to read this information and discuss it with others if you wish. If there is anything that is not clear, or if you would like more information please ask us. Participation in this additional study visit is entirely voluntary.

What is the purpose of the study?

To understand what happens in the long term to women who have prolapse operations with regards to the prolapse coming back, symptoms of prolapse and bladder symptoms.

Why have I been invited?

You have previously participated in the above study. Due to increased regulatory and media interest in operations such as the one you had for your prolapse, investigators involved in the study have recently decided to invite study participants for a further visit, six years following their operation. We want to reassure you that we continue to undertake this operation with regulatory approval, and the available evidence suggests it is safe to do so. We are hoping to see you again to gain further information, not because we anticipate you having a problem. Most women who have had this operation do not have any problems related to the mesh.

Do I have to take part?

No, you do not have to attend this study visit. You do not have to provide a reason for this, it will not affect any future care and you may withdraw at any time.

What will happen if I take part?

You will have two options. One will involve attendance at the clinic at the John Radcliffe Hospital in Oxford, where you will be seen by one of the doctors in the Urogynaecology Department. You will have a pelvic examination to assess for the presence of prolapse and complete questionnaires as you have done previously. This will take approximately 30 minutes. Alternatively, you can opt to have a telephone consultation only to complete the questionnaires, taking approximately 30 minutes.

What should I consider?

You will need to consider whether or not you are happy to return to the John Radcliffe Hospital, to see one of the members of the gynaecology team. This will involve seeing a doctor, answering questionnaires and undergoing a routine pelvic assessment.

Alternatively, you may opt to speak to one of the doctors over the phone to complete questionnaires.

If anything is found at the clinical visit or telephone follow-up that requires gynaecological input, you will be assessed by a member of the clinical team and a routine treatment pathway commenced. Non-gynaecological issues, not related to your surgery, will need to be addressed by your general practitioner.

Are there any disadvantages from attending?

This will require a visit to the hospital which may be inconvenient. Additionally, some people find an internal examination or completing questionnaires distressing. You will be seen by a gynaecologist at this visit who is familiar with these types of visits and will provide a sensitive study visit.

What are the possible benefits from taking part?

You will have the opportunity to exclude any problems related to your previous surgery and discuss your pelvic floor health with a gynaecologist.

Will my GP be notified?

No, we will not be informing your GP routinely as we are not altering your care. Should you raise any problems at your visit, then we will inform your GP as part of routine care.

Will I be reimbursed for taking part?

No, unfortunately we are not in a position to provide reimbursement.

What will happen to my data?

Collected data will include responses to questionnaires and examination results as part of your study visit, as well as a review of your medical records. This data will be compared to responses that you have previously supplied as part of the study. All information from your visit will be kept confidential in accordance with NHS practices and according to the study documentation as provided previously.

We will be using information from the questionnaires you complete, the results of your examination and your medical records, in order to undertake this study. Research is a task that we perform in the public interest. Oxford University Hospitals NHS Foundation Trust, as sponsor, is the data controller. This

means that we, as Oxford University Hospitals NHS Foundation Trust researchers, are responsible for looking after your information and using it properly. We will use the minimum personally-identifiable information possible. We will keep identifiable information about you for 6-12 months after the study has finished. We will store the anonymised research data and any research documents with personal information, such as consent forms, securely at the Oxford University Hospitals NHS Foundation Trust for three years after the end of the study.

The Oxford University Hospital will use your personal information to [give contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. They will keep identifiable information about you from this study for three years after the study has finished.

Your rights to access, change, or move your personal information may be limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. Can also include: Further information about your rights with respect to your personal data is available at <https://www.ouh.nhs.uk/privacy/default.aspx>

You can find out more about how we use your information by contacting m.izett@nhs.net.

Responsible members of the Oxford University Hospitals NHS Foundation Trust may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

What happens if I don't want to continue with the study?

Participation is entirely voluntary and you may change your mind at any stage. Withdrawal will not affect your care. Your clinical care team will be able to see you outside of the study visit if there are any issues that need medical attention.

What will happen to the results of this study?

You will not be identified in any report or publication. The results will be published in a research journal.

What if there is a problem?

If you wish to complain or have any concerns about any aspect of the way you have been approached or treated during the course of this study, you should contact Mr Simon Jackson on 01865 221626. You will also be able to contact the Patient Advice and Liaison Service (PALS) in the first instance (01865 221473).

There are no special compensation arrangements. Oxford University Hospitals NHS Foundation Trust will provide indemnity for this study. If you are harmed due to someone's negligence, then you may have grounds for legal action but you may have to pay for it.

NHS bodies are legally liable for the negligent acts and omissions of their employees. If you are harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the study team this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University Hospitals NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

Who is organising and funding this study?

This study is organised and sponsored by Oxford University Hospital NHS Foundation Trust, there is no funding of this study.

Who has reviewed this study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect participants' interests. This study has been reviewed and given favourable opinion by _____ Research Ethics Committee.

Further Information

Please contact Dr Matthew Izett – m.izett@nhs.net.

Thank you for considering to continue participation in this study.

Appendix 8. PROMS utilised for study in Chapter 3.

Initial number

ICIQ-VS 10/05

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VAGINAL SYMPTOMS QUESTIONNAIRE

Many people experience vaginal symptoms some of the time. We are trying to find out how many people experience vaginal symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

Please write in today's date:

DAY MONTH YEAR

Please write in your date of birth:

DAY MONTH YEAR

Vaginal symptoms

1a. Are you aware of dragging pain in your lower abdomen?

- never 0
occasionally 1
sometimes 2
most of the time 3
all of the time 4

1b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

2a. Are you aware of soreness in your vagina?

- never 0
occasionally 1
sometimes 2
most of the time 3
all of the time 4

2b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

Pre-op Post-op

3a. Do you feel that you have reduced sensation or feeling in or around your vagina?

not at all 0
a little 1
somewhat 2
a lot 3

3b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

Prolapse is a common condition affecting the normal support of the pelvic organs, which results in descent or 'dropping down' of the vaginal walls and/or the pelvic organs themselves. This can include the bladder, the bowel and the womb. Symptoms are usually worse on standing up and straining (e.g. lifting, coughing or exercising) and usually better when lying down and relaxing.

Prolapse may cause a variety of problems. We are trying to find out how many people experience prolapse, and how much this bothers them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

4a. Do you feel that your vagina is too loose or lax?

not at all 0
a little 1
somewhat 2
a lot 3

4b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

5a. Are you aware of a lump or bulge coming down in your vagina?

never 0
occasionally 1
sometimes 2
most of the time 3
all of the time 4

5b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

6a. Do you feel a lump or bulge come out of your vagina, so that you can feel it on the outside or see it on the outside?

never 0
occasionally 1
sometimes 2
most of the time 3
all of the time 4

6b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

7a. Do you feel that your vagina is too dry?

never 0
occasionally 1
sometimes 2
most of the time 3
all of the time 4

7b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

8a. Do you have to insert a finger into your vagina to help empty your bowels?

never 0
occasionally 1
sometimes 2
most of the time 3
all of the time 4

8b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

9a. Do you feel that your vagina is too tight?

never
occasionally
sometimes
most of the time
all of the time

9b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

Sexual matters

We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

10. Do you have a sex life at present?

yes 1

no, because of my vaginal symptoms 0

no, because of other reasons 2

If NO, please go to question 14

11a. Do worries about your vagina interfere with your sex life?

not at all 0

a little 1

somewhat 2

a lot 3

11b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10

not at all a great deal

12a. Do you feel that your relationship with your partner is affected by vaginal symptoms?

not at all 0

a little 1

somewhat 2

a lot 3

12b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10

not at all a great deal

13. How much do you feel that your sex life has been spoilt by vaginal symptoms?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10

not at all a great deal

Quality of life

We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

14. Overall, how much do vaginal symptoms interfere with your everyday life?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
not at all a great deal

Thank you very much for answering these questions.

VAGINAL SYMPTOMS QUESTIONNAIRE

SCORING

(This section is for administrative use only)

Patient number

--	--	--	--	--	--	--	--

Vaginal symptoms score

Vaginal symptom score = 2×(dragging pain) + 2×(soreness in vagina) + (reduced sensation) + 2×(vagina too loose) + 2×(lump felt inside) + 2×(lump seen outside) + 2×(vagina too dry) + (faecal evacuation)

symptom*	score	weighted score
Q1. 'dragging pain'		x 2 =
Q2. 'soreness in vagina'		x 2 =
Q3. 'reduced sensation'		x 1 =
Q4. 'vagina too loose'		x 2 =
Q5. 'lump felt inside'		x 2 =
Q6. 'lump seen outside'		x 2 =
Q7. 'vagina too dry'		x 2 =
Q8. 'faecal evacuation'		x 1 =
Total vaginal symptoms score		

*(Note: Q9, 'vagina too tight', is primarily for detecting a potential post-treatment complication and is therefore not included in the scoring)

Sexual matters score

Sexual matters score = (sex-life spoilt) + 8×(worries about vagina interfere with sex-life) + 8×(relationship affected)

sexual matter	score	weighted score
Q11. 'worries about vagina interfere with sex-life'		x 8 =
Q12. 'relationship affected'		x 8 =
Q13. 'sex life spoilt'		x 1 =
Total sexual matters score		

Quality of life score

quality of life	score
Q14. 'quality of life affected'	

<input type="text"/>					
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Initial number

ICIQ-FLUTS 08/04
CONFIDENTIAL

<input type="text"/>					
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DAY MONTH YEAR
Today's date

Urinary symptoms

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:

<input type="text"/>					
----------------------	----------------------	----------------------	----------------------	----------------------	----------------------

DAY MONTH YEAR

2a. During the night, how many times do you have to get up to urinate, on average?

none 0
 one 1
 two 2
 three 3
 four or more 4

2b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

3a. Do you have a sudden need to rush to the toilet to urinate?

never 0
 occasionally 1
 sometimes 2
 most of the time 3
 all of the time 4

3b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

4a. Do you have pain in your bladder?

never 0
 occasionally 1
 sometimes 2
 most of the time 3
 all of the time 4

4b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

5a. How often do you pass urine during the day?

1 to 6 times 0
 7 to 8 times 1
 9 to 10 times 2
 11 to 12 times 3
 13 or more times 4

5b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

F score: sum scores 2a-5a

6a. Is there a delay before you can start to urinate?

never 0
 occasionally 1
 sometimes 2
 most of the time 3
 all of the time 4

6b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

7a. Do you have to strain to urinate?

never 0
 occasionally 1
 sometimes 2
 most of the time 3
 all of the time 4

7b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

8a. Do you stop and start more than once while you urinate?

never 0
 occasionally 1
 sometimes 2
 most of the time 3
 all of the time 4

8b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

V score: sum scores 6a+7a+8a

9a. Does urine leak before you can get to the toilet?

never 0
 occasionally 1
 sometimes 2
 most of the time 3
 all of the time 4

9b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

10a. How often do you leak urine?

never 0
 once or less per week 1
 two to three times per week 2
 once per day 3
 several times per day 4

10b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

11a. Does urine leak when you are physically active, exert yourself, cough or sneeze?

never 0
 occasionally 1
 sometimes 2
 most of the time 3
 all of the time 4

11b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

12a. Do you ever leak urine for no obvious reason and without feeling that you want to go?

never 0
 occasionally 1
 sometimes 2
 most of the time 3
 all of the time 4

12b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

13a. Do you leak urine when you are asleep?

never 0
 occasionally 1
 sometimes 2
 most of the time 3
 all of the time 4

13b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 10
 not at all a great deal

I score: sum scores9a-13a

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Thank you very much for answering these questions.

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**Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire
(PISQ-12)**

DATE: _____

NAME: _____ DATE OF BIRTH: _____

Instructions: Following are a list of questions about you and your partner's sex life. All information is strictly confidential. Your answers will be used only to help doctors understand what is important to patients about their sex lives. Please check the box that best answers the question for you. While answering the questions, consider your sexuality over the past six months. Thank you for your help.

1. How frequently do you feel sexual desire? This feeling may include wanting to have sex, planning to have sex, feeling frustrated due to lack of sex, etc.
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
2. Do you climax (have an orgasm) when having sexual intercourse with your partner?
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
3. Do you feel sexually excited (turned on) when having sexual activity with your partner?
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
4. How satisfied are you with the variety of sexual activities in your sex life?
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
5. Do you feel pain during sexual intercourse?
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
6. Are you incontinent (leak urine) with sexual activity?
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
7. Does fear of incontinence (either stool or urine) restrict your sexual activity?
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
8. Do you avoid sexual intercourse because of bulging in the vagina (either bladder, rectum or vagina falling out)?
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
9. When you have sex with your partner, do you have negative emotional reactions such as fear, disgust, shame or guilt?
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
10. Does your partner have a problem with erections that affects your sexual activity?
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
11. Does your partner have a problem with premature ejaculation that affects your sexual activity?
 Always (4) Usually (3) Sometimes (2) Seldom (1) Never (0)
12. Compared to orgasms you have had in the past, how intense are the orgasms you have had in the past six months?
 Much less intense (4) Less intense (3) Same intensity (2) More intense (1) Much more intense (0)

Appendix 9. REC approval for study in Chapter 3



South Central - Oxford C Research Ethics Committee

Level 3, Block B
Whitefriars Building
Lewins Mead
Bristol
BS1 2NT
Tel: 020 7104 8049

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

08 January 2019

Mr Simon Robert Jackson
Consultant Gynaecologist
Oxford Radcliffe Hospitals Trust
Women's Centre, John Radcliffe Hosp
Headley Way, Headington, Oxford
OX3 9DU

Dear Mr Jackson

Study title:	Laparoscopic hysteropexy versus vaginal hysterectomy for treatment of uterovaginal prolapse: a prospective randomised study.
REC reference:	09/H0606/28
EudraCT number:	N/A
Amendment number:	1
Amendment date:	18 December 2018
IRAS project ID:	11721

The Committee considered an amendment to include a longer term six year follow up. The study will therefore be extended until 01/09/2019 to allow for all study participants to attend for follow up.

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Covering letter on headed paper [REC Cover Letter 14.9 MI]		18 December 2018
Letters of invitation to participant [Cover Letter 17.9.2018]	1	17 September 2018
Notice of Substantial Amendment (non-CTIMP) [AmendmentForm_ReadyForSubmission]	1	18 December 2018
Participant information sheet (PIS) [PIS 15.11]	1	14 September 2018
Research protocol or project proposal [28.11.2018 V2 VHvLSH]	2	14 September 2018
Validated questionnaire [Gen PISQ12]		
Validated questionnaire [ICIQ-FLUTS]		
Validated questionnaire [ICIQ-VS]		
Validated questionnaire [PGI-I]		

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at <http://www.hra.nhs.uk/hra-training/>

09/H0606/28:	Please quote this number on all correspondence
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Yours sincerely
PP



Mr David Carpenter
Chair

E-mail: nrescommittee.southcentral-oxfordc@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to:

Appendix 10. Codes and sub codes.

Name of codes and sub-codes	Frequency of code
1- Patient concerns	59
1a- safety of mesh	17
1b- further surgery	1
1c- the future	14
1d- worries	17
1e- anxieties	5
1f- inadequate information	3
1g- uncertainty	1
1h- Not concerned	1
10- Information giving	36
10a- leaflets	2
10b- inadequate	17

Name of codes and sub-codes	Frequency of code
10c- patient involvement	0
10d- not reflective of individual care journey	3
10e- the use of mesh	3
10f- seeking reassurance	6
10j - Offer of alternatives	2
10k-Informed choice	3
10l - positive about it	1
11- Satisfied with outcome	142
12- Functional outcomes	126
12a- ability to exercise	14
12b- inability to exercise	7
12c- restrictions	18
12d- enhanced	34

Name of codes and sub-codes	Frequency of code
12e- activities of daily living	43
12f- work-related positive	2
12g- work-related negative	4
12h- social engagement	2
13- Follow-up	32
13a- inadequate follow up	10
13b- uncertainty	2
13c- length of follow up	0
13d- comprehensive follow up	1
13e- mesh safety	0
13f- ongoing	8
13h- desired	8
13i barriers to secondary care	1

Name of codes and sub-codes	Frequency of code
14- Recovery period	80
14a- longer than expected	19
14b- shorter than expected	11
14c- as expected	12
14d- more painful than expected	10
14e- length of stay	2
14f- information leaflets	0
14f- use of pain relief	2
14g- use of laxatives	0
14h - Issues with	2
14i - normal or uneventful	8
15- Relationships - interpersonal	5
15a- positive effect	0

Name of codes and sub-codes	Frequency of code
15b- negative effect	3
15c- relationship breakdown	1
15d- inability to start new relationships	1
15e- relationship status unchanged	0
16- Psychological status	78
16a- self image	3
16b- anxiety	2
16c- anger	4
16d- improved	9
16e- happiness	46
16f- depression	1
16g- regret	0
16h- concerns	4

Name of codes and sub-codes	Frequency of code
16i- sad	9
16j- coping	0
17- Further medical management	37
17a- repeat surgery prolapse	12
17b- repeat surgery incontinence	0
17c- mesh removal	1
17d- bowel complications	3
17e- bladder complications	0
17f- desired	4
17g- planned	11
17h- successful	0
17i- unsuccessful	1
17j- undesired	5

Name of codes and sub-codes	Frequency of code
18- Comments about study	11
18a- positive	2
18b- negative	1
18c- interested	1
18d- gratitude	1
19- Emphasising importance	25
19a- capitalisation	1
19b- exclamation	14
19c- repetition]	0
19d- positive	5
19e- negative	3
19f- provided further information	1
2- Bladder symptoms	179

Name of codes and sub-codes	Frequency of code
2a- stress incontinence	43
2b- voiding dysfunction	7
2c- incomplete emptying	7
2d- altered sensation	3
2e- leakage	48
2f- painful bladder	1
2g- catheters	0
2h- UTI	8
2i- control	7
2j- use of pads	12
2k- Improved	2
2l - OAB	10
20- Other medical conditions	43

Name of codes and sub-codes	Frequency of code
20a- autoimmune conditions	1
20b- chronic pain	0
20c- mental health	0
20d- predating surgery	6
20e- subsequent to surgery	21
20f- attributed to mesh	1
20g - Not attributed to mesh	10
20h - Weight gain	1
21- Left blank	0 (we could not code for this as the software did not allow it)
22- Physiotherapy	43
22a- ongoing	17
22b- preoperative physio	0
22c- postoperative physio	9

Name of codes and sub-codes	Frequency of code
22d- positive	12
22e- negative	3
22f- access	0
23- Ongoing use of medication	18
23a- laxatives	6
23b- pain management OTC	2
23c- pain management prescribed	2
23d- bladder medication	3
23e- bowel medication	2
23f- intolerance to medication	0
23g- adverse events from medication	0
24- Stated no further comments	21
25- Other	20

Name of codes and sub-codes	Frequency of code
25a - Regret	1
26 - Pregnancy	1
27-Menstrual Dysfunction	2
28 Quality of life	6
28a - Negative	2
28b - Positive	4
29 - Asking questions	1
3- Bowel symptoms	79
3a- incontinence	10
3b- rectocele	11
3c- constipation	20
3d- laxatives	3
3e- pain when opening bowels	9

Name of codes and sub-codes	Frequency of code
3f- straining	5
3g- bowel surgery	1
3h- investigation of bowel symptoms	5
3i- use of pads	1
4- Prolapse symptoms	200
4a- recurrent symptoms	99
4b- recurrent operation	23
4c- recurrent diagnosis	38
4d- successfully treated	14
4e- pessary	7
4f- never treated	4
4g - Initially better	5
4h - Asymptomatic	9

Name of codes and sub-codes	Frequency of code
5- Pain symptoms	201
5a- back	35
5b- bladder	3
5c- vaginal	11
5d- chronic	13
5e- acute	8
5f- resolved	0
5g- pain management	9
5h- hip and sacral	7
5i- menopausal-like symptoms	1
5j- mesh associated pain	13
5k- non mesh associated pain	8
5l- pain leading to functional or psychological sequelae	1

Name of codes and sub-codes	Frequency of code
5m- preventing sex	4
5n-Pelvic	7
5o - Lower Limb	1
5p -Dysmenorrhoea	1
5q - None	5
5r - Dyspareunia	3
6- Consultant care	71
6a- positive comments	30
6b- negative comments	4
6c- gratitude	15
6d- thankfulness	19
6e- consultant acknowledgement of outcome	2
7- General Care	70

Name of codes and sub-codes	Frequency of code
7a- negative comments about MDT	2
7b- positive comments about MDT	30
7c- post-operative care	7
7d- pre-operative investigations	1
7e- satisfaction	22
7f- dissatisfaction	7
7g- administrative	1
8- Sexual Function	36
8a- dyspareunia	16
8b- obstruction	2
8c- positive disruption	2
8d- negative disruption	12
8e- frequency	0

Name of codes and sub-codes	Frequency of code
8f- satisfaction	1
8j - altered sensation	1
9- Surgical mesh	102
9a- concerns about mesh	25
9b- mesh in the media	20
9c- awareness of mesh	6
9d- safety of mesh	8
9e- adverse events due to mesh	6
9f- non specific symptoms attributed to mesh	17
9g- other medical conditions and mesh	1
9h- patient awareness and mesh surgery	3
9i- desire for non mesh alternatives	4

Name of codes and sub-codes	Frequency of code
9j- mesh regret	6
9k - Mesh Controversy	3
Miscellaneous non-coded sub-codes	
Cosmesis	0
Abdomen	1
Disappointment	8
Recognised different mesh types	1
Hysterectomy avoidance	3
No problems reported	13
Non-specific health problem	4
Outcome	41
Outcome negative	14
Outcome positive	27

Name of codes and sub-codes	Frequency of code
Personal health narrative	15
Surgery	60
Avoiding further	1
Hysterectomy	4
issues attributed to op	7
Issues not attributed to op	1
No issues	4
Recommend	6
Specifically references as positive	30
Specifically references as negative	4
Wish had op earlier	2
Weight gain	1

