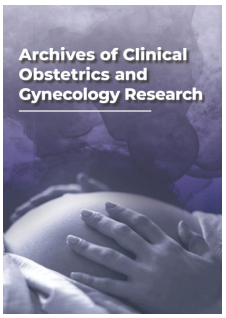
Archives of Clinical Obstetrics and Gynecology Research

Original Article



Feasibilty of a Double Blind Randomised Controlled Trial to Compare Post-operative Recovery following Laparoscopic Hysterectomy with Post-operative Recovery following Laparoscopic Sub-total Hysterectomy - The LaHoST Study

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- Received Date: 25 Aug 2024
- Accepted Date: 15 Sep 2024
- Publication Date: 18 Sep 2024

Abbreviations: BSO: Bilateral Salpingo-oophorectomy; CES-D: Centre for Epidemiology Scale for Depression; e-PAQ: electronic Personal Assessment Questionnaire; FSFI: Female Sexual Function Index; HRT: Hormone Replacement therapy; IBS: Irritable Bowel Syndrome; LAVH: Laparoscopic Assisted Vaginal Hysterectomy; LH : Laparoscopic Hysterectomy; LSH: Laparoscopic Supracervical (Sub-total) Hysterectomy; RCT: Randomised Controlled Trial; SAH: Supracervical (Sub-Total) Abdominal Hysterectomy; SF-36: Short Form 36; STAI: State Trait Anxiety Index;TAH: Total Abdominal Hysterectomy; TLH: Total Laparoscopic Hysterectomy; USI: Urinary Stress Incontinence; WHQ: Womens Health Questionnaire

Abstract

Observational studies suggest faster recovery and quicker return to normal activities following laparoscopic supracervical hysterectomy (LSH) compared with laparoscopic hysterectomy (LH) in women with benign uterine disease. Data from the only randomised controlled trial (RCT) on the topic does not support this observation.

We have investigated the feasibility of a double blind RCT comparing post-operative recovery following LH with that following LSH. 70 women were invited to participate from a single gynaecological surgeon's caseload 20 women were excluded. Web based randomisation was carried out at the time of study laparoscopy. Surgery was performed using a standardised technique.

Participants and the data handler were blinded to treatment allocation.

Primary outcome was feasibility of recruitment. Secondary outcomes included validated post-operative recovery and mood questionnaires at baseline, prior to discharge and at weekly intervals for 12 weeks. Validated questionnaires regarding pelvic floor function and sexual function were assessed at baseline, 6 weeks and 6 months. Recruitment and treatment of 50 women was completed within 18 months. Less than 30% of eligible invitees were excluded and the commonest reason for exclusion was a strong opinion regarding conservation or removal of the cervix (8/70 = 11.4%). 96% of participants received treatment according to randomisation. Data collection was complete at 6 weeks for 88%. Recovery scores were similar to pre-op at 3 weeks for LSH and at 4 weeks for LH. Subjects had returned to normal activity 'all of the time' by 6 weeks for LSH and by 8 weeks for LH.

In conclusion the definitive study appears feasible. The observed advantage in short term recovery following LSH compared to LH appears to be supported. If a difference in QoR score of 5 is clinically significant and power is set at 0.8 with α at 0.05 the definitive study will require 186 women in either arm.

Background

Historical Perspective

Charles Clay is credited with the first hysterectomy in the United Kingdom in 1843 [1]. The procedure was a subtotal hysterectomy performed for an incorrect diagnosis without anaesthesia. A similar operation in another part of Manchester the same month was performed by A.M. Heath [2]. In both instances the women died from massive haemorrhage within a few hours. It was not for another 20 years that the operation was performed for the correct diagnosis and the woman survived.

The early operations to remove the womb were all sub-total abdominal hysterectomies, a technically simpler procedure avoiding opening of the vagina with perceived reduced risks of infection and urinary tract injury. Around the turn of the last century Johannes Pfannenstiel introduced the low transverse incision [3] with a reduction in wound dehiscence rates and shorter recovery. In 1929 Richardson advocated total abdominal hysterectomy (TAH) in order to prevent cancer in the retained cervical stump [4].

In England and Wales approximately 36000 hysterectomies are performed per year and 58% of these are performed abdominally [5]. Over 40% of the uteri removed are histologically normal. Hysterectomy is also a treatment for malignant disease of the uterus which is not the subject of this study.

Citation: Ahmed AIH. Feasibilty of a Double Blind Randomised Controlled Trial to Compare Post-operative Recovery following Laparoscopic Hysterectomy with Post-operative Recovery following Laparoscopic Sub-total Hysterectomy - The LaHoST Study. Arch Clin Obs Gyn Res. 2024;3(1):1-24.

Total versus Subtotal Hysterectomy Debate

The default towards total hysterectomy persisted until a Scandanavian prospective study suggested that retention of the cervix may be important in subsequent sexual function [6]. The findings were not confirmed by a number of authors including a subsequent study by the same group. Even prior to effective cervical screening the incidence of cervical stump carcinoma was as low as 0.4% [7]. With the advent of cervical cancer screening programmes the incidence of cervical stump cancer has reduced further [8]. If the endocervical mucosa is coagulated the incidence of stump carcinoma is as low as 0.11% [9]. It follows that in women at low risk for cervical carcinoma supracervical hysterectomy is a realistic option.

The observed advantages of subtotal abdominal hysterectomy (SAH) compared to total abdominal hysterectomy (TAH) on sexual function [6,10,11] are unsubstantiated by a randomised trial [12]. Outcomes using the EQ5D were significantly better in the SAH compared to the TAH arms in a more recent RCT (no significant difference at baseline compared to a difference at 1year of 0.15, $p<0.05$ [13]. There was improvement of health related quality of life in both the SAH and TAH groups but the improvement was more pronounced in the SAH group in the Gorlero study. Similarly the previously observed benefit of SAH on urinary function compared to TAH [14] was actually reversed following an RCT [15]. The St George's Hospital group in South London attempted to address the controversy. Two hundred and seventy nine women who were awaiting abdominal hysterectomy were randomised to SAH or TAH. Quality of life was assessed with short form 36 (SF-36) and general health questionnaire 28 (GHQ-28) at 6 and 12 months. No significant differences were found [16,17]. Later questionnaires with a response from 64% of the original cohort showed no significant difference [18]. Analysis of secondary outcomes showed statistically significant more multiple orgasms in the SAH arm and reduced coital frequency in the TAH arm. A non-significant higher rate of dyspareunia was noted in the TAH arm. There were more vault haematomas in the SAH group and, somewhat surprisingly, an increased rate of cervical prolapse. Others have previously reported that pelvic organ prolapse post hysterectomy is rare and does not appear to be related to the method of hysterectomy [19]. Theoretically cervical prolapse following SAH should be uncommon as the uterosacral cardinal complex supports of the cervix are preserved. This raises the question as to whether some of the participants in the St Georges study may have had pre-exisitng uterine prolapse and may have been more suitable for vaginal hysterectomy perhaps with a vault suspension procedure.

Short term recovery following TAH and SAH was the subject of a recent Swedish RCT [20,21]. Of the 200 recruits 178 completed the study. Participants were assessed daily using visual analogue scores for wellbeing, and 4 validated questionnaires from 7 days before the hysterectomy until 35 days after. No significant differences were noted between the groups at 6 weeks, 6 months and 12 months.

The comparison of TAH and SAH has been the subject of a number of systematic reviews. A Cochrane review reported in 2006 included only 3 randomised controlled trials with 733 participants [15,16,22]. The Author's concluded that the perception of better sexual, urinary and bowel function following SAH when compared to TAH remained unproven [23]. Scandinavian countries have led the way in terms of preference for SAH over TAH with 56% preference for the former in Sweden [24] and 22% preference for SAH in Denmark [25]. Helga Gimbel performed a meta-analysis using Cochrane methodology on data from 4 RCTs, the 3 reported in the earlier Cochrane review plus a small RCT, [26] and 11 observational studies [27]. Counter-intuitively the meta-analyses showed an advantage in TAH over SAH with regards to urinary incontinence and prolapse. SAH was shown to be a somewhat faster operation with less operative blood loss but there were more complications related to cervical stump problems in keeping with the Lethaby review [23]. Most importantly, no difference was noted in sexual function or psychiatric symptoms between the 2 groups. The better sexual function argument had been the main driver for the drift towards SAH rather than TAH in the Scandinavian countries (Finland, Norway, Sweden and Denmark).The Cochrane review has recently been updated [28] and now includes 9 RCTs with 1593 participants but not all of the participants were included for the analysis of all parameters. The analysis of the additional data supported the findings of the previous review of 2006. Once again the perceived better outcomes in terms of sexual, urinary and bowel function in women undergoing SAH compared to those undergoing TAH were unsubstantiated. The small difference with regards to shorter operating times of 11 minutes on average, and less blood loss of 57mls on average in SAH compared with TAH, are not clinically relevant. The incidence of post-operative febrile illness was higher in TAH compared with SAH which is clinically important but should easily be amenable to correction with appropriate antibiotic therapy. The incidence of post-operative vaginal bleeding for up to two years was, on average, 16 times more likely following SAH compared to TAH. In summary extensive examination of data with regards to the abdominal approach to hysterectomy has failed to show a clinically important advantage of cervical conservation. The most recent Cochrane review included 2 studies using the laparoscopic route to hysterectomy [29,30] but the studies were underpowered to detect some differences. This leads us on to a detailed discussion of laparoscopic hysterectomy.

Enter the Laparoscope

Since the 1960s the laparoscope has formed a central part of the armamentarium available to the gynaecologist. With improved instrumentation therapeutic techniques have emerged using small incisions associated with less post-operative pain and faster recovery in the 'era of keyhole surgery'. Gynaecologists led the way with both laparoscopic appendicectomy [31] and laparoscopic cholecystectomy [32].

The first total laparoscopic hysterectomy (TLH) was performed by Harry Reich in Pennsylvania in 1988 [33]. Despite this early start uptake of the laparoscopic approach to hysterectomy has been relatively slow and the majority of hysterectomies worldwide are still performed abdominally [34]. Since the first reported vaginal hysterectomy by Langenbekke in 1813 the relative merits of vaginal versus abdominal hysterectomy have been debated [2]. In ancient writings the first vaginal hysterectomy may have been as early as 120 AD by Soranus of Ephesus [35] and perhaps represents the first example of Natural Orifice Transluminal Surgery.

Laparoscopic hysterectomy (LH) was included in the debate relatively recently with Garry's seminal 'eVALuate study' [36] comprising of 2 randomised parallel comparisons of laparoscopic hysterectomy with vaginal and abdominal routes. The design of the study included a 2:1 randomisation in both

arms in favour of the laparoscopic route. Indeed the Author's stated in the introduction 'there was urgent need to define the role of the laparoscopic approach to hysterectomy before this was introduced extensively into clinical practice'. Whether participants were recruited onto the abdominal or vaginal arm of the study was left to the clinical discretion of the investigator. Primary outcomes were predefined major complications, both immediate and short term. Secondary outcomes included predefined minor complications, pain scores with analgesic requirement and data from 3 validated questionnaires. The study showed a clear benefit in the vaginal hysterectomy group but the laparoscopic arms of both the vaginal and abdominal trials were associated with longer operating times and significantly higher complication rates, especially with regards to urinary tract injuries. The crucial question is why were there so many complications in the laparoscopic arms of both studies? Laparoscopic hysterectomy was a very new procedure having been reported in the literature for the first time in 1989. The new technique was being compared to abdominal hysterectomy which was at least 150 years old and vaginal hysterectomy which had been practised for even longer. The study was recruiting when laparoscopic hysterectomy was just beginning to be introduced by enthusiasts. The minimum experience required for a surgeon to recruit to this study was 25 laparoscopic hysterectomies. The surgeon with the most experience with the new technique need not have been the primary surgeon and no standard technique was specified. In a very simple observational study based on data from the Finnish Hospital Registry, outcomes following laparoscopic hysterectomies performed between 1992 and 1999 were compared with outcomes following laparoscopic hysterectomies performed between 2000 and 2005 [37]. Approximately 14000 women were in each cohort and the overall incidence of major complications reduced from 1.8% in the earlier cohort to 1% in the later cohort. Specifically urinary tract injuries reduced by half (1.4 to 0.7%) and ureteric injuries reduced to one third (0.9% to 0.3%) when the earlier cohort was compared with the later cohort. This is very compelling evidence that the learning curve for laparoscopic hysterectomy is much longer than the 25 cases required to be eligible to recruit to the eVALuate study. The lack of standardisation of technique is particularly relevant as 43 gynaecological surgeons were involved from 30 different centres. Almost 25% of all major complications in the laparoscopic arms of the study occurred when suturing was the method of securing haemostasis of the ovarian pedicle. Almost 75% of all major complications in the laparoscopic arms of the study occurred when suturing was the method of securing haemostasis of the uterine pedicle. Laparoscopic suturing was being used by only 2 of the 43 participating surgeons, was not the recognised technique and significantly skewed the results. The more commonly used 'safer' techniques of the time were bipolar diathermy and linear staplers. On closer analysis almost all of the ureteric injuries occurred in the centre that employed laparoscopic suturing. Unintended conversion to laparotomy was considered a major complication and occurred in 32 intended laparoscopic procedures. Appropriate conversion to laparotomy for the safety of the patient should be considered good surgical technique and not a major complication. Another significant challenge to the study was under recruitment. The original power calculations required 1800 patients in total split into 1048 in the abdominal arm and 752 in the vaginal arm. The study recruited 1380 in total and was underpowered to find any difference in the vaginal arm. The eVALuate study confirmed the advantages of avoiding laparotomy for hysterectomy seen in previous smaller studies but concluded that this was at a cost of higher major complications. In the same issue of the BMJ Jacques Donnez et al [36] reported their observational single centre data with much lower major complication rates of 0.6% in laparoscopic supracervical (sub-total) hysterectomy (LSH) and 2% in TLH. Professor Donnez's major criticism of the high complication rates in the eVALuate study was the lack of experience of many of the surgeons involved and the use of poor technique. The issue was the subject of a Cochrane review [38] incuding 27 randomised controlled trials (RCT)s and 3643 participants. The largest number of patients were from the eVALuate study and the conclusions, not surprisingly, were in line with those of the eVALuate study. The Author's concluded that where possible vaginal hysterectomy is the method of choice but where vaginal hysterectomy is not deemed possible consideration should be given to LH as long as the higher risk of major complications are acceptable. The eVALuate study may, in part, explain the slow uptake of laparoscopic hysterectomy in gynaecology when our colleagues in gastrointestinal and urologic surgery were moving on at pace. The Donnez group have updated their single centre data [39] to include 4505 patients between 1990 and 2006 with 0.19% ureteric injury rate in LSH and 0.32% in laparoscopic total hysterectomy (LTH) a conglomerate of laparoscopic assisted vaginal hysterectomy (LAVH), LH and TLH. The Cochrane review has also been updated [40] to include 34 studies with 4495 women. The additional data has not changed the Author's conclusions but the increased power allowed some comparison of LAVH and TLH. This leads us on to a discussion of the debate around LSH and LH.

Total versus Subtotal Laparoscopic Hysterectomy Debate

The late pioneering German gynaecological surgeon, Kurt Semm, published a 'classic intrafascial supracervical hysterectomy' using 'pelviscopy' in 1989 [41]. Semm's technique involved a novel 'calibrated uterine resection tool' to core out the cervix with removal of the uterus via a 'serrated edged macro-morcellator'.

This technique in a variety of forms has been reported in observational studies as leading to faster recovery and faster return to normal activities when compared to laparoscopic hysterectomy when both the body of the uterus and cervix are removed [42-44]. If this advantage is real the implications to women undergoing this surgery may be important, both in terms of patient morbidity but perhaps even more relevant in the current financial climate: with respect to faster return to work and contribution to the wider society. In hospital stay was not significantly different whether subtotal hysterectomy was performed abdominally or laparoscopically in one Scandinavian study which employed a form of the enhanced recovery programme to the abdominal arm [45]. However, Oscarrson and colleagues did confirm greater disability days following discharge from hospital in the SAH group versus the LSH group. Observational [46] and randomised studies [47] from Oslo University hospital confirm that LSH is consistently possible within the outpatient setting. However, the RCT found a deleterious effect on quality of life measures in the patients operated on as day cases. Others routinely discharge LSH patients home the same day [48-50] with no apparent increase in readmission rates.

Theoretically in the LSH technique less extensive separation

of the bladder from the cervix and removing the uterus at the level of the internal os should, intuitively, be associated with fewer bladder and ureteric injuries than in LTH. More recent observational comparisons of the two techniques have produced conflicting results. Two retrospective studies have shown fewer baldder injuries in LSH compared with LTH [51,52] but in a Canadian smaller retrospective study bladder injury rates were comparable between the two groups [53]. None of the studies showed a difference in ureteric injury rates but much larger numbers would be required to show a real difference. A prospective comparison has shown no difference in operating time between LSH and LTH [54] in keeping with the largest retrospective review [51] but Cipullo reported longer operating times with LTH compared to LSH [52]. An earlier study showed longer operating times with LAVH compared to LSH [55]. In the largest retrospective study the hospital stay was on average 5 hours longer for LTH compared to LSH [51]. Although the difference was statistically significant this does not constitute a clinically important difference. Of much more relevance is days taken to return to normal activities which was not examined in the study. In a small prospective study no difference in quality of sexual life was found between the 2 techniques [56]. In a smaller RCT sexual function improved in both LTH and LSH groups compared to non-hysterectomised controls but there was no difference according to the type of hysterectomy performed [57]. These findings were in keeping with an earlier RCT and parallel observational study [58]. In a larger more recent RCT a definite advantage was observed following SAH with regards to sexual pleasure and orgasm frequency but the authors encourage caution when interpreting the results [59]. The inclusion criteria were narrower than many other studies and enrolled only premenopausal women in whom the ovaries were to be conserved. There is no clear consensus regarding laparoscopcic conservation of the cervix at the time of hysterectomy and subsequent sexual function.

The advantage of LSH versus LH seen in some observational studies has not been confirmed in the only published randomised comparison of LSH with TLH which examined short term outcomes including recovery [30]. The study had a number of limitations. The study screened 529 women but only 154 premenopausal women with abnormal uterine bleeding or symptomatic fibroids were assessed as eligible, of which 141 agreed to randomisation. The Authors did not present the reasons for exclusion of 388 women, over 73% of those screened, which may represent selection bias. 6 patients in each group did not have the intended intervention due to technical/clinical reasons (8.4-8.6%) and it is not clear whether the outcomes were analysed according to intention to treat. With regards to post-operative recovery, the Authors did not stipulate the tool used to assess recovery and whether this is validated. Furthermore the participants were assessed at 3 monthly intervals from operation for 24 months. Case series suggest recovery from LSH occurs much earlier with return to normal quoted from within 3-21 days [60,61]. It follows that in order to detect a difference in recovery between the 2 treatment groups frequent assessments are necessary during the first 3 months following surgery. More minimally invasive techniques for treatment of menstrual disorders have been the subject of randomised comparisons against LSH. Although endometrial resection and thermal balloon ablation are effective treatments for menometrorrhagia, overall satisfaction following LSH is significantly better [61,62].

The question of whether SAH has advantages over TAH appears to have been answered and no advantage has been confirmed. However, the same question with regards to the laparoscopic route is far from answered. We aim to address this enormous gap in the literature by conducting a feasibility study of an RCT to compare recovery, pelvic floor and sexual function following LSH with LH. To our knowledge this question has not been adequately addressed.

Feasibility Study Rationale

The current study is reported according to the published Consolidated Standards for Reporting Trials [63].

One definition of a feasibility or pilot study includes preliminary test or trial run of an investigation designed to test the feasibility of methods and procedures for later use on a large scale or to search for possible effects and associations that may be worth following up in a subsequent larger study' [64]. The British Medical Research Council explicitly recommends the use of feasibility studies prior to Phase III trials [65]. Phase 3 studies are large, double-blind, randomized, controlled trials on large patient groups designed as the definitive assessment of a new therapy's efficacy, especially in comparison with currently available alternatives (www.geovax.com/technologyandproducts/glossary.php). The main goal of a feasibility study is to avoid embarking on a large scale study which may fail to recruit or fail to complete, thereby wasting resources in terms of time and effort.

Aims and Objectives

In keeping with these recommendations we set out to assess the feasibility of conducting a randomised, double blinded comparison of post-operative recovery following laparoscopic hysterectomy (LH) with that following laparoscopic supracervical hysterectomy (LSH). The paucity of grade 1 evidence on the topic was established following a systematic review of the literature as described in Appendix 1and is detailed in the background section.

The primary aims of the feasibility study are in keeping with examination of process, resources, management and scientific factors which have previously been defined as the cardinal aspects of pilot studies [66]. The process was investigated in terms of recruitment rate, refusal rates, completion rates and non-compliance with protocol rates. Resources and management were investigated in terms of time to obtain informed consent, time to administer and input questionnaires, hardware, software requirements and time for statistical analysis. Scientific factors which were examined included immediate/short term complications, quality of recovery, depression scores, pelvic floor and sexual function using validated questionnaires. The primary aim of the definitive study is to detect a clinically important difference in quality of recovery between women undergoing the 2 types of laparoscopic hysterectomy under study. The corresponding null hypothesis is that there is no difference in recovery and short term outcomes in women undergoing laparoscopic hysterectomy (LH) when compared with women undergoing laparoscopic supracervical hysterectomy (LSH).

To our knowledge there has been no published RCT comparing LSH with LH. The approach of choice for extirpation of the uterus for benign indications is vaginal hysterectomy (VH). When VH is not practicable LH should be offered but there is paucity of evidence with regards to which type of laparoscopic hysterectomy should be offered. The feasibility study outlined is designed to assess whether it is realistic and practicable to recruit to an RCT aimed at addressing this enormous gap in

the literature.

The primary outcomes of the definitive RCT are post-operative recovery, post-operative mood states, intermediate term urinary, bowel and sexual functioning. The feasibility study will allow detailed assessment of recruitment to the proposed RCT in a single centre (Author's main hospital of practice) with a single primary surgeon (Author).

The quantitative results of the feasibility study will be used to inform power calculations to estimate numbers required for the definitive study. Secondary aims of the definitive study would include long term comparisons of pelvic floor and sexual function between women undergoing LH and LSH. Although these outcomes have been extensively investigated with regards to abdominal hysterectomy, no comparisons exist for the laparoscopic approach. The feasibility study was granted approval from the National Research Ethics Committee and the Local Research Ethics committee (Appendix X).

It is important to predefine the criteria for success of a feasibility study at the outset [67]. The feasibility study was set up to recruit 50 participants over 12 months and complete all surgery within 6 months of recruitment. All outcome data would be collected within a further 6 months. The number of participants was arbitrarily based on the principal investigators clinical caseload (approximately 75 eligible women per year). Predefined criteria for determining success of the feasibility study are listed below.

Recruitment and data collection should be completed within 2 years of study commencement.

More than 70% of eligible women approached to take part should agree to randomisation.

A minimum of 95% of participants should have treatment according to randomisation.

All data should be complete at baseline (QoR-40, CES-D, e-PAQ and FSFI).

The randomisation procedure used should reliably rule out selection bias and be simple to administer.

The study protocol should ensure reliable blinding of treatment allocation from the patient and the data handler.

A minimum of 85% should have complete recovery data at 6 weeks.

A minimum of 75% should have complete recovery data at 12 weeks.

A minimum of 85% should have complete e-PAQ and FSFI data at 6 weeks.

A minimum of 70% should have complete e-PAQ and FSFI data at 6 months.

The process of completing the questionnaires should be simple to understand and be completed within 10 minutes for the short questionnaires (QoR-40 and CES-D) and within 30 minutes for the longer questionnaires (e-PAQ and FSFI).

Materials and Methods

Setting

The setting was a district general hospital in the Southeast of England, Medway Foundation Hospital, an associate University Hospital to the University of London.

Inclusion Exclusion Criteria

The recruits were premenopausal women who had completed their families and had a benign indication for hysterectomy. Women were excluded if the uterine size was estimated as greater than that of a 16 week pregnancy at the time of surgery or if there was greater than first degree uterine prolapse at examination under anaesthetic. Recruits were required to be up to date with cervical cytology screening and on a routine recall schedule. If a smear was due this was taken at the initial invitation to the study. The recruits were from a single clinician's caseload and the surgery was completed by the named clinician.

Inclusion criteria are summarised below.

- Benign indication for hysterectomy
- Uterine size < 16/40
- Normal cytology & on routine screening schedule
- No more than 1st degree prolapse
- Premenopausal
- Family complete

Exclusion criteria are summarized as

- Postmenopausal women
- Undiagnosed abnormal vaginal bleeding
- History of high grade cervical intraepithelial neoplasia
- Uterovaginal prolapse > stage I [68]
- Previous gynaecological malignancy
- Previous extensive pelvic surgery
- Current use of antidepressant/antipsychotic treatment
- Inability to read or write fluently in English.

Potential recruits were invited to participate in the clinic setting at the time of discussion regarding treatment by laparoscopic hysterectomy. Hysterectomy as a treatment was discussed in general as per the principal investigators normal clinical practice. The two different types of laparoscopic hysterectomy on offer (Stage 4 and stage 6 Garry and Reich classification)[69] were discussed in detail and written information was supplied to support the discussion (Appendix II). Potential recruits were formally invited to take part by letter (Appendix IIIa) and were given specific information about the study (Appendix IIIb and IV). Potential recruits were seen again at an interval of 2 to 4 weeks for completion of consent. Those women agreeing to take part were formally invited onto the study at the time of consent. The informed consent process was in keeping with good clinical practice and it was made absolutely clear that the participants were at liberty to withdraw consent from the study at any time.

Standardised Surgical Technique

A standardised surgical technique was used for both arms of the study. There are numerous descriptions for LSH and LH in the literature. The procedures were carried out according to the usual practise of the principal investigator who was the primary surgeon for all 50 cases. A large part of both procedures are the same and will be described first. General anaesthesia is induced and maintained by a single anaesthetist.

A size 12 Foley catheter is inserted into the bladder and a PelosiTM (CooperSurgical, Connecticut USA) manipulator is used to cannulate the endometrial cavity.

A 5mm primary bladeless, dilating tip trocar (Excel™, Ethicon, Cinncinati, USA) is inserted into the umbilicus under direct vision. Once intraperitoneal placement is confirmed a carbon dioxide pneumoperitoneum is established at a pressure of 15mmHg. The patient is placed in 30° Trendelenberg and 3 accessory ports are inserted under direct vision. The position

of the ports are lateral at the level of the umbilicus on either side and the third, 2 fingers breadth above the symphysis pubis. The two lateral accessory ports are 5 mm in diameter and the suprapubic port is 12mm in diameter. Smart bipolar tissue fusion via a single use 5mm diameter blunt tip forcep with tissue sensing (LigasureTM Covidien, Mansfield Massachusetts, USA) is used to coagulate the proximal portion of the left Fallopian tube and utero-ovarian ligament, if the ovary is to be conserved, or the left infundibulopelvic ligament if removal of the ovary is desired, after identification of the position of the ureter at the pelvic brim. Coagulation and dissection are continued through the round ligament to gain access to the space between the 2 leaves of the broad ligament. The uterovesical fold of peritoneum is dissected with scissors and monopolar diathermy at 30W cutting. The bladder flap is reflected caudad. A posterior peritoneal flap is similarly dissected and reflected to mobilise the ureters caudad. The ascending branch(es) of the left uterine arteries are coagulated but not transected with the tissue sensing bipolar forceps. The steps are repeated on the right side of the pelvis after delineation of the pelvic course of the right ureter. The remainder of the procedure differs according to treatment allocation.

For LH the main trunk of the uterine artery is coagulated and transected superomedially to the course of the ureter. The uterosacral ligaments are coagulated close to the arch of the uterosacrals. The remainder of the procedure is carried out via the vagina after removal of the uterine manipulator. Forty mls of 1:200 000 adrenaline in normal saline solution is infiltrated into the subcuticular space around the cervix taking care to avoid intravascular injection. The cervix is circumscised with a monopolar angled needle using blended diathermy of 100W cutting and 60W coagulation. The supra-vaginal septum is divided to allow cranial reflection of the bladder. The Pouch of Douglas is entered with a single cut into the peritoneum underlying the vaginal skin in the posterior vaginal fornix. The uterosacral ligaments are clamped with curved Zeppelin clamps, cut, transfixed and ligated with 1 Vicryl® (Ethicon division of Johnson & Johnson, New Jersey, USA) prior to removal of the uterus and cervix. The vaginal skin and peritoneum are sutured en-masse with locking 0 Vicryl® and suspended to the uterosacral ligaments.

In the case of LSH the ascending branches of the uterine arteries are coagulated but not transected at just below the junction of the uterine corpus and cervix. The Pelosi uterine manipulator is removed. A 100W monopolar diathermy loop (Lap Loop™, Roberts Surgical, Worcester, UK) is used to amputate the body of the uterus from the cervix. The uterus is morcellated and removed piecemeal with a 15mm disposable morcellator (Morcellex Gynecare division of Johnson & Johnson, New Jersey, USA) which is inserted suprapubically with a dilating tip blunt trocar. The endocervical canal and cervical stump are coagulated with bipolar diathermy.

The remainder of the procedure is the same for both techniques. Haemostasis is confirmed laparoscopically. A 4.7mm (14 gauge) RedivacTM drain is left in the pelvis through the right lateral port, secured with a silk suture and clamped for 30 minutes. 30mls 2.5% chirocaine is instilled intraperitoneally. The accessory ports are removed under direct vision. The 12-15mm suprapubic port site is closed with 1 Vicryl® on Endoclose® (Tyco, Hampshire UK).The pneumoperitoneum is deflated and the laparoscope and primary trocar are removed under direct vision. The skin is closed with subcuticular 3-0 Vicryl Rapide® (Ethicon). 10mls 2.5% chirocaine is injected subcuticularly at the port sites. The Redivac drain is removed when there is less than 100mls drained in 6 hours after mobilisation out of bed. Analgaesia is commenced per-operatively with intravenous diclofenac 75 mg and paracetamol 1g together with 8 mg dexamethasone and 4mg ondansetron as antiemetic.

Patients are transferred to the ward after recovery from anaesthesia. Hourly vital signs are maintained until stable and then reduced to 4 hourly observations. The catheter is removed once the patient is able to mobilise out of bed. The majority of patients are discharged within 1-2 days of admission with simple analgaesia.

Randomisation

Randomisation was conducted at the time of laparoscopy using a web based computer generated randomisation service (www.sealedenvelope.com/freerandomiser/v1).The reason for randomisation after laparoscopy was so that only recruits in whom both techniques were deemed practicable were randomised.

Outcomes

Participants were asked to complete a number of validated questionnaires prior to randomisation and then again prior to discharge after surgery. Two short questionnaires were used, the Quality of Recovery 40 (QoR-40 Appendix VI) [70] and the Center for Epidemiologic Studies Depression Scale (CES-D, Appendix VII) [71]. In a systematic review of 'Recovery Specific Quality of Life Instruments' [72] the QoR-40 was the best validated tool with regards to short term post-operative recovery.

Operative findings were completed by the surgeon immediately post procedure using a proforma (Appendix V). The participants were requested to fill in the pair of short questionnaires preoperatively, at discharge and at weekly intervals from the first post-operative week up to and including the 12th post-operative week (fourteen pairs of questionnaires in total). A fifteenth pair of questionnaires were requested at the sign off visit at 6 months. The QoR-40 poses 40 questions to the recipient, each of which are scored from a minimum of 1 to a maximum of 5. The global QoR-40 score may vary between 40 (worst possible recovery) and 200 (best possible recovery) and the Author of the questionnaire has previously shown that a difference in scores of 5 is clinically important [70]. The CES-D includes 20 questions scored from 0 to 3 with minimum total score of 0 and a maximum possible score of 60. A score of over 16 signifies depression. The majority of the short questionnaires were completed electronically via secure e-mail (44 patients). The remainder were collected in hard copy via stamped, self-addressed envelopes (6 patients).

A further 2 validated questionnaires were used, a paper version of the electronic Personal Assessment Questionnaire version 10 (e-PAQ [73] Appendix VIII) and the Female Sexual Function Index (FSFI [74] Appendix IX). The pair of long questionnaires were given to the participants in paper format to fill out prior to admission, at 6 weeks and at 6 months.

The e-PAQ is available in electronic format but in view of the cost (£6000 p.a. recently reduced to £2000 p.a.) a paper format was used. This questionnaire has questions divided into 4 domains. Namely these are urinary, bowel, vaginal and sexual. The domains are subdivided into 5 sub-domains in the case of urinary, bowel, and sexual domains and 4 sub-domains in the case of the vaginal domain. The score from each sub-

domain is multiplied by a factor to give a score out of a possible maximum score of 100 (worst possible score) and a minimum score of 0 (perfect score). The scores for each sub-domain are amenable to numerical comparison longitudinally i.e. at baseline, 6 weeks and 6 months and between treatment groups. The FSFI questionnaire consists of 19 questions which can score between 1-5 (questions 1 & 2 desire domain) and between 0-5 for the remaining questions (3-6 arousal domain, 7-10 lubrication domain, 11-13 orgasm domain, 14-16 satisfaction domain and 17-19 pain domain). The scores for each domain are multiplied by a factor to give a maximum possible score of 6. The total score for the questionnaire may vary from 2 (worst possible sexual function) to 36 (best possible sexual function). Scores are amenable to intra-individual numerical comparison longitudinally and between treatment groups.

The questionnaire data was inputted onto an Excel spread sheet and imported onto SPSS version 19 (SPSS Inc. Chicago, Illinois) for statistical analysis. The inputting of the data was undertaken without prior knowledge of treatment group allocation.

Results

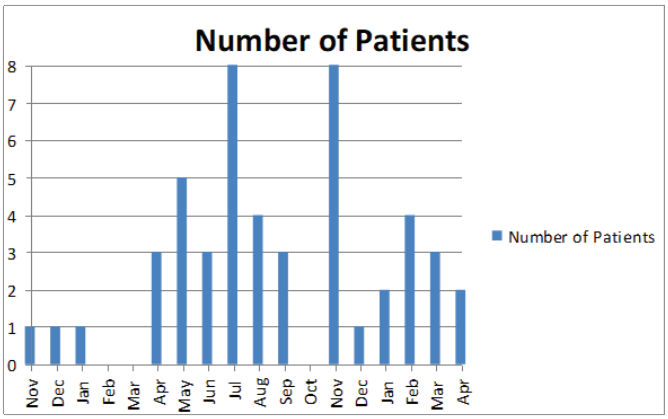


Chart 1. *Recruitment Time line*

Recruitment and surgery was completed in 18 months and data collection was concluded within 2 years of study commencement (see chart 1 recruitment time line).

Recruitment was slower than anticipated, particularly at the outset (50% longer to reach 50 recruits) but the predefined overall time to complete data collection was not exceeded so this part of the study was deemed feasible. In the first 5 months only 6 patients were recruited. If the intial slow months are excluded the average recruitment rate was 4 participants per month with peak recruitment of 8 in month.

50 participants were randomised from a potential 70 recruits. Reasons for exclusion are summarised in table 1.

The commonest single reason for exclusion was a strong opinion regarding cervical conservation. Two women did not want the cervix removed and 6 could not contemplate having the cervix conserved (40% of all exclusions and 11.5% of total invitees). Technically these were the only eligible women who went on to have hysterectomy that refused randomisation. This is a refusal rate of 8/58 (13.8%). In 5 patients the symptoms had resolved and a further 2 changed their mind regarding major surgery. One patient was excluded on the basis of abnormal cervical screening cytology taken at the invitation clinic visit. One patient became pregnant whilst awaiting surgery as part of the study; she returned for surgery after the baby had been delivered but was out of time with regards to the feasibility study. Three patients were excluded under anaesthetic. In one case the cervix was inaccessible secondary to cervical fibroids, in another case a vaginal hysterectomy was performed; in the third case the patient was found to have a frozen pelvis and hysterectomy was deferred until she had received formal bowel preparation. A fourth patient was excluded at the time of laparoscopy because of an inadvertent injury to the transverse colon at the time of insertion of the primary trocar. She had previously had a laparoscopic cholecystectomy and the transverse colon was adherent under the umbilicus. The injury was immediately recognised and sutured without spillage of bowel content. She made an uneventful recovery and went home on the second post-operative day. She subsequently re-enrolled on the study at an interval of 3 months. On the second

Table 1. *Reasons for Exclusion*

Reason for exclusion	Number	% total patients (n=70)
Symptoms resolved	5	7.1%
Declined conservation of cervix	6	8.6%
Declined removal of cervix	2	2.9%
Changed mind and declined major surgery	2	2.9%
Cervix inaccessible	1	1.4%
Severe dyskaryosis at baseline cytology	1	1.4%
Suitable for vaginal hysterectomy	1	1.4%
Pregnant	1	1.4%
Frozen Pelvis at index laparoscopy	1	1.4%
Included	50	71.4%
Total	70	100.0%

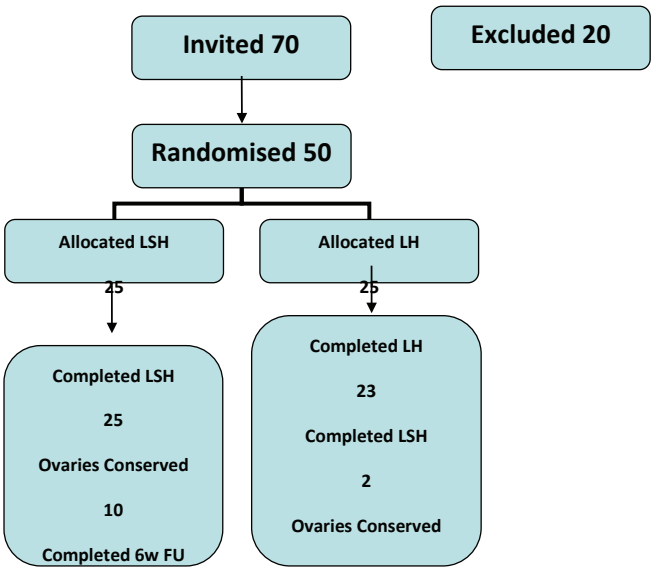


Chart 2. *Participant Flow*

Table 2. *Baseline Characteristics*

Variable	LH (n=25)	LSH (n=25)	Not randomized (n=19)	P value
Age in years	44 (38-46)	44 (40-47)	47 (42-49)	0.298
Body mass index in kg/m^2	26 (23-34)	29 (24-30)	27 (25-32)	0.841
Parity				
Nulliparous, n (%)	2 (8.0)	3 (12.0)	1 (5.3)	
Para 1 or 2, n (%)	13 (52.0)	12 (48.0)	13 (68.4)	0.607
Para 3 or more, n (%)	10 (40.0)	10 (40.0)	5 (26.3)	0.872
Previous CS				
None, n (%)	20 (80.0)	19 (76.0)	11 (57.9)	
One CS, n (%)	2 (8.0)	4 (16.0)	4 (21.1)	0.368
Two or more CS, n (%)	3 (12.0)	2 (8.0)	4 (21.1)	0.344

Table 3. *Baseline Characteristics*

Variable	LH (n=25)	LSH (n=25)	P value
Pre-operative hemoglobin (g/dL)	13.8 (13.2-14.4)	13.1 (12.7-14.1)	0.063
Post-operative hemoglobin (g/dL)	11.8 (11.3-12.5)	11.5 (10.9-12.4)	0.691
Oophorectomy			
Conserved, n (%)	7 (28)	10 (40)	0.551
Unilateral oophorectomy, n (%)	3 (12)	0 (0)	0.235
Bilateral oophorectomy, n (%)	15 (60)	15 (60)	1.000
Duration of surgery (minutes)	105 (81-129)	80 (63-99)	0.014
Estimated blood loss (mL)	200 (125-300)	100 (100-200)	0.011
In-patient stay (days)	2 (1-2)	1 (1-2)	0.326
Histology of specimen			
Fibroids, n (%)	7 (28)	9 (36)	0.762
Adenomyosis, n (%)	4 (16)	5 (20)	1.000
Endometriosis, n (%)	1 (4)	2 (8)	1.000
Endometrial hyperplasia, n (%)	3 (12)	0 (0)	0.235
Normal histology, n (%)	10 (40)	9 (36)	1.000

occasion a Palmer's point entry was used which facilitated avoidance of her midline adhesions. She was randomised to LH but during the course of the procedure it became clear that LSH was a safer option. After the initial protocol violation data collection was completed uneventfully. Patient flow is summarised in chart 2.

All surgery was performed by one surgeon (principal investigator). The participant was unaware of which procedure had been undertaken and this was revealed after 1 year from the operation so that participants could continue on the cervical screening programme if necessary. Data was put onto an Excel data base without prior knowledge of treatment status by the data handler.

The distribution of the quantitative data obtained from all the questionnaires was tested using Komolgorov-Smirnov for the first 6 weeks. Pre-op QoR-40 scores were not normally distributed (K-S z=1.807, p<0.05) and week 2 QoR-40 scores were also not normally distributed (K-S z=1.398, p<0.05). Based on these observations we applied non-parametric statistical tests to the data. The Wilcoxon signed ranks test was used to compare scores with preoperative baseline and the Mann-Whitney U test was used to compare scores between treatment allocation groups at baseline. All analysis was according to intention to treat.

Pre-op (baseline scores) were compared between treatment groups for all the questionnaires and subdomains using the Mann-Whitney U test. There were significant differences at baseline for QoR-40: U=197, p=0.025 (LSH have a higher score), e-PAQ-B(IBS): U=195, P=0.022 (LH group have a higher score) and e-PAQ-B (Constipation); U=190, p=0.014 (LH group have a higher score) (Table 5). There were no statistically significant differences between treatment allocation groups at baseline with regards to CES-D scores, the remaining 17 sub-domain scores in e-PAQ and FSFI scores. This supports the randomisation method which has resulted in largely homogenous groups at baseline. Baseline characteristics for both treatment groups and excluded patients are summarised in tables 2 & 3.

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	N of Valid Cases	50
Pearson Chi-Square	.802[a]	1	.370		
Continuity Correction[b]	.357	1	.550		
Likelihood Ratio	.805	1	.370		
Fisher's Exact Test				.551	.276

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 8.50.

b. Computed only for a 2x2 table

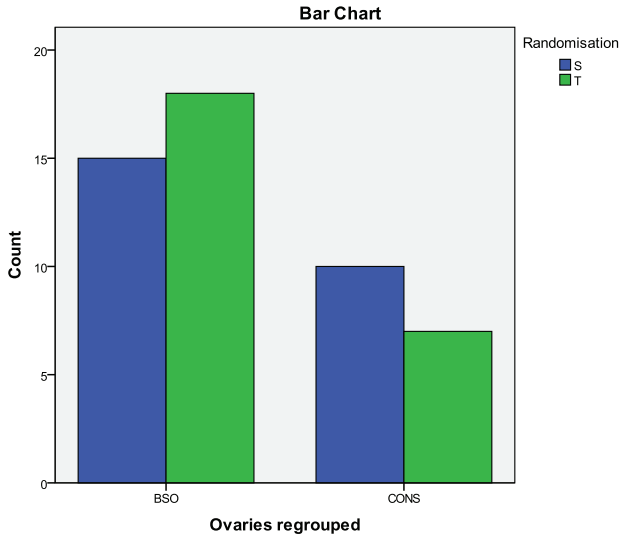


Chart 3. *Baseline Characteristics according to oophorectomy*

There was no significant difference between the groups at baseline with respect to age, parity and previous caesarean sections. There was no significant difference at baseline with respect to pre-operative haemoglobin concentration according to treatment allocation. Whether the patient was left with any ovaries following surgery was a clinical decision between the patient and the surgeon. However there was no significant difference according to treatment allocation (chi square .802, p=0.370 2 sided with 1df chart 3).

Indications for hysterectomy are summarised in table 4

There was no difference at baseline with regards to primary indication for surgery and treatment allocation (chi square 3.429, p=0.489 2 sided with 4 df chart 4).

These findings are supportive of the randomisation procedure employed and we would plan to use this method in the definitive study.

96% of the participants had treatment according to randomisation; criterion for success was predefined as greater than 95% treatment according to randomisation. Two patients randomised to LH actually received LSH. In one case this was a simple human error in interpreting the web generated randomisation code. The second protocol violation was intentional and is dealt with in the discussion. The quantitative analyses were according to intention to treat to correct for selection bias.

A number of participants required additional procedures at the time of surgery. In 4 cases adhesiolysis was performed. In one case a transobturator tape continence procedure was performed at the end of her surgery. Two women required removal of contraceptive implants at the end of surgery. The additional procedures were excluded from calculation of the

Indication1 * Randomisation Crosstabulation

Count

		Randomisation		Total
		S	T	
Indication1	Menorrhagia only	9	8	17
	Menorrhagia and dysmenorrhea	13	14	27
	Dysmenorrhea only	2	0	2
	Pelvic pain	1	2	3
	Irregular bleeding	0	1	1
Total		25	25	50

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	3.429[a]	4	.489
Likelihood Ratio	4.595	4	.331
N of Valid Cases	50		

a. 6 cells (60.0%) have expected count less than 5. The minimum expected count is .50.

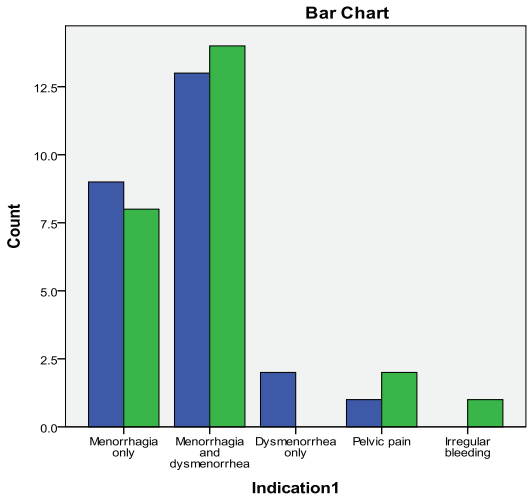


Chart 4. *Indication for Hysterectomy*

operative time which was taken from the initial abdominal (umbilical excision) until the last abdominal skin suture.

Estimated blood loss was statistically significantly less in the LSH group (100mls) compared to the LH group (200mls), p=0.011. However the volumes involved are not clinically important. Two participants received 2 unit blood transfusions each. The first woman suffered a primary post-operative haemorrhage and was taken back to theatre 6 hours after the initial surgery. A repeat laparoscopy revealed bleeding from both uterine arteries and the vaginal vault. The bleeding was controlled with a combination of bipolar diathermy and laparoscopic extracorporeal sutures. She was nursed in the surgical High Dependency Unit overnight but made an uneventful recovery and was discharged home on the 3rd post-operative day. The second woman had a pre-operative haemoglobin concentraton of 9.2 g/dl secondary to hermenorrhagia.

Table 4. *Indications for hysterectomy*

	LH		LSH		Excluded	
Menorrhagia only	8	32%	9	36%	4	21%
Menorrhagia &Dysmenorrhea	14	56%	13	52%	9	47%
Dysmenorrhea only	0	0%	2	8%	1	5%
Pelvic pain	10	40%	10	40%	10	53%
Irregular Bleeding	14	56%	14	56%	4	21%
Abdominal mass	1	4%	3	12%	3	16%
Premenstrual Syndrome	0	0%	2	8%	2	11%
Ovarian cyst	1	4%	1	4%	0	0%
Anaemia	0	0%	0	0%	2	11%

Operative time was shorter in the LSH group (average 81 minutes) compared to the LH group (average 105 minutes) p=0.014. Hospital stay was not significantly different according to treatment group (1-2 days).

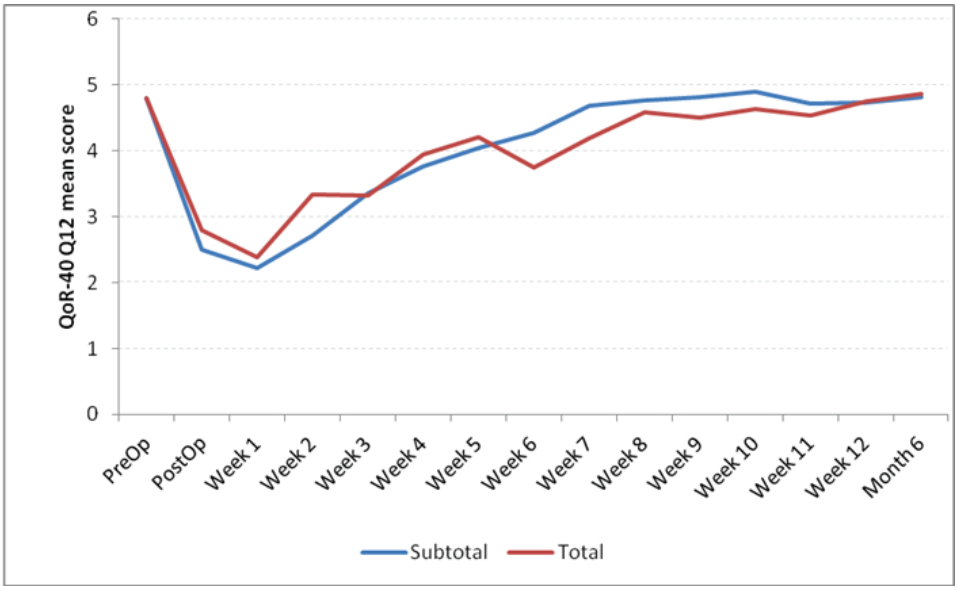
Questionnaire data was complete at baseline with progressive attrition as the study progressed. At 6 weeks recovery data (QoR-40 and CES-D) was complete for 44 participants or 88% in keeping with predefined requirement for feasibility (>85% complete data at 6 weeks). Beyond 6 weeks there was incremental missing data and at 12 weeks only 60% of recovery data was complete (tables 6 and 7). We aimed to collect complete data in at least 75% of participants at 12 weeks. This part of the feasibility study was unsuccessful according to our predefined feasibility success criteria. Mean combined QoR-40 and CES-D scores are shown week by week in tables 6 and 7. QoR scores fell below baseline but returned to preoperative levels at 4 weeks. With regards to CES-D the mean peak scores are at post-op, week 1 and week 2 (greater than average score of 16 corresponding to clinical depression) with a rapid fall to a score of, on average, 10 or less by week 5. The study is feasible with regards to week by week data up to and including 6 weeks. After 6 weeks both QoR-40 scores and CES-D scores remained relatively flat so the missing data form 6 weeks onwards does not appear discriminatory. A second peak of CES-D scores was observed at week 9 but did not reach the threshold of 16 which defines depression in accordance with the authors of CES-D.

The time to fill in the short recovery questionnaires (QoR-40) and depression scores (CES-D) was, on average, less than 10 minutes.

Filling in the paper version of e-PAQ and FSFI took over 30 minutes on average and a number of questionnaires were incompletely filled in. The data were complete at baseline. At 6 weeks 90% of e-PAQ and FSFI data were complete (in keeping with the requirement to confirm feasibility. At 6 months 76% of e-PAQ and FSFI data were complete which was within the required 70% for success of feasibility.

However, on closer inspection of the responses a number of points of confusion were discovered with the e-PAQ. The paper version of the e-PAQ is unacceptably cumbersome and difficult to administer. The FSFI questionnaire is simpler than the e-PAQ and as the name suggests is designed to assess sexual function in a reproducible way. The long term aspects of pelvic floor and sexual function were not reliably assessed in this feasibility study. Reasons and possible improvements are explored in the discussion.

In view of the fact that there were significantly higher QoR-40 scores at baseline in those randomised to LSH compared to those randomised to LH, we compared in allocation group scores with baseline using the Wilcoxon signed ranks test (Table 8). In the LSH group there is no significant difference



Tables 6 and 7 Combined QoR-40 and CES-D scores

Group	Pre-op	Post-op	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Month 6
Subtotal Descriptives															
Mean	187.2	174.625	173.4783	178.0476	183.913	184.52	187.0909	188.28	189.4737	191.7647	190.1176	191.3889	191.9412	192.3333	186.1538
Standard deviation	11.55422	13.64077	12.46402	13.62159	11.41336	14.56915	13.16167	8.885944	10.28142	9.463941	10.94236	10.16418	10.04658	9.309493	14.67904
Median	190	175.5	172	182	186	187	187.5	190	193	193	194	195	193	193	193
Difference from baseline															
p value (related samples Wilcoxon signed ranks test)		0.001	0.001	0.003	0.322	0.922	0.434	0.615	0.371	0.073	0.552	0.041	0.102	0.157	0.388
Significant?		Y	Y	Y	N	N	N	N	N	N	N	Y	N	N	N
Total Descriptives															
Mean	173.12	164.3333	166.1364	163.8571	173.1429	175.7	177.5789	179.1	179.6316	174.7059	167.2105	176.7647	177.4118	166.7333	180
Standard deviation	38.2724	19.25722	15.80023	39.97535	21.2068	22.32087	23.05625	20.4628	21.60044	22.90678	45.73666	22.0015	20.88378	51.43716	16.71077
Median	181	163.5	169	175	182	181	184	185.5	185	177	177	180	185	188	181
Difference from baseline															
p value (related samples Wilcoxon signed ranks test)		0.005	0.001	0.002	0.046	0.121	1	0.643	0.635	0.331	0.422	0.552	0.981	0.754	0.138
Significant?		Y	Y	Y	Y	N	N	N	N	N	N	N	N	N	N

from baseline at 3 weeks and in the LH group there is no significant difference from baseline at 4 weeks. This suggests that the advantage with respect to short-term recovery in the LSH group may only mean a difference of 1 week. Comparison of CES-D scores showed no discernible pattern (Table 9).There were no statistically significant differences between the treatment allocation groups according to whether the participant had any remaining ovary after the procedure or not (Chart 3). There were no significant differences between treatment allocation groups according to primary indication for hysterectomy. These observations further support the randomisation method used.

Recovery and mood scores were analysed longitudinally and compared with baseline according to whether any ovarian tissue was conserved or not. Recovery was not significantly different according to ovarian status (statistically significant worse QoR-40 scores compared to baseline in both ovarian conservation and extirpation groups for post-op, week 1 and week 2, table 10). However, there appeared to be a statistically significantly better CES-D score compared to baseline in those women undergoing oophorectomy at week 5, week 12 and month 6 (Table 11).

The 12th question in QoR-40 concerns 'return to work or usual home activities'. We analysed this comparing each score to baseline (chart 6) for this specific question using Wilcoxon Signed Ranks test. Normal activity was denoted by a maximum score of 5. Our findings show a statistically significant difference from baseline in the LSH group until 7 weeks whereas this persists in the LH group until 8 weeks. Alternatively the median score was consistently 5 (denoting normal activity all of the time) from week 6 onwards in the LSH group whereas a median score of 5 was not consistently reached in the LH group until week 8 (Tables 12 and Chart 5).

The long questionnaire data (e-PAQ and FSFI) satisfied all the criteria for feasibility with 100% complete data at baseline, 90% complete data at 6 weeks and 74% complete data at 6 months.

The 19 sub-domains from e-PAQ and overall FSFI scores were compared to baseline at 6 weeks and 6 months (Tables 13- 32).

Scores for urinary incontinence and overall urinary quality of life were statistically significantly better at 6 weeks in the group randomised to LSH but this was not observed at 6 months.

Scores for bowel continence were also statistically significantly better at 6 weeks compared to baseline in the group randomised to LSH but this was not seen at 6 months.

Scores relating to vaginal pain were statistically significantly better than baseline at 6 weeks and 6 months in the group randomised to LSH. Scores relating to vaginal prolapse symptoms were statistically significantly better at 6 weeks in the group randomised to LH. Overall quality of life with respect to vaginal symptoms was statistically significantly better at 6 weeks for both groups and at 6 months in the group randomised to LH.

Sexual function and urinary symptoms were statistically significantly better than baseline at 6 weeks in the group randomised to LSH but this was not observed at 6 months. Sexual problems associated with vaginal symptoms were statistically significantly better than baseline at 6 weeks in both groups but not at 6 months. Dyspareunia was statistically significantly better than baseline at 6 weeks in the group randomised to LSH but this was not observed at 6 months. Overall sexual function was statistically significantly better

***Table 13**. Bladder Sub domain pain*

e-PAQ-U-Pain				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives**			
	Mean	6.67	9.78	8.15
	Standard deviation	12.422	16.455	14.221
	Median	.00	.00	.00
	Difference from baseline			
	p value (related samples Wilcoxon signed ranks test)		0.208	0.705
	Significant?		N	N
Total	**Descriptives**			
	Mean	8.44	13.89	16.16
	Standard deviation	14.084	16.071	15.996
	Median	.00	5.56	11.11
	Difference from baseline			
	p value (related samples Wilcoxon signed ranks test)		0.098	0.4
	Significant?		N	N

***Table 14**. Bladder Subdomain voiding*

e-PAQ-U-Voiding				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives**			
	Mean	2.66656	2.66656	4.44427
	Standard deviation	5.226149	5.753191	8.253257
	Median	.00	.00	.00
	Difference from baseline			
	p value (related samples Wilcoxon signed ranks test)		1	0.461
	Significant?		N	N
Total	**Descriptives**			
	Mean	5.99976	7.49970	16.16
	Standard deviation	9.166300	13.759082	15.488053
	Median	.00	5.56	11.11
	Difference from baseline			
	p value (related samples Wilcoxon signed ranks test)		0.098	0.4
	Significant?		N	N

***Table 15**. Bladder subdomain overactive symptoms*

e-PAQ-U-Overactive B				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives**			
	Mean	10.33292	6.66640	9.44407
	Standard deviation	20.451249	13.607732	13.312945
	Median	.00	.00	.00
	Difference from baseline			
	p value (related samples Wilcoxon signed ranks test)		0.157	0.398
	Significant?		N	N
Total	**Descriptives**			
	Mean	11.66620	12.91615	18.93864
	Standard deviation	10.205799	13.910975	18.667002
	Median	8.33300	8.33300	16.66600
	Difference from baseline			
	p value (related samples Wilcoxon signed ranks test)		0.805	0.758
	Significant?		N	N

***Table 16**. Bladder subdomain stress incontinence symptoms*

e-PAQ-U-SUI				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives**			
	Mean	15.20076	7.73372	11.11
	Standard deviation	18.411867	11.333900	14.837
	Median	6.66700	.00000	.00
	Difference from baseline			
	p value (related samples Wilcoxon signed ranks test)		0.007	0.439
	Significant?		Y	N
Total	**Descriptives**			
	Mean	14.13404	12.66730	18.18
	Standard deviation	15.907933	15.583045	24.055
	Median	13.33400	6.66700	6.67
	Difference from baseline			
	p value (related samples Wilcoxon signed ranks test)		0.838	1
	Significant?		N	N

***Table 17**. Bladder subdomain overall quality*

e-PAQ_U_Quality				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	11.11100 18.975645 .00000	3.99996 10.081868 .00000	8.14807 14.220757 .00000
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.028 Y	1 N
Total	**Descriptives** Mean Standard deviation Median	10.66656 15.869682 .00000	10.55545 26.113649 .00000	22.22200 36.174795 11.11100
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.72 N	0.776 N

***Table 18**. Bowel subdomain irritable bowel syndrome*

e-PAQ-B-IBS				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	23.67 24.729 16.67	21.33248 18.332600 16.66600	20.55473 19.635457 24.99900
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.97 N	0.36 N
Total	**Descriptives** Mean Standard deviation Median	37.00 24.541 33.33	30.41545 19.917714 33.33200	35.60464 26.896598 24.99900
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.5863 N	0.726 N

***Table 19**. Bowel subdomain constipation*

e-PAQ-B-Constipation				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	13.78 15.140 11.11	16.44 21.062 11.11	9.62953 11.778758 11.11100
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.458 N	0.68 N
Total	**Descriptives** Mean Standard deviation Median	23.56 16.140 22.22	23.89 18.478 22.22	20.20182 20.974897 11.11100
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.091 N	0.34 N

***Table 20**. Bowel subdomain evacuation*

e-PAQ-B-Evacuation				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	15.80984 11.882757 14.28600	11.61928 10.743562 9.52400	10.47640 9.891083 9.52400
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.171 Y	0.08 N
Total	**Descriptives** Mean Standard deviation Median	19.04800 15.183737 14.28600	15.95270 14.433529 11.90500	17.31636 14.170087 14.28600
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.592 N	0.282 N

***Table 21**. Bowel subdomain continence*

e-PAQ_B-Continence				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	9.14304 9.005931 4.76200	6.10 6.073 4.76	9.52400 14.510990 4.76200
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.045 Y	0.673 N
Total	**Descriptives** Mean Standard deviation Median	11.42880 8.248026 9.52400	12.62 11.693 9.52	15.15182 11.028566 14.28600
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.167 N	0.213 N

***Table 22**. Bowel subdomain overall quality*

e-PAQ-B-Quality				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	4.89 10.183 .00	2.67 9.229 .00	6.67 17.718 .00
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.34 N	0.68 N
Total	**Descriptives** Mean Standard deviation Median	6.67 8.486 .00	9.44 14.543 .00	10.10 13.567 .00
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.141 N	0.67 N

***Table 23**. Vaginal subdomains* Pain

e-PAQ-V-Pain				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	17.66596 14.296216 16.66600	8.99964 11.764984 8.33300	11.66620 14.014737 8.33300
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.009 Y	0.042 Y
Total	**Descriptives** Mean Standard deviation Median	18.66592 17.226013 16.66600	9.58295 12.173628 8.33300	16.66600 18.256688 8.33300
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.067 N	0.107 N

***Table 24**. Vaginal subdomains* Capacity

e-PAQ-V-Capacity				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	1.78 5.251 .00	.00 .000 .00	1.48147 3.909581 .00000
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.102 Y	0.317 N
Total	**Descriptives** Mean Standard deviation Median	6.22 15.739 .00	3.33 7.299 .00	5.05045 9.113237 .00000
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.414 N	0.317 N

***Table 25**. Vaginal subdomains* Prolapse

e-PAQ_V-				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	3.66652 7.248592 .00000	1.00 3.664 .00	3.33320 8.796293 .00000
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.135 N	1 N
Total	**Descriptives** Mean Standard deviation Median	6.33308 9.090230 .00000	2.08 4.584 .00	3.78773 7.784678 .00000
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.046 Y	0.146 N

***Table 26**. Vaginal subdomains* Quality

e-PAQ-V-Quality				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	16.44428 27.984137 .00000	1.78 6.939 .00	3.70367 9.072094 .00000
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.005 Y	0.108 N
Total	**Descriptives** Mean Standard deviation Median	24.88864 33.221704 11.11100	5.56 13.727 .00	2.02018 4.494621 .00000
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.026 Y	0.026 Y

***Table 27**. Sexual domains* Sex and Urinary

e-PAQ-S-Sex and Urinary				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	12.99948 26.1396 0	3.3332 10.48546 0	2.222133 5.864195 0
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.043 Y	0.144 N
Total	**Descriptives** Mean Standard deviation Median	7.99968 14.12519 0	4.58315 15.64227 0	15.15091 28.82259 0
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.715 N	0.273 N

***Table 28**. Sexual domains* Sex and bowel

e-PAQ-S-Sex and bowel				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	4.66648 14.64808 0	0.66664 2.307303 0	2.777667 7.497495 0
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.141 N	0.655 N
Total	**Descriptives** Mean Standard deviation Median	6.6664 12.02765 0	2.4999 6.677355 0	0 0 0
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.068 N	0.102 N

***Table 29**. Sexual domains* Sex and Vagina

e-PAQ-S-Sex and Vagina				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	18.66592 25.71555 0	4.9998 11.02352 0	7.221933 18.05636 0
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.018 Y	0.235 N
Total	**Descriptives** Mean Standard deviation Median	24.33236 26.45208 16.666	11.24955 24.2231 0	15.15091 30.68947 0
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.05 Y	0.161 N

***Table 30**. Sexual domains* Dyspareunia

e-PAQ-S-Dyspareunia				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	17.86756 21.66519 13.334	4.80024 9.133222 0	9.778267 13.53879 6.667
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.001 Y	0.053 N
Total	**Descriptives** Mean Standard deviation Median	17.86756 21.23346 13.334	9.3338 12.68668 6.667	15.75836 22.16669 6.667
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.063 N	0.128 N

***Table 31**. Sexual domains* -General

e-PAQ-S-General				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	28.3322 30.6174 16.666	14.33276 15.31248 16.666	18.88813 27.72106 8.333
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.051 N	0.141 N
Total	**Descriptives** Mean Standard deviation Median	33.66532 28.30768 24.999	25.41565 26.55504 16.666	16.666 24.15133 8.333
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.086 N	0.014 Y

***Table 32**. Overall FSFI score*

FSFI				
Group		Pre-op	Week 6	Month 6
Subtotal	**Descriptives** Mean Standard deviation Median	25.5125 8.063137 27.8	18.91739 11.44845 19.3	26.55 9.054925 31.55
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.033 Y	0.139 N
Total	**Descriptives** Mean Standard deviation Median	22.3875 11.0269 24.25	17.21053 14.17282 8.4	26.86 10.60107 31.45
	Difference from baseline p value (related samples Wilcoxon signed ranks test) Significant?		0.024 Y	0.017 Y

than baseline in the group randomised to LH at 6 months. With regards to FSFI overall sexual function was statistically significantly better than baseline in both groups at 6 weeks but an improvement at 6 months was only observed in the group randomised to LH.

In summary a double blind RCT to compare short and intermediate term outcomes of LSH with LH appears feasible. Recruitment rates, adherence to protocol rates and response rates were in keeping with the predefined criteria for feasibility. With regards to secondary outcomes, recovery appears quicker in LSH compared with LH, 3 weeks versus 4 weeks, with complete return to normal activities at 6 weeks in LSH versus 8 weeks in LH. Considering primary outcomes of a future definitive study urinary symptoms may be better following LSH but prolapse symptoms appear better following LH. Overall sexual function appears improved with LH rather than with LSH.

With regards to a power calculation for a future definitive study, if a difference of 5 in QoR-40 score is clinically significant, as has previously been established (Myles 2006), then 186 women will be needed in either arm for a power of 0.8 with α=0.05.

Discussion

Our study shows that a double blind, randomised comparison of short and intermediate term outcomes following LH with outcomes following LSH is feasible but raises some important factors to consider prior to roll out of a larger multicentre study. There are no published guidelines on what the criteria for success of a feasibility study should be. Each feasibility study will have specific questions to answer in the subsequent definitive study. The criteria for success are based on whether the definitive study can answer the research questions posed within a reasonable time frame and within reasonable resource constraints. We set our criteria for success based on what we would like to achieve in the definitive study in order to obtain meaningful results. If a feasibility study fails the investigators have the option to adjust the limits of time and resources for the proposed definitive study or abandon the definitive study. The methodology of the current study has not been used previously so no data were available to benchmark the current study against. Many aspects of the feasibility study are, by definition, path finding and success criteria are based on educated 'guesstimates'.

Evaluation of feasibility involves assessment of the processes that are key to the success of the definitive study, consideration of the time and resource challenges that may occur during the definitive study, human and data management problems, and lastly the scientific observations of treatment effect and variance of effect [67].

Process

Recruitment was slower than anticipated. One contributory factor for slower than anticipated recruitment was a change in the local Primary Care Trust's referral and treatment criteria for menstrual disorders. The result was a reduction in rate of referrals from primary care to secondary care for women suffering with menstrual disturbances than had been observed prior to the new directive. Primary care physicians were encouraged to try a number of conservative options for appropriate patients. The approach is recommended because it is in keeping with good clinical practice. The absolute number of referrals were not reduced but the time to enter the secondary care pathway was prolonged.

With regards to the slow start to recruitment, this was while clinician's working alongside the principal investigator were becoming accustomed to the inclusion and exclusion criteria and were in the process of identifying eligible women to bring to the attention of the principal investigator. Once all the clinic staff were familiar with the eligibility criteria, the rate of recruitment significantly improved. This may be addressed by holding start-up meetings prior to the first recruitment date to widely publicise the eligibility and recruitment criteria. This would certainly be planned for any centre recruiting to the definitive study. With the appropriate support it should be possible to recruit at least 1 woman a week from an average gynaecological caseload. As with all large multicentre studies it would be important to encourage collaboration from centres with an established track record for clinical research. A prerequisite to success is a research philosophy that potential contributing centres are signed up to; this is as, if not more, important as the resources and support to carry out the research [75].

The exclusion rates for the study were acceptable and within the predefined criteria for success of this feasibility study i.e. less than 30% approached were excluded from the study. Only 8 women who were eligible and had surgery actually refused randomisation from a total of 58 women who were eligible for randomisation and who underwent surgery (13.8%). Given that other than in Scandinavia [25], and some parts of the United States [76], rates of subtotal hysterectomy are less than 10% of all hysterectomies, one might have assumed a greater reluctance to conserve the cervix. In the light of such emotive concerns surrounding cervical cancer and the need for regular screening [77] one might postulate that the majority of women in the United Kingdom would request removal of the cervix at the time of hysterectomy. We were pleasantly surprised that, in our caseload, women with a benign indication for hysterectomy were largely open to the concept of cervical conservation despite warning them of an up to 20% chance of ongoing vaginal bleeding and the need to continue on the cervical screening programme. Whether this would be observed in other geographical areas of the United Kingdom is unclear but the prospect appears promising.

The inclusion and exclusion criteria were clear and did not give rise to confusion. The woman who was found to be suitable for vaginal hysterectomy and the woman whose cervix was inaccessible making the study procedure impracticable could have been excluded with a better assessment in the clinic setting. This would have avoided the disappointment to all concerned of exclusion after general anaesthetic. Strict adherence to the exclusion criteria should be possible with careful assessment in the clinic setting.

The initial explanation of the study to eligible subjects was carried out in the setting of a normal gynaecology clinic. The explanation added, on average, 15 minutes to the total consultation to allow the potential recruits some time to ask questions. This is somewhat disruptive to the clinic but if we are aiming, on average, to invite 1-2 eligible women per clinic, the overall disruption is minimal. The alternative would be to simply identify eligible recruits in the clinic setting, provide the information about the study and invite them back to a dedicated clinic set-up for the study. The latter approach has merit in removing time-pressure but causes the inconvenience to the patient of an extra visit. For those women expressing an interest to participate, they were invited back at an interval of 4-6 weeks, on average, to inform the investigator of their decision and provide informed consent. The interval visit was arranged to coincide with an anaesthetic preassessment appointment to avoid inconvenience to the patient of an

extra visit. The enrolment visit took, on average, 30 minutes to allow the patient to ask questions and sign the appropriate consents. This is longer than a routine surgical preassessment appointment by, on average, 15 minutes and reflects the time required to go through the research questionnaires in detail and allow time for questions. The latter process would be easier in a dedicated clinic but would add a visit with the associated resource implications and patient inconvenience. In any definitive study we would plan to cover public transport or mileage costs to the participants which is standard practice for many phase III studies.

The randomisation procedure appears to have been successful at removing selection bias given the similarity between groups at baseline. The process of randomisation was simple to administer and the only requirement was internet access in the operating theatre. Despite the simplicity 1 patient was treated inappropriately due to misinterpretation of the randomisation code and represents a simple human error. The patient who was initially excluded due to an injury to the transverse colon was readmitted 3 months after the first surgery. She was randomised to LH but during the course of the surgery, the size and shape of the uterus made LSH less technically challenging. Given her history of surgical complication we opted to perform LSH to avoid unnecessary hazards. These protocol violations were addressed by analysing the data according to intention to treat. The randomisation procedure was otherwise robust. It is somewhat cumbersome to wait until the initial laparoscopic survey had been completed prior to randomisation but this was an important step to avoid randomisation of women in whom both techniques were not technically feasible. There was reliance on other members of the theatre team to perform the randomisation and relay the information to the operating surgeon. In the definitive study the surgeon should view the computer screen to reduce the risk of erroneous interpretation of the randomisation code.

The short questionnaires were relatively quick to fill in. There did not appear to be any misunderstanding of the QoR-40, which sets out the question scores for all domains with 1 signifying the worst possible recovery and 5 the best. The CES-D has 20 questions 16 of which score a maximum of 3 for symptoms associated with depression and 4 questions with a minimum score of 0 for symptoms associated with depression. The inversion of the scales were poorly understood and many respondents had a tendency to circle a column of zeros even though the symptoms were incongruent e.g. question 16 'I enjoyed life' score zero corresponding to'rarely or none of the time' and question 18 'I felt sad' score zero corresponding to 'rarely or none of the time'. The CES-D has been validated but in view of the confusing questions we will consider alternative measures of mood in the definitive study such as the Women's Health Questionnaire [78] or the State-Trait Anxiety Index (STAI)[79]. The alternative measures of psychological welbeing have been used in a previous RCT comparing day by day recovery following STAH with TAH [21].

Recovery data until the 6 week mark was complete in 88% of those enrolled (greater than 85% complete data predefined as satisfactory outcome). After 6 weeks there was a progressive fall off in completeness of data to 60% at 12 weeks. However, the data up to 6 weeks appears discriminatory whereas data from weeks 7 to 12 does not; the data from week 7 to 12 was analysed by excluding missing data on a case by case basis. Our pilot data show a fall in mean QoR-40 scores at post-op, weeks 1 to 4 with return to mean pre-operative scores by week 4 (Table 5). From week 5 onwards the QoR-40 scores are relatively flat although the data must be viewed with caution as the missing data exceeds 30% from week 8 onwards. The week by week data between 7 and 12 weeks appears non-discriminatory both within the treatment group longitudinally and between the treatment groups at weekly intervals. This data does not appear to add value to the analysis and could be omitted in the definitive study. With regards to the specific question regarding return to normal activities in QoR-40 (12th question), there was no significant difference from baseline by 6 weeks in the LSH group and by 8 weeks in the LH group. Therefore a case can be made to continue week by week recovery and mood data until 8 weeks in any future definitive study.

Resources

The paper version of e-PAQ is rather cumbersome to administer. There are 4 domains and in the paper version it is necessary to answer every question which takes 30 minutes, on average, but is rather confusing. For example if the answer to question U1a: do you have any bladder problems or concerns? is no, none of the next 12 pages are relevant. However in the paper version there was a natural tendency to answer every question which is confusing. Conversely the electronic version is very user friendly and intuitive such that if the answer to U1 a is no then the participant is automatically taken to the next domain. The e-PAQ is used in many urogynaecology clinics routinely. The electronic version produces graphical representations of patient symptoms in four domains. Namely these are urinary, bowel, vaginal and sexual function domains. The e-PAQ is particularly helpful in assessing changes in each of the domains following an intervention such as physiotherapy, drug therapy or surgery. The electronic version of e-PAQ is an essential part of any assessment of pelvic floor function in longitudinal studies. We would have liked to have used the electronic e-PAQ for the feasibility study but cost constraints did not allow this. There is currently an on-line format such that participants can input the data in the comfort of their own homes. This would certainly be the way forward for any future definitive study looking at a comprehensive assessment of a woman's pelvic function symptoms.

Management

Inputting data onto an Excel spreadsheet was a painstaking and laborious process. On average it took the data handler 1 hour and 15 minutes to input all relevant data from 1 participant. During the process several breaks were required to avoid erroneous data entry. Ideally the loading of the data should be automated electronically as in the electronic version of e-PAQ. This would reduce the time required and should be less prone to data transcription error. For any data that has to be entered manually a minimum of double data entry with examination of incongruent entries is an established method of reducing errors.

With regards to missing data there is a well-established principal that the sooner a piece of missing data is chased the more likely it is that the data will be completed.

In a busy clinical setting timely chasing of missing data is labour intensive. Estimates from the current study suggest at least 8 hours per week need to be assigned to chasing missing questionnaires either by e-mail or by phone. Ideally reminder questionnaires should be automated which would reduce the time required to chase missing data. An investigator need only be involved if there is no response to a predefined number of reminders e.g. 2. It is crucial to remember that participants are at complete liberty to ignore questionnaires and a balance must be maintained between collecting complete data and

perception of bothersome irritation to participants.

Collection of data at 6 weeks was relatively straight forward as this was the time of a scheduled post-operative visit to the clinic. At the 6 week milestone almost all participants were back to normal activity and most had returned to work. It is not surprising that the timely completion of questionnaires progressively fell after the 6 week post-operative milestone as most participants had returned to their busy lives.

Scientific outcomes

The treatment allocation groups were similar at baseline. Our pilot data appear to confirm faster recovery and faster return to normal activities following LSH compared to LH. The difference, on average, appears to be in the order of 1-2 weeks. This is probably an important difference if it allows women to return to work 2 weeks earlier following hysterectomy. Observational studies have suggested return to work within 10 – 14 days following LSH [80,81] which was echoed in a prospective RCT comparing LSH with hysteroscopic endometrial resection [61]. Anecdotally one of the women who was randomised to and underwent LSH in the current study was riding a horse within 10 days of LSH (against medical advice) with no apparent ill effects.

Perhaps the most important single question with regards to post-operative recovery is when is a patient able to return to all normal activity including work 'all of the time'. This is the 12th question in the QoR-40 and the results are shown in tabular and graphical form (Table 12, Chart 4). Our results show a 1-2 week advantage with return to complete normal activity in the participants randomised to LSH.

Somewhat surprisingly the differences in QoR-40 scores to pre-treatment were similar whether ovarian tissue was conserved or not. Previous investigators have shown worse quality of life if premenopausal women undergo BSO at the time of hysterectomy [82]. At 6 months, the BSO group demonstrated less improvement than women with ovarian conservation on scales for body image), sleep problems and the SF-36 Mental Component Summary. The women undergoing BSO were on average older than the conservation group in the Teplin study and the observed differences were no longer present at 2 years.

Some women in the current study had cyclical symptoms prior to surgery particularly in the progestogenic phase of the menstrual cycle. Extirpation of the ovaries reliably abolishes the menstrual cycle and one might expect an advantage with respect to progestogenic symptoms. Any potential advantage of removing the ovaries might be negated due to the onset of vasomotor symptoms. The latter may be reliably addresed with appropriate oestrogen replacement which was offered to all women who were having their remaining ovaries removed. A large retrospective study has shown poorer psychosexual health 5 years after hysterectomy by any method which was worst of all in the women who had their ovaries removed [83]. In the McPherson study hormone replacement therapy was not associated with uniform beneficial effects in the women who had undergone BSO at the time of hysterectomy.

Given that cyclical symptoms have a significant psychological component one may have expected an observed advantage in mood in the women who had their ovaries removed. Statistically significant better CES-D scores were observed at week 5, week 12 and month 6 in the women who had their ovaries removed which is suggestive of an advantage to some women. Regardless of the findings the decision to remove ovaries will remain a clinical decision which is complex and multifactorial. The only randomised study of LSH and TLH with ovarian conservation designed specifically to investigate psychosocial outcomes showed no difference in both groups [29] but hysterectomy by either method resulted in reduction in abdominal pain and some improvement in sexual function. The CES-D questionnaire in the current study demonstrated a number of limitations and we would propose alternatives as mentioned earlier in the discussion.

The only RCT comparing recovery following LSH and TLH has not shown any significant differences [30]. However, the Italian study has a number of limitations. A total of 529 women were screened of whom 154 premenopausal women with symptomatic menses and/or leiomyomata were assessed as eligible. Only 141 of those eligible agreed to randomisation but there is no explanation regarding the 388 women who were excluded. This may represent selection bias. In 12 cases the participants did not receive the treatment they were randomised to due to technical/clinical reasons. Whether outcome measures were analysed according to intention to treat is not clear. Assessment of post-operative recovery is not detailed so the validity of the tool is unclear. Moreover the participants were assessed at 3 monthly intervals for 2 years. If recovery to full normal activity occurs within a matter of weeks, far more frequent assessments would be required to show a difference. Our feasibility study used validated instruments at weekly intervals. Perhaps daily assessment would be more discriminatory as used by Persson et al in their comparison of recovery following SAH and TAH [20]. Since the current study was designed Kirsten Kluivers and colleagues have compared the QoR-40 and 2 other instruments for assessment of post-operative recovery [84]. They concluded that the Recovery Index-10 (RI-10) should be the recommended instrument to measure short term post-operative recovery. We would aim to use the RI-10 in any future studies to assess recovery from surgery which appears simpler to administer and more reliable.

Detailed analysis of the e-PAQ and FSFI results have shown a number of interesting findings. The return rates were in keeping with prerequisites for feasibility. We obtained 100% returns at baseline, 90% at 6 weeks and 74% at 6 months. The returns were facilitated because the majority of participants agreed to complete the long questionnaires while they were present at the clinic (pre-op visit, post-op visit, sign off visit). The sign off visit was extra to standard clinical practice and was offered on a voluntary basis. The 6 month returns were comprised of 70% who chose to attend and only 4% (2 patients) who responded by post. In the definitive study we would plan to routinely add in the 3rd visit and maintain the possibility to send questionnaires at longer intervals, for example annually. The web based e-PAQ interface would facilitate this longer term review and allow women to fill in data on-line in the comfort of their own homes. There is an assumption around familiarity with use of a computer screen but access and tuition could be provided to the small minority who lack this. Strategies to include non-English speaking participants and those with impaired sight would need to be considered and is beyond the scope of this discussion.

The e-PAQ paper version was somewhat confusing to the participants as discussed earlier in the process section. As such the results should be viewed with some caution.

There appeared to be some benefit to the participants randomised to LSH with regards to quality of life and urinary

symptoms, particularly stress incontinence. Limited dissection of the bladder in LSH compared to LH has long been postulated as reducing subsequent urinary symptoms [26] but the findings have not been substantiated for the abdominal approach to sub-total hysterectomy. This would be an important long term outcome of the definitive study.

Similarly there appeared to be some advantage at 6 weeks to the group randomised to LSH with regards to bowel continence. The mechanism is more complex than the dissection issue but the effect may not be real as this was not seen at 6 months and did not appear to effect quality of life.

There appeared to be less vaginal pain in the group assigned to LSH compared to baseline at 6 weeks and 6 months. No significant reduction in vaginal pain was observed in the group assigned to LH. The latter however appeared to have lower vaginal prolapse symptoms which was accompanied by an improvement in overall quality of life. Greater rates of prolapse have previously been reported following SAH compared with TAH [17,27] which was contrary to the postulated greater support when the uterosacral ligaments and pericervical ring are left intact. This would be an important secondary outcome of the definitive study.

There appeared to be significant improvement in all sexual function domain scores at 6 weeks in the group assigned to LSH compared to baseline except in the sex and bowel subdomain but this did not translate to an improvement in general sexual matters. In the group assigned to LH an improvement was observed at 6 months for the general sexual matters subdomain.

The FSFI scores show overall improvement in the group assigned to LH at both 6 weeks and 6 months whereas an improvement was only observed at 6 weeks for the group assigned to LSH. This is the opposite to what has been postulated [9] and appears to have been the major drive towards subtotal hysterectomy in Scandanavia. This is certainly an important outcome to include in the definitive study and would allow correlation between the FSFI and e-PAQ with regards to sexual function. Perhaps the real value of the e-PAQ is to assess the individuals response to treatment of pelvic symptoms which can be represented graphically and inform discussions between clinicians and their patients. The electronic version with web based interface would be essential to administer a large multicentre study.

Caution should be excercised when interpreting the results of feasibility studies. The observations may not be generalisable. A major weakness of the current study is that we evaluated only one centre or, more precisely, 1 surgical team. The challenges of replicating uniform protocols in more than 1 centre are recognised [85]. The advantage of increasing study power to reduce the risk of a type II error is at the cost of potential loss of uniformity [86]. Robust measures are required to assure data quality. One of the major criticisms of the eVALuate study [87] was the lack of standardisation of techniques leading to a potential comparison of 'apples with pears'.

Problems with quality assurance and strict adherence to study protocol are proportional to the number of centres in a multicentre trial. Increasing the number of centres improves recruitment rates but requires careful management and a structured approach [88]. Based on our power calculation from the QoR-40 data a definitive study would require 186 women in each arm. We would recommend a maximum of 4 centres all of which should have a track record of regularly performing LSH and LH; a track record in participating in research trials would also be desirable.

'Cherry picking' centres with an established track record of collaboration in good quality research carries other risks. Using such centres restricts the setting such that interventions are carried out by enthusiasts. Enthusiasts are likely to have a thorough knowledge of the intervention under study, be familiar with good clinical practice and biostatistics but may have preformed ideas of which intervention is better (bias). The results may not be representative of the 'average' district general hospital. Perhaps the correct setting for the definitive study would include 2 centres of excellence and 2 district general hospitals.

Furthermore, study participants may be inherently different to non-participants [89] and the results may not be generalisable to the non-study population. The study participants represent a sample which should be representative of the larger population to confer external validity. A number of epidemiological studies have shown that study participants may enjoy better general health than non-participants due to motivation, better awareness of health nutrition and, as yet, undefined factors [90,91]. Reliable randomisation and blinding is the method employed to correct for potential bias.

In this feasibility study the randomisation and blinding procedures were simple to administer and appear reliable.

During the time when this feasibility study was being planned, the Author's standard practice was to offer either LH or LSH for those women requiring hysterectomy for a benign indication and in whom there was no history of high grade cervical intraepithelial neoplasia. Since conducting the feasibility study the Author has changed to Total Laparoscopic Hysterectomy (TLH) instead of (LH) as the method of choice for removing both corpus and cervix. A large proportion of the Author's caseload is made up of postmenopausal women with low grade endometrial carcinoma. The women tend to have high body mass indices and poor vaginal access. TLH is an elegant method to avoid a struggle to remove the uterus vaginally in such patients. Having become proficient at this technique this is now the method employed for all women who elect to have the uterine corpus and cervix removed and who are not suitable for simple vaginal hysterectomy. When planning the definitive study we would aim to compare primary and secondary outcomes between LSH and TLH. Observational data from Medway Maritime Foundation Hospital suggest comparable short term recovery. Retrospective studies of others suggest some short term advantages of LSH compared to TLH [92,93] but this appears to be at the cost of greater long term complications in the LSH group, largely related to the cervical stump [92,94]. Although bleeding from the cervical stump may be present in up to 24% of those undergoing LSH [95] the vast majority of patients found this a minor inconvenience (median VAS bothersome score zero) and 92% of respondents were satisfied or very satisfied with the surgery. In a retrospective comparison of TLH and LSH with regards to reoperation, method specific indications for reoperation were observed in 2.7% of the LSH group (late reoperation for extirpation of cervical stump) and 0.7% of TLH group (early reoperation to repair vaginal vault dehiscence) Einharrson and colleagues [96] have compared LSH and TLH prospectively and concluded advantages in the LSH group in terms of both physical and psychological quality of life measures. However, in their study this did not translate to any advantage with

respect to return to normal activities post-surgery. The current feasibility study remains very pertinent as the recruitment process, trial management and practicality of the instruments used were the main focus.

The power calculation presented in the results may not be appropriate as the magnitude of observed differences may be different when comparing TLH and LSH.

Power of the definitive study needs to be set such that a clinically important difference can be reliably detected. This is dependant upon the research hypothesis. The original research hypothesis was that there is a clinically important difference in time to full recovery in women undergoing LSH compared to those undergoing LH.

Our new research hypothesis would be that there is a clinically important difference in time to full recovery in women undergoing LSH compared to those undergoing TLH.

We estimate the difference in time to recovery from LSH compared with TLH to be 30% less in magnitude than the difference observed between LSH and LH (based on assumptions following local observations of surrogate markers including analgaesic requirement and time to mobilisation). As such we would propose multiplying the numbers required to treat by a factor of 1.3 to avoid a type II error. The definitive double blind RCT to compare LSH with TLH would require 240 women in each arm if power is kept at 0.8 and α at 0.05. It would be prudent to increase this to 275 to allow for 12% drop out rate (88% returned recovery questionnaires at 6 weeks). Total recruits needed would be 550

A single blind RCT of LSH versus TLH is currently being recruited for in the Brigham Women's Hospital under the supervision of Chief Investigator Jon Einarsson (www.clinicaltrials.gov/ct2/show/study/NCT00734812?term=Brigham+Women's+Laparoscopic+Hysterectomy+trial&rank=1). Recruitment started in May 2008 and the study is due to complete in October 2013. Primary outcomes are return to normal activities, measured by daily diary, with an expected range of 3-6weeks. Secondary outcomes include urinary symptoms assessed by 3IQ and sexual function measured by FSFI. The trial is planned to recruit 172 women which in our opinion will be underpowered.

A smaller RCT comparing LSH and TLH is due for completion of recruitment in December 2012 entitled 'Long Term Outcomes following Total Laparoscopic Hysterectomy and Laparoscopic Supracervical Hysterectomy' (www.http://clinicaltrials.gov/ct2/show/NCT01289314?term=Laparoscopic+AND+Hysterectomy+AND+Lieng&rank=1). The planned recruitment is for 62 patients (31 in each arm) with primary outcome measures of pain relief requirement and satisfaction with the surgery. Based on the feasibility study presented the study will be underpowered with regards to post-surgical recovery.

Conclusion

Observational data suggest that in women undergoing laparoscopic hysterectomy for a benign indication with no history of high grade cervical intra-epithelial neoplasia, conservation of the cervix is associated with faster recovery. This was not confirmed in the only randomised comparison of LSH with TLH [30]. However the Italian study had a number of limitations as summarised in the discussion.

No randomised comparisons of LH versus LSH have been found following an extensive search of the literature. We present the results of a feasibility study of a double blind RCT comparing recovery and mood following LSH with LH.

A double blind randomised controlled trial to compare short term outcomes and recovery following laparoscopic supracervical hysterectomy with those following laparoscopic hysterectomy is feasible.

Randomisation using a web based computer generated block randomisation sequence is easy to use and results in relatively homogenous groups.

Recruitment, treatment and data collection can be achieved within 2 years of commencement for 50 patients from 1 surgeon participant.

Return of 85% data at 6 weeks and 75% data at 6 months is achievable.

Return of short questionnaires are good in the first 6 weeks with progressive drop in return rates to 60% at 12 weeks. Data from 8 to 12 weeks does not appear discriminatory and would be omitted from the definitive study.

The data collected appear to be non-parametric following Komolgorov- Smirnov analysis. Mann Whitney U and Wilcoxon Signed Ranks analysis is appropriate for quantitative outcomes.

The QoR-40 was a good choice to assess post-operative recovery but appears to have been superceded by the RI-10. Conversely CES-D is confusing and alternative measures of mood such as the WHQ or STAI would be preferred for the definitive study. Lengthy paper questionnaires are confusing and electronic versions with an online interface should facilitate data quality. None-the–less return rates of paper questionnaires are good if participants fill them in at a clinic attendance (90% at 6 weeks, 74% at 6 months). The e-PAQ and FSFI are informative with regards to pelvic and sexual function. The e-PAQ may be most valuable in assessing changes in pelvic function longitudinally in individuals following an intervention. Analysis may be repeated at various intervals to assess, short, intermediate and long term outcomes.

Secondary outcomes of the feasibility study included quantitative analysis of QoR-40 scores and CES-D scores. Secondary outcomes suggest a 1-2 week advantage with respect to recovery from LSH versus LH, which is clinically important in terms of returning to normal activity including work. LSH takes, on average, 25 minutes shorter operative time which is probably important in terms of theatre time costs.

LSH is associated with less blood loss but the volume (100mls difference on average) is not clinically relevant.

LSH may be associated with better outcomes with regards to urinary symptoms but LH appears to be associated with better outcomes with regards to post-operative symptomatic prolapse. No advantage was suggested with regards to sexual function and LSH but study design precludes direct comparisons between treatment allocation groups. Indeed, findings from this feasibility study suggest an advantage in the group allocated to LH with regards to sexual function.

We would plan to replicate this study as a multicentre definitive double blind RCT to compare outcomes following different methods of laparoscopic hysterectomy. However, we would recommend a comparison of LSH and TLH. TLH is now the preferred method of removing both the uterine corpus and cervix at the Author's main Hospital of practice.

Whether conservation of the cervix at laparoscopic

hysterectomy confers any short, intermediate or long term benefit remains unclear and the definitive study is essential to address this important clinical question.

Findings from this feasibility study will be used to inform a grant application for the definitive study. In order to show a difference we guesstimate needing to recruit 550 women from an estimated total of 4 centres.

Two much smaller trials are recruiting at the moment at Brigham women's hospital, Boston Massachusetts USA (estimated n=172) and the University Hospital in Oslo, Norway (estimated n=62). From the data presented in this feasibility study the trials are likely to be significantly underpowered to detect any differences with regards to post-surgical recovery and return to normal activities.

Acknowledgements

This study was supported by a research grant from JOHNSON & JOHNSON MEDICAL LIMITED.

Thanks to my unit at Medway Maritime Hospital for providing the environment and the wealth of clinical material to study.

I am grateful to Hany Wisa, my speciality Doctor for his invaluable help with developing an online interface for questionnaires, data transcription and chasing missing returns.

Finally I wish to thank all the women who took part in the study and painstakingly filled in the questionnaires. Ladies, without you, none of this would have been possible.

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