THE PRACTICE OF OFFICE HYSTEROSCOPY

by

PAUL PHILIP SMITH

A thesis submitted to the University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

School of Clinical and Experimental Medicine

College of Medical and Dental Science

University of Birmingham

January 2015

UNIVERSITY OF
BIRMINGHAM

University of Birmingham Research Archive

e-theses repository

This unpublished thesis/dissertation is copyright of the author and/or third parties. The intellectual property rights of the author or third parties in respect of this work are as defined by The Copyright Designs and Patents Act 1988 or as modified by any successor legislation.

Any use made of information contained in this thesis/dissertation must be in accordance with that legislation and must be properly acknowledged. Further distribution or reproduction in any format is prohibited without the permission of the copyright holder.

Abstract

Advances in technology have led to the miniaturisation of hysteroscopes without compromising optical performance. This development has facilitated the routine use of diagnostic hysteroscopy in an outpatient setting without the need for general anaesthesia. Further developments have expanded hysteroscopy from a simply diagnostic intervention to an operative one with a plethora of hysteroscopic surgical procedures. The work in this thesis has adopted a mixed methodological approach to rigorously evaluate patient selection, feasibility and efficacy of office hysteroscopy. Based on the results of this thesis we recommend:

1) Women with recurrent PMB should be investigated with either hysteroscopy or saline infusion sonography.
2) Vaginoscopy should probably be used in preference to other techniques to introduce the hysteroscope into the uterine cavity.
3) Women who have a uterine cavity >9cm or dysmenorrhoea should be warned they are more likely to require further intervention after endometrial ablation.
4) There appears to be no difference between the effectiveness of bipolar radiofrequency ablation and thermal balloon ablation at five years of follow up.
5) Women who present with abnormal uterine bleeding and an endometrial polyp should have it removed.
6) The hysteroscopic morcellator should be used in preference to bipolar resection for endometrial polyp removal.

Dedication

I dedicate this thesis to my dad, who always gave more than he took from life. We will always miss you.

Acknowledgements

Thank you to Natalie Cooper for acting as a second reviewer for the systematic review.

Thank you to the team at Birmingham Clinical Trials Unit for their support, but in particular Jane Daniels who gave advice on running trials and Lee Middleton for advice and help with statistical analysis.

Thank you to Mary Connor, Shilpaja Karpate and Siobhan O'Connor for helping with recruitment of patients and data collection.

Thank you to Professor Arri Coomarasamy for his supervision and mentorship through this PhD.

Thank you to Mr Justin Clark for helping with recruitment of patients, data collection, supervision and mentorship. Without his enthusiasm and knowledge of office hysteroscopy the completion of this thesis would not have been possible.

Finally, I would like to thank my parents, Philip and Jane Smith, my sister, Sarah Smith and my fiancé, Rima Dhillon for their love, support and encouragement.

Abbreviations

aOR	Adjusted Odds Ratio
AUB	Abnormal Uterine Bleeding
BCTU	Birmingham Clinical Trials Unit
BMI	Body Mass Index
BSGE	British Society for Gynaecological Endoscopy
BWH	Birmingham Women's Hospital
CI	Confidence Interval
COAT	Comparison of Office endometrial Ablation Techniques
D&C	Dilation and Currettage
EB	Endometrial Biopsy
EEC	Endometrial Echo Complex
GCP	Good Clinical Practice
GnRHa	Gonadotrophin Releasing Hormone
HMB	Heavy Menstrual Bleeding
HR	Hazard Ratio
HRT	Hormone replacement therapy
IMB	Inter-menstrual bleeding
LNG-IUS	Levonorgestrel Intrauterine Systems
MERT	Morcellation vs Electrical Resection Trial
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service

OH	Office Hysteroscopy
OR	Odds Ratio
PBAC	Pictorial Bleeding Assessment Chart
PMB	Post Menopausal Bleeding
RCOG	Royal College of Obstetrics and Gynaecology
RCT	Randomised Controlled Trial
R&D	Research and Development
SAQ	Sexual activity questionnaire
SD	Standard Deviation
SIS	Saline Infusion Sonography
TVS	Transvaginal Sonography
UAE	Uterine Artery Embolisation
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale
VAST	Vaginoscopy Against Standard Technique

Table of Contents

List of Tables

List of figures

CHAPTER 1: THESIS OVERVIEW AND OBJECTIVES

Background

Hysteroscopy describes a technique where a small endoscope called a 'hysteroscope' is placed into the vagina, advanced to pass through the cervix and into the uterine cavity allowing direct visualisation of normal anatomy and pathological conditions. Hysteroscopy is the commonest surgical intervention in gynaecology being used to diagnose and treat problems with abnormal uterine bleeding and reproduction; in the financial year between 2012 and 2013, 37,543 diagnostic hysteroscopies and 27,127 therapeutic hysteroscopic procedures were performed in the NHS[1].

Advances in technology have led to the miniaturisation of hysteroscopes without compromising optical performance. This development has facilitated the routine performance of diagnostic hysteroscopy in an office setting in dedicated hysteroscopy facilities, within hospital endoscopy departments or in community based settings[2–4]. There has thus been a paradigm shift with this most common of gynaecological procedures moving from an inpatient, general anaesthetic setting, within a formal operating theatre, to a convenient and flexible office environment. Further developments have expanded hysteroscopy from a simply diagnostic intervention to an operative one with a plethora of hysteroscopic surgical procedures to treat abnormal bleeding and reproductive problems[5–8]. This changing paradigm has been incentivised through economic changes in favour of office based procedures reflected in improved Department of Health procedure tariffs[9]. Moreover, in a recent trial comparing inpatient and office endometrial polypectomy, in those patients that expressed a preference, 80% choose to have

an office procedure (OPT, personal communication Clark). Thus there is both economic and patient demand for increasing office hysteroscopic services. This is reflected in the British Society for Gynaecological Endoscopy (BSGE) and Royal College of Obstetrics and Gynaecology (RCOG) Greentop guideline 59, which recommends that all NHS trusts should offer office hysteroscopic services[4]. Office hysteroscopy has been shown to be a safe, feasible and accurate diagnostic test[3]. Moreover, common gynaecological procedures traditionally the preserve of inpatient hospital based treatment are now achievable in a convenient office setting. Such office hysteroscopic therapeutic interventions include removal of uterine polyps, fibroids, adhesions and sterilisation procedures using specially designed miniaturised health technologies[7,8]. Evidence is mounting for the feasibility, effectiveness and cost-effectiveness of office hysteroscopic interventions[3,4,10].

Identifying the right patients and offering the best treatments are of key importance to optimise clinical outcomes. Moreover, with the continuous rapid development of technology extending the repertoire of office hysteroscopic procedures, it is essential that we critically evaluate current practice and new health technologies before they become embedded in clinical practice. The work presented in this thesis has adopted a mixed methodological approach to rigorously evaluate patient selection, feasibility and efficacy of office hysteroscopic interventions for common gynaecological conditions in order to help identify best practice and enhance clinical outcomes (Table 1).

Objectives

1. To improve patient selection for procedures in office hysteroscopy in order to optimise clinical outcomes.

2. To identify the most effective health technologies for the treatment of common gynaecological conditions.

Table 1. Summary of research studies within the PhD thesis.

Chapter	Title	Population	Intervention	Comparator	Study Type	Objectives
Chapter 2	The role of hysteroscopy in recurrent post-menopausal bleeding	Women with postmenopausal bleeding	Investigation pathway for postmenopausal bleeding	N/A	Observational Study	To estimate the prevalence of genital tract pathologies in women presenting with initial and recurrent postmenopausal bleeding (PMB) to help inform diagnostic pathways
Chapter 3	Vaginoscopy versus traditional hysteroscopy: a pilot study	Women having a diagnostic hysteroscopy in the office setting	Vaginoscopy	Standard Hysteroscopy	Randomised Controlled Trial	To evaluate whether vaginoscoopy or standard hysteroscopy is more favourable in an office setting in terms of feasibility, complications, pain, and acceptability.
Chapter 4	Prognostic factors that predict success in office endometrial ablation	Women receiving endometrial ablation in the office setting	Failed treatment defined as further surgical intervention	Successful treatment defined as no further surgical intervention	Observational Study	To identify factors within the patient history, demographics and examination findings that may predict the chance of a satisfactory result from endometrial ablation

Chapter 5	A randomised controlled trial to compare the effectiveness of office endometrial ablation: a five year follow-up	Women receiving endometrial ablation in the office setting	Bipolar Radiofrequency Ablation	Thermal Balloon Ablation	Randomised Controlled Trial	To estimate the longer-term effectiveness of office based bipolar radiofrequency ablation compared with thermal balloon ablation of the endometrium for the treatment of heavy menstrual bleeding at five years follow-up.
Chapter 6	Uterine polypectomy for the treatment of abnormal uterine bleeding	Women with endometrial polyps associated abnormal uterine bleeding	All available therapeutic interventions	No intervention	Systematic Review	To assess the effictiveness of uterine polypectomy in the treatment of abnormal uterine bleeding.
Chapter 7	Hysteroscopic morcellation of intrauterine polyps: a randomised controlled trial	Women with benign endometrial polyps for removal in the office setting	Hysteroscopic Morcellation	Electrical Resection	Randomised Controlled Trial	To evaluate whether hysteroscopic morcellation or bipolar electrosurgical resection is more favourable for removing endometrial polyps in an office setting in terms of feasibility, speed, pain, and acceptability.

CHAPTER 2: THE ROLE OF HYSTEROSCOPY IN RECURRENT POST-MENOPAUSAL BLEEDING

Publication

The work has been published with the Journal of Minimally Invasive Gynecology; Smith P, O'Connor S, Gupta J, Clark TJ. Recurrent postmenopausal bleeding: a prospective cohort study. J Minim Invasive Gynecol, September 2014

Abstract

Objective

The aim of this study was to estimate the prevalence of genital tract pathologies in women presenting with initial and recurrent postmenopausal bleeding (PMB) to help inform diagnostic pathways.

Methods

A prospective cohort study was conducted in a large, urban teaching hospital in Birmingham, UK. A total of 1938 consecutive women presented with postmenopausal bleeding, of which, 106 (5%) women were investigated for a recurrent episode after previously having normal investigations. All women underwent a pelvic examination and ultrasound scan. An endometrial biopsy was performed when endometrial thickness was >4mm in women presenting for the first time with PMB, with recourse to office hysteroscopy following correlation between clinical and pathological findings. All women had an endometrial biopsy and office hysteroscopy with a recurrent PMB presentation.

Results

The chance of having endometrial cancer or hyperplasia with atypia was significantly lower in women who presented with recurrent PMB as compared to those presenting with PMB for the first time (0% and 8% respectively, $P = 0.002$). However, those with recurrent PMB were significantly more likely to have benign

endometrial polyps compared to women presenting with PMB for the first time (28% and 19% respectively, RR 1.47 [95% CI 1.07, 2.02], *P* = 0.02).

Conclusion

Investigations of women with recurrent PMB are less likely to show pre-malignant or malignant endometrial disease, but one in four women have endometrial polyps as a cause of PMB. First line investigation for women with recurrent PMB should be with tests that have a high accuracy for diagnosing focal pathologies such as office hysteroscopy or saline infusion sonography.

Introduction

Background

Postmenopausal bleeding (PMB) is a common condition affecting between 7-15% of the postmenopausal population[11]. Women with PMB are most likely to present in the sixth decade of life, with consultation rates in primary care of 14.3/1000 population[12]. Prompt investigation is needed because there is a 3-10% risk of endometrial cancer[13]. Guidelines[14,15] recommend first line investigation with transvaginal sonography (TVS) to measure endometrial thickness. The prevalence of malignancy is reduced to <1% when the endometrial echo complex (EEC) is ≤4mm and it is regular with no fluid in the uterine cavity. Under these circumstances further testing is usually not required[16–18]. Above this cut-off endometrial sampling is recommended[14,15] because the risk of malignancy is higher[19]. In contrast to the standardised approach to investigating initial presentations of PMB, the management of women that re-present with PMB is more ambiguous. This is despite recurrence being common with estimated rates ranging between 19.4 and 33%[20–22].

Need for cohort study looking at recurrent PMB

All investigations for PMB carry a false negative rate so it is important to re-investigate women who remain symptomatic or who have recurrent symptoms[23]. However, evidence on when and how these women should be investigated is lacking. Research and published guidance[14,15] has concentrated on the diagnosis of endometrial malignancy following first presentation with PMB, which may not be

applicable to those presenting with recurrent PMB. It is likely that the prevalence of malignant and benign uterine pathologies, such as polyps, fibroids, endometrial hyperplasia and endometritis, differs between those women with PMB presenting for the first time and those with recurrent PMB. Therefore, the emphasis on rapid referral and investigation to evaluate for endometrial cancer may result in these benign conditions being overlooked resulting in a failure to adequately treat these undetected benign pathologies. Thus, the aim of this study was to estimate and compare the prevalence of all underlying genital tract pathologies in women with first presentation and women with recurrent PMB to help inform diagnostic pathways and the need for ongoing surveillance.

Objectives

1. To estimate the prevalence of genital tract pathologies in women who present for the first time after PMB.
2. To estimate the prevalence of genital tract pathologies in women with recurrent PMB who did not have malignant or premalignant pathology identified on previous investigation.
3. Construct management pathway for women presenting with recurrent PMB.

Methods

Study design

A prospective cohort study of the incidence of genital tract pathology associated with PMB, comparing those who present initially to those with recurrent symptoms and previous normal investigations.

Study setting

1938 women were seen consecutively in the postmenopausal bleeding clinic at the Birmingham Women's Hospital between 27th February 2007 and 27th July 2011.

Participants

PMB was defined as an episode of vaginal bleeding 12 months or more after the last menstrual period. Recurrent PMB was defined as any repeat presentation of bleeding after previously being investigated for PMB. Women taking HRT with unscheduled bleeding were also considered to have PMB. Some clinicians may consider re-presentation over 12 months to represent a 'new' episode of PMB rather than a 'recurrence' of the initial problem, so we further subdivided recurrent PMB into those women that presented ≤12 months and those that presented >12 months. Women were excluded from the recurrent cohort if they were diagnosed with cancer, hyperplasia or an untreated polyp during the first episode of bleeding.

Investigation

All women with PMB underwent TVS as a first-line screening test. Final diagnosis for PMB was made using the following reference standards:

1. *Transvaginal sonography (TVS)*: if the endometrium was regular, ≤4mm on TVS with no evidence of fluid, the patient was considered to have an atrophic endometrium and sampling was not performed. The patient was reassured after performing a lower genital tract examination and consequently discharged. A trained sonographer who was not blinded to the clinical symptoms performed all TVS. Colour Doppler was used when endometrial irregularities were seen.
2. *Endometrial biopsy (EB):* women who screened positive i.e. TVS with EEC >4 mm or irregular endometrium (even if the EEC was ≤4mm), or incomplete visualisation of the endometrium, underwent aspiration endometrial biopsy (EB). A senior pathologist reviewed all histology and was not blinded to the clinical symptoms.
3. *Office hysteroscopy (under conscious sedation):* where an outpatient endometrial biopsy (EB) failed (defined as failure to instrument the uterus or a non-diagnostic sample) an office hysteroscopy was arranged and a further biopsy taken unless the cavity seemed atrophic on hysteroscopic visualisation. Atrophy on hysteroscopic visualisation was defined as a pale, avascular uterine surface with visible underlying stroma with no endometrial tissue avulsed following contact with the tip of the hysteroscope. Office hysteroscopy was performed on all patients with a recurrent presentation of PMB. An office hysteroscopy was also performed where focal pathology

(polyps, submucous fibroids) were suspected on TVS or EB reports. If confirmed on office hysteroscopy, they were removed and sent for histological confirmation. All office hysteroscopy was performed by a senior gynaecologist or a specialist nurse who was not blinded to the clinical symptoms.

Diagnosis

For the purposes of this study we restricted final diagnosis to a single pathology. When more than one endometrial histological diagnosis was made the patient was categorised using the following hierarchy: Endometrial cancer / hyperplasia with atypia > hyperplasia without atypia > polyps > infection > functional > atrophic. Cancer and hyperplasia with atypia were included together because of the high rate of under-call and progression to cancer where complex hyperplasia is found with cytological atypia[24–26].

Statistical methods

We prospectively collected standardised data on a specially designed password protected Microsoft™ Access Database. The relative proportion of different pathologies in women with first and recurrent PMB was compared using Chi-square test or Fisher's exact test when the expected frequency was less than five. For the purpose of working out relative risk, values of zero were replaced with 0.5. Statistical analysis was performed using SPSS™ version 15.

Results

Participants

Over the 53 month study period, 1832 women with a median duration of follow up of 35 months (range 1–56 months), presented with PMB for the first time to the Birmingham Women's Hospital. Of this cohort, 106 (5%) women had recurrent PMB. The median follow up in this subgroup of women with recurrent PMB was 12 months (range 1–45 months). All had previously been investigated for PMB and had endometrial cancer or hyperplasia excluded. When comparing baseline characteristics for women with first presentation versus those with recurrent PMB results were similar: mean age (62.9 vs 61.1); body mass index (BMI) (30.7 vs 31.8 kg/m^2), EEC (8.3 vs 7.7 mm) and percentage taking HRT (11.7% vs 12.3%) was similar in women with first or recurrent PMB.

Outcome data

Endometrial cancer or hyperplasia with atypia was diagnosed in 152/1832 (7.8%) women with first presentation PMB but no cases were found in the 106 women with recurrent PMB. In contrast, benign endometrial polyps were found to be significantly more prevalent in the recurrent PMB group compared with first presentation PMB (30/106, 28.3% vs 349/1832, 19.6%, P = 0.02 respectively). The prevalence of all other endometrial pathologies was equivalent between initial and recurrent PMB groups (Table 2). Because of a possible association between HRT and the development of polyps[27], we re-analysed the data after removing the women taking HRT. Endometrial polyps remained more prevalent in women with

recurrent PMB, but the difference was no longer significant (25/94, 27% in recurrent PMB presentation vs 313/1616 19%, in initial PMB presentation, *P* = 0.09). Removing the women taking HRT had no effect on the significant decrease in cancer and atypia in recurrent PMB presentation. No significant differences in the prevalence of endometrial pathologies were noted in women with recurrent PMB when stratified into re-presentation within and beyond 12 months of initial presentation (Table 3).

Table 2. Comparison of endometrial pathology rates between women with PMB presenting for the first time or recurrently after previously normal investigations.

	Initial PMB presentation	Recurrent PMB presentation	RR (95% CI)	P value[1]
Infection	20 (1%)	0 (0%)	0.42 (0.03 to 6.86)[2]	0.3
Polyps	349 (19%)	30 (28%)	1.47 (1.07 to 2.02)	0.02
Hyperplasia	97 (5%)	7 (7%)	1.24 (0.59 to 2.59)	0.6
Cancer and Atypia	152 (8%)	0 (0%)	0.06 (0.00 to 0.90)[2]	0.002
Functional[3]	348 (19%)	18 (17%)	0.93 (0.62 to 1.42)	0.7
Atrophy	866 (47%)	51 (48%)	1.01 (0.82 to 1.24)	0.9
Total	1832	106		

PMB = postmenopausal bleeding; RR = relative risk

1) Chi square test, presented to one significant figure

2) For the purpose of working out relative risk values of 0 were replaced with 0.5.

3) Functional = included histology described as weakly proliferative and weakly secretary

Table 3. Comparison of endometrial pathology rates stratified by time to re-presentation in women with recurrent PMB.

	Recurrent PMB ≤12 months	Recurrent PMB >12 months	*P* value[1]
Average follow-up time in months (range)	7.5 (2-12)	21.8 (13-45)	
Infection	0 (0%)	0 (0%)	No value
Polyps	13 (25%)	17 (32%)	0.5
Hyperplasia	4 (8%)	3 (6%)	0.7
Cancer and Atypia	0 (0%)	0 (0%)	No value
Functional[2]	12 (23%)	6 (11%)	0.2
Atrophy	24 (45%)	27 (51%)	0.2
Total	53	53	

PMB = postmenopausal bleeding

1) Chi square test, presented to one significant figure

2) Functional = included histology described as weakly proliferative and weakly secretary

Discussion

Key results

In our study, 106 (6%) women had recurrent PMB over a 4.5 year period, but no cases of endometrial cancer or hyperplasia with atypia were detected. However, women with recurrent PMB had a significantly increased risk of having benign endometrial polyps irrespective of the time to recurrence.

Interpretation

The apparent increased prevalence of endometrial polyps with recurrent PMB may reflect the higher accuracy of office hysteroscopy for detecting focal pathologies.[28,29] This was undertaken routinely in the recurrent PMB group, but only selectively in women presenting with PMB for the first time. Alternatively, women with recurrent PMB may have more frequently developed polyps *de novo* accounting for further bleeding symptoms. In either case, the finding that benign endometrial polyps are more prevalent has potential implications for how to best manage women with recurrent PMB. With it's focus on diagnosing endometrial cancer, the current consensus for working up women with PMB using first-line TVS EEC measurement[14,15,30], may be inappropriate in women with recurrent PMB. Although the vast majority of endometrial polyps are benign[31,32], and the consequences are less serious to health than endometrial cancer, they are associated with abnormal uterine bleeding and removal by polypectomy frequently resolves symptoms[31,33]. Thus, diagnostic pathways in recurrent PMB should be developed with the aim of diagnosing benign as well as malignant endometrial disease.

Proposed pathway for investigation of recurrent PMB

Figure 1. illustrates a potential testing pathway for women presenting with recurrent PMB based upon the findings from our study. We propose that office hysteroscopy should be incorporated because it is more accurate in diagnosing discrete pathologies such as endometrial polyps[29,34]. Moreover, structured interviews exploring women' preferences in the evaluation of PMB have shown that women are prepared to undergo more invasive hysteroscopy to evaluate for any additional pathology, rather than adopt the currently recommended expectant management after ultrasound[35]. It is possible that this preference for additional testing may be even more likely with recurrent PMB because of increased anxiety associated with repeated symptoms, even though paradoxically the risk of endometrial cancer appears to be low.

The low risk of serious endometrial disease in recurrent PMB after previous normal investigation is reassuring and so reinvestigation of women who have already had endometrial polyps excluded by office hysteroscopy may be unnecessary. However, if the nature of bleeding has changed (i.e. increased quantity or persistence) or other relevant symptoms such as pain have developed then it would seem prudent to undertake timely re-investigation to exclude endometrial cancer (Figure 1). We found no difference in the likelihood of endometrial cancer or hyperplasia in women with recurrent PMB according to whether re-presentation was within or beyond 12 months of initial negative testing. However, the median duration of follow up in our series was only 12 months. Therefore a cautious approach should be adopted, especially in women with recurrent symptoms and longer time intervals from

previously negative testing. For this reason the proposed diagnostic algorithm recommends re-investigation for all women with recurrent PMB after 12 months, regardless of previous testing history (Figure 1).

Comparison with other studies

Several other studies have estimated recurrence rates for PMB and evaluated the prevalence of malignant although not benign uterine pathology[20,22,36–38]. One study evaluated 126 women presenting with recurrent PMB and reported an 8% recurrent PMB[38] rate in keeping with our observed estimate of 6%. In contrast to our findings, no significant difference in the incidence of cancer or atypical hyperplasia were observed compared to women presenting for the first time. However, initial diagnostic work up was not in line with current recommendations[14,15] such that two of the five women with endometrial cancer in the recurrent group re-presented within a year, but neither had undergone initial endometrial sampling despite having an EEC >9mm. The likelihood of recurrent bleeding has been reported to be as high as 33%[22] and the rates of cancer and atypical hyperplasia up to 22.7% (15/66)[20]. These differences may be explained by differences in patient selection and referral criteria, variations in initial diagnostic work-up and the sample size and duration of follow-up. Closer analysis of these studies revealed that significant pathology usually occurred 12 months after initial investigation[20,21,38]. When cancer or atypical hyperplasia did present within 12 months, endometrial sampling was either not normal, inadequate or not performed at first presentation[20,38]. It is for this reason that in our suggested pathway (**Figure 1**) all patients with recurrent PMB are

investigated with office hysteroscopy with an attempt at biopsy irrespective of the EEC and that a full review of previous investigations is undertaken. Larger studies are needed to externally validate our findings before we can make robust clinical recommendations.

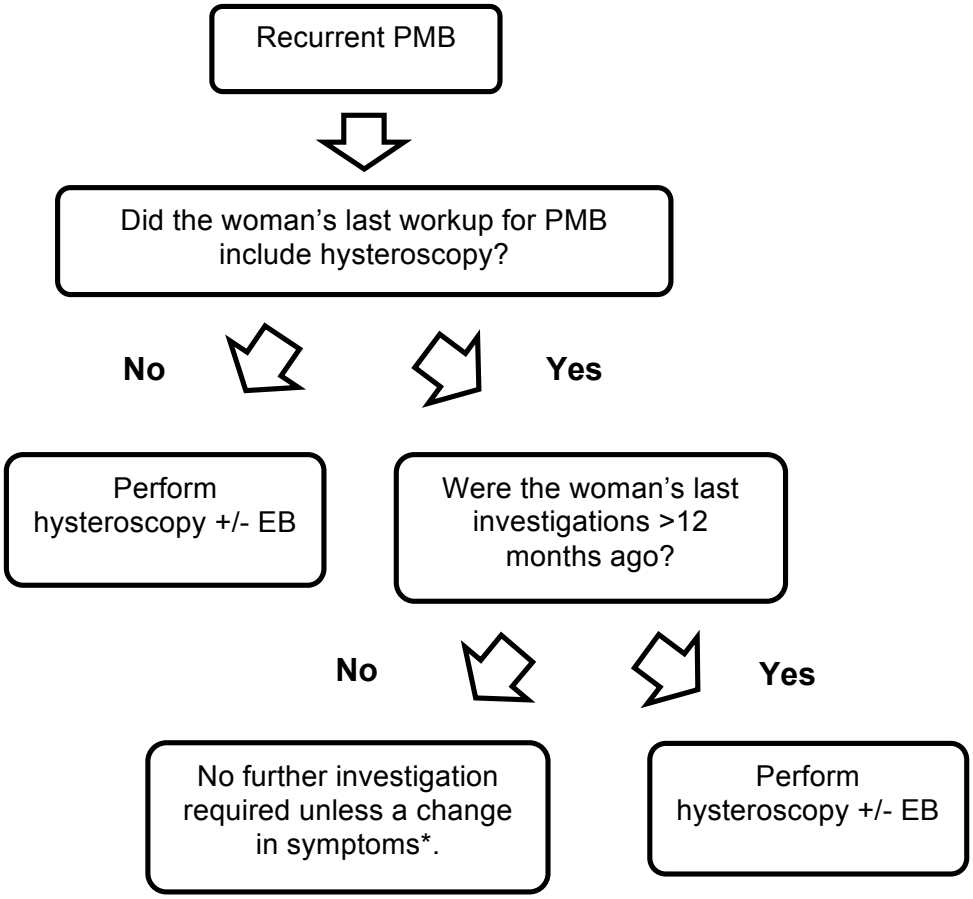
Strengths and limitations

A strength of our study is that the data were collected prospectively, consecutively and in a standardised fashion minimising bias from incomplete data. However, whilst the generalisability of our findings are limited because they are derived from a single centre, we believe that they are likely to mirror other centres because we adopted testing for PMB in line with current guidelines[14,15] from a large, unselected, general postmenopausal population.

Although we did not follow up apparently asymptomatic women, it is unlikely that that our low prevalence of serious endometrial disease in women with recurrent PMB reflects high rates of loss to follow up. This is because PMB is an alarming symptom so women are unlikely to ignore it and general practitioners are well educated in the need to rapidly refer. Furthermore, postmenopausal women are not a particularly itinerant population and our hospital is the largest provider of gynaecological care in Birmingham. A potential criticism of our study is the lack of a common reference standard for diagnosing endometrial disease. Our study was pragmatic, with data collected within a clinical setting such that the indication for further testing with office hysteroscopy, after the standard use of TVS and EB if EEC≥4mm[14,15], was based upon clinico-pathological correlation in the absence of

uniform guidance. We also restricted diagnosis to a single pathology so that we may have underestimated the prevalence of some pathologies. However, in the presence of multiple endometrial pathologies, we based our final diagnosis according to the most significant pathology and so the clinical implications of our simplification are likely to be negligible.

Figure 1. Proposed diagnostic pathway for recurrent PMB



EB = Endometrial Biopsy; PMB = Postmenopausal Bleeding; * increased quantity or persistence of bleeding, pain, weight loss, bowel or urinary symptoms.

Conclusions

At least one in twenty women with PMB will have recurrent symptoms. Compared to women presenting for the first time with PMB, the risk of endometrial cancer in recurrent PMB in women who have had previously normal investigations in line with current diagnostic guidelines[14,15] appears to be much lower, but the risk of having benign endometrial polyps is significantly higher. All women with recurrent PMB, irrespective of when they re-present after their initial negative investigations, should undergo a test with a high sensitivity for focal pathology such as office hysteroscopy.

CHAPTER 3: A RANDOMISED CONTROLLED TRIAL OF VAGINOSCOPY AGAINST STANDARD TREATMENT

Abstract

Objective

To evaluate whether vaginoscopy or standard hysteroscopy was more successful in the office setting by comparing rates of failure, complications, infection, patient acceptability, and pain scores.

Methods

A single centre randomised controlled trial of vaginoscopy compared with standard hysteroscopy was conducted. A total of 200 women were randomly allocated to one of the two methods in an office setting. The primary outcome was “success”; this was a composite outcome defined as: a complete procedure, no complications, a level of pain acceptable to the patient and no sign of infection two weeks after the procedure. Secondary outcomes consisted of the individual elements of a successful procedure, duration and pain, measured using a 100mm electronic visual analogue scale.

Results

Vaginoscopy was significantly more successful than standard hysteroscopy (OR 4.28 [95% CI; 1.52 to 12.09]). One (1%) women receiving vaginoscopy reported the procedure unacceptable, compared to two (2%) women in the standard hysteroscopy group (OR 0.20 [95% CI; 0.01 to 4.14]). Vasovagal reactions

occurred in two women receiving vaginoscopy and five women receiving standard hysteroscopy (OR 2.58 [95% CI; 0.48 to 13.62]). There were two (2%) women undergoing vaginoscopy and five (6%) after standard hysteroscopy who met the criteria for having a post-procedural infection. Significantly more procedures failed with standard hysteroscopy compared to vaginoscopy (eight [8%] versus one [1%] respectively; OR 8.61 [95% CI; 1.05 to 70.20]). The median time taken to complete vaginoscopy was two minutes compared to three minutes for standard hysteroscopy ($P < 0.001$). The median pain measured on a 100mm electronic visual analogue scale was 33 for vaginoscopy compared to 38 standard hysteroscopy ($P = 0.3$).

Conclusions

There is evidence to suggest that vaginoscopy is quicker to perform and more successful than standard hysteroscopy and therefore should be considered the technique of choice for office hysteroscopy.

Clinical Trial Registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01972945

Introduction

Background

Office hysteroscopy can be associated with significant anxiety, pain and patient dissatisfaction[4]. One technical modification identified to potentially reduce pain at hysteroscopy is 'vaginoscopy', otherwise known as the 'no touch' technique[3,39,40]. This describes a technique where the hysteroscope is guided into the uterus without the need for potentially painful vaginal instrumentation. Pain is often experienced by the patient at a number of stages during the standard hysteroscopy practice, these include passage of a vaginal speculum to separate the vaginal walls in order to visualise the cervix, cleansing of the cervix and sometimes application of traumatic forceps to the ectocervix in order to stabilise it. Vaginoscopy could be less traumatic because the approach minimises potentially painful manoeuvres in the lower genital tract.

Recent technological advances have led to the miniaturisation of hysteroscopes, which facilitates vaginoscopy by reducing resistance to advancement of the hysteroscope through the relatively narrow and often tortuous cervical canal. However, despite these modifications in instrumentation, few clinicians use vaginoscopy routinely preferring more invasive traditional approaches. This may reflect a lack of familiarity with the technique as well as concerns over the ability to identify and traverse the cervical canal in order to access the uterine cavity.

We therefore designed a randomised controlled trial (RCT) to compare standard approach to hysteroscopy against vaginoscopy evaluating important clinical outcomes such as pain, feasibility, acceptability, vasovagal responses and infection. To inform the study design we conducted pilot work including a survey of gynaecological endoscopists, and a systematic review of the current evidence.

Survey of members of the British Society of Endoscopy

We surveyed the members of the British Society of Endoscopy (BSGE) to identify the most popular techniques and the most important questions for a trial in vaginoscopy.

Methods

A series of questions were distributed via email to all the members of BSGE using surveymonkey. Participants were identified through the BSGE electronic database of members (as of January 2013). In order to enhance response rates we restricted the survey to six questions with closed responses. The questions were formulated to help identify current practice, to assess the likely impact of a comparative trial comparing vaginoscopy and standard technique and to inform selection of primary and secondary outcomes.

Results

A total of 128/658 (20%) of participant responded to the email questionnaire. Table 4 shows the responses to the questions.

Table 4. Answers to survey of BSGE members

Question	Answer options	Response
Q1. Do you perform outpatient or office hysteroscopy (ie. hysteroscopy without general anaesthesia)?	Yes	115/128 (90%)
	No	13/128 (10%)
Q2. Which technique do you use most often?	Hysteroscopy using a speculum with or without cervical instrumentation to steady the cervix	36/88 (41%)
	Hysteroscopy with local anaesthetic	10/88 (11%)
	Vaginoscopy (hysteroscopy without a speculum or cervical instrumentation to steady the cervix)	32/88 (36%)
	Flexible hysteroscopy	10/88 (11%)
Q3. Do you employ more than one technique and if so which ones?	Traditional Hysteroscopy	59/85 (69%)
	Traditional Hysteroscopy with local anaesthetic	49/85 (58%)
	Vaginoscopy	51/85 (60%)
	Flexible hysteroscopy	20/85 (24%)
Q4. What is the approximate diameter of the hysteroscopes that you are currently using in mm?	Size in mm	Mean 4.06
Q5. If one technique was shown to be superior based on patient orientated outcomes, would it change your practice?	Yes	76/84 (90%)
	No	8/84 (10%)
Q6. When comparing different techniques which outcomes are most important? (You can choose more than one).	Pain scores	83/87 (95%)
	Failure rates	81/87 (93%)
	Infection rates	23/87 (26%)

	Complication rates	33/87 (38%)

Discussion

Office hysteroscopy is established practice within BSGE members, with 90% of respondents performing the procedure. The most common first line technique for performing office hysteroscopy, using a speculum and no anaesthesia.

The survey showed that only 60% of BSGE members are familiar with vaginoscopy. These estimates, based upon enthusiasts for endoscopy are likely to be much lower within the general gynaecological community and so the potential benefit to patients would be even greater if widely adopted, subject to vaginoscopy being shown to be beneficial. Our survey reported that over 90% of respondents were willing to change their practice, if vaginoscopy was shown to be superior to traditional approaches based on patient orientated outcomes. Therefore, a well conducted and designed RCT has the potential to change practice in one of the commonest surgical instruments in gynaecological practice. The respondents considered pain to be the most important clinical outcome and whilst infection was considered important, 26% of respondents identified it as an important endpoint to evaluate.

There are several limitations to our questionnaire. Firstly, to make the questionnaire quick we only asked six questions with closed responses. More questions with open responses may have generated more information on current

practice and the impact of a trial. Also, the survey was distributed amongst enthusiasts of endoscopy, which affects the generalisability of the results to the wider gynaecological community. Furthermore, given the response rate of 20% it is difficult to determine if those that did not respond would have answered the questions differently.

The findings from our cross-sectional survey suggests that an RCT comparing vaginoscopy and standard approaches is feasible and likely to influence current practice for a common procedure. Based on current practice it appears that hysteroscopy using a speculum without local anaesthesia should be the comparator against which vaginoscopy is compared and that the outcomes of pain, feasibility and complications including rates of infection should be evaluated.

Systematic review and meta-analysis

We have previously completed and reported a systematic review and meta-analysis of vaginoscopy compared to standard hysteroscopy[39]. The databases searched included MEDLINE, EMBASE, and CINAHL using a combination of the keyword 'hysteroscopy', 'vaginoscopy', vaginoscop*', 'no-touch', and their associated word variants and medical subject headings. The Cochrane Library was searched using the keywords 'hysteroscopy', 'vaginoscopy', 'vaginoscopic' and 'no-touch'.

Of the 1167 citations retrieved, six studies met the criteria for inclusion and in four there was suitable data for meta-analysis. Vaginoscopy was found to be less painful than traditional approaches, with a standard mean difference in visual

analogue scales (VAS) pain scores of -0.44 (95% CI -0.65 to -0.22)[39]. However there was statistically significant heterogeneity and this was also seen in the wide variation in procedure feasibility (failure rates varying from 2% to 17%)[39]. This inconsistency reflected the lack of standardisation of approach both in relation to vaginoscopy and traditional speculum based approaches where there was variation between studies in the administration of local cervical anaesthesia, application of cervical tenaculum forceps, and the size and angle of the rigid hysteroscope employed. None of these small RCTs [41–46] had optimal randomisation processes in terms of using computer generated random number sequences and third party concealment. The review and subsequent BSGE and RCOG guideline [4,39] recommended further higher quality adequately powered RCTs to examine more comprehensively the role of vaginoscopy in terms of pain, feasibility, acceptability and complications.

The need for a RCT comparing vaginoscopy to standard hysteroscopy

The current restricted use of vaginoscopy is likely to be the result of a lack of experience with the technique and uncertainty as to whether the technique is associated with a worthwhile reduction in procedural pain and improvement in patient acceptability. Furthermore, there is concern that vaginoscopy is technically more challenging leading to prolonged procedures which may fail to be completed,

lead to more vaso-vagal fainting episodes and a higher likelihood of post-operative infection of the uterus.

In view of the uncertainty over the effectiveness of vaginoscopy we designed an RCT. The aim was to evaluate whether vaginoscopy or standard hysteroscopy was potentially more successful in the office setting by comparing failure rates, complications, infection rates, patient acceptability, and pain scores. In the first instance we designed a feasibility pilot trial (**VA**ginoscopy versus **S**tandard **T**eloscope for office hysteroscopy trial; **VAST**) to inform the design, conduct and feasibility of a larger scale RCT.

Objectives

1. To estimate whether the vaginoscopic technique is potentially more successful compared to traditional approaches where success is defined as a completed diagnostic hysteroscopy with an acceptable level of patient reported pain without a vasovagal episode or post-operative uterine infection.

2. To test the hypothesis that in women undergoing an office hysteroscopy, a vaginoscopic technique is associated with on average at least 10% less pain (as measured by visual analogues scores) compared to traditional approaches.

3. To test the hypothesis that in women undergoing an office hysterosocpy, a vaginoscopic technique is associated with fewer vaso-vagal episodes compared to traditional approaches.

4. To test the hypothesis that in women undergoing an office hysteroscopy, there is no difference in the rates of failure to complete the procedure between vaginoscopy and traditional approaches.

5. To test the hypothesis that in women undergoing an office hysteroscopy, there is no difference in the incidence of post-operative infection between vaginoscopy and traditional approaches.

6. To test the hypothesis that in women undergoing an office hysteroscopy, a vaginoscopic technique is associated with better patient acceptability.

Methods

Study design

A parallel-group unblinded RCT comparing vaginoscopy versus standard hysteroscopy was conducted.

Study setting

Women were recruited from office hysteroscopy clinics within Birmingham Women's Hospital Foundation Trust.

Patient eligibility

Inclusion criteria

All women over 16 attending for an office hysteroscopy were approached to participate in the trial. All participating women gave written informed consent.

Exclusion criteria

Women were excluded from participation if they preferred the procedure under general anaesthesia, or if it was known that cervical dilation would be needed based upon previous reports of severe cervical stenosis or that they would not tolerate a speculum prior to the procedure beginning e.g. history of vaginismus, virgins and severe lichen sclerosis.

Trial registration

This trial was registered on clinicaltrials.gov (identifier: NCT01972945). The National Research Ethics Service, UK, granted ethical approval (identifier: 13/WM/0471). Research and Development approval was sought and granted at Birmingham Women's Hospital. The trial was conducted according to the principles of Good Clinical Practice (GCP)[47]. Appendix 1 shows the consent form that women had to complete before entering the trial. Prior to hysteroscopy all women were provided with evidence based patient information leaflets (Appendix 2).

Randomisation

Women were allocated in a 1:1 ratio to either of the interventions through a telephone-based system managed by the Birmingham Clinical Trials Unit. The randomisation blocks were kept centrally in the Birmingham Clinical Trials Unit and the sizes varied so that the allocation could not be deduced pre-randomisation. Blocks were stratified by menopausal status (premenopausal versus post-menopausal) to ensure we achieved balance between groups for this variable. Menopausal status was chosen because of the influence of oestrogen has on the elasticity of the female genital tract.

Interventions

All procedures were performed in the office setting without general anaesthesia or conscious sedation. Three practitioners experienced in both vaginoscopy and

standard hysteroscopy performed all surgical procedures (TJC, SOC, PS). Vaginoscopy consisted of guiding the hysteroscope into the uterus without the need for any vaginal instrumentation or vaginal antiseptic preparation. Standard hysteroscopy consisted of passage of a vaginal speculum to separate the vaginal walls, cleansing of the ectocervix and when necessary the application of traumatic forceps to the ectocervix in order to stabilise it. All procedures were done using either the 3.1mm 0^0 Single-flow hysteroscopy system (Storz Endoscopy, Tuttlingen, Germany) or a 3.5mm 0^0 Alphascope hysteroscopy system (Gynecare; Ethicon Inc., New Jersey, USA). No cervical preparation was used prior to the procedure. Normal Saline (0.9% w/v NaCl) was instilled from a 50ml syringe, controlled by a nursing assistant, to provide distension and irrigation of the uterine cavity. In line with departmental protocols, fluid deficit was not calculated for office hysteroscopy because procedures were short and performed through small diameter operating hysteroscopes [3]. The use of local anaesthesia (direct cervical block using 6.6ml of 3% Mepivacaine) placed in four quadrants[3] was restricted to procedures where dilatation of the cervix was required to pass the hysteroscope through the endocervical canal. Where the allocated technique failed the operator could revert to the alternative technique if they considered it appropriate.

For a procedure to be considered satisfactorily completed the operator must have done the following:

- Obtained a panoramic view of the uterine cavity from the position of the internal cervical os.
- Identified both tubal ostia or cornual recesses under magnification.

- Inspected the endometrium over the fundus and all four uterine walls (anterior, posterior, right lateral and left lateral) under magnification.
- Identified the origin of focal lesions (polyps/submucous fibroids)
- Inspected the endocervical canal and ectocervix.

Outcomes

Procedure failure

This was defined as an inability to enter the uterine cavity and obtain a satisfactory view for a duration of time sufficient to allow complete systematic examination of the uterine cavity and cervical canal. The reason for failure was documented: patient (pain, anxiety), adverse anatomy (cervical stenosis, inability to identify cervix, acute uterine deviation, adhesions), or suboptimal visualisation.

Complications

Serious complications in the office setting such as uterine perforation are rare, but vaso-vagal reactions (defined physiologically as a sudden drop in heart rate and blood pressure leading to syncope) can complicate between 2.3 – 9.0% of procedures[8,39,48]. For the purpose of this trial vaso-vagal reactions were defined clinically as a woman being unable to leave the operating couch within five minutes of cessation of the procedure due to feeling faint, dizzy or nauseous.

Procedural pain & patient acceptability

These data were collected on a ipad mini™ (Apple™, California, USA) device. We designed a novel system, programming the ipad device to allow easy patient input; all patients were familiarised with the system before they got changed for their procedure. Additionally, all women were informed that their responses were confidential and once completed the screen would become 'blank' at which point the device should be returned to the clinical team. In this was we hoped that the validity of the patient response would be optimised by facilitating an immediate response (minimal recall bias) and blinding their response from the clinical trial (reducing observer bias). This was administered to the participating women immediately after the diagnostic procedure but before any further intervention (e.g. endometrial biopsy, polypectomy or levonorgestrel intrauterine device (LNG-IUS, Bayer, Leverkusen, Germany) insertion. To assess acceptability women were asked 'Did you find the procedure acceptable?' 'Yes'; 'No'. Pain was assessed using a slider on a 100mm visual analogue scale (0 for no pain and 100 for worst imaginable pain) (Appendix 3).

Infection rates

The patients were contacted via email or telephone two weeks after the procedure. An infection was defined as any of the following i) if the woman had received antibiotics for a urinary tract infection or vaginal discharge; ii) if the women had two out of the following three symptoms: offensive vaginal discharge, pelvic pain and pyrexia.

Surgical technique

Surgeons completed a standard form following the procedure to record technical aspects of the procedure including time taken and peri- or post-operative complications. Data collected by the operator at the time of hysteroscopy included: the use of local anaesthesia; the need for dilatation of the cervix; the use of a vaginal speculum; the use of a tenaculum; completeness of procedure; any further procedures after the diagnostic hysteroscopy; the time taken to complete the procedure (defined as the time from insertion of vaginal instrumentation post-randomisation until the end of the diagnostic procedure); details of any adverse events (Appendix 4).

Primary clinical outcome

The primary clinical outcome was success, which was defined as a composite outcome of a completed hysteroscopy with an acceptable level of pain for the patient without a vasovagal episode or post-operative uterine infection. A composite outcome was chosen as it was felt that all of these factors were important to classify a hysteroscopy as 'successful' based upon the evidence from the literature[39] and data from our cross-sectional survey of the BSGE (see preceding section on the survey of British Society of Endoscopy members). Each of the individual constituents of the primary clinical outcome was also examined individually as a secondary outcome.

Serious and unexpected adverse events

Office hysteroscopy is performed widely across the NHS and regarded as a safe procedure. However, all *serious adverse events* (SAE) were to be reported as soon as possible (Appendix 5). For the purposes of this study, "serious" adverse events were those that were fatal, life-threatening, disabling or caused prolonged hospitalisation and resulted from the hysteroscopy, or associated procedures.

Data management

All data were inputted into the electronic VAST database by PS. At the end of the trial, a random 10% sample of all of the trial data were re-entered by the Chief Investigator JC to verify correct data input. Any discrepancies between originally entered data and re-entered data were reviewed and checked against the original paper copy. An initial data entry error rate of >5% would have triggered a requirement to re-enter the entire data set from that questionnaire. This was not found to be necessary.

Sample size

A recent review of the vaginoscopy approach compared with traditional methods[39] found the proportion of failed procedures to be similar for both approaches: 7% for former compared with 5% for the later. The same review found pain levels (on a visual analogue scale) to be lower with vaginoscopy (-0.44, 95%CI: -0.65 to -0.22; $P < 0.001$), but did not include details on the other components of our primary composite outcome measure (rates of unacceptable pain levels, vasovagal episodes and genital tract infections). Trial data is available from other sources for

the traditional outpatient approach for these components (but not for vaginoscopy); a randomised controlled trial found that 16% of women found the procedure to be unacceptable (30% required some sort of pain relief on the day)[49]. Vasovagal response rates were also reviewed in a recent systematic review found to be around 9%[39]. Genital tract infections rates are thought to be around 1%[50,51].

Given pain levels have been shown to be lower with vaginoscopy (notwithstanding the poor quality of the current evidence) our hypothesis is that we expect this to translate to lower rates of unacceptable pain and vasovagal responses. Rates of genital tract infection could be slightly higher than the traditional approach. Obviously there is some potential for overlap in the four components of the primary outcome. If a conservative figure of 24% is assumed for the 'failure' rate in the traditional hysterosocpy arm (16% unacceptable plus a further 8% either failure of procedure, vasovagal response or infection). To be able to detect a 25% relative reduction from this rate (i.e. reduced to 18%) with 80% power (P = 0.05) we would require 1500 women. To allow for loss to follow-up and incomplete data we would aim to recruit at least 10% more than the target above. However, given the uncertainties in our composite outcome we felt a pilot trial needed not just to ascertain feasibility and trial procedures, but also to estimate the likely magnitude of effect and confirm or refute whether our estimate for N = 1500 are correct.

Statistical analysis

Analysis for all parameters was intention to treat. The primary outcome was a combined measure of acceptable pain, procedure completion, no vasovagal

episodes and no infection. This was a dichotomous outcome and was compared using chi-squared tests. The individual components were compared as secondary outcomes using t-test and chi squared test as appropriate. Mean differences/relative risks and 95% confidence intervals were presented alongside results of significance testing for all parameters. All analyses were carried out using SPSS software version 21 (IBM, Armonk, NY, USA).

Results

Participants

In total, 200 women requiring hysteroscopy were randomised over 8 months between April 2014 and August 2014. There were 182/200 (91%) that responded to follow-up 2 weeks after the procedure to check for infection. Figure 2. summarises the flow of participants through the trial in line with the recommendations of the consolidation standards of reporting trials (CONSORT) statement [52].

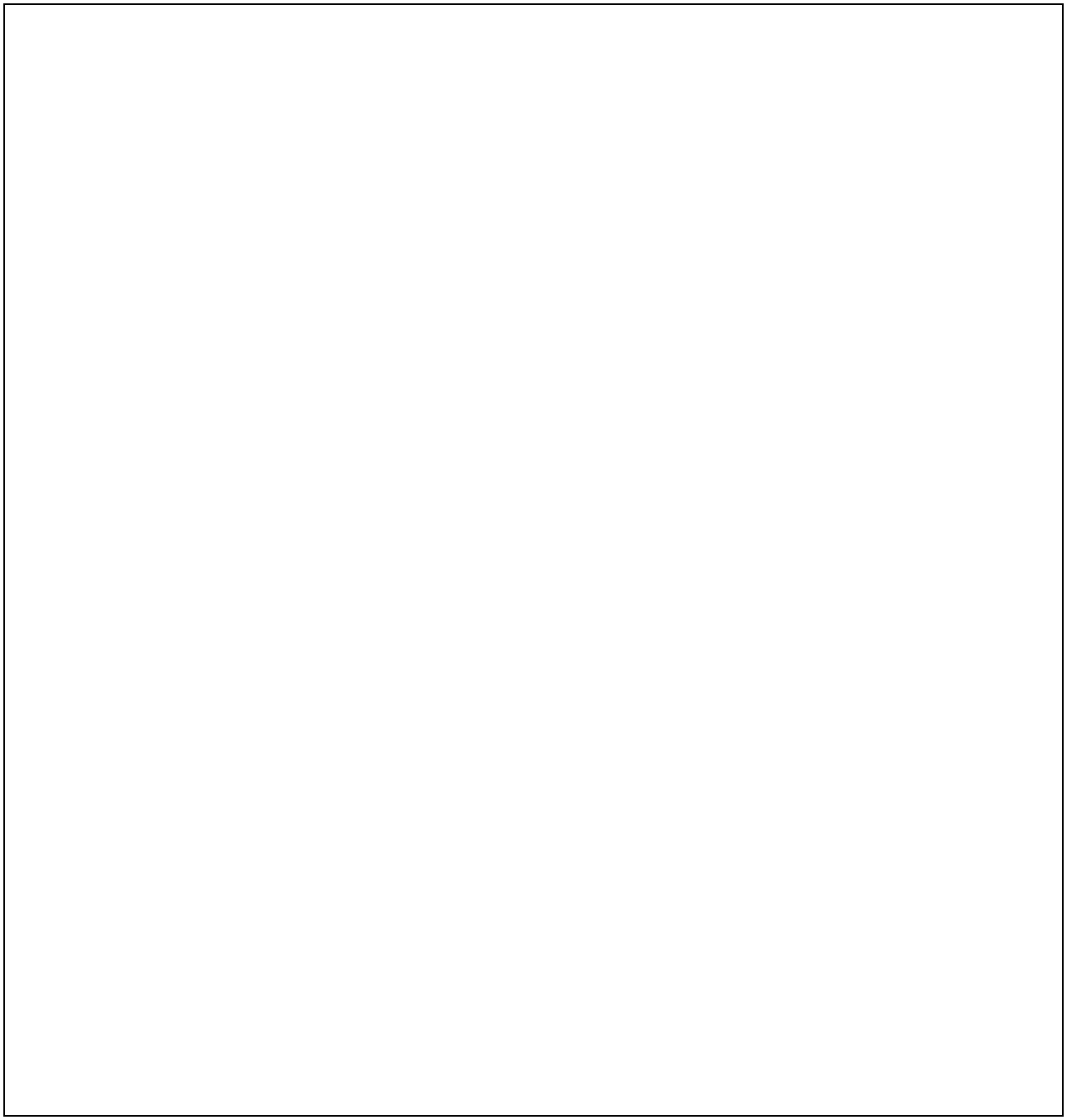


Figure 2. CONSORT flow diagram of women in trial.

Baseline characteristics

The baseline variables were balanced between the groups post-randomisation (Table 5).

Table 5. Baseline characteristics of trial participants.

		Vaginoscopy (N=100)	Standard Hysteroscopy (N=100)
Age (years)	Mean (SD)	44.3 (12.3)	44.2 (13.4)
BMI (kg/m2)	Mean (SD)	28.4 (7.6)	28.0 (6.8)
Parity	Mean (SD)	1.6 (1.7)	1.5 (1.5)
Previous caesarean	Yes	13	17
	No	87	83
Menopausal status	Premenopausal	70	70
	Postmenopausal	30	30
Indication	Bleeding	61	61
	Dysmenorrhoea	2	1
	Fertility	20	15
	Lost intrauterine device	5	6
	Pregnancy loss	0	2
	Abnormal imaging	11	15
	Amenorrhoea	1	0
Practitioner	J Clark	31	30
	P Smith	48	49
	S O'Connor	20	22

BMI = body mass index; SD = standard deviation

Outcome data

Overall, 99% of women found office hysteroscopy to be acceptable; with no women receiving vaginoscopy reporting the procedure as unacceptable, compared to 2 (2%) women in the standard hysteroscopy group (OR 0.20 [95% CI 0.01 to 4.14]) (Table 6). The only complications to occur during the trial were vasovagal reactions, which occurred in two women receiving vaginoscopy and five women receiving standard hysteroscopy (OR 2.58 [95% CI; 0.48 to 13.62]) (Table 6). There were two (2%) women for vaginoscopy and five (6%) for standard hysteroscopy who were classified as having an infection (Table 6). Of the seven (4%) women who had an infection 1 (14%) was treated with antibiotics, while (86%) had at least two of the following: offensive discharge, pyrexia and pelvic pain in the two weeks after the procedure. Significantly more procedures failed with standard hysteroscopy eight (8%) compared to vaginoscopy one (1%); (OR 8.61 [95% CI; 1.05 to 70.20]) (Table 6). The primary outcome was a successful procedure that was defined as a composite score of an acceptable level of pain, with no complications, no infection and no failures. Vaginoscopy was significantly more successful than standard hysteroscopy (OR 4.28 [95%; 1.52 to 12.09]) (Table 6). There was no strong evidence for a difference in the median pain measured on a 100mm visual analogue scale between the two techniques (33 for vaginoscopy versus 38 for standard hysteroscopy; $P = 0.3$). However, the median time taken to complete vaginoscopy was 2 minutes compared to 3 minutes for standard hysteroscopy ($P < 0.001$).

Table 6. Outcome data for vaginoscopy compared to standard hysteroscopy.

Outcome	Vaginoscopy n/N (%)	Standard Hysteroscopy n/N (%)	OR (95% CI)
Acceptable	100/100 (100)	98/100 (98)	0.20 (0.01 to 4.14)
Complications			
Vasovagal reactions	2/100 (2)	5/100 (5)	2.58 (0.48 to 13.62)
Others	0/100 (0)	0/100 (0)	
Infection			
Women meeting criteria for infection[1]	2/92 (2)	5/90 (6)	2.65 (0.50 to 14.01)
Antibiotics for UTI	0/92 (0)	0/90 (0)	
Antibiotics for discharge	1/92 (1)	0/90 (0)	
Offensive discharge	3/92 (3)	5/90 (6)	
Pelvic pain	20/92 (22)	16/90 (18)	
Pyrexia	3/92 (3)	5/90 (6)	
Procedure Failed	1/100 (1)	8/100 (8)	8.61 (1.05 to 70.20)
Composite score[2]	5/92 (5)	18/90 (20)	4.28 (1.52 to 12.09)

n/N = number with positive outcome/total number reported with outcome; OR = odds ratio; CI = confidence interval; UTI = urinary tract infection

1) Criteria for infection = either antibiotics for UTI or vaginal discharge or 2 of the following: offensive discharge, pelvic pain, pyrexia.

2) Composite score of failure, were success was defined as an acceptable procedure, with no complications, no infections and complete procedure.

Subgroup analysis

A subgroup analysis was only done for the stratification variable of menopausal status for the primary outcome of successful procedure. In premenopausal women significantly more procedures failed with standard hysteroscopy (9/63; 14%) compared to vaginoscopy (2/65; 3%) (OR 5.25 [95% CI; 1.09 to 25.35]). For postmenopausal women there were more failures with standard hysteroscopy (9/29; 31%) compared to vaginoscopy (3/28; 11%), but this did not reach statistical significance (OR 3.75 [95% CI; 0.90 to 15.72]).

Discussion

Key findings

This RCT provides evidence to suggest that vaginoscopy is quicker to perform and more successful than standard hysteroscopy. That is more procedures were fully completed with an acceptable level of pain and without complications. Vaginoscopic hysteroscopy was associated with a lower procedure failure rate but procedural pain scores were comparable and both approaches were equally safe and acceptable. The improved performance of vaginoscopy may be attributed to the avoidance of instrumentation of the lower genital tract.

Interpretation

One of the advantages of office hysteroscopy is that it allows the investigation of women without the risks of a general anaesthetic. However, it is the women for whom avoiding a general anaesthetic is most advantageous, i.e. the elderly or obese, that can provide the biggest challenges when performing office hysteroscopy. For instance, increasing age is associated with decreased elasticity of the vaginal tract, and so passing a speculum maybe associated with increased pain and anxiety for elderly women. Access can be compromised within the lower genital tract in women with increased BMI's and increased soft tissue that can make identifying the cervix difficult and painful with a speculum. Thus, avoiding instrumentation of the genital tract by utilising a vaginoscopic approach could be particularly beneficial in these groups of patients, in addition to the general female population. However, the decreased elasticity that is associated with increasing

age can also be associated with stenosis of the cervix. In this situation a speculum is necessary to allow local anaesthetic infiltration and cervical dilatation, so vaginoscopy may not always the appropriate technique. A subgroup analysis in postmenopausal participants did not show a significantly more failed procedures for standard hysteroscopy compared to the vaginoscopy (OR 3.75 [95% CI; 0.90 to 15.72]). Although this could of been explained by the smaller number of participants who were postmenopausal (60/200; 30%).

Only 9/200 (4.5%) of office procedures failed. However, it is of interest that in all procedures where the procedure failed with the allocated treatment, the procedure was ultimately successful with the other technique. This shows the importance of becoming proficient in both vaginoscopy and standard hysteroscopy if one is to perform procedures in the office setting. However, vaginoscopy failed in only 1/100 (1%) case, when a stenosed cervix was identified and a speculum was needed to perform cervical anaesthesia to allow dilatation, compared to 8/100 (8%) cases with standard hysteroscopy. It appears to be the preferential technique to adopt. Standard hysteroscopy most commonly failed because of pain associated with insertion of the speculum. Also, it may be that removing the speculum, and other vaginal instrumentation, enables the manoeuvrability of the camera to be improved allowing more successful and quicker procedures (median time 2 minutes for vaginoscopy compared to 3 minutes for standard hysteroscopy). Also, less torque on the cervix may minimise pain and vasovagal responses, although our relatively small study did not show these effects. The size of the hysteroscope used may influence the pain and feasibility of the procedure. In clinical settings were different

sized hysteroscopes are employed the results may be different. However, a larger randomised study would be needed to have sufficient power to provide subgroup analysis of different hysteroscope sizes. Whilst further work is needed to improve patient selection, the evidence suggests that vaginoscopy should be the default technique unless it is known that cervical dilatation is needed.

One potential advantage of having access to the cervix using the standard technique is that the cervix can be cleaned, hypothetically reducing the incidence of ascending infection. However, infection rates in relation to office hysteroscopy are very few[50,51] and this had not been investigated in a rigorous RCT. We used broad criteria aimed to detect all infections associated with hysteroscopy including: uterine endometritis, tubal infection, pelvic infection and tuboovarian abscess. Reassuringly, we have demonstrated no significant difference in the rate of infection using thorough follow-up, although given the small incidence a very large sample would be needed.

Comparison with other studies

Previous work comparing vaginoscopy to standard hysteroscopy has focused on pain scores [41–46]. A meta-analysis of this work concluded that vaginoscopy significantly reduced pain compared to standard hysteroscopy. This study showed a trend for decreased pain with vaginoscopy, which did not reach significance. In this study the average pain scores for the standard technique were lower than in previous trials [39]. This could be explained because all the studies included within the meta-analysis used a tenaculum for standard hysteroscopy in addition to vaginal

speculum and avoiding cervical instrumentation may confer a significant pain reduction. Another difference in our study compared to the studies in the meta-analysis was the lower procedural failure rate in the vaginoscopy group compared to the standard group. This could have been because the hysteroscopes used in the current study were of a smaller diameter, thus negating the need for cervical dilatation in some cases. We also developed and used a normal patient reported outcome measure for estimating the degree of procedural pain; the electronic VAS allowed immediate, blinded responses limiting recall and observer bias.

Strengths and limitations

The main strength of our trial was the strict randomisation and the completeness of follow-up, with 91% of women having complete data. The hysteroscopic evaluation of the uterine cavity was standardised and we evaluated a range of outcome measures identified as important to women and gynaecologists, which included an assessment of post-operative infection, an outcome not previously reported.

One of the main limitations was the lack of blinding. Operating in conscious patients makes it difficult to blind participants to their allocated intervention unless they are indistinguishable. In the VAST trial, we did not inform the women of the allocated procedural technique, but it is likely that most women were aware of the particular intervention they underwent in view of the pre-randomisation verbal and written information provided describing the techniques. Moreover, a vaginal speculum examination is familiar to most women over 25 years who are eligible for cervical screening.

The small sample size also restricts the inferences we can draw. However, this RCT is more rigorously conducted and nearly as large as the biggest RCT to date[42] (sample size 400). However, this RCT is a pilot to help design and inform a larger, more generalisable multicentre study. Such a study would also allow investigation of subgroups of women e.g. post-menopausal, nullliparous, high BMI who may benefit more from one or other approaches to hysteroscopy. The generalisability of the results would also be improved if there had been a multicentre design. However, our general unselected population of women is likely to be representative of the demography of women undergoing office hysteroscopy in many units.

Our adoption of a composite outcome, in addition to evaluating outcomes individually helped aid interpretation and inform clinical decisions regarding choice of technique for this very common gynaecological intervention. This is because the procedure is established as safe and feasible and is generally acceptable with moderate to low pain scores[39,40]. Thus, we anticipated that distinguishing between the different approaches would be difficult if looking at individual components of an office hysteroscopy in isolation whereas evaluating the procedure in totality, using outcome measures deemed by gynaecologists a-priori to influence their practice, we believe aids interpretation.

Conclusion

Advances in medical technologies have facilitated increasingly convenient but invasive office procedures. Instrumenting the uterine cavity requires intimate genital tract examination and can be associated with substantial pain. Thus, in view of the ubiquity and importance of office hysteroscopy in day-to-day gynaecological practice, it is important to minimise pain, complications and failure associated with the procedure to benefit patients, stream-line management and ethically utilise healthcare resources. In centres already providing office services, vaginoscopy could offer a potential benefit to patients undergoing hysteroscopy with minimal training and could save resources by reducing the need for subsequent inpatient procedures under general anaesthesia because of failed office procedures. A larger, multicentre RCT is now needed to confirm these preliminary findings and to allow subgroup analysis to estimate types of women that may particularly benefit from vaginoscopy.

CHAPTER 4: PROGNOSTIC FACTORS THAT PREDICT SUCCESS OF ENDOMETRIAL ABLATION IN THE OFFICE SETTING

Publication

The work has been submitted to the Journal of Gynecolgoical Surgery to be considered for publication.

Abstract

Objective

To identify clinical factors that influence the rate of further surgical intervention in women who have endometrial ablation.

Methods

Prospectively held electronic databases and patient records were scrutinised to obtain historical, examination, investigative and procedural data considered to be potentially predictive of the need for further surgical intervention after endometrial ablation in the office setting.

Results

A total of 391 consecutive women were identified who received endometrial ablation in the office setting between July 2005 and December 2012, with an average follow-up of 4.3 years. Univariable and multivariable logistic regression were used to estimate the influence of these variables on prognosis. Factors predictive of further surgical treatment were dysmenorrhoea (aOR 4.82; 95% CI 1.81 to 12.82) and a uterine cavity length >9cm OR (aOR 3.13; 95% CI 1.52 to 6.43).

Conclusion

Dysmenorrhoea before treatment or a uterine cavity length >9cm are associated with the need for further surgical interventions after office endometrial ablation.

These findings should help inform clinician and patient decision making when considering treatment options for heavy menstrual bleeding.

.

Introduction

Background

Heavy menstrual bleeding is a common gynaecological condition that has a significant impact on the morbidity of premenopausal women[53,54]. In the majority of cases no organic cause is found and this is termed dysfunctional uterine bleeding. The first line therapy for dysfunctional uterine bleeding is pharmacological treatment[55]. If this fails it is appropriate to perform an endometrial ablation[55]. The uterine sparing ablative procedure has the advantage that it can be performed in the office setting and does not have the costs, morbidity and mortality associated with major surgery[56].

Endometrial ablation

Endometrial ablation is targeted destruction of the endometrial lining in the uterine cavity. It should only be considered in women who have completed their family. The first generation hysteroscopic techniques included resection of the endometrium, endometrial laser ablation and roller ball ablation. These were rigorously evaluated against hysterectomy in number of RCTs[57,58]. The first-generation techniques still provide a treatment option in women with irregular endometrial cavities due to submucous fibroids or congenital abnormalities. However, they have been replaced by the second-generation techniques that have been developed for smoother cavities. These have included thermal balloon devices, bipolar radiofrequency and microwave ablation. They are safer and technically easier to learn than the hysteroscopy based techniques and can be

performed in the office setting. Women undergoing endometrial ablation should have endometrial histology prior to the procedure to ensure that malignant or premalignant disease is not responsible for bleeding symptoms. They should also have a hysteroscopy before and after the procedure to make sure there is no perforation. Potential complications include: infection, uterine perforation, visceral burns, haematometra and fluid overload due to absorption of distension media[57,58].

The need to look for prognositic factors that predict failure with endometrial ablation

In contrast to hysterectomy, endometrial ablation cannot guarantee amenorrhoea and the need for further surgical intervention, usually in the form of a hysterectomy, is well recognised[59]. A randomised controlled trial (RCT) comparing the two most commonly used second generation ablative devices in a novel office setting, bipolar radiofrequency ablation and thermal balloon ablation, showed satisfaction rates of 90% and 79% respectively at 1 yr follow-up[60]. However, after five years there were eight women in the bipolar radiofrequency group (9.8%) and five in the thermal balloon ablation group (12.9%) who had undergone a hysterectomy[60].

If it were possible to predict the chance of such treatment failure following endometrial ablation, then alternative, potentially more effective, treatment interventions could be considered. Two earlier studies evaluating treatment outcomes after second generation endometrial ablation performed in a traditional

inpatient setting under general anaesthesia have provided evidence that prognostic variables may be identified from information gleaned from the patient history, examination and uterine imaging[61,62]. Both studies identified dysmenorrhoea and enlarged uterine cavity size as predictive of treatment failure, although the results for age, parity and tubal sterilisation were conflicting[61,62]. While a network meta-analysis of second generation endometrial ablation found only uterine cavity length >8cm had an adverse impact on patient satisfaction[63].

In light of these inconsistent findings and the increasing adoption of the office setting to conduct endometrial ablation[64,65], we studied our cohort of office endometrial ablations.

Objectives

1. To establish which women having an endometrial ablation at Birmingham Women's Hospital needed further intervention.

2. To identify treatment clinical factors associated with further intervention.

Methods

Study design

We performed an observational analysis of 391 patients.

Study setting

All women who underwent endometrial ablation in the office setting at the Birmingham Women's Hospital, between July 2005 and December 2012 were included in the analysis.

Participants

Women who had undergone office endometrial ablation for heavy menstrual bleeding were identified through the surgical logbooks.

Interventions

Endometrial ablations were done using either thermal balloon ablation (Thermachoice^{TM}; Gynecare^{TM}; Ethicon^{TM} Inc., New Jersey, USA), or bipolar radiofrequency ablation (NovaSure^{TM}; Hologic^{TM} Bedford, MA, USA). The office endometrial ablative procedure has been previously described[6,64]. In short, women were pre-medicated one hour before the procedure with either 100mg Diclofenac rectal suppository (or 100mg oral Tramadol Hydrochloride if contraindicated), two oral tablets of Co-dydramol 10mg/500mg and 50mg of oral Cyclizine. A direct intracervical block was administered by infiltrating 2.2ml of 3% Mepivicaine into the 12 and 6 o'clock position before infiltrating 1.1ml into the 3 and 9 o'clock positions,

using a 35mm, 27 gauge dental syringe; the majority of the solution was infiltrated at the level of the internal os with the rest evenly distributed along the length of the cervix on withdrawal of the needle. A preliminary diagnostic hysteroscopy was performed to exclude pathology that would distort the intrauterine cavity and to ascertain likely compliance to the procedure and the uterine length was sounded. This was followed by endometrial ablation with bipolar radiofrequency ablation or thermal balloon ablation, performed according to the recommended manufacturers instructions for use.

Data collection

The analysis included the following data parameters for each patient: age, body mass index (BMI), caesarean section, ablation type, duration of symptoms, uterine size, regularity of cycle, dysmenorrhea, premenstrual syndrome, anti-platelet medication, failed medical therapy, cycle phase, uterine axis, fibroids on imaging or examination, hysteroscopy findings and further surgical intervention. Data for 81 patients were collected prospectively as part of the Comparison of Office Ablation Techniques trial[6,64], while data for the remaining 310 patients were collected retrospectively by scrutinising medical records.

Statistical methods

Data were analyzed using the SPSS statistical software version 21 (IBM, Armonk, NY, USA). Univariable logistic regression analysis was used to determine the influence of individual prognostic factors on the odds of requiring further surgical or radiological intervention i.e. endometrial ablation, myomectomy, hysterectomy or

uterine artery embolisation (UAE), which were considered to be consistent with treatment failure. The relative importance of the above covariates was determined with multivariate regression analysis using the stepwise backward likelihood ratio method.

Results

Baseline characteristics

The average follow-up for the 391 women undergoing office endometrial ablation during the study period was 4.3 years (range 0.2 to 8.9 years). Table 1 shows the baseline demographics and clinical characteristics of the women. Of the 360/391 (92%) who had been unsuccessfully treated with medical therapy, 216/360 (60%) had a hormonal therapy (including the levonorgestrel releasing intrauterine system), 95/360 (26%) had a non-hormonal therapy and in 49/360 it was not stated which medical treatment they had received. Of the 64 women who had abnormalities on hysteroscopy before treatment: 18/64 (53%) had fibroid changes (either small submucous fibroids or slight distortions by intramural fibroids), 8/64 (23%) had endometrial polyps, 8/64 (14%) had congenital abnormalities (mildly arcuate) and 6/64 (9%) had synechiae.

Further surgery

Further surgical intervention after the office ablation was subsequently reported in 49 women: 46 (12%) underwent hysterectomy, two (1%) had a uterine artery embolisation and one woman had a myomectomy (<1%). The majority of interventions were performed within 24 months of endometrial ablation; 41% of interventions by one year of follow up and 75% performed by two years. Of those women that had a hysterectomy, pain alone was the most common indication (19/46; 41%), followed by bleeding alone (17/46; 37%), then bleeding and pain (7/46; 15%), 2/46 (4%) had bleeding with an ovarian mass, 1/46 (2%) had a

persistent watery discharge and 1/46 (2%) was diagnosed with complex endometrial hyperplasia. Two other women had a hysterectomy, but were not considered as treatment failures; one woman had a hysterectomy for uterine prolapse, while the other woman had a hysterectomy for an ovarian mass discovered as incidental finding after investigation for upper abdominal symptoms.

Abnormal findings were found in 32/46 (70%) of the hysterectomy specimens, while 14/46 (30%) were normal (except for endometrial scarring secondary to the endometrial ablation). The most common abnormality found was adenomyosis alone (14/46; 30%). The remainder comprised of: fibroids and adenomyosis (6/46; 13%), fibroids alone (5/46; 11%), fallopian tube endometriosis (4/46; 9%), endometrial polyps 2/46 (4%) and malignant ovarian mass 1/46 (2%). The uterus of the woman who had a hysterectomy because of complex hyperplasia showed complete regression of disease.

Pre-operative predictors of the need for further surgery

Table 7 shows the results of univariable analysis. Both increased uterine cavity length (OR 2.28, 95% CI 1.20 to 4.33; *P* = 0.01) and presence of dysmenorrhoea before treatment (OR 3.30, 95% CI 1.50 to 7.26; *P* = 0.003), demonstrated evidence for an association with the need for further surgical intervention. These findings remained independently predictive of further surgical intervention after multivariable analysis; dysmenorrhoea (aOR 4.82, 95% CI 1.81 to 12.82; *P* = 0.002) and uterine size >9cm (aOR 3.13, 95% CI 1.52 to 6.43; *P* = 0.002).

Table 7 Factors assessed for prediction of further uterine surgical intervention after office endometrial ablation.

Characteristic		No Intervention (n=340)	Further Intervention (n=51)	Univariable analysis Odds Ratio (95% CI)	*P*[1]	Multivariable analysis Odds Ratio (95% CI)	*P*[1]
Age	>45	110 (33)	17 (35)	reference			
	40 to 45	135 (40)	12 (25)	0.59 (0.27 to 1.27)	0.2		
	<40	96 (28)	20 (41)	1.36 (0.67 to 2.75)	0.5		
BMI	<18.5	1 (0)	0 (0)	not recordable			
	18.5 to 25.0	95 (28)	7 (14)	reference			
	25.1 to 30.0	103 (30)	18 (37)	2.37 (0.95 to 5.93)	0.07		
	>30.0	143 (42)	24 (49)	2.28 (0.94 to 4.570)	0.07		
Previous caesarean		82 (24)	14 (29)	1.27 (0.65 to 2.47)	0.5		
Endometrial ablation technique (Bipolar Radiofrequency vs Thermal Balloon)		189 (55)	29 (59)	1.17 (0.64 to 2.16)	0.6		
Failed medical treatment		364 (92)	44 (90)	0.72 (0.26 to 1.98)	0.8		
Phase of cycle	Secretory	110 (32)	17 (35)	reference			
	Proliferative	120 (35)	12 (25)	0.65 (0.30 to 1.42)	0.3		
	Menses	33 (10)	6 (12)	1.18 (0.43 to 3.23)	0.8		

	Progesterone effect	79 (23)	14 (29)	1.15 (0.53 to 2.46)	0.7		
Uterine Axis	Anteverted vs Other	50 (15)	8 (16)	1.14 (0.51 to 2.57)	0.8		
Abnormal hysteroscopy findings[2]		57 (17)	7 (14)	0.83 (0.36 to 1.95)	0.7		
Presence of fibroids[3]		276 (81)	38 (78)	0.83 (0.40 to 1.70)	0.6		
Duration of symptoms (months)		40.0 (43.4)[4,5]	32.9 (32.0)[4,6]	1.00 (0.99 to 1.00)	0.3		
Uterine Size >9cm[7]		65 (20)[8]	18 (37)	2.28 (1.20 to 4.33)	0.01	3.13 (1.52 to 6.43)	0.002
Menstrual Cycle Irregular		137 (41)[9]	17 (37)[10]	0.84 (0.45 to 1.59)	0.6		
Dysmenorrhea		208 (61)	41 (84)	3.30 (1.50 to 7.26)	0.003	4.82 (1.81 to 12.82)	0.002
Premenstrual syndrome		90 (26)	15 (31)	1.24 (0.64 to 2.37)	0.5		
Antiplatelet drugs or anticoagulants		8 (2)	2 (4)	1.78 (0.37 to 8.62)	0.5		

Data are n (%) unless otherwise specified

1) *P* = one significant figure

2) Of the 64 women who had abnormalities on hysteroscopy: 53% had fibroid changes (either small submucous fibroids or slight distortions by intramural fibroids), 23% had endometrial polyps, 14% had congenital abnormalities (mildly arcuate) and 9% had synechiae.

3) Fibroids of any location found on imaging, hysteroscopy or clinical examination

4) Data are mean average (standard deviation)

5) Data missing for 24 cases

6) Data missing for 5 cases

7) Measured on a uterine sound

8) Data missing in 22 cases

9) Data missing in 8 cases

10) Data missing in 3 cases

Discussion

Key findings

This study has provided evidence to show that women with pre-existing dysmenorrhoea or a uterine cavity size above 9cm are more likely to require further intervention after having endometrial ablation in the office setting. Knowledge of these unfavourable features following history taking and examination should help inform patient counselling and decision making regarding the appropriateness of endometrial ablation in comparison to other medical and surgical treatment options for heavy menstrual bleeding.

Comparison with other studies

The most important risk factor for further intervention identified within this study was dysmenorrhoea before treatment. This is consistent with previous studies that have shown similar findings[61,62]. Higher rates of further intervention among those women with pre-existing dysmenorrhoea could be caused by coexisting conditions such as adenomyosis. This contention could be supported by the finding of adenomyosis in 43% of all failed treatment hysterectomy specimens. However, 41% of all women undergoing subsequent hysterectomy did so because of menstrual pain, so it is possible that the ablative procedure could have induced or exacerbated this symptom because of (i) iatrogenic adenomyosis (as has been reported following first generation hysteroscopic ablation procedures[66]) or (ii) formation of intrauterine adhesions obstructing menstrual outflow i.e. haematometra. The second most important risk factor for further surgery after ablation was a uterine cavity depth

>9cm. In a larger cavity there is a more endometrium to destruct and the ablation devices may not be optimised for treatment of more capacious uterine cavities.

There were no significant differences in hysterectomy rates based on age. This is consistent with one previous case-controlled study[6] but contrasts with other research that identified age under 40 as significantly associated with increased hysterectomy rate[67,68]. Having a previous caesarean section, taking anticoagulants or anti-thrombotics, irregular menstrual bleeding, uterine axis, duration of symptoms and BMI were not associated with an increased hysterectomy rate consistent with previous work[61,7]. The phase of menstrual cycle has not been previously assessed but we did not find an association with subsequent hysterectomy.

Previous work identified submucous fibroids as being associated with treatment failure and higher hysterectomy rates[62,68,69] following ablation. This observation is thought to reflect suboptimal endometrial coverage by the ablation device because of uterine cavity distortion. However, a recent meta-analysis of second generation techniques did not find the presence of submucous fibroids and intrauterine polyps predictive of patient satisfaction[63]. Our study found no association between uterine fibroids and further intervention, but we did not restrict our analysis to submucous fibroid locations. This was because the prevalence of submucous fibroids was low in the current study and where they did exist they were <1cm with negligible cavity distortion. Whilst many second generation ablative devices only consider submucous fibroids of >3cm as contraindications, in our unit most women have had a pre-treatment transvaginal ultrasound or office hysteroscopy and this thorough

diagnostic work up may have selectively removed women with any degree of cavity distortion by fibroids thought to impact upon the feasibility of endometrial ablation.

This study showed no difference between the need for surgical intervention according to the type of ablative procedure, bipolar radiofrequency ablation or thermal balloon ablation, at a mean follow up of 4 years. This finding is consistent with two RCTs that have reported similar rates of hysterectomy and satisfaction health related quality of life measures at five years of follow up[60,64].

Strengths and limitations

This cohort study original in that it is the first to look specifically at endometrial ablations performed in the office setting. Other strengths of the study include the exploration of a wide range of possible prognostic factors for subsequent surgical intervention within a large population of women undergoing office endometrial ablation. Although the generalisability of the findings may be limited because data were derived from a single treatment centre, we believe that the findings are likely to be representative because standardised procedures were used in a large, diverse population of women with heavy menstrual bleeding.

A limitation of this study is that it does not show if women who did not have further intervention were completely satisfied after treatment. There may have been women who were not satisfied with treatment but were not willing, or considered not suitable, for a further surgical procedure. Furthermore, we considered women undergoing a hysterectomy because of premalignant endometrial disease to have

failed treatment even if asymptomatic. These patients were included because surveillance of endometrial hyperplasia can be hampered subsequent to endometrial ablation due to the formation of uterine adhesions (Asherman's syndrome). Also, without formal follow-up for all women some may have moved or decided to be treated in a different hospital. However, it was reassuring that the hysterectomy rate was the same for the women who had data collected prospectively as part of the Comparison of Office Ablation Techniques trial[6,64], and those who's data was collected retrospectively by scrutinising medical records.

The majority of the data were collected retrospectively, so results in this paper depended on the quality of the data obtained from clinical records. However, the clinical information required was recorded as standard in the medical notes and so most of the data were complete; the variable with the most missing data was duration of symptoms, and this was only missing in 7% of cases.

Conclusions

This study showed that one in eight women had further uterine surgery after office endometrial ablation and that dysmenorrhoea before treatment and a uterine cavity length >9cm were predictive of this need for subsequent surgery. These findings, derived from endometrial ablation performed in an innovative and increasingly utilised office, local anaesthetic setting, corroborate earlier studies performed with a variety of second generation ablative systems under general anaesthesia in hospital[61,62,68]. Women with pre-existing dysmenorrhoea or enlarged uteri should be counselled about their increased chance of requiring additional uterine surgery after endometrial ablation. This knowledge should help women and their clinicians formulate more informed decisions regarding treatment for heavy menstrual bleeding refractory to previous medical therapy.

CHAPTER 5: FIVE YEARS FOLLOW-UP OF A RANDOMISED CONTROLLED TRIAL TO COMPARE THE EFFECTIVENESS OF OUTPATIENT ENDOMETRIAL ABLATION.

Publication

This work has been published in the Green Journal; Smith PP, Malick S, Clark TJ. Bipolar radiofrequency compared with thermal balloon ablation in the office: a randomized controlled trial. Obstet Gynecol. 2014 Aug;124(2 Pt 1):219-25.)

Abstract

Objective

To estimate the effectiveness of office based bipolar radiofrequency ablation compared with thermal balloon ablation of the endometrium for the treatment of heavy menstrual bleeding at five years follow-up.

Methods

A single blind randomised controlled trial (RCT) was conducted in an office hysteroscopy clinic in a university teaching hospital. A total of 81 women were randomly allocated to either bipolar radiofrequency ablation or thermal balloon ablation in an office setting avoiding use of general anaesthesia or conscious sedation. The main outcome measures were amenorrhoea rates, patient satisfaction, health related quality of life and incidence of further uterine surgery at five year follow up.

Results

At five years follow-up 59 (73%) of women responded to postal questionnaires. Amenorrhoea was reported in 60% of thermal balloon ablation and 62% of bipolar radiofrequency ablation (OR 1.09; 95% CI 0.38 to 3.11) and satisfaction with treatment outcome in 96% of thermal balloon ablation and 96% of bipolar radiofrequency ablation (OR 0.92; 95% CI 0.05 to 25.59). Further surgical intervention was needed in 3/29 (7%) women treated with bipolar radiofrequency ablation compared to 4/30 (13%) of women treated with thermal balloon ablation (*P*

= 0.7). There was no significant difference in either condition specific or generic health related quality of life measures.

Conclusions

There was no difference in the effectiveness of bipolar radiofrequency ablation and thermal balloon ablation performed in an office setting at five years follow-up.

Introduction

Various methods exist to destroy the endometrium as a way of controlling HMB (heavy menstrual bleeding). The range of chemicals and substances used to create an iatrogenic Asherman's syndrome has even extended to the use of radiotherapy[70]. However, endometrial ablation only gained real popularity with the introduction of the first generation techniques, which included rollerball endometrial ablation, transcervical resection of the endometrium and endometrial laser ablation. Trials, mainly in comparison to hysterectomy, proved these techniques were associated with increased patient satisfaction and decreased HMB[57,71–77]. Unfortunately, the first-generation techniques needed a high level of operator skill and took a long time to complete. Moreover, national audits showed that they were associated with uterine perforations and fluid overload syndrome with electrolyte imbalances[78,79].

The introduction of the global endometrial ablation devices heralded the beginning of the second-generation minimally invasive treatments for HMB. Not only were these devices shown to be more favourable to traditional resectoscopic methods in amenorrhoea and patients satisfaction, but they also had the advantage of being quicker, faster to learn and have decreased complication rates[58,80]. These advantages led clinicians to consider the feasibility of using these methods in the office setting with local anaesthetic or conscious sedation.

The safety, feasibility, acceptability and short-term effectiveness of endometrial ablation for the treatment of heavy menstrual bleeding in an office setting has been demonstrated [6,65]. The results of longer-term follow-up are important so that women can be counselled properly about the results of the hysterectomy sparing surgery on heavy menstrual bleeding. Whilst five and ten year effectiveness data have recently been published for conventional inpatient endometrial ablation under general anaesthesia [60,81–83], there is a lack of any longer-term data for office based endometrial ablation.

We have previously published the results of an randomised controlled trial (RCT) showing that office-based bipolar radiofrequency ablation (NovaSure™; Hologic™ Bedford, MA, USA) was significantly quicker and achieved a greater degree of endometrial destruction than the thermal balloon ablation (Thermachoice III™; Gynecare™; Ethicon™ Inc., New Jersey, USA), although there was no significant difference in amenorrhoea rates at six months[6].

Objectives

1. To compare thermal balloon and bipolar radiofrequency ablation in the office setting at 3 months, 6 months, 12 months and 5 years follow-up in terms of bleeding amount and patient satisfaction.
2. To assess the effects of thermal balloon and bipolar radiofrequency ablation in the office setting at 3 months, 6 months, 12 months and 5 years follow-up in terms of quality of life
3. To compare thermal balloon and bipolar radiofrequency ablation in the office setting at 3 months, 6 months, 12 months and 5 years follow-up in terms of further uterine surgery, namely repeat endometrial ablation or hysterectomy.

Methods

Study design

A single-blinded, parallel-group, RCT comparing bipolar radiofrequency ablation to thermal balloon ablation for the treatment of heavy menstrual bleeding.

Study setting

This was a single centre study conducted in the office hysteroscopy clinic of Birmingham Women's Hospital Foundation Trust between May 2006 to October 2007.

Eligibility

Inclusion criteria

To be included in the trial women needed to have heavy menstrual bleeding that impacted on their quality of life and opt for ablative treatment in the office setting. It should be noted that HMB is defined objectively as menstrual loss in excess of 80ml per menstrual cycle[84]. In clinical practice, it is not possible to routinely perform an objective quantitative assessment of menstrual loss or semi-quantitative assessment using pictorial charts. Moreover, HMB is a subjective perception[85], which will vary from individual to individual, and so inclusion or exclusion of women without regard for clinical practice would have impacted on the external validity of study findings. For these reasons, eligibility criteria were a subjective complaint of excessive menstrual loss refractory to medical treatment.

Exclusion criteria

Women were excluded if they had pathology that distorted the uterine cavity, previous classical caesarean section or myomectomy, were younger than 25 years, were perimenopausal (defined as follicle-stimulating hormone level of ≥40 international unit/L), or there was suspicion of genital tract infection. Endometrial sampling was performed prior to the procedure to rule malignant and premalignant causes for bleeding. All participating women gave written informed consent after reading a patient information leaflet (Appendix 6 – 8).

Trial registration

This trial was registered on clinicaltrials.gov (identifier: NCT01124357). The National Research Ethics Service (NRES), UK, granted ethical approval (identifier: 06/q2709/34). Research and Development approval was sought and granted at Birmingham Women's Hospital Community Trust.

Randomisation

Women were allocated in a 1:1 ratio to either of the interventions through a telephone-based system managed by the University of Birmingham Clinical Trials Unit. The randomisation blocks were kept centrally in the Birmingham Clinical Trials Unit and block sizes varied so that the allocation could not be deduced pre-randomisation. Blocks were stratified by age (<40 or ≥40) and uterine cavity length (≤8cm or >8cm) to ensure we achieved balance between groups for these variables. Uterine cavity length was chosen because it could influence the area ablated and

age was chosen because of its association with an ensuing menopause (Appendix 9).

Interventions

All women were treated in the office setting without general anaesthesia and were informed not to fast to prevent hypoglycaemia and reduce vasovagal episodes. Premedication was given one hour prior to the procedure and consisted of: 100mg diclofenac rectal suppository (oral if the patient did not want rectal suppository), two tablets of co-dydramol and an antiemetic (usually 50mg of cyclizine orally). If the patient could not tolerate non-steroidal analgesics then Tramadol Hydrocholoride 100mg orally was given instead. During the procedure there was a designated nurse who stayed with the patient to offer support and distraction, providing "vocal-local". The patient was positioned in the dorso-lithotomy position before being administered with a cervical block. This was achieved by infiltrating 2.2ml of 3% mepivicaine into the 12 and 6 o'clock position before infiltrating 1.1ml into the 3 and 9 o'clock positions, using 35mm, 27 gauge dental syringe. The majority of the solution was infiltrated at the level of the internal os with the rest evenly distributed along the length of the cervix on withdrawal of the needle. A preliminary diagnostic hysteroscopy was performed to exclude pathology that would distort the intrauterine cavity and to ascertain likely compliance to the procedure. Gynaecologists with suitable training and experience in both thermal balloon and bipolar radiofrequency ablation carried out all procedures. The allocated ablative technologies were performed according to manufacturer's instructions using a standard departmental protocol for office endometrial ablation.

Thermal Balloon ablation

The Thermachoice III^{TM} consists of a disposable catheter with a silicone balloon at its distal end. The diameter is 4.5mm before the balloon is instilled with up to 30ml of sterile fluid, so cervical dilation is not always necessary. The balloon catheter is primed ready for use using a syringe to purge air from the system and deflate the balloon. It is then inserted into the uterine cavity to the level of the fundus and the cavity length noted from the graduated catheter. The balloon is then inflated with sterile 5% dextrose until the pressure is stabilised between 160-180mmHg. This pressure allows optimal contact between the balloon and tissue ensuring an even heat penetration through the tissue thereby destroying the endometrium and underlying myometrium to a depth of 3-10mm. Intrauterine pressure fluctuation occurs as a result of contraction and relaxation of stimulated myometrial smooth muscle. The amount of intrauterine fluid required will depend upon cavity size, but is between 10-15ml on average. No more than 30mls of dextrose should be instilled and the procedure abandoned if therapeutic pressure not reached. The system is then switched on so that fluid within the balloon is heated to a pre-set temperature of 87°C, which takes 30-45 seconds on average (depending upon the amount of fluid instilled). The system then begins a standard 8-minute treatment cycle. On completion of the treatment cycle, the balloon is deflated and removed.

Bipolar radiofrequency ablation

The NovoSure^{TM} system consists of single-use bipolar radio-frequency ablation device, which is inserted into the uterine cavity after cervical dilatation to 8mm.

Once inside the cavity the fan-shaped bipolar electrode is deployed with tips in each cornua. A cavity integrity test is then performed, before the power is delivered which is imputed by the cavity size determined by uterine length (sound) and width (integral measuring device – cornu to cornu distance) measurements. Active treatment is for a maximum of 120 seconds, during which suction maintains opposition between the electrode array and endometrium and removes steam, blood and endometrium from desiccated tissue. After automatic termination the device is closed and removed from the cavity.

Outcomes

Baseline characteristics

The baseline characteristics of the patient were collected by the surgeon on a specially designed form (Appendix 10).

Assessment of menstrual bleeding

The objective of any treatment for HMB is to substantially reduce the amount of menstrual blood loss. The aim of endometrial ablation is to provide destruction of the entire endometrium so that cyclical endometrial regeneration is prevented and menstruation suppressed thereby inducing amenorrhoea (complete cessation of menstrual blood loss). Continuing menstrual loss occurs when the entire endometrial surface is not removed and islands of endometrium remain functional, the amount is dependant upon the surface area of functional endometrium remaining. For this reason amenorrhoea rates are often chosen as the primary outcome measure in clinical trial of the effectiveness of endometrial ablation in

women with HMB. Also, the complete absence of bleeding (amenorrhoea) is relatively objective when compared to the subjective concepts of light blood loss ('hypomenorrhoea') or restoration of 'normal' menstrual blood loss ('eumenorrhoea') following treatment. Therefore, the primary outcome was the proportion of women with amenorrhoea. This was assessed using the following Likert scale: 'How would you describe your menstrual periods?': 'No bleeding', 'Spotting or discharge only', 'Light bleeding', 'Moderate bleeding', 'Heavy bleeding'. Satisfaction with treatment was also measured using a Likert scale using the following response categories: 'Compared to before treatment, would you say that your heavy menstrual bleeding is: 'Much better, 'A little better', 'Same', 'Worse'.

Dysmenorrhoea and premenstrual pain

HMB can be associated with a number of other symptoms such as dysmenorrhoea and mood disturbances, either as a direct result of the bleeding, or because of coexisting diseases. Moreover, successful endometrial ablation should avoid ablating the glandular lining of the endocervical canal because this may lead to cervical stenosis and subsequent problems with haematometra and pelvic pain. For these reasons dysmenorrhoea measured using a Likert scale using the following response categories: 'Compared to before treatment, would you say that your period pain is: 'Much better', 'A little better', 'Same', 'Worse', 'Never had period pain'. While premenstrual pain was measured using the following Likert scale: 'If you had pre-menstrual symptoms before treatment please complete the following: 'Improved', 'Same', 'Worse'.

Further intervention

Women were asked directly in the questionnaire if they had undergone any further surgical treatment for gynaecological problems.

Assessment of sexual function

Sexual function is an important aspect of life quality in patients with heavy menstrual bleeding. HMB is an anti-aphrodisiac and it impacts upon sexual function. Most of the available sexual functioning questionnaires are designed specifically to investigate sexual dysfunction. These were deemed unnecessarily detailed for the purposes of assessing the impact of treatments for HMB. The sexual activity questionnaire (SAQ) was developed as a self-report questionnaire for use in gynaecological clinical trials, which would be quick to complete and acceptable to the majority of women [86,87]. The SAQ has been extensively field-tested for this purpose. The SAQ has excellent internal consistency and test retest reliability [86]. It also has excellent concurrent and construct validity and has been shown to be acceptable to women in other clinical trials[87]. The SAQ measures sexual function using a scale from 0 to 18 for pleasure and 0 to 6 for discomfort[86,87], with higher scores indicating more pleasure and less discomfort. In the questionnaire it was clearly stated that the measure of sexual function covers material that was sensitive and personal. Patients were reassured that their responses would be kept completely confidential and that if they do not wish to answer any questions, they were allowed to leave the questionnaires blank.

Generic quality of life measures

General health related quality of life was measured using the EuroQoL-5D scale (best possible score was 1 for utility and 100 for the health thermometer)[88,89]. It provides a single index value for health status that can be used in a wide range of health conditions and treatments. Responses will be given valuations derived from published UK population tariffs.

Disease specific quality of life measures

Disease specific quality of life was measured using the menorrhagia multi-attribute utility assessment score (Shaw score)[90] and the menorrhagia outcomes questionnaire[91]. The menorrhagia multi-attribute utility assessment score gives a maximum score of 100, which indicates no problems with the monthly cycle. For the menorrhagia outcomes questionnaire the lower the score the better; no baseline measurement was taken and the results were standardised to a mean of 50 as recommended by the author.

Follow-up

Data were collected using postal questionnaires, which were posted to women at 3, 6, 12 and 60 months follow-up. In cases were there was no reply a second questionnaire was sent. If there was still no reply, the women were phoned and a third questionnaire sent with their permission.

Sample size

The sample size for this trial was originally chosen to give statistical power to detect a significant difference in the primary measure of amenorrhoea at six months follow-up and has been previously described. It was assumed that there would be a 10% rate of amenorrhoea in the control ablation group and a 40% rate in the experimental group (clinically important difference equal to 30%). This meant a sample of 62 patients was required (31 patients in each group) based on a α = 0.05, β= 0.2 (80% power) and a moderate to large (0.65 SD) effect. To account for a 30% loss to follow-up the sample size was inflated to 80 patients (40 in each group).

Statistical methods

Analysis was performed by intention-to-treat. For the purpose of analysis all women who had undergone hysterectomy were considered to have amenorrhoea although a sensitivity analysis was performed in which they were considered not to have amenorrhoea. Furthermore, hysterectomised women were excluded from the comparison of age between ablation groups because the relationship between age and menopause was no longer relevant. Logistic regression was employed for the dichotomous outcomes amenorrhoea, reduction in bleeding, dysmenorrhoea, premenstrual syndrome and further intervention rates. Odds ratios and 95% confidence intervals were derived with a chi-squared test used to assess statistical significance. Mean differences and corresponding 95% confidence intervals were calculated for the EuroQoL-5D, health thermometer, menorrhagia multi-attribute utility assessment, menorrhagia outcomes questionnaire and sexual activity

questionnaire. A t-test was used to assess statistical significance. All analyses were carried out using SPSS software version 21 (IBM, Armonk, NY, USA).

Results

Participants

Between May 2006 to October 2007, 39 women were randomised to thermal balloon ablation and 42 women were randomised to bipolar radiofrequency ablation (Figure 3) At five years follow-up 59 (73%) women responded to postal questionnaires.

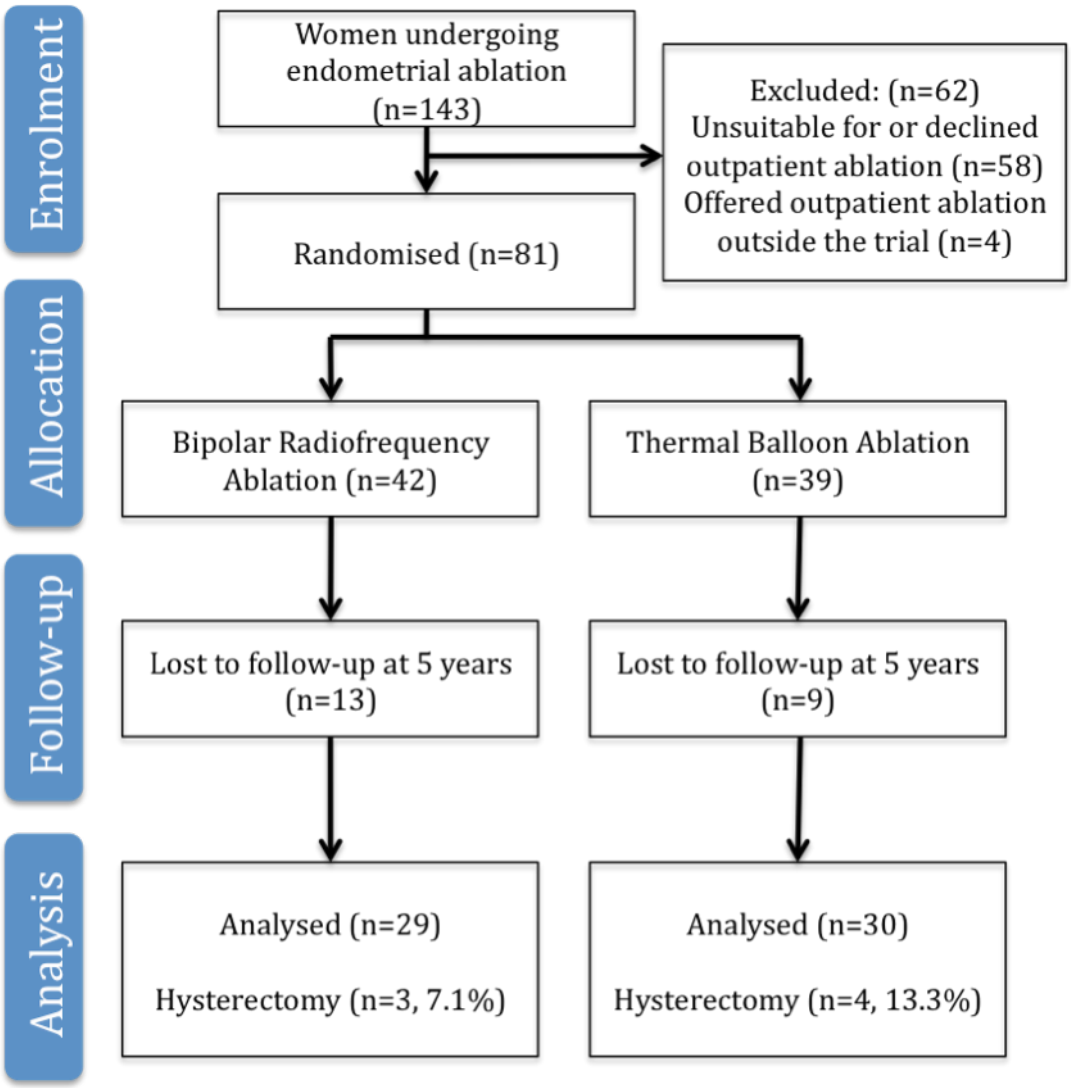


Figure 3. A randomised controlled trial of office ablation techniques

Baseline characteristics

There were 29 (69%) women who responded in the bipolar radiofrequency group compared to 30 (77%) who responded in the thermal balloon ablation group. The baseline characteristics were comparable between the two groups, although there was a mean 2.2yr gap between those treated with thermal balloon ablation compared to bipolar radiofrequency ablation (49.2yrs versus 47.0yrs; Table 8). There was no significant difference in baseline characteristics between the women that returned the questionnaires compared to those that did not.

Table 8. Baseline characteristics of those followed up for five years

	Thermal Balloon (n=30)	Bipolar Radiofrequency (n=29)	*P*
[#]**Age at 5 yrs fu** (SD)	49.2 (4.6)	47.0 (4.4)	NS
(min,max)	(41,59)	(35,55)	
Parity (SD)	2.5 (1.2)	2.7 (1.2)	NS
(min,max)	(0,6)	(1,5)	
Caesarean Section (%)	5 (17)	6 (21)	NS
BMI (kg/m^2) (SD)	29.3 (6.6)	29.7 (5.9)	NS
Folicle Stimulating Hormone (internation units/L) (SD)	7.2 (6.4)	5.7 (5.0)	NS
(min,max)	(2.1, 31.4)	(1.5, 26.4)	
Uterine cavity length (cm) (SD)	8.6 (1.2)	8.1 (0.6)	NS
(min, max)	(6, 11)	(7, 9.5)	
Uterine axis			
Anteflexed (%)	22 (73)	23 (82)	NS
Retroflexed (%)	8 (27)	5 (18)	NS
Axial (%)	0 (0)	0 (0)	NS
Endometrium			
Proliferative (%)	12 (40)	9 (32)	NS
Secretory (%)	9 (30)	10 (35)	NS
Menstrual (%)	8 (27)	9 (32)	NS
Atrophic (%)	1 (3)	0 (0)	NS
Dysmenorrhoea (%)	25 (83)	21 (75)	NS
Premenstrual Syndrome (%)	21 (70)	22 (79)	NS

[#] = does not include the age of those that had hysterectomy; NS = not significant (*P* > 0.05).

Outcome data

Assessment of menstrual bleeding

Over the five-year follow-up there was an increase in rates of amenorrhoea for both treatment groups (Table 9). At three, six and twelve months follow-up there were higher amenorrhoea rates in the bipolar radiofrequency ablation group, but this only reached a significant difference at twelve-months follow-up. However, this difference in amenorrhoea rate had disappeared at five years follow-up; bipolar radiofrequency ablation 18/29, 62% compared to thermal balloon ablation 18/30, 60% (OR 1.09 [95% CI 0.38 to 3.11]). Similarly, no difference in amenorrhoea was observed when an adjusted odds ratio was calculated to account for the age difference noted in respondents and the possible effects of menopause on the results (OR 1.39 [95% CI 0.42 to 4.62]). Of the women who returned questionnaires at 12 months, 45 (90%) returned questionnaires at 5 years. A further sensitivity analysis was performed to check for a response bias by presuming that those who did not return the questionnaires at five years had the same symptoms as they did at 12 months (OR 1.21 [95% CI 0.43 to 3.42]). For the purpose of these analyses, women who had hysterectomy were considered to be amenorrhoeic. A sensitivity analysis was performed in which those women with hysterectomy were considered not to have amenorrhoea (OR 1.22 [95% CI 0.44 to 3.40]; $P = 0.7$).

Table 9. The effect of office radiofrequency and thermal balloon ablation of the endometrium on rates of amenorrhoea

Time point	Thermal Balloon	Bipolar Radiofrequency	*P* value	Odds Ratio (95% Confidence Interval)
Amenorrhoea				
3 month	7/36 (19%)	12/36 (33%)	0.2	2.07 (0.71 to 6.09)
6 months	7/34 (21%)	11/28 (39%)	0.1	2.50 (0.81 to 7.69)
12 months	6/26 (23%)	14/25 (56%)	0.02	4.24 (1.27 to 14.18)
5 years	18/30 (60%)	18/29 (62%)	0.9	1.09 (0.38 to 3.11)
			[#]0.6	1.39 (0.42 to 4.62)
Amenorrhoea + spotting				
3 month	15/36 (42%)	19/36 (53%)	0.3	1.56 (0.62 to 3.97)
6 months	14/34 (41%)	17/28 (61%)	0.1	2.21 (0.80 to 6.13)
12 months	15/26 (58%)	17/25 (68%)	0.4	1.56 (0.50 to 4.90)
5 years	22/30 (73%)	23/29 (79%)	0.6	1.39 (0.42 to 4.67)

Data are n/N (%)

[#] = value at five years adjusted for age

Further surgical intervention

At five years follow-up there were 3/29 (10%) women treated with bipolar radiofrequency ablation underwent hysterectomy compared to 4/30 (13.3%) of women treated with thermal balloon ablation (*P* = 0.7). Two of the four women treated with thermal balloon ablation who ultimately had a hysterectomy had also undergone a repeat thermal balloon ablation procedure in the interim. Indications for hysterectomy in those who had thermal balloon ablation included: one woman who had complex hyperplasia on biopsy and three women who had persistent heavy menstrual bleeding. While indications for hysterectomy in those who had bipolar radiofrequency ablation included: one woman who had cyclical pelvic pain, one woman who had offensive watery vaginal discharge and one woman who had persistent heavy menstrual bleeding.

Patient satisfaction, dysmenorrhoea and premenstrual syndrome

Significant improvement in heavy menstrual bleeding, premenstrual syndrome and dysmenorrhoea symptoms were observed following both treatments throughout the five-year follow-up period, but there was no evidence of difference between the groups (Table 10).

Table 10. The effects of office radiofrequency and thermal balloon ablation of the endometrium on menstruation, dysmenorrhea and premenstrual syndrome.

Time point	Thermal Balloon	Bipolar Radiofrequency	*P* value	Odds Ratio (95% Confidence Interval)
Heavy bleeding now improved:				
3 month	33/36 (92%)	34/36 (94%)	0.6	1.54 (0.24 to 9.85)
6 months	30/33 (91%)	28/28 (100%)	0.2	#6.54 (0.32 to 132.29)
12 months	24/26 (92%)	23/23 (100%)	0.3	#4.80 (0.22 to 105.26)
5 years	26/27 (96%)	24/25 (96%)	0.9	0.92 (0.05 to 25.59)
Period pain now improved:				
3 month	22/29 (76%)	23/30 (77%)	0.9	1.05 (0.32 to 3.47)
6 months	21/29 (72%)	20/24 (83%)	0.3	1.90 (0.50 to 7.33)
12 months	12/21 (57%)	16/21 (78%)	0.2	2.40 (0.64 to 9.03)
5 years	18/21 (86%)	17/21 (81%)	0.7	0.71 (0.14 to 3.64)
Improvement in emotional symptoms of premenstrual syndrome				
3 month	9/21 (43%)	17/26 (65%)	0.1	2.52 (0.77 to 8.22)
6 months	11/22 (50%)	11/18 (61%)	0.7	1.57 (0.44 to 5.56)
12 months	10/16 (63%)	10/20 (50%)	0.5	0.60 (0.16 to 2.29)
5 years	13/21 (62%)	14/22 (64%)	0.9	1.08 (0.31 to 3.71)

Improvement in physical symptoms of premenstrual syndrome

3 month	12/21 (57%)	15/25 (60%)	0.8	1.13 (0.35 to 3.65)
6 months	14/21 (67%)	12/17 (71%)	0.8	1.20 (0.30 to 4.78)
12 months	8/16 (50%)	13/20 (65%)	0.4	1.86 (0.48 to 7.12)
5 years	14/22 (64%)	15/21 (71%)	0.6	1.43 (0.40 to 5.16)

Data are n/N (%)

[#] = for the purpose of working out the odds ratio a value of 1 was used instead of 0.

Quality of life assessment

At five years follow-up there was no significant change from baseline for generic health related quality of life or sexual activity scores for either technique. The disease specific health related quality of life (multi-attribute utility score) was significantly higher at all time points compared with baseline for both techniques, but there was no significant difference between techniques (Table 11).

Table 11. The effects of office radiofrequency and thermal balloon ablation of the endometrium on quality of life measures

Time point	Thermal balloon	Bipolar Radiofrequency	Difference (95% CI, *P*)*
Euroqol change from baseline			
3 month	0.13±0.3 (36)	0.14±0.3 (35)	0.01 (-0.13 to 0.15, 0.9)
6 months	0.14±0.3 (32)	0.16±0.4 (27)	0.02 (-0.15 to 0.20, 0.8)
12 months	0.12±0.3 (24)	0.15±0.4 (25)	0.03 (-0.16 to 0.23, 0.7)
5 years	0.54±1.9 (28)	1.5±1.9 (22)	-0.94 (-2.0 to 0.15, 0.09)
Health Thermometer change from baseline			
3 month	6.7±18.7 (32)	4.8±18.7 (30)	-1.9 (-11.4 to 7.6, 0.7)
6 months	7.6±20.8 (29)	7.7±21.2 (26)	0.1 (-11.2 to 11.5, >0.99)
12 months	3.7±22.2 (21)	8.5±27.4 (22)	4.9 (-10.5 to 20.3, 0.5)
5 years	10.6±30.9 (26)	7.5±29.0 (25)	2.7 (-14.5 to 20.0, 0.8)
Multi-attribute utility score change from baseline			
3 month	41.1±27.4 (36)	46.2±26.8 (35)	4.8 (-8.0 to 17.6, 0.5)
6 months	38.8±24.9 (33)	48.8±24.9 (27)	9.9 (-3.0 to 22.8, 0.1)
12 months	39.5±24.0 (25)	48.3±30.0 (26)	8.9 (-6.5 to 24.2, 0.3)
5 years	52.7±23.5 (26)	48.7±22.3 (24)	4.0 (-9.4 to 17.1, 0.6)
Menorrhagia Outcome Questionnaire[#]			
3 month	50.3±5.8 (36)	49.9±5.6 (36)	-0.4 (-3.1 to 2.3, 0.8)
6 months	51.4±6.8 (33)	48.3±4.2 (28)	-3.1 (-6.1 to -0.1, 0.04)
12 months	50.2±6.1 (25)	49.6±5.8 (26)	-0.6 (-3.9 to 2.8, 0.7)

5 years	50.7±7.5 (28)	49.0±5.8 (21)	1.9 (-2.1 to 5.9, 0.3)
Sexual Activity Questionnaire pleasure change from baseline			
3 month	2.1±4.0 (22)	2.2±5.9 (15)	0.1 (-3.2-3.4, 0.9)
6 months	3.1±3.9 (18)	1.0±4.5 (13)	-2.1 (-5.1 to 1.0, 0.2)
12 months	2.4±3.3 (14)	-1.9±7.7 (11)	-4.3 (-9.0 to 0.4, 0.07)
5 years	-1.00±4.6 (20)	-0.46±5.2 (13)	-0.5 (-4.1 to 3.0, 0.8)
Sexual Activity Questionnaire discomfort change from baseline			
3 month	0.35±1.34 (23)	-0.38±1.54 (16)	-0.72 (-1.66-0.22, 0.1)
6 months	0.00±0.84 (18)	0.25±1.3 (12)	0.25 (-0.54 to 1.04, 0.5)
12 months	-0.20±1.08 (15)	0.40±1.35 (10)	0.60 (-0.41 to 1.61, 0.2)
5 years	-0.15±1.5 (20)	-0.75±1.5 (12)	0.60 (-0.50 to 1.70, 0.3)
Sexual Activity Questionnaire increase in habit change from baseline‡			
3 month	11/27 (41)	8/20 (40)	1.0 (0.3 to 3.2, >0.99)
6 months	3/21 (14)	6/19 (32)	2.8 (0.6 to 13.2, 0.2)
12 months	7/17 (41)	5/17 (29)	0.6 (0.1 to 2.5, 0.5)
5 years	10/21 (48)	4/13 (31)	0.5 (0.1 to 2.1, 0.3)

CI = confidence interval

Data are mean ± standard deviation (n) unless otherwise stated

* Those more than 0 favour bipolar radiofrequency ablation, those less than 0 favour thermal balloon ablation, apart from menorrhagia outcome questionnaire, for which less than 0 favours bipolar radiofrequeny ablation.

Menorrhagia outcome questionnaire standardised to a mean of 50. Post-treatment scores only

‡ "Much or somewhat more" compared with "the same or less". Odds ratio shown

Discussion

Key findings

This RCT has shown that both bipolar radiofrequency ablation and thermal balloon ablation are equally effective at treating heavy menstrual bleeding, dysmenorrhoea, premenstrual syndrome and improving health related quality of life at five years following treatment.

Comparison with other studies

The 62% amenorrhoea rate for bipolar radiofrequency ablation at five years reported in this trial is similar to longer term follow up rates previously reported for bipolar radiofrequency ablation performed under general anaesthesia [60,83]. However, the 60% rate of amenorrhoea for thermal balloon ablation was almost double that of other studies where rates of 29-32% have been reported[60,92]. This improvement in thermal balloon ablation may be explained in part by our use of Thermachoice III™, in contrast to earlier studies that have employed the previous, now no longer available model (Thermachoice I™), which did not distribute heat so evenly throughout the balloon. The only other RCT comparing bipolar radiofrequency ablation and thermal balloon ablation was conducted under general anaesthesia and used the older thermal balloon ablation technology. Whilst the authors reported that bipolar radiofrequency ablation was superior to thermal balloon ablation at five years follow-up, this conclusion was not substantiated by their results that showed no significant differences in rates of amenorrhoea (RR 1.6 [95% CI, 0.9 to 2.6])[60]. This group have just reported their ten year follow up data

and again identified no differences in longer term rates of amenorrhoea (RR 1.1 [95% CI, 0.83-1.5])[81].

It was reassuring to note that other pertinent clinical outcomes supported the sustained and comparable effectiveness of bipolar radiofrequency ablation and thermal balloon ablation at five years; condition specific health related quality of life was substantially improved from baseline in both groups and nine in every ten women treated avoided hysterectomy. Our surgical re-intervention rates for heavy menstrual bleeding were consistent with rates reported in other trials of second generation ablative technologies at five years[60,82]. Two of the four women in the thermal balloon ablation group who had a hysterectomy also had a preceding repeat thermal balloon ablation, suggesting that that there may not be any clinical benefit to this strategy.

Strengths and limitations

The strength of this trial includes its strict randomisation and its originality, with no other RCTs to our knowledge, comparing ablative technologies in the office setting. Although we achieved more complete follow up at five years than at 12 months[6], the 27% loss to follow-up may have affected the validity of our findings to an uncertain degree. However, there were no significant differences in baseline characteristics between responders and non-responders to postal-questionnaires at five years. In keeping with other RCTs evaluating endometrial ablation, our primary outcome was amenorrhoea[83,93,94]. However, whilst this outcome is relatively objective, it may not be the most relevant clinical outcome when evaluating long-term successful

treatment. This is because a proportion of women will enter menopause during follow up, thereby increasing amenorrhoea rates indirectly. The older mean age of the thermal balloon ablation group could explain the blunting of treatment effect seen at five years compared to that observed earlier at twelve months. However an adjusted analysis using increasing age as a surrogate marker for menopause provided no evidence to support this contention. It should be noted that the mean ages of women in both treatment groups were under 51 years, the average age of female menopause[95].

Conclusions

Office endometrial ablation may be convenient, but it is important that women are fully counselled about the longer-term effects of treatment. They should understand that clinical outcomes appear equivalent to data from inpatient procedures performed under general anaesthesia and that approximately 10% of women will require subsequent hysterectomy within five years. Such information will facilitate clinical decision making for women and their clinicians.

CHAPTER 6: A SYSTEMATIC REVIEW OF UTERINE POLYPECTOMY FOR THE TREATMENT OF ABNORMAL UTERINE BLEEDING

Publication

This work will be published as part of the outpatient versus inpatient polypectomy trial (OPT, http://www.opt.bham.ac.uk, ISRCTN65868569) Health Technology Assessment report. The OPT trial has been accepted for publication by the British Medical Journal; Cooper NAM, Clark TJ, Middleton L, Diwaker L, Smith P, Denny E, et al. A randomised trial of outpatient versus inpatient uterine polyp treatment for abnormal uterine bleeding. BMJ. 2015;In Print.

Abstract

Objective

The aim of the study was to assess the efficacy of uterine polypectomy in the treatment of abnormal uterine bleeding

Methods

A systematic review of uterine polypectomy for abnormal bleeding was conducted. MEDLINE, EMBASE and CINAHL were searched (from inception to 2013) using MeSH headings for polyps combined with word variants for endometrium (endometri* OR uter*) and surgical polypectomy (surgery OR curettage OR hysteroscopy OR polypectomy). Furthermore, all the bibliographies of relevant studies were hand searched to identify articles not captured by the electronic searches. Two reviewers independently selected trials. Data were extracted for relief of abnormal bleeding symptoms measured in general terms (improvement from baseline, normalisation of bleeding patterns) and patient satisfaction. Secondary outcomes included technical feasibility and complications. Due to a lack of studies with a comparative group meta-analysis could not be performed and the data were tabulated to allow qualitative analysis.

Results

17 studies met our inclusion criteria enrolling a total of 1829 patients between 1989 and 2009. There were two randomised controlled studies and 15 observational studies, only two of which were controlled. All the studies reported an improvement in abnormal uterine bleeding following uterine polypectomy in the range of 60 - 100%.

Conclusions

The evidence collated in this review supports the notion that removing uterine polyps is effective at improving symptoms of abnormal uterine bleeding. However, most of the evidence was derived from observational studies that reported high success rates, but in general the quality of the research was poor. The highest quality studies, the two randomised controlled trials, reported more modest improvements in symptoms.

Introduction

Background

Endometrial polyps are focal outgrowths that can occur anywhere within the uterine cavity. Uterine polyps are composed of either functional and/or basal endometrium. They are typically a mixture of dense fibrous tissue (stroma), large and thick walled vascular channels, and elongated glandular spaces of varying shapes[96,97], which protrude into the uterine cavity. The underlying cause of uterine polyp formation remains unclear, but is believed to be multifactorial [98].

The prevalence of uterine polyps in a general adult female population without abnormal uterine bleeding (AUB) is generally estimated to be around 10%[3]. Case series of asymptomatic women are generally small and estimates of prevalence imprecise; following transvaginal ultrasound, uterine polyps were detected incidentally in 12% of premenopausal women[99] and in 6%-11% of infertile women without AUB[100,101]. In asymptomatic postmenopausal women, prevalence of between 13%[99] and 16%[102] have been reported following investigation with ultrasound and hysteroscopy respectively. However, they are found with increasing frequency in women undergoing investigation for problems with abnormal uterine bleeding. In addition to AUB, risk factors for uterine polyp development are thought to include obesity, late menopause and the use of the partial oestrogen agonist Tamoxifen [99,103–105]. The role of hormone replacement therapy (HRT) on polyp formation is unclear with some studies supporting an association [99,103] and others not [106,107].

Once a uterine polyp has been diagnosed, the current clinical consensus is to remove it [108]. The rationale for this approach is based upon (i) a belief that they are unlikely to spontaneously resolve, (ii) a desire to alleviate AUB symptoms or optimise fertility and (iii) a need to exclude serious endometrial disease [3]. The vast majority of uterine polyps are benign and endometrial cancer originating within the polyp is a rare occurrence. Case series of varied populations report a cancer prevalence of approximately 0.5-3% [109–116].

Since the introduction of diagnostic hysteroscopy and high-resolution pelvic ultrasound it has become apparent that uterine polyps are highly prevalent during investigation of AUB. The reported prevalence of endometrial polyps in general is considered to be between 20-30% [106,117,118], this variation reflects the criteria used to define a polyp, the diagnostic test used and the type of population studied. Whilst the prevalence of uterine polyps may be increased after the menopause [99], polyps are found to commonly affect both pre- and postmenopausal women across all age groups [119]. In recognition of the frequency in which uterine polyps are discovered in women of reproductive age, the International Federation of Gynecology and Obstetrics have recently accepted a new classification system for causes of abnormal uterine bleeding in the reproductive years, based on the acronym 'PALM-COEIN' with the 'P' denoting a 'polyp' i.e. describing AUB associated with the presence of uterine polyps[120].

With more endometrial polyps being diagnosed there has been an increase in surgical removal of polyps ('polypectomy'). This is the accepted practice for the

majority of gynaecologists, not only to treat symptoms, but also to obtain tissue for histological analysis to ensure the polyp is benign[108].

Treatment of uterine polyps

Traditionally, investigation and treatment of endometrial polyps was done under general anaesthetic using blind dilation and curettage ('D&C'). This involves dilating the cervix to allow the blind insertion of polyp forceps or a curette to explore the uterine cavity. This technique is still employed by many gynaecologists today, although a diagnostic hystesteroscopy is usually performed beforehand to identify the location of the polyp and guide blind avulsion [35,108]. Due to the discomfort associated with D&C, it is necessary to perform the procedure under a general anaesthesia, which is associated with significant use of health care resources. In the United Kingdom there is an increasing trend for more endometrial polypectomies; between 2011-2012 there were 25,000 procedures which was an increase of over 4,000 procedures from 1998-1999 (Department of Health, Hospital Episode Statistics) [121].

Expectant management

The observation that polyps are an incidental finding in around 5-15% of women [99–102], that the majority of polyps are benign [122,123], and that some may naturally regress [119,124] has led some to question whether removal of uterine polyps is necessary [125]. Furthermore, removal of polyps may subject women to unnecessary

morbidity and wastage of scarce health service resources. Two RCTs have addressed this issue randomising women with AUB and uterine polyps to expectant management or surgical removal [122,125]. One trial failed to recruit women with PMB because neither doctors nor patients were in equipoise and so were unwilling to participate [125]. This finding is consistent with postmenopausal women having a preference for hysteroscopic diagnosis and treatment where an abnormality is found [35]. The other RCT randomised 150 women with uterine polyps, of which 60% had AUB symptoms. Overall, no reduction in periodic blood loss was demonstrated at 6 months follow up, but inter-menstrual bleeding (IMB) symptoms were significantly improved [122]. However, it should be noted that the findings from this study are limited for a number of reasons: the study was restricted to pre-menopausal women, the sample size was small, only 60% of the population included were symptomatic, their presenting complaints were heterogeneous and the study length of follow up was short.

Medical management

Medical management is widely adopted for the treatment of menstrual complaints and includes the use of hormonal contraceptives. Whilst some of these women may have undiagnosed uterine polyps, evidence for the use of medical therapy is lacking and not recommended[55]. Gonadotrophin releasing hormone analogues (GnRH-a) have been used prior to hysteroscopic resection of focal pathologies in pre-menopausal women [126], but the costs and menopausal side effects are difficult to justify for the removal of uterine polyps. This is because polyps are successfully removed in the majority of cases without the need for adjunctive medical

preparation, in contrast to submucous fibroids. One small series evaluated different HRT regimens to see whether some have a reduced propensity to polyp formation[127]. The use of levonorgestrel releasing intrauterine system in women taking Tamoxifen has been reported to reduce the incidence of endometrial polyps [128].

Surgical management (Polypectomy)

A UK national survey [108] and two subsequent Dutch surveys [129,130] confirmed that the vast majority of gynaecologists advocated surgical removal of polyps from the uterus after diagnosis with 854/918 (93%)[108] 455/553 (83%)[129] and 411/585 (91%) respondents performing polypectomy [130]. In the UK, the predominant method for removal of uterine polyps was by blind avulsion or curettage, after hysteroscopic location of the focal lesion under general anaesthesia [108] whereas in the Netherlands removal under direct hysteroscopic vision under general or regional anaesthesia [129,130] was the favoured approach.

Blind methods to retrieve focal intrauterine pathology included blind curettage of the endometrium or avulsion with polyp forceps. These approaches can be associated with potential uterine trauma which can be unrecognised and lead to serious complications from intra-abdominal damage [131,132]. Failure to remove polyps and problems with incomplete removal are well recognised [28,132–136].

Advances in hysteroscopic equipment have enabled polyps to be removed under direct vision. Fine mechanical instruments, such a scissors, biopsy cups, forceps

and snares can be used down a 5 or 7 Fr working channel of a rigid operative hysteroscope and the safety and feasibility of such approaches have been reported [3,33,137,138]. Potential drawbacks of mechanical instrumentation are the fragility of the instruments, limited manipulation, difficulty with cutting or avulsing large and fibrous pathology and in some instances bleeding [3,139].

The adoption of electrosurgical technologies may help overcome these difficulties. Large diameter hysteroscopic resectoscopes, developed originally to resect the endometrium for the treatment of HMB [140], can also be used to resect focal pathologies such as submucous fibroids [126,141], or polyps [142,143]. They have the advantage of speed and manipulation, but the large diameter of the instruments necessitates general anaesthesia, specialised skills are required [144,145] and potential serious complications from fluid overload and inadvertent electrosurgical injury can occur [78].

In contrast to firm submucous fibroids of myometrial origin, polyps are generally softer structures derived from the underlying endometrium. Thus, it has been recognised that smaller, less traumatic electrosurgical instruments would suffice. A miniature bipolar electrosurgical system has been developed (Versapoint® (Gynecare, Ethicon, Somerville, NJ, USA)) to cut away polyps and the safety, acceptability and feasibility of this approach has been reported [146–148]. However, retrieval of the tissue specimen from the uterine cavity can be problematic and usually requires the additional use of mechanical instruments to effect [3]. Other technologies including monopolar electrosurgical snares [138] and more recently

morcellation technologies (TRUCLEAR™, Smith & Nephew, Andover, MA, USA) and Myosure (Hologic, Marlborough, MA USA)), which allow simultaneous tissue cutting and extraction have been developed [149,150].

Evidence for uterine polyp treatment in abnormal uterine bleeding

We have undertaken a systematic review of the effectiveness of uterine polypectomy building on a previously published systematic review [33], using updated methodological advances in search strategies, quality assessment and statistical analysis [151,152].

Objectives

1. To systematically review the literature to evaluate the effectiveness of uterine polypectomy for the treatment of AUB.
2. Our secondary aims were to establish if the type of AUB, setting or technique influenced outcome.

Methods

Search strategy

We performed searches on the general bibliographic databases Medline (1950-2013), EMBASE (1980-2013) and CINAHL (1981-2013). Based on published advice, our search term combination for electronic databases was MeSH headings for polyps combined with word variants for endometrium (endometri* OR uter*) and surgical polypectomy (surgery OR curettage OR hysteroscopy OR polypectomy). Furthermore, all the bibliographies of relevant studies were hand searched to identify articles not captured by the electronic searches (Appendix 11).

Study selection

Two reviewers (PPS and NAMC) independently selected articles in a two-stage process. Firstly, abstracts obtained by either the electronic database searches or bibliography inspections were reviewed and articles that could possibly fulfill the following criteria were selected for full text review:

Inclusion criteria

- Population – Women with intrauterine polyps and AUB
- Intervention – Uterine polypectomy
- Outcome – Relief of AUB symptoms*

  *measured in general terms - e.g. objective, semi-objective or subjective measures of change in AUB; normalisation of bleeding patterns; satisfaction with AUB outcome; change in quality of life scores from baseline.

Once articles were selected, both reviewers used specially designed data extraction forms to collect data on the main outcome measure that was relief of AUB symptoms. Secondary outcomes included technical feasibility, complications and polyp histology. Differences in article and information selection were solved by deliberation. Where a consensus could not be found a third reviewer (TJC) made the final judgment. No language restrictions were applied and translation available where necessary.

The strength of agreement between reviewers taking into account the play of chance was computed using kappa statistic (agreement is considered good if > 0.6 and very good if > 0.8)

Type of study included

All relevant randomised controlled studies (RCTs) were included. Due to the small number of RCTs, non-randomised studies including both prospective and retrospective observational studies were also included.

Study quality assessment

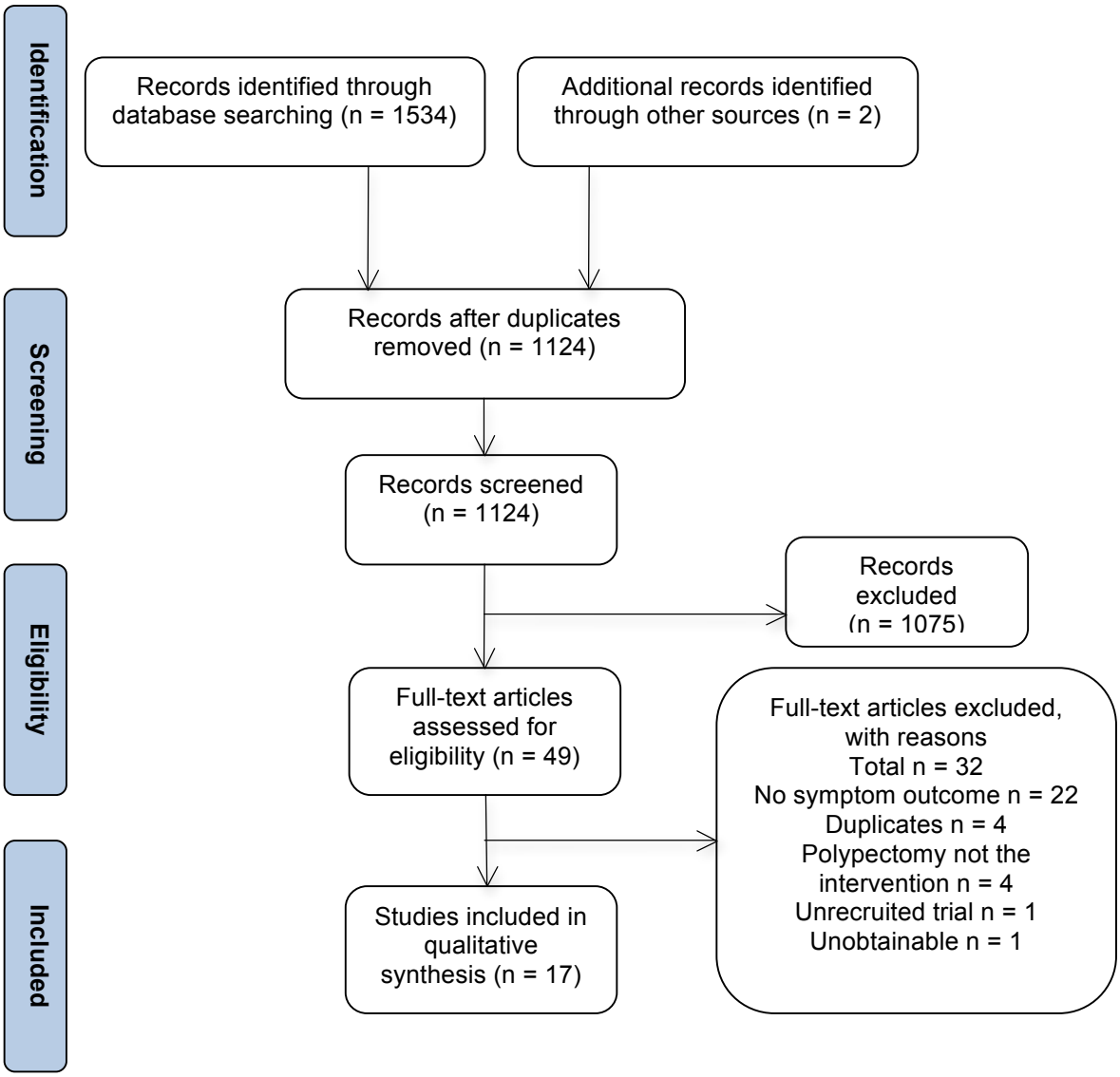
The 2007 STROBE checklist was used to assess the quality of the observational studies [153], while the Cochrane risk of bias tool checklist was used to assess the quality of the randomised controlled studies [151]. Two reviewers independently scrutinised the articles against each element of the relevant checklist.

Synthesis of results

Originally, in the absence of heterogeneity, data pooling and meta-analysis was planned. However, due to a lack of controlled studies this could not be performed. All extracted data were tabulated to allow qualitative analysis.

Results

Figure 4. Study selection process.



Results of search

From the electronic search we obtained 1122 citations and a further two from searching reference lists of relevant articles. At this stage 1075 citations were excluded based on a review of the abstracts and titles. An attempt was made to retrieve the remaining 49 articles for further scrutiny. One article could not be retrieved either online or via the British Library. Review of these articles showed that 32 did not meet the selection criteria. The characteristics of the excluded articles are described in **Figure 4**. There was a high level of agreement between reviewers for which articles should be retrieved for further scrutiny (Kappa agreement = 0.92; $P = < 0.001$).

Included studies

The 17 studies that met our inclusion criteria [21,122,142,147,154–165] enrolled a total of 1829 patients between 1989 and 2009. The population size ranged from 8 to 311 with only 5 studies having a population size of over 100 [122,142,154,157,161].

Study quality and design

There were two RCTs: one comparing inpatient versus outpatient treatment [165], while the second compared polyp removal with observation for six months [122]. The RCTs were assessed for quality using the validated Cochrane risk of bias tool [151] (**Figure 5**). Of the remaining 15 observational studies, only two had a comparative group: one compared inpatient versus office treatment [147] and the second compared hysteroscopic morcellation to electrical resection [154]. The remaining 15 articles were non-comparative observational studies. Only six of the studies were

prospective although the majority of the studies collected the data consecutively [21,122,147,163–165]. All observational studies meeting the selection criteria were assessed for quality using the validated tool STROBE[153] (Figure 6).

Figure 5. Study quality of the randomised controlled trials using the Cochrane risk of bias tool.

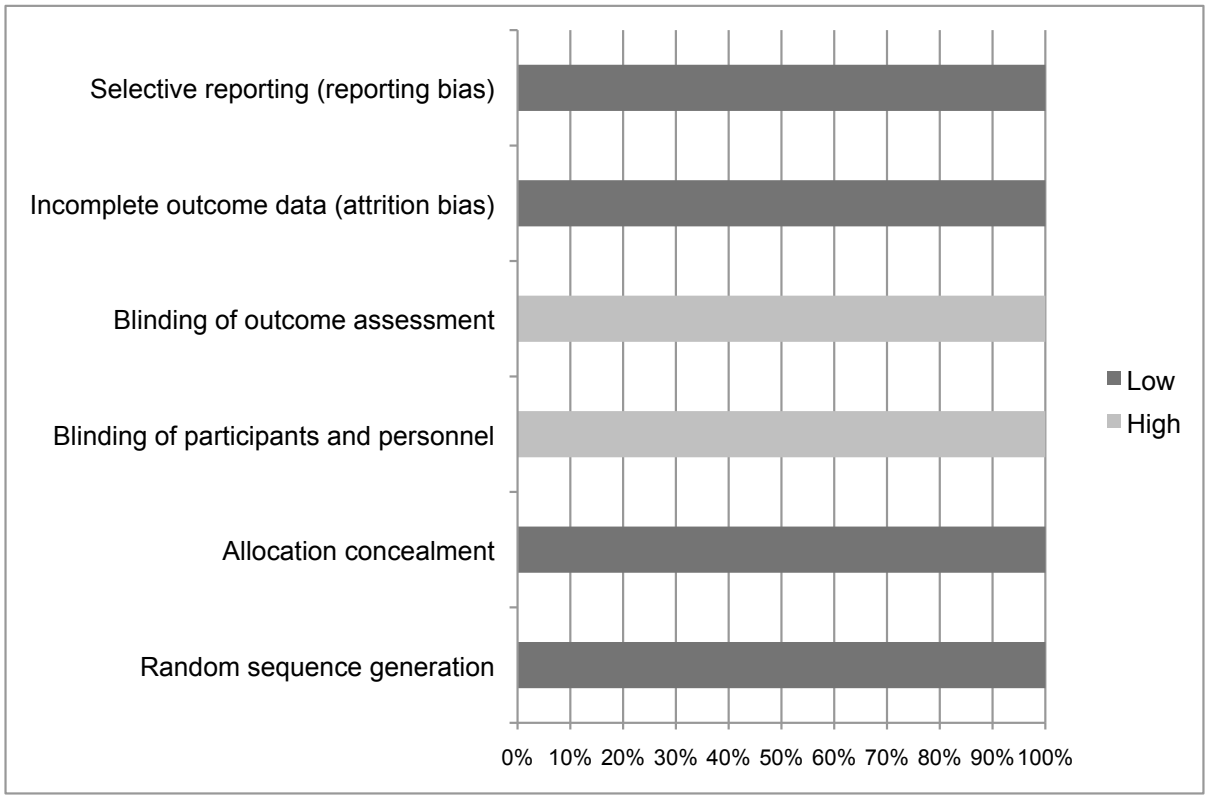
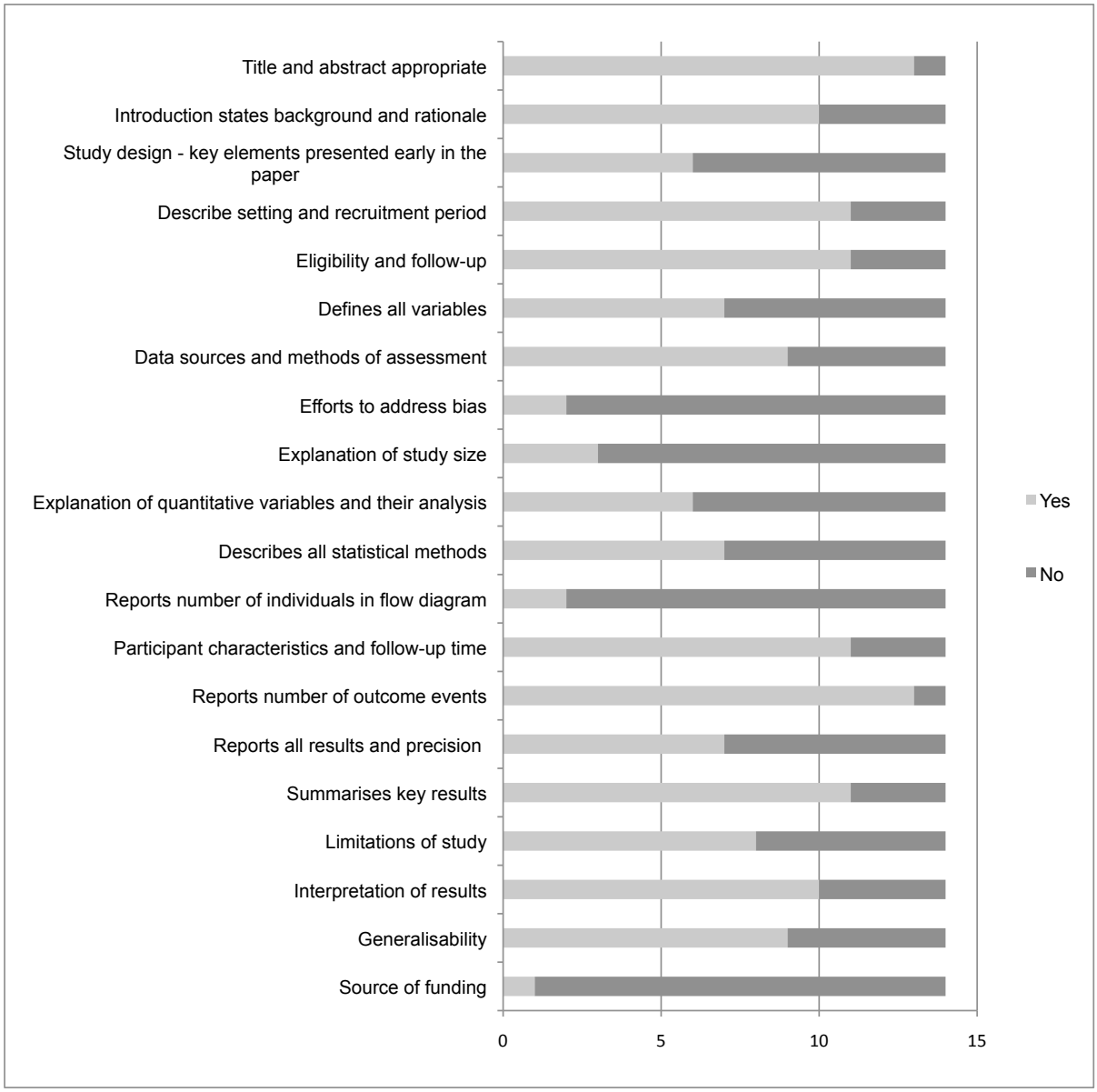


Figure 6. Quality of observational studies using the STROBE guidelines**.**



Participant characteristics

One study looked exclusively at women suffering from PMB[21], seven studies looked at only women who were premenopausal[122,155,156,158,161,162,164] and the remaining 9 studies examined mixed populations of women with AUB (Table 12).

Interventions

When the operative technique was described, polypectomy was performed under direct vision (hysteroscopically) with the exception of two studies that had inpatient arms in which blind avulsion was used [147,165] (Table 13). There were a variety of techniques and instruments described for polyp removal under direct vision including: scissors, polyp forceps, morcellator devices and a variety of bipolar instruments.

Outcomes

There were large differences in the time of follow-up, ranging from two months [160] to over nine years [142] (Table 14). Only two studies used a validated tool for measuring efficacy of polypectomy: both studies used a visual analogue scale (VAS) [147,164]. The majority of studies defined the primary outcome as an improvement in symptoms of AUB as perceived by the patient. All the studies reported an improvement in symptoms from 60-100% [21,122,142,147,154–166]. The study looking exclusively at postmenopausal patients presented a survival analysis curve[21]. The

seven studies looking at premenopausal patients reported improvements in 60-100% of participants [122,155,156,158,161,162,164]. The remaining nine studies looking at mixed populations reported 65-100% symptomatic improvements [142,147,154,157,159,160,163,165,166]. Two of these studies further explored recurrent AUB symptoms for those that were pre and postmenopausal at treatment [154,159]. One of the studies found no significant difference in AUB at 1 year, although the numbers were small (27 of 34 premenopausal patients versus 12 of 12 postmenopausal patients; $P = 0.2$)[159]. While a larger study found that premenopausal women were more likely to have recurrence of symptoms (Hazard Ratio [HR] 2.42 [95% CI 1.42-4.11])[154]. Another study examined symptom outcome by types of AUB in premenopausal women; no differences in outcome were observed for those women complaining of HMB or IMB, although the study population was small (HR 1.29 [0.61 to 2.73]; $P = 0.50$ and HR 0.42 [0.09 to 1.76] $P = 0.24$) [158].

The two studies comparing inpatient to office treatment reported no difference in symptom improvement, although the study sizes were small: 11 of 12 (92%) after office treatment compared with 13 of 14 (93%) after inpatient treatment [147]; and 18/22 (82%) after outpatient treatment compared with 17/26 (65%) after inpatient uterine polypectomy RR 1.25 (95% CI 0.88 – 1.83) [165]. In both studies the office polypectomies were performed under direct vision, while inpatient polypectomy was performed 'blindly'.

There was one other controlled observational study and that compared mechanical polyp resection (using a morcellator) versus electrical resection. Overall, 36 of 172

patients (20.9%) undergoing electrical resection and 21 of 139 patients (15.1%) undergoing intrauterine morcellation reported recurrence of AUB [154].

The randomised controlled study comparing resection of polyps with observation for six months reported no difference in periodic blood loss using the pictorial blood assessment chart (PBAC), but did report a significant decrease in recurrence of gynaecological symptoms (e.g. IMB and vaginal discharge) in those women having polypectomy (7/75 patients [9.3%] versus 28/75 control patients [37.3%]; $P < 0.001$) [122].

Table 12. Methodology of the included studies

Study	Methodology		Patient	Population - polyps and AUB		
Author	**Study design**	**Data collection**	**Selection**	**Number**	**Type (%)**	**Follow-up (%)**
Clark *et al*[165]	Randomised controlled trial	Prospective	Consecutive	60	Unspecified menstrual; PMB	80
Lieng *et al*[122]	Randomised controlled trial	Prospective	Consecutive	150	Intermenstrual (47); Menorrhagia (13); Irregular (8); Discharge (7); asymptomatic (25)	95
AlHilli *et al*[154]	Controlled Observational	Retrospective	Consecutive	311(IUM 139, HSR)	Menorrhagia (19%), menometrohagia (10%), postmenopausal bleeding (44%)	100
Barisic *et al*[155]	Observational	Unreported	Unreported	8	Unspecified menstrual	100
Brooks *et al*[156]	Observational	Unreported	Unreported	9	Excessive menstrual	89
Clark *et al*[147]	Controlled Observational	Prospective	Consecutive	58	Unspecified menstrual (10); PMB +/- HRT (90)	58
Cravello *et al*[157]	Observational	Retrospective	Consecutive	195	Unspecified menstrual (60); PMB + HRT (12); tamoxifen (2); PMB (26)	89
Henriquez *et al*[158]	Observational	Retrospective	Consecutive	56	Unspecified	100
Nagele *et al*[159]	Observational	Unreported	Unreported	33	Excessive menstrual (47); intermenstrual bleeding (13); PMB 40	100
Pace *et al*[160]	Observational	Unreported	Consecutive	87	Unspecified menstrual/PMB (86); subfertility (14)	87;49
Polena *et al*[161]	Observational	Retrospective	Consecutive	367	Menorrhagia, metrorrhagia, intermenstrual	83

					bleeding	
Preutthipan *et al*[142]	Observational	Retrospective	Unreported	155	Metrorrhagia(31), hypermenorrhea(29), IMB(19), menorrhagia (11) and menometrorrhagia(10)	100
Stamatellos *et al*[162]	Observational	Retrospective	Unreported	83	Unspecified	100
Timmermans *et al*[21]	Observational	Prospective	Consecutive	49	PMB	100
Towbin *et al*[163]	Observational	Prospective	Consecutive	14	Menorrhagia, metrorrhagia. Postmenopausal	100
Tjarks *et al*[166]	Observational	Retrospective	Unreported	34	Unspecified menstrual (64); PMB (36)	100
van Dongen *et al*[164]	Observational	Prospective	Consecutive	21	Menorrhagia, metrorrhagia, intermenstrual bleeding	90

AUB = abnormal uterine bleeding; ECA = endometrial cancer; EH = endometrial hyperplasia; EH+A = endometrial hyperplasia + cytological atypia; HRT = hormone replacement therapy; HSR = hysteroscopic resection; IUM = intrauterine morcellation; NR = not recorded; PBAC = pictoral blood assessment chart; PMB = post menopausal bleeding; SD = standard deviation; VAS = visual analogue scale

Table 13. Operative details of included studies.

Study Author	Technique (%)	Anesthesia (%)	Mean operation time	Polyp number (%)	Mean polyp size (range)	Polyp histology (%)
Clark *et al*[165]	Outpatient = hysteroscopic; inpatient = blind	Outpatient = local (93), none (7); Inpatient = General (100)	Outpatient (consultation time) 29min; Inpatient 24min	NR	NR	NR
Lieng *et al*[122]	Hysteroscopic resection or observation	General	NR	NR	16.5 mm (5.3SD)	EH (1.5) Benign (98.5)
AlHilli *et al*[154]	Hysteroscopic resection	General	NR	Single (65); multiple (35)	2.1cm	EH + ECA(7)
Barisic *et al*[155]	Hysteroscopic resection	General	NR	Single (100)	(1.8-3cm)	EH (13); benign (87)
Brooks *et al*[156]	Hysteroscopic resection	General	NR	NR	NR	NR
Clark *et al*[147]	Hysteroscopic (Versapoint) (50); or hysteroscopy + blind avulsion (50)	Local (50); general (50)	NR	NR	0.9cm	NR
Cravello *et al*[157]	Hysteroscopic resection	General	19 min	Single (90); multiple (10)	1.4cm(0.5-4cm)	EH+A (1); benign (99)
Henriquez *et al*[158]	Hysteroscopic	General or spinal	NR	single (62); multiple (39)	17.5 mm(SD 8.3)	NR
Nagele *et al*[159]	Hysteroscopic resection or mechanical excision (scissors)	Local (20); general (80%)	NR	Single; "some" multiple	(1-5cm)	EH+A(2); ECA (2); benign(96)

Pace *et al*[160]	Hysteroscopic resection	General	22 min	Single (86); multiple (14)	(<1.5cm[45%]; >1.5cm[55%])	EH(1); benign(99)
Polena *et al*[161]	Hysteroscopic resection	General	NR	Single (81); multiple (19)	NR	ECA(0.05); benign(99.5)
Preutthipan *et al*[142]	Hysteroscopic resection	General	23.1+/-4.7 microscissors; 20.9 +/-3.9 grasping forceps; 25.2+/-4.9electric probe; 31.9+/-8.3	single (74);	3.4+/-0.9cm premenopausal; 2.5+/-0.8cm postmenopausal	EH (3); benign (97)
Stamatellos *et al*[162]	Hysteroscopic resection	General or none	NR	single (41); multiple (59) same as polyp size data	<1cm[41]; >1cm[59]	NR
Timmermans *et al*[21]	NR	NR	NR	NR	NR	NR
Towbin *et al*[163]	NR	NR	NR	NR	NR	NR
Tjarks *et al*[166]	NR	General	NR	Single (88); multiple (12)	(<1cm[13%]; >1cm[87%])	NR
van Dongen *et al*[164]	Hysteroscopic resection	General or spinal	NR	single (38.1); multiple (61.9)	13.2 mm (4.7SD)	NR

Table 14. Treatment outcomes of included studies

Study Author	Failure rate/ complication rate	Outcome assessment (time)	Outcome measure	Treatment success (%)
Clark *et al*[165]	Outpatient 2/1; Inpatient 0/0	Postal questionnaire (6 months)	Improvement in VAS	Outpatient 18/22(82); 17/26(65) inpatient
Lieng *et al*[122]	0/1	Postal questionnaire (6 months)	No gynecological symptom	68/75(91) resection; 47/75(63) observation
AlHilli *et al*[154]	NR	Clinical interview	Recurrence of AUB	118/139(85) IUM; 136/172(79) HSR; 254/311(81) both
Barisic *et al*[155]	NR/NR	NR (first 3 menstrual cycles)	Normalisation of AUB	8/8 (100)
Brooks *et al*[156]	NR/0	NR (>3 months)	Improved vs not improved	7/8 (88)
Clark *et al*[147]	0/0	Postal questionnaire at 6 months	Better vs not better; satisfied vs not satisfied	Outpatient 11/12 (92); inpatient: 13/14(93); Outpatient: 14/18 (78); inpatient: 14/16 (88) 156/175 (89)
Cravello *et al*[157]	0/2	Telephone interview with patients or referring clinicians (NR)	Normalisation of AUB	156/175 (89)
Henriquez *et al*[158]	NR	Review of clinical notes	Persistence of AUB requiring medical therpay or surgical intervention	33/56 (60) 1yr
Nagele *et al*[159]	0/0	Clinical interview (3 months); postal questionnaire (5-52 months)	Short-term "cure" of AUB; maintenace of "cure" (no recurrence of AUB)	44/49 (90); 38/49 (78)
Pace *et al*[160]	0/1	Clinical interview (2 months); clinical interview (12 months)	Normalisation of AUB (no "relapse" of symptoms)	85/87 (98);100

Polena *et al*[161]	1/4 (out of total population of 367)	Telephone interview and postal questionnaire	Normalisation of AUB	91/97(94)
Preutthipan *et al*[142]	NR/21	Clinical interview 9 years 2 months	Normalisation of AUB	144/155 (93)
Stamatellos *et al*[162]	NR/2	Telephone interview or examination when indicated (3-18 months)	Normalisation of AUB	76/83(91)
Timmermans *et al*[21]	NR/NR	Patients self reported symptoms	Recurrence of PMB	Survival curve
Towbin *et al*[163]	NR	Clinical interview	Recurrence of AUB	14/14(100)
Tjarks *et al*[166]	NR/NR	Telephone interview (5-24 months)	Menorrhagia score (scale 0-3); number of days bleeding/month; satisfied vs not satisfied	Significant reduction $P<0.05$; significant reduction $P<0.05$; 23/26(88)
van Dongen *et al*[164]	NR/NR	Questionnaire	Improvement of symptoms; menstrual chart score; VAS quality of life	18/21(86); improvement $P = <0.001$; improvement $P = <0.001$

Discussion

Key findings

The evidence collated in this review supports the notion that removing uterine polyps is effective at improving symptoms of AUB. However, most of the evidence was derived from observational studies that reported high success rates, but in general the quality of the research was poor. The highest quality studies, the two randomised controlled trials, reported more modest improvements in symptoms [122,165]. However, it was unclear whether menopausal status or the exact nature of the presenting AUB complaint influences treatment outcome.

Strengths and limitations

The strengths of this review included the rigorous, systematic approach to literature searching; independent selection of studies and data extraction in duplicate; and use of recommended study quality assessment tools [151,153]. The included studies were however, small and many contained heterogeneous populations of women who were both pre and postmenopausal. In addition, follow up was often incomplete and short-term, such that the strength of any clinical inference drawn is limited. Meta-analysis was precluded because of the observed heterogeneity within and between the study populations, as well as variation in follow-up and outcome assessment.

Comparison with other studies

The majority of studies reported hysteroscopic polyp resection under direct vision. However, although hysteroscopic polypectomy is increasing in popularity, a large number of clinicians continue to use blind techniques such as dilation and curettage (D&C) affecting the generalisability of the results presented in this review [108,129,130]. To better ascertain the effect of polyp removal on AUB we decided not to include data in which patients had concomitant or subsequent medical or surgical treatments e.g. insertion of the LNG-IUS which may also affect generalisability.

Conclusions

Larger randomised controlled studies are necessary to elucidate if certain groups of patients benefit more from uterine polypectomy. However, recruitment may be hampered by the unwillingness of both gynaecologists and patients to participate in placebo controlled trials [125]. A further consideration is the increasing move to office polypectomy observed in many units, driven by technological advances in instrumentation, patient expectation and scarcity of health care resources [3]. Only two randomised studies were identified in this review. Large RCTs comparing conventional inpatient with novel outpatient approaches to polyp treatment are needed to identify best practice before opinion is solidified. It is also important to note that alleviation of AUB is not the only reason why uterine polypectomy is performed. Other reasons include the optimisation of fertility and concerns about the potential for polyps to turn malignant. Further work is needed in these areas to inform decisions on how and when to treat uterine polyps.

CHAPTER 7: A RANDOMISED CONTROLLED TRIAL OF HYSTEROSCOPIC MORCELLATION OF INTRAUTERINE POLYPS

Publication

This work has been peer reviewed and published in the Green Journal; Smith P, Middleton L, Connor M, Clark J. Hysteroscopic Morcellation Compared With Electrical Resection of Endometrial Polyps: A Randomized Controlled Trial. Obstetrics and Gynecology 2014 April, Vol 123, No 4 pg 745 – 751

Abstract

Objective

To evaluate whether hysteroscopic morcellation or bipolar electrosurgical resection is more favourable for removing endometrial polyps in an office setting in terms of feasibility, speed, pain, and acceptability.

Methods

A multicenter, single-blind, randomised controlled trial of office hysteroscopic morcellation compared with electrosurgical resection was conducted. A total of 121 women were randomly allocated to polyp removal by one of the two methods in an office setting. The outcomes assessed were time taken to complete the endometrial polypectomy, defined as the time from insertion to removal of vaginal instrumentation, completeness of polyp removal, acceptability, and pain measured on a 100mm visual analogue scale.

Results

The median time taken to complete the procedure was 5 minutes, 28 seconds for morcellation compared to 10 minutes, 12 seconds for electrosurgical resection ($P < 0.001$). The polyp(s) were completely removed in 61/62 (98%) of women assigned to morcellation compared to 49/59 (83%) of women treated with electrosurgical resection (OR 12.5; 95%CI: 1.5 to 100.6, $P = 0.02$). The mean pain scores during the procedure favoured morcellation by 16.1 points on average (35.9 vs. 52.0;

95%CI for difference: -24.7 to -7.6, $P < 0.001$). Overall, 99% of women found office polypectomy to be acceptable with only one woman in the electrosurgical resection group considering the procedure unacceptable.

Conclusions

In comparison to electrosurgical resection during hysteroscopic polypectomy, morcellation was significantly quicker, less painful, more acceptable to women and more likely to completely remove endometrial polyps compared with electrosurgical resection.

Clinical Trial Registration: ClinicalTrials.gov, www.clinicaltrials.gov, NCT01509313.

Introduction

Background

The miniaturisation of hysteroscopes and ancillary instrumentation coupled with enhanced visualisation has enabled hysteroscopic surgery to be performed in an office setting without the need for general anaesthesia or hospital admission [3]. The most common operative hysteroscopic procedure is endometrial polypectomy [121] i.e. surgical removal of an endometrial polyp. The feasibility of office hysteroscopic polypectomy has been demonstrated [147]. Traditionally these procedures were performed using miniature mechanical instruments, but the small size and fragility of these ancillary instruments limited office treatment to smaller, isolated focal lesions [137]. In recent years those mechanical approaches have been superseded by the introduction of a disposable miniature bipolar electrosurgical system that has been developed to be used down standard operating hysteroscopes to cut away polyps. The safety, acceptability and feasibility of this approach has been reported [146–148]. However, as with mechanical technologies retrieval of the detached polyp tissue from within the uterine cavity requires additional instrumentation, which may prolong the procedure and affect patient tolerability.

Recently, a new technology has been developed to overcome their limitations of currently available hysteroscopic instrumentation. This technology, called the hysteroscopic morcellator, incorporates a disposable mechanical cutting device that simultaneously cuts and aspirates polyp tissue. The ability to both cut and retrieve polyps avoids the need for additional instrumentation of the uterine cavity and may

also improve visualisation during surgery by avoidance of bubble formation or the production of tissue fragments ('chips') associated with the electrosurgical approach. Avoidance of thermal injury may also confer safety and tolerability benefits compared with electrosurgical resection.

In view of the development of hysteroscopic morcellation and potential advantages associated with this innovation, we designed a randomised controlled trial (RCT).

Endometrial polyps

Endometrial polyps are localised overgrowths of endometrial tissue that can occur anywhere in the uterine cavity. They contain variable amounts of glands, stroma and blood vessels that are covered by a layer of epithelium [110]. Most commonly they are attached to the uterus by an elongated pedicle (pedunculated), but they may also have a large flat base (sessile). They range in size from a few millimeters to several centimeters. There is some evidence to suggest that some smaller polyps (<10mm) may regress naturally without treatment, but most polyps will persist [119,124]. Normally polyps are benign, with the prevalence of cancer reported in the range of 0.5-3% [109–116].

Review of hysteroscopic morcellation

After searching four electronic databases (Medline, EMBASE and CINAHL), four citations were identified for polyp morcellation. Of these, two articles were retrospective descriptive studies[149,167]; one was a randomised-controlled pilot study amongst residents in training [150] and the last was an abstract describing histo-

pathological outcomes [168]. Emanuel et al [149] compared traditional electrosurgical resection with hysteroscopic morcellation for the removal of focal lesions within the uterus, namely endometrial polyps and submucous fibroids (benign smooth muscle tumours arising from the underlying myometrium and protruding into the uterine cavity). Electrosurgical resection is a technique where large diameter hysteroscopes incorporate a monopolar electrosurgical cutting loop, a set up known as a 'resectoscope' which removes uterine pathology in a piecemeal fashion, in contrast to hysteroscopic morcellation which simultaneously cuts and aspirates tissue. All procedures were carried out under a spinal or general anaesthetic. Twenty-seven women had their lesions removed by morcellation with a significantly shorter average operating time of 8.7 minutes (95% CI: 7.3 to 10.1) compared with 30.9 minutes (95% CI: 27 to 34.8) for the 44 women who had their lesions removed by traditional resection. A single RCT pilot study has also compared hysteroscopic morcellation with resection of fibroids and polyps under either spinal or general anaesthetic. Again, morcellation was found to be significantly quicker compared with resection (10.6 minutes vs 17.0 minutes) [150]. Unfortunately, it did not breakdown the operating times for fibroids and polyps separately. In an uncontrolled series of 278 hysteroscopic polyp morcellations under general anaesthesia, the reported total installation and operating times were 7.3 minutes and 6.6 minutes respectively [167]. One conference abstract was identified assessing the use of hysteroscopic morcellation. The study examined the quality of histological specimens and found no difference between morcellated or resected tissue specimens [168].

The need for a randomised trial comparing hysteroscopic morcellation with bipolar electrosurgical resection in an outpatient setting

The current literature shows that the hysteroscopic morcellation using a large diameter (9mm) apparatus is feasible and safe procedure for removal of endometrial polyps and is quicker to perform than monopolar electrosurgical techniques under general anaesthesia. However, contemporary practice is moving to performing hysteroscopic surgery, especially polypectomy, with miniature instruments in the office setting without the need for general anaesthesia. It should be noted that this morcellator system is designed for use under a general or regional anaesthesia because of its large diameter requiring significant cervical dilatation.

The technology most commonly used to perform outpatient polypectomy is the Versapoint® bipolar electrosurgical system (Gynecare™; Ethicon Inc., New Jersey, USA) a 1.8mm (5F) electrode which can be passed down standard <5.5mm continuous flow operating hysteroscope. A 5mm miniature TRUCLEAR™ hysteroscopic morcellator (Smith&Nephew, Andover MASS, USA) has recently become available for use in the office setting without anaesthesia and offers potential advantages over traditional electrosurgical resection of polyps. The ability to both cut and retrieve polyps avoids the need for additional instrumentation of the uterine cavity in order to retrieve the detached polyp specimen i.e. a single insertion

of the hysteroscope is required only. This may enhance the efficacy, tolerability and feasibility of office hysteroscopic polypectomy. The use of mechanical morcellation may also improve visualisation during surgery by avoidance of bubble formation or the production of tissue fragments ('chips') associated with the electrosurgical approach.

Thus, this new technology has potential advantages for the patient (acceptability, pain, infection, safety), the surgeon (speed, feasibility, completeness of the procedure) and health service (avoidance of second stage procedures under general anaesthetic). However, the established single use bipolar electrode is smaller than the disposable morcellator cutting device (1.6mm vs. 2.9mm). Moreover, the bipolar electrode can be used down the operating channel of a variety of continuous flow hysteroscopes which are longer and smaller in diameter and in day-to-day use in gynaecological practice in outpatient settings (outer diameter 4.1mm (Gynecare; Ethicon Inc., New Jersey, USA), 5mm Storz Bettocci hysteroscope (Karl Storz Endoscopy-America inc., California, USA) or Olympus 5.5mm (Olympus Corporation, Shinjuku-ku, Tokyo, Japan). In contrast, the hysteroscopic morcellator system is larger (5.6mm outer diameter) and requires acquisition of specific hysterscopes with an offset proximal eyepiece to allow the rigid mechanical cutting device to be inserted in direct alignment with the barrel of the hysteroscope. Thus in an office setting, the bipolar electrode may have advantages over the larger hysteroscopic morcellator in terms of ease of uterine instrumentation.

Endometrial polypectomy is one of the commonest procedures in modern gynaecological practice. In light of this and to answer uncertainties about potential benefits in terms of feasibility and effectiveness of office hysteroscopic morcellation compared with current office bipolar electrosurgical resection, we believed that there was an urgent need to undertake a robust health technology assessment. We therefore designed an adequately powered RCT to assess the speed, effectiveness (in terms of completed procedures) and acceptability of endometrial polyp removal between treatment modalities. Long-term outcomes such as the effect of polyp removal on abnormal uterine bleeding (AUB) were not evaluated because a large randomised controlled trial comparing inpatient to office polypectomy on alleviation of AUB symptoms had recently been completed[169]. However, this trial did identify increased failure of polypectomy in the office setting with one in five procedures being incomplete[169] and a lower patient acceptability compared with inpatient procedures under general anaesthesia. Thus, this finding added further support to an RCT evaluating a potentially more effective hysteroscopic surgical method.

Objectives

1. To determine if hysteroscopic morcellation is faster than bipolar electrosurgical resection.
2. To assess if hysteroscopic morcellation is more likely to completely remove endometrial polyps in the office setting.
3. To determine if hysteroscopic morcellation is less painful than bipolar electrosurgical resection.
4. To compare hysteroscopic morcellation to bipolar electrosurgical resection in terms of patient acceptability.
5. To compare hysteroscopic morcellation to bipolar electrosurgical resection in terms of complications.

Methods

Study design

A multicenter, single-blinded, parallel-group RCT comparing hysteroscopic morcellation versus electrosurgical resection was conducted.

Study setting

Women were recruited from office hysteroscopy clinics within two large urban teaching hospitals; Birmingham Women's Hospital Foundation Trust and the Royal Hallamshire, Sheffield Teaching Hospital.

Patient eligibility

Inclusion criteria

All women attending for an office hysteroscopy or who had a hysteroscopically diagnosed endometrial polyp and in whom polypectomy was indicated [3] were approached to participate in the trial. All participating women gave written informed consent after reading the patient information leaflet (Appendix 12 – 13).

Exclusion criteria

Women were excluded from participation if they preferred the procedure under general anaesthesia or were considered by the surgeon to be unable to tolerate an office hysteroscopic polypectomy based upon their response to the office diagnostic hysteroscopy. Women with polyps suspected at hysteroscopy to be malignant were also excluded. The number and size of polyps were not exclusion criteria.

Centre eligibility

To take part in the trial the centres needed to meet the following eligibility criteria: 1) be willing to attend collaborative meetings 2) have staff proficient in both electrical resection and morcellation of endometrial polyps in the office setting 3) have the equipment to perform both electrical resection and morcellation.

Originally recruitment was planned in three centres: Birmingham Women's Hospital Community Trust, Sheffield University Hospital and Bradford University Hospital. However, the clinicians in Bradford University Hospital were not willing to randomise all suitable patients so they were not included to maintain the integrity of the trial.

Trial registration

This trial was registered on clinicaltrials.gov (identifier: NCT01509313). The National Research Ethics Service, UK, granted ethical approval (identifier: 12/WM/0058). Research and Development approval was sought and granted at Birmingham Women's Hospital and Sheffield Teaching Hospital. The trial was conducted according to the principles of Good Clinical Practice (GCP).

Randomisation

Women were allocated in a 1:1 ratio to either of the interventions through a telephone-based system managed by the Birmingham Clinical Trials Unit. The randomisation blocks were kept centrally in the Birmingham Clinical Trials Unit and

the sizes varied so that the allocation could not be deduced pre-randomisation. Blocks were stratified by the location of polyp (fundal versus non-fundal) to ensure we achieved balance between groups for this variable. Location was chosen because access to the base of fundal polyps can be problematic with standard mechanical or electrosurgical hysteroscopic instruments[3]. Women were not told which intervention they had been allocated to until after they had completed the post-operation questionnaire.

Interventions

All surgical procedures were performed in the office setting without general anaesthesia or conscious sedation. Three surgeons experienced in outpatient endometrial polypectomy performed all surgical procedures (TJC, MEC, PS). Participating surgeons were proficient in both methods of polypectomy, although all three had greater experience with the more established technique of electrical resection. Office polypectomy was performed (i) immediately following diagnosis ('see & treat') or (ii) scheduled within 8 weeks of diagnosis, depending upon local circumstances and patient preference. Vaginoscopy (i.e. passage of the hysteroscope into the uterine cavity without the use of a vaginal speculum or instrumentation of the ectocervix) was the standard approach, with recourse to instrumentation of the lower genital tract where vaginoscopy failed. No cervical preparation was used prior to the procedure. Normal Saline (0.9% w/v NaCl) was instilled from a three litre bag within a pressure cuff set at 180mmHg which was hung from a 180cm stand to provide distension and irrigation of the uterine cavity. In line with departmental protocols, fluid deficit was not calculated for office

polypectomy because procedures were short, limited to the endometrium, relatively avascular and performed through small diameter operating hysteroscopes [3]. The use of local anaesthesia (direct cervical block using 6.6ml of 3% mepivacaine) was restricted to procedures where dilatation of the cervix was required to pass the hysteroscope through the endocervical canal and / or to facilitate retrieval of the polyp specimen from the uterine cavity [3].

Hysteroscopic morcellation

Morcellation was carried out under direct hysteroscopic vision using the TRUCLEAR™ 5.0 (Smith & Nephew, Andover MA, USA) hysteroscopy system incorporating a 2.9mm rotary style hysteroscopic morcellator. The hysteroscopic morcellator technology has been previously described; in short it incorporates a disposable cutting device that consists of 2 hollow metal tubes that fit inside each other. There is a window or aperture and tissue is sucked into the opening by means of vacuum and is shaved as the inner tube is rotated within the outer tube [149].

Bipolar electrosurgical resection

Bipolar electrosurgical resection was carried out under direct vision using the VersaPoint™ (Gynecare; Ethicon Inc., New Jersey, USA) disposable bipolar electrosurgical system. The electrode was placed down a 5Fr operating channel within either the 3.5mm ALPHASCOPE™ (Gynecare; Ethicon Inc., New Jersey, USA) or the 5mm Bettocchi (KARL STORZ™, Tuttlingen, Germany) operating hysteroscope. After electrosurgical resection ancillary mechanical instruments are

used the specimen(s) from the uterine cavity. These can be either hysteroscopic instruments (miniature grasping forceps, snares) or standard blind polyp forceps [3].

Outcomes

Time taken to complete the endometrial polypectomy

This was defined as the time from insertion to removal of vaginal instrumentation post-randomisation. In addition, the total time the hysteroscopic morcellator generator was activated according to the TRUCLEAR™ operating system was collected at the Birmingham Women's Hospital site.

Completeness of polyp removal

A complete endometrial polypectomy was defined as the detachment and retrieval of all visible polyp tissue (single or multiple polyps), such that no polyp remnants remained within the uterine cavity. An incomplete procedure included any of the following: (a) *failure to detach* any polyp tissue from the uterine wall; (b) *partial detachment* of polyp(s) from the uterine wall and (c) *failure to retrieve* the detached specimen from the uterine cavity.

Procedural pain & patient acceptability

These data were collected using previously piloted self-completed questionnaires. A pre-operative questionnaire was completed by all women before the procedure to collect baseline pain scores and a second questionnaire was given to patients immediately after the procedure (Appendix 15 – 16). Women were asked to

complete the questionnaire prior to discharge from hospital in order to limit recall bias and increase response rates. To assess acceptability, a four point ordinal scale was used with the following response categories: 'Would you describe the procedure as "Totally acceptable"; "Generally acceptable"; "Fairly acceptable"; "Unacceptable". Pain was assessed using a 100mm visual analogue scale (0 for no pain and 100 for worst imaginable pain). Women were asked to assess their pain during the procedure and also their short-term post-operative pain just prior to discharge from hospital or after 15 minutes of completing the procedure, whichever came first.

Surgical technique and complications

Surgeons completed a standard form following the procedure to record technical aspects of the procedure including time taken and peri- or post-operative complications (Appendix 14).

Data collected by the operator at the time of polypectomy included: parity, indication for polypectomy, menopausal status (pre or postmenopausal), the make and size of hysteroscope, the size and number of endometrial polyps, the location of the polyp(s), the type of polyp(s) (sessile or pedunculated), the consistency (fibrous or glandulo-cystic), the use of local anaesthesia (none, direct cervical, paracervical, topical), the need for cervical dilatation, the use of a speculum (as compared with pure vaginoscopy), completeness of polyp removal (defined as complete detachment and retrieval of all polyp tissue from the uterine cavity for histological assessment), details of any adverse events (Genital tract trauma, haemorrhage,

vaso-vagal reactions, severe pain etc.). Vaso-vagal reactions were defined clinically as the patient being unable to leave the operating couch within five minutes of cessation of procedure due to feeling faint or dizzy or nauseous.

Serious and unexpected adverse events

There may be complications associated with either electrical resection or morcellation of endometrial polyps (Appendix 17). In this trial, "*serious*" adverse events (SAE) were defined as those that were life threatening, fatal, disabling or caused prolonged hospitalisation as a result of the hysteroscopy or endometrial polypectomy. Any SAE were to be reported immediately to the trial office, followed within 2 working days by a completed SAE form (Appendix 18).

Data management

Anonymised data from Sheffield University Hospital was sent to Birmingham Women's Hospital Community Trust via post. All data were inputted into the electronic Morcellation versus Electrical Resection Trial (MERT) database by PS. At the end of the trial, a random 10% sample of all of the trial data were re-entered by the Chief Investigator JC to verify correct data input. Any discrepancies between originally entered data and re-entered data were reviewed and checked against the original paper copy. An initial data entry error rate of >5% would have triggered a requirement to re-enter the entire data set from that questionnaire. This was not found to be necessary.

Trial steering committee

The trial was originally expected to take 18 months to complete and the first meeting was planned at 12 months. The trial was complete at 10 months so the trial steering committee did not convene.

Sample size

The sample size for this trial was chosen to give high statistical power to detect a significant difference in the primary measure of time taken to complete the endometrial polypectomy. This size of difference was based upon evidence reported from a randomised pilot study among resident in training evaluating the hysteroscopic morcellator with formal transcervical resection under traditional general anaesthesia[150]. The results here showed the mean operating time for morcellation to be 10.6 minutes compared with 17.0 minutes for resectoscopy with a standard deviation of 9.5 minutes over both groups. This size of difference reflected an overall operating time reduction of approximately one third which we considered to be clinically meaningful difference in the office setting. To detect a difference of this size (6.4 minutes) with 90% power (P = 0.05) would require 48 participants per group, 96 in total. To account for attrition we aimed for 120 participants in total.

Statistical methods

Analysis was performed by intention-to-treat. Mean differences and corresponding 95% confidence intervals were calculated for treatment times and pain scores. A t-

test was used to assess statistical significance, although in the presence of some skewness of distribution for treatment times, a non-parametric Mann-Whitney U test was also performed. Logistic regression was employed for dichotomous outcomes such as completeness of polyp removal. Odds ratios and 95% confidence intervals were derived with a chi-squared test used to assess statistical significance. Fisher's exact test was used to compare treatment failure because sample sizes were small. Regression analysis was used to compare trends across the different responses to acceptability. All analyses were carried out using SPSS software version 21 (IBM, Armonk, NY, USA).

Results

Participants

In total, 121 patients requiring removal of an endometrial polyp(s) as part of their standard care were randomised from 2 hospitals over 11 months between July 2012 and May 2013. There were 98 women recruited from Birmingham Women's Hospital and 23 women from Sheffield Teaching Hospital. Figure 7 shows total recruitment along with the contribution from each site. Figure 8 summarises the flow of participants through the trial in line with the recommendations of the consolidation standards of reporting trials (CONSORT) statement [52].

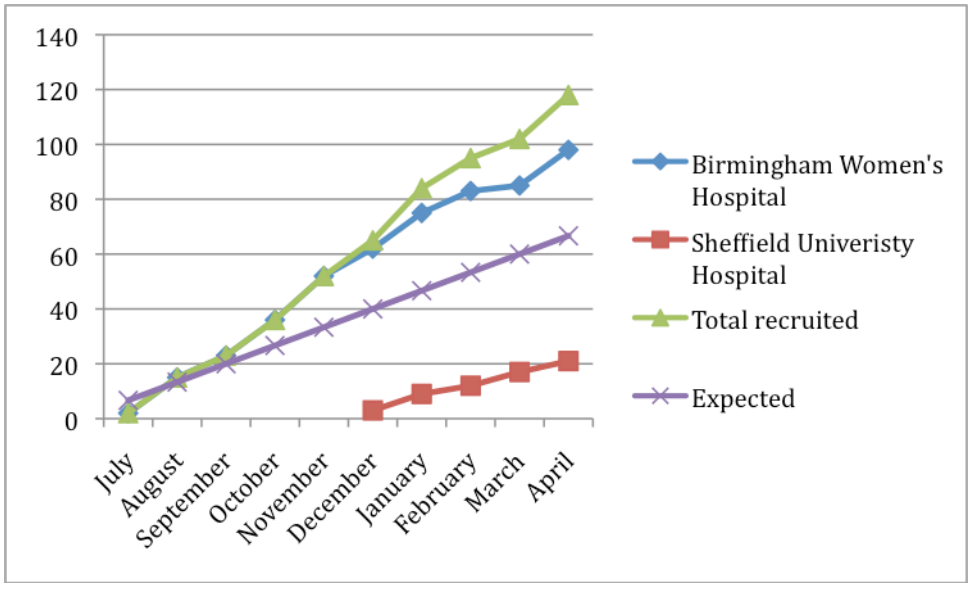


Figure 7. Trial recruitment over time.

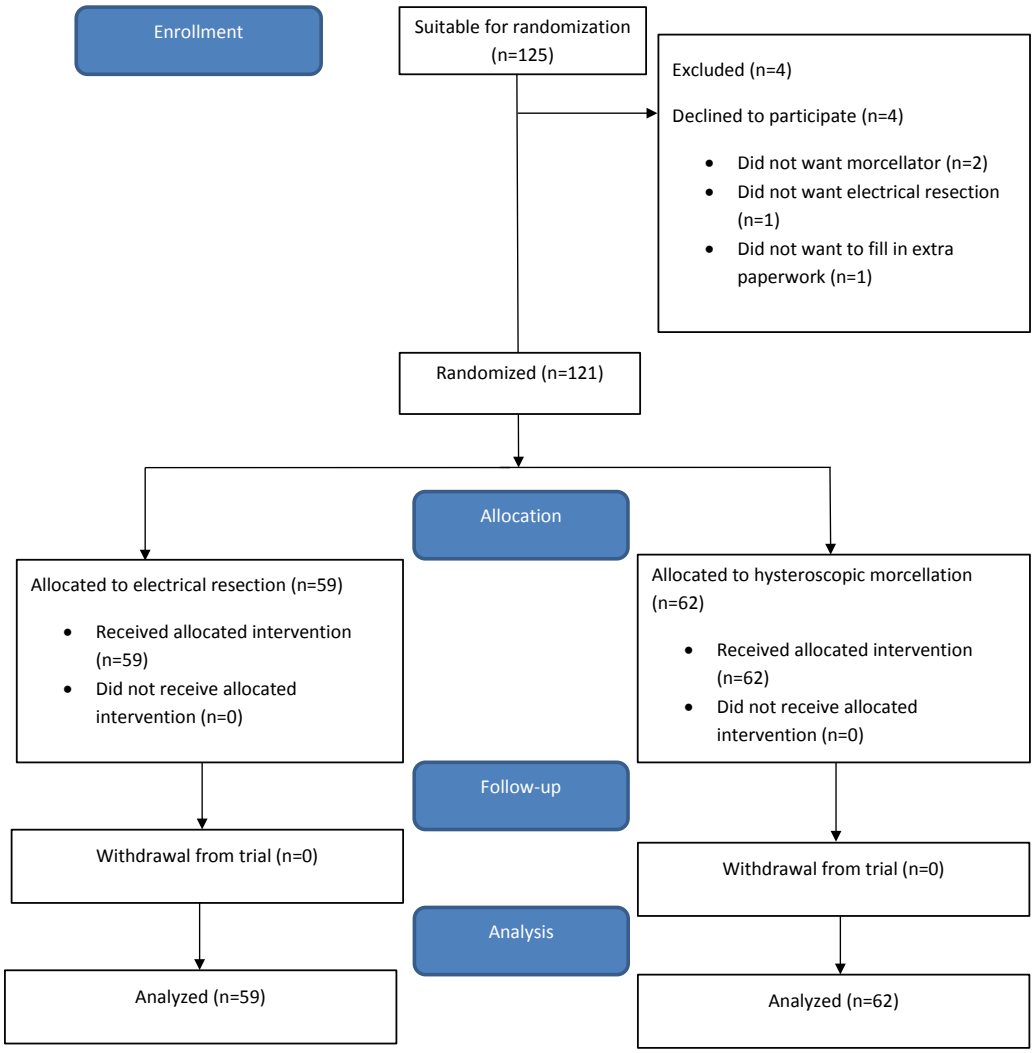


Figure 8. Flow diagram of women in the hysteroscopic morcellation versus electrical resection trial.

Baseline characteristics

The majority of baseline variables were balanced between groups post-randomisation (Table 15). However, women randomised to hysteroscopic morcellator had more polyps on average than those randomised to electrical resection and proportionately more women were allocated hysteroscopic morcellator in Sheffield Teaching Hospital compared with Birmingham Women's Hospital.

Table 15. Baseline Characteristics of Trial Participants

		Hysteroscopic Morcellation (n=62)	Electrical Resection (n=59)
Age (years)	Mean (SD)	54.3 (12.7)*	54.9 (14.2)†
BMI (km/m^2)	Mean (SD)	31.7 (6.6)‡	31.5 (8.4)§
Parity	Mean (SD)	1.9 (1.6)	2.2 (1.8)
Previous cesarean	Yes	5 (8%)	4 (7%)
	No	57 (92%)	55 (93%)
Menopausal status	Premenopausal	26 (42%)	28 (47%)
	Postmenopausal	35 (56%)	31 (53%)
	Missing	1 (2%)	0 (-)
Indication	Bleeding	51 (82%)	52 (88%)
	Fertility	1 (2%)	4 (7%)
	Dysmenorrhoea	0 (-)	2 (3%)
	Incidental radiological	3 (5%)	1 (2%)
	Vaginal discharge	1 (2%)	0 (-)
	Missing	6 (10%)	0 (-)
Number of polyps	Mean (SD)	1.8 (0.9)	1.2 (0.5)
	(min, max)	(1,4)	(1,3)

BMI = body mass index; SD = standard deviation; BWHCT = Birmingham Women's Hospital Foundation Trust; STH = Sheffield Teaching Hospital.

* Four values missing

† Three values missing

‡ Eleven values missing

§ Twelve values missing

Outcome data

Time taken to complete the procedure

The median time taken to complete the polypectomy procedure was 5 minutes and 28 seconds for hysteroscopic morcellator compared with 10 minutes and 12 seconds for electrical resection ($P < 0.001$).

Completeness of polyp removal

Complete polyp removal was achieved in 61/62 (98%) women for hysteroscopic morcellation compared with 49/59 (83%) in electrosurgical resection (OR 12.5; 95% CI: 1.5 to 100.6, $P = 0.02$) (Table 16). There was no singular reason why there were more failures in the electrosurgical resection group; reasons given were equally distributed between inability to locate polyps using blind instruments (i.e. where removal under hysteroscopic vision had failed), inadequate visualisation and patient discomfort.

Table 16. Surgical Technique and Complications

	Hysteroscopic Morcellation (n=62)	Electrical Resection (n=59)	Odds Ratio (95% CI)	*P*
Surgical technique				
Speculum used	28 (45%)	37 (63%)	0.5 (0.2 to 1.0)	0.05
Cervical dilatation	30 (48%)	31 (53%)	0.8 (0.4 to 1.7)	0.8
Cervical anaesthesia	31 (50%)	34 (58%)	0.7 (0.4 to 1.5)	0.4
Removal success				
Total removal	61 (98%)	49 (83%)	12.4 (1.5 to 100.6)	0.02
Partial removal	0 (-)	7 (12%)[*]		
Failed removal	1 (2%)[†]	3 (5%)[*]		
Complications				
Vasovagal reactions	1 (2%)	6 (10%)	0.1 (0.0 to 1.2)	0.08
Others	0 (-)	0 (-)		

CI, confidence interval.

[*]Partial/failed removal reasons: unable to locate blindly (n=4); patient discomfort (n=3); inadequate visualisation (n=3)

[†]Partial/failed removal reasons: inadequate visualisation (n=1)

Pain scores and acceptability

The mean pain scores for morcellation compared with electrosurgical resection were significantly lower both during the procedure and at 15 minutes following the procedure (Table 17).

Table 17. Pain Scores (Measured on a 100-Point Visual Analogue Scale)

	Hysteroscopic Morcellation, mean (SD, n)	**Electrical Resection, mean (SD, n)**	**Mean Difference (95% CI)**	***P***
Baseline	8.1 (9.4, 60)	5.1 (9.7, 58)	-3.0 (-6.4 to 0.5)	0.1
During procedure	35.9 (23.5, 60)	52.0 (23.5, 58)	16.1 (7.6 to 24.7)	<0.001
Postprocedure	23.9 (21.2, 60)	31.0 (23.9, 59)	7.1 (-1.1 to 15.3)	0.09

SD, standard deviation; CI, confidence interval.

Overall, over 99% of women found office polypectomy to be at least 'fairly acceptable' (Table 18) with only one woman in the electrosurgical resection group reporting the procedure as unacceptable. There was a significant trend towards increased acceptability in women receiving morcellation rather than electrosurgical resection (*P* = 0.009). There was also a significant difference between techniques when we dichotomised the acceptability response to totally acceptable/generally acceptable versus fairly acceptable/unacceptable.

Table 18. Patient Acceptability

	Hysteroscopic Morcellation (n=61)	**Electrical Resection (n=58)**	***P****
Totally acceptable	44 (72)	33 (57)	
Generally acceptable	15 (25)	12 (21)	0.009
Fairly acceptable	2 (3)	12 (21)	
Unacceptable	0	1 (2)	

* Using a logistic regression test for trend.

Data are n(%).

Complications

The only surgical complications observed in either treatment group were vasovagal reactions occurring in 1/62 (2%) and 6/59 (10%) of hysteroscopic morcellation and electrosurgical resection procedures respectively (P = 0.08) (Table 16). One serious adverse event occurred. This was in a woman treated in the morcellation group who was admitted two weeks after treatment because of vaginal bleeding and pain. She was diagnosed as having an endometritis and treated with broad-spectrum antibiotics.

Discussion

Key findings

This RCT provides strong evidence to suggest that hysteroscopic morcellation is quicker to perform, more successful at completing polyp removal, less painful, and more acceptable to women than traditional electrosurgical resection for the removal of endometrial polyps.

Interpretation

The improved performance of morcellation relative to electrosurgical resection may reflect its ability to simultaneously cut and extract polyp tissue under vision. In addition, acquiring proficiency with the hysteroscopic morcellator is rapid[150] and this relative ease of use may also have contributed to obtaining favourable outcomes.

We used a rigorous definition of what constituted a successfully completed procedure. Data from this trial suggests that the increased success of morcellation compared with electrosurgical resection arises from a combination of factors. Firstly, failures due to inadequate visualisation were reduced. Although this trial did not evaluate reasons behind enhanced visualisation, it may have arisen because steam bubble formation from electrically heating saline was avoided. Alternatively it may have reflected better continuous irrigation because the morcellator system used a larger diameter hysteroscope with greater inflow of saline and the disposable morcellator provided suction when activated. Secondly, failures because of inability to blindly locate specimens within the uterine cavity were avoided

because simultaneous tissue cutting and extraction under direct hysteroscopic vision from the uterine cavity was integral to the morcellation system. Thirdly, failures due to patient discomfort were circumvented. Conventional mechanical or electrical instruments necessitate additional hysteroscopic or blind mechanical instrumentation of the uterus to retrieve resected polyp tissue via the narrow endo-cervical canal. It is likely that the need for these further manoeuvres contributed to prolongation of the electrosurgical resection procedure and increased peri-operative pain compared with morcellation. Although the clinical significance of the differences in procedural pain are uncertain without further qualitative research, the findings appear consistent with the observed increase in acceptability with morcellation. The integration of cutting and aspiration with morcellation may also explain why the need for cervical dilatation and local anaesthesia was comparable between interventions, despite the larger diameter of the hysteroscopic morcellator. The size and number of polyps did not seem to affect the success of morcellation although the study was not powered to provide adequate analysis of these subgroups.

The need for cervical dilatation and local anaesthesia was similar in both arms of the trial. This may seem counterintuitive due to the smaller diameter of the electrosurgical resection tools in comparison to the hysteroscopic morcellator. Reasons are likely to reflect the practice of using local anaesthetic if it is anticipated that there will be difficulties retrieving the polyp tissue after detachment. Secondly, our practice is to remove the specimen en bloc, because this generates quicker procedures that are less likely to result in deteriorating vision. We believe this

technique it more successful than alternative techniques (slicing)[170], which requires a longer procedure and multiple passes of the hysteroscope. Therefore, these units that routinely adopt slicing techniques may have a decreased rate of dilatation, but may have a decreased success rate.

Comparison with other studies

In a recently completed multi-centre RCT in the UK[169], bipolar electrosurgical resection was the most commonly adopted modality, but recruitment to this trial predated widespread commercial availability of the hysteroscopic morcellator. Treatment times and failure rates for electrosurgical resection were comparable to those noted in the current study[169]. Moreover, the results presented here are consistent with data from two trials comparing the morcellator to electrosurgical resection using a resectoscope under general anesthetic[149,150], both of which found the morcellator to be quicker. In keeping with these data, our trial supported the apparent safety of office polypectomy, with adverse events limited to self-limiting vaso-vagal episodes affecting a minority of women. One post-operative complication was observed in a woman who developed endometritis after morcellation, which resolved with oral antibiotics. All retrieved specimens underwent histopathological examination and a diagnosis was provided in all cases consistent with another study[171]. Thus, concerns over the ability to histologically analyse morcellated tissue specimens seem unfounded

The economic advantages of the office compared with the traditional inpatient setting for polypectomy is primarily driven by the avoidance of expensive inpatient

bed and theatre facilities[172,173]. We did not conduct a cost-effectiveness evaluation alongside this RCT because symptom outcome data were not collected (these shortly to be published data have been collected in the larger Office Polypectomy Trial[169]). In addition, the known wide variation in costs between different healthcare systems, would limit the transferability of findings from such an economic evaluation. Despite these caveats, it is likely that the use of hysteroscopic morcellation will be more cost effective compared to electrical resection in terms of successfully removing polyps given the magnitude of the observed odds ratio in favour of morcellation.

Strengths and limitations

The strengths of our trial include strict randomisation, the multicentre design and full completeness of data collection both pre and post-treatment. While we did not collect longer term clinical follow up data, a retrospective cohort study comparing morcellation with electrosurgical resection found that morcellation may be associated with lower recurrence of endometrial polyps, although the incidence of recurrent abnormal uterine bleeding was unaffected by the technique used [154]. The shortly to be published Office Polypectomy Trial[169] should also provide data pertaining to longer-term outcomes following endometrial polypectomy for abnormal uterine bleeding. Our trial does have some limitations. Randomisation did not equally distribute the potential confounders of polyp number and surgical site. However, the distribution of these confounders would be expected to bias against hysteroscopic morcellation by prolonging treatment time as women randomised to morcellation had slightly more polyps and were more likely to have been performed

at Sheffield Teaching Hospital where there was an overall longer procedure time than at Birmingham Women's Hospital (5 mins 7 secs). Another potential source of bias was inability to blind the surgeon from the intervention and indeed whilst every effort was made to blind the patient from the allocated intervention, it is probable that some women would have been aware of the treatment they received given that they were awake and had received thorough pre-trial patient information which included a description of morcellation and electrosurgical resection.

Conclusion

The new technology of hysteroscopic morecellation has been shown to have advantages for the patient (acceptability, pain, safety), the surgeon (speed, feasibility, completeness of the procedure) and health service (avoidance of second stage procedures under general anaesthetic). While advances in technology are increasingly allowing more gynaecologic procedures to be performed in the office setting, it is important to critically appraise new technologies such as hysteroscopic morcellation before they become more widely embedded into clinical practice. Assessments of larger patient cohorts are required to more reliably assess the relative safety of hysteroscopic morcellation in the wider population.

CHAPTER 8: DISCUSSION

Diagnostic office hysteroscopy

Hysteroscopy has become an essential tool in gynaecological practice. The conventional approach to hysteroscopy involved a scheduled admission to hospital so that theatre facilities could be used to conduct the operation under general anaesthesia. Advances in technology, including the development of miniature endoscopic equipment and in particular enhanced optics and imaging, has facilitated the procedure being performed in the office (outpatient) setting without the need for general anaesthesia. Studies have shown that women who undergo hysteroscopy in the office setting, compared with those in a day case setting, have a more rapid return to normal activities and less need for post-operative analgesia[49]. There are also substantial economic benefits to patients, employers and health care systems in performing hysteroscopy in the office setting[174]. Avoiding a general anaesthetic can be safer for the patient, not only because of the risks of anaesthesia, but also because the patient can give feedback to reduce the chances of serious complications such as uterine perforation and fluid overload.

The economic and patient benefits have resulted in an increasing number of hospitals providing such services and this was reflected in a survey of the British Society of Gynaecological Endoscopy (BSGE) members, which found that 90% of respondents were performing office hysteroscopy (**Chapter 3**).

The most common indication for investigation with office hysteroscopy is abnormal uterine bleeding, a term that encompasses heavy menstrual bleeding, non-menstrual bleeding and post-menopausal bleeding (PMB). The work in **Chapter 2**

showed that women with recurrent PMB who had previously had normal investigations could benefit from hysteroscopy to identify and treat endometrial polyps. Although endometrial polyps are invariably benign and so not as serious to health as a diagnosis of premalignant endometrial hyperplasia or endometrial cancer the morbidity associated with the bleeding caused by endometrial polyps should not be ignored. This morbidity includes anxiety and ongoing symptoms impacting adversely on health related quality of life and may result in unnecessary further testing because of failure to diagnose the underlying, albeit benign, causative uterine pathology. Current PMB diagnostic pathways[14,15] prioritise the diagnosis of endometrial cancer, but over 90% of women[13] with PMB have benign disease, most prevalent of which are endometrial polyps. Thus, current testing algorithms may be ignoring the morbidity and health resource utilisation of undiagnosed and thus untreated benign uterine pathologies such as endometrial polyps. Furthermore, previous work exploring women's preferences in the evaluation of PMB has shown women are willing to undergo more invasive hysteroscopy to evaluate additional pathology, rather than adopt the currently recommended expectant management after ultrasound[35]. Patient preferences along with the decreasing cost of office hysteroscopy, could lead to office hysteroscopy being incorporated as a first line investigation for women who present with PMB.

The biggest obstacle to successful, universal implementation of office hysteroscopy remains patient discomfort, which can have an adverse impact on acceptability and success rates. A variety of techniques have been used to try to decrease the pain

of the procedure[39,175–178]. These have mainly focused on traversing the tight and often acutely angled or tortuous endocervical canal. Research work continues in this area and recent RCTs that have looked at pre-procedural cervical preparation[179–181], and intra-operative cervical anaesthesia[182] and bladder distension[178] to ease negotiating of the cervical canal thereby decreasing the pain associated with office hysteroscopy. As hysteroscopes become smaller it has become easier to pass the hysteroscope through the cervical canal avoiding the precipitation of noxious stimuli arising from resistance to passage of the endoscope. Thus the discomfort associated with the aforementioned interventions may obviate any potential benefit. However, vaginoscopy is a technique that avoids the use of a speculum and tenaculum to access the uterine cavity in an attempt to minimise pain. Vaginoscopy would still benefit women even with the use of smaller diameter hysteroscopes and indeed should become even more feasible as resistance to a correctly aligned hysteroscope from the approximated endocervical canal should be substantially reduced. In **Chapter 3** vaginoscopy was shown to be more successful than standard hysteroscopy using a speculum with or without cervical instrumentation for diagnostic procedures. A large multicentre RCT is needed to confirm these preliminary findings and facilitate adequately powered a-priori subgroup analyses to ascertain groups of women (e.g. nulliparous, post-menopausal, previous caesarean section) who may particularly benefit from adoption of vaginoscopy. Further research is also needed to establish whether vaginoscopy is beneficial for operative hysteroscopy in which larger diameter instruments are used and greater manipulation of the cervix is necessary.

Therapeutic office hysteroscopy

Currently, many hospitals restrict office hysteroscopy to diagnostic procedures. However, office hysteroscopy has a bigger role than just diagnosis with a number of common therapeutic procedures now being done in the office setting. Such therapeutic procedures are often done in conjunction with diagnostic hysteroscopy in so called 'see and treat' clinics. Providing seamless diagnostic hysteroscopy followed by immediate therapeutic services in 'see and treat' clinics, not only has economic benefits to the health service by efficient use of resources, but can also reduce inconvenience and social costs such as transport, childcare, absenteeism and business costs. Operative procedures include sterilisation, Levonorgestrel intrauterine system (LNG-IUS) fitting, retrieval of 'lost' intrauterine contraceptive devices, endometrial ablation and the removal of polyps, fibroids and adhesions.

Endometrial ablation

Traditionally, hysterectomy was the preferred surgical treatment for heavy menstrual bleeding. There are a wide variety of medical treatments for heavy menstrual bleeding, but only the LNG-IUS has been proven to be as effective as hysterectomy[183]. Endometrial ablation represents a surgical alternative to hysterectomy and has been shown to be cheaper, have lower morbidity and shorter hospital stay times[57,58]. Research has also shown that endometrial ablation is tolerated and effective in the office setting[6,65].

Our group's publication of an RCT comparing bipolar radiofrequency ablation to thermal balloon ablation in an office setting had shown no significant difference between pain scores and acceptability during thermal balloon and bipolar radiofrequency ablation procedures[6]. However, bipolar radiofrequency ablation was more effective in alleviating heavy menstrual bleeding at 12 months follow-up. In contrast, our five year follow-up data presented in this thesis has shown no difference in the effectiveness of bipolar radiofrequency ablation and thermal balloon ablation performed in an office setting, but importantly the majority of treated women were effectively treated with amenorrhoea rates increasing over time and only a minority of women ultimately requiring further intervention usually in the form of hysterectomy (**Chapter 5**). This finding of blunting of relative treatment effects is consistent with other longer-term follow-up data from RCTs of different endometrial ablation techniques performed in a conventional inpatient general anaesthetic setting[60,82]. Therefore, there is no evidence to suggest that bipolar radiofrequency ablation should be used in preference to thermal balloon ablation in the office setting on the basis of improved symptomatic results.

Office endometrial ablation may be convenient, but it is important that women are fully counselled about the relative advantages and disadvantages of office as compared to inpatient treatment. Whilst such doctor-patient discussions will focus around procedural factors and patient experience between settings, clinical outcomes may not be so readily addressed in the absence of longer-term efficacy data. Our five year follow-up data should reassure patient and clinicians that clinical outcomes appear equivalent to data from inpatient procedures performed

under general anaesthesia and that approximately 10% of women will require subsequent hysterectomy within five years (**Chapter 5**). In particular, women with pre-existing dysmenorrhoea or enlarged uteri should be counselled about their increased chance of requiring additional uterine surgery after endometrial ablation (**Chapter 4**). This information should be used following clinical assessment (history and patient examination) to inform shared clinical decision making.

Endometrial Polypectomy

The majority of gynaecologists advocate the removal of endometrial polyps. The rationale behind this is: 1) to exclude sinister pathology; 2) the perception that they are unlikely to spontaneously resolve and 3) that removal will alleviate AUB symptoms or increase fertility. However, some of these beliefs maybe misplaced because endometrial polyps are found in up to 10% of asymptomatic women[117], some polyps may spontaneously regress[119] and sinister pathology such as endometrial cancer and hyperplasia is rare in premenopausal women[109–116].

We tried to address whether removal of polyps alleviates AUB symptoms by performing a systematic review of the literature (**Chapter 6**). However, the systematic review showed there is a paucity of quality literature assessing the efficacy of uterine polypectomy. All studies showed an improvement in symptoms, but the percentage of women that improved ranged from 60 to 100%[122,155,156,158,161,162,164]. Large and thoroughly designed RCTs are needed to establish whether all polyps need to be removed particularly in premenopausal

women. Such trials should assess clinically relevant outcomes such as alleviation of bleeding symptoms and fertility outcomes.

A survey of UK gynaecologists in 2001, found that the default technique for removing endometrial polyps was by blind avulsion or curettage after hysteroscopic location of the lesion under general anaesthesia[108]. Hysteroscopic removal of polyps under direct vision was generally restricted to those gynaecologists with an interest in endoscopic surgery[108]. Although it is possible to the remove endometrial polyps using blind curettage and avulsion techniques, such approaches usually require general anaesthesia and are associated with increased uterine trauma and discomfort[3,28,131–136]. However, most polyps removed in the office setting are done under direct hysteroscopic vision, because avoiding potentially traumatic abrasive techniques, with the necessity to dilate the cervix, is especially important in the conscious patient. For this reason it will be increasingly important for gynaecologists to acquire the skills necessary for hysteroscopic polyp removal under direct vision as more hospitals adopt office hysteroscopy.

A recently completed large RCT found office polypectomy was non-inferior to inpatient polypectomy and more cost-effective for treating women with abnormal bleeding ('OPT' http://www.opt.bham.ac.uk, ISRCTN65868569)[169]. However, failure to remove a uterine polyp was more likely and procedure acceptability was slightly lower. The OPT study recommended further work to identify and develop strategies to decrease the pain and failure rate while increasing acceptability of hysteroscopic polyp removal in the office setting.

The main technique used for office polypectomy in the OPT trial was Versapoint® bipolar electrosurgical system (Gynecare™; Ethicon Inc., New Jersey, USA). The development of a new group of instruments called hysteroscopic morcellators may help overcome some of the difficulties of bipolar electrical resection, namely extraction of the intrauterine tissue specimen. We therefore designed and performed a randomised controlled trial comparing polypectomy using the new TRUCLEAR™ hysteroscopic morcellator (Smith&Nephew, Andover MASS, USA) to Versapoint® bipolar electrosurgical system (Gynecare™; Ethicon Inc., New Jersey, USA) (**Chapter 7**). This trial provided strong evidence that morcellation is faster, less painful, more acceptable and more likely to completely remove the polyp than the current standard of electrical resection in the office setting (**Chapter 7**)[8]. A previous randomised controlled trial comparing morcellation to conventional resectoscopy under general anaesthetic for the removal of intrauterine polyps and myomas found that hysteroscopic morcellation was quicker and easier to learn when used by residents in training[150]. In view of the mounting evidence supporting the superiority of morcellation, when compared to electrosurgical treatment, it is likely that endometrial polyp removal in the office setting will increasingly be performed using hysteroscopic morcellators.

Research and Future Developments in Office Hysteroscopy

Cervical preparation

The role of cervical preparation on the patient experience in the office setting has been, and continues to be, the subject of much research. A systematic review and meta-analysis of six studies showed there maybe a benefit of using prostaglandins for postmenopausal women and there is some evidence that prostaglandins reduce the force and requirement for dilatation of the cervix beyond 5 mm[175]. They concluded that cervical priming with vaginal prostaglandins may be considered in postmenopausal women if using hysteroscopic systems >5 mm in diameter.

Since the completion of the systematic review further trials with conflicting results have been completed[179–181]. The conflicting results may reflect heterogeneity in the patient cohort, operative technique and equipment. If Misoprostal is to be used, current opinion is that it should be given 3-4 hours prior to the procedure, although it may work quicker than this. In fact, both pharmaceutical and mechanical dilation of the cervix require time. To be compatible with modern office hysteroscopy, which aims to avoid the need for hospital admission, future developments and research will have to focus on a faster mechanism of action. With no obvious method currently meeting the criteria of speed, cervical preparation will probably only be suitable for selected cases in the office setting.

Analgesia

A systematic review and meta-analysis looked at local anaesthesia for pain control during office hysteroscopy[176]. They were able to meta-analyse 15 trials, showing intracervical and paracervical injections of local anaesthetic significantly reduced pain (Standard Mean Difference (SMD) -0.36; 95% CI -0.61 to -0.10 and SMD -1.28; 95% CI -2.22 to -0.35 respectively) in women undergoing office hysteroscopy, whereas transcervical and topical application did not. Since the review, a small RCT with a sample size of 58 women has been completed with similar results[182]. However, as the techniques for introducing hysteroscopes into the uterine cavity improve in conjunction with ever decreasing hysteroscope diameters, inevitably trauma and stretching of the cervix will reduce. This may then make it counter productive to use local anaesthetic, because the process of injecting local anaesthetic in itself can be painful.

Cervical anaesthesia does not address pain generated by the upper third of uterus which is innervated from the thoracic nerves, largely derived from the sympathetic fibres of the superior hypogastric plexus T8-T10 and L1 roots [184]. Using a cyctoscopy needle through the operating channel of a hysteroscope, local anaesthetic can be injected to target these nerves to create an intrauterine cornual block[185]. This has the potential to make operative procedures, such as endometrial ablation, more acceptable to women and future research should look to perform a placebo controlled RCT to evaluate the efficacy of this technique.

Hysterocopic technique

There have been many alternative methods to minimise patient discomfort. Recently an RCT has been completed which assessed the role of bladder distension on patient comfort and ease of cervical entry[178]. Women in the intervention group were asked to drink 500mL of water prior to the procedure and asked not to empty their bladder. In contrast, the control group of women were asked to ensure an empty bladder prior to the procedure. The status of the bladder (full or empty) was checked by ultrasound prior to the procedure. They found bladder distension prior to office hysteroscopy was associated with significantly less pain (P = 0.01), quicker procedure times (P = 0.03) and easier cervical entry (P = 0.01). However, the practicalities of introducing bladder distension into a busy clinic where there can be delays in appointments is yet to be proven, although it is routine for women to attend gynae/early pregnancy scans with a full bladder.

The pilot RCT in chapter 3 provided evidence to suggest that vaginoscopy is quicker to perform and more successful than standard hysteroscopy. A larger, multicentre RCT is now needed to confirm these preliminary findings and to allow subgroup analysis to estimate types of women that may particularly benefit from vaginoscopy.

Biopsy

The idea of the vaginoscopic approach has also extended to global biopsy tools. The H Pipelle can be used after a hysteroscope has been introduced into the

uterine by withdrawing the optic from the diagnostic sheath, then passing the H Pipelle into the uterus through the sheath, before removing sheath allowing a biopsy to be taken in the usual way. An RCT comparing the H Pipelle to the standard Pipelle found that endometrial sampling with the H Pipelle was significantly quicker (median times: 39 seconds for H Pipelle versus 102 seconds for Pipelle; P <0.001) and less painful (median visual analogue scale: 1 for H Pipelle and 5 for the Pipelle; P = 0.01) [186]

Hysteroscopes and instruments

New developments in hysteroscopes and sheaths have traditionally been dominated by miniaturisation and it is likely that future developments will also be focused on miniaturisation. Fundamental to the decrease in diameter of hysteroscopes are improvements in optics, and more can be expected from the introduction of optical chip technology in hysteroscopes, such as the Invisio Digital Hysteroscope (GyrusACMI/Olympus, Tokyo, Japan)

In chapter 7 we showed that morcellation appears to be better than electrosurgical resection for the removal of endometrial polyps. Future work with morcellators is likely to lead to the development of products with smaller outer diameters. Furthermore, there is a need to establish the efficacy and safety of morcellators for the treatment of fibroids and other intrauterine pathology, such as retained products of conception.

The hysteroscopic resectoscopes were developed from the cystoscopic resectoscopes used in urology and consist of a movable cauterisation loop. These versatile tools can be used to resect fibroids, polyps and endometrium for heavy menstrual bleeding. Initially these devices used monopolar cutting energy and required a non-conducting distension media. Non-conducting distension media are not isotonic so are more likely to cause electrolyte imbalances than normal saline. Recently, bipolar electrosurgical devices have been made which allow normal saline irrigation, which reduces the effects of fluid intravasation. Future developments in resectoscopy will involve devices with smaller outer diameters. However, the skills needed to perform resectoscopy, along with serious electrosurgical complications that occur, may mean that surgeons increasingly look to safer alternatives such as the morcellators.

Hysteroscopic sterilisation

Since the introduction of hysteroscopic sterilisation in 2001, it has increasingly gained popularity over laparoscopic sterilisation. Hysteroscopic sterilisation has several advantages over laparoscopic sterilisation, that includes avoiding an abdominal entry and avoiding a general anaesthetic (by performing the procedure in the office setting). The most commonly applied technique is ESSURE^{TM}, which involves the placement of microcoils into the fallopian tubes. It has recently been improved by the introduction of new catheters with better microcoil release mechanisms. The main competitor for ESSURE^{TM} was the Adiana^{TM}. The Adiana^{TM} involved inserting a catheter into the fallopian tube that emitted radiowaves causing injury to the tubal lining. Subsequent scarring was promoted by the insertion of a

silicon stent. However, it was removed from market in 2012 to resolve patent infringement claims.

The main disadvantage of hysteroscopic sterilisation compared to laparoscopic sterilisation is that it is not immediately effective; at least 3 months is required before tubal fibrosis and occlusion to occur for the procedure to be effective. After 3 months a post-procedure hysterosalpingogram or pelvic ultrasound is required to check for placement and occlusion. Patients need to use an alternative contraception and occlusion does not occur in 1-12% of cases[7,187,188]. Future advancements in hysteroscopic sterilisation will include methods that do not require the gradual fibrosis and occlusion of tubes, but instead will have an immediate effect.

Ablation devices

There have been few surgical techniques that have been evaluated as rigorously as endometrial ablation. The first generation techniques have been superseded by the second-generation techniques, which are easier to learn and associated with fewer complications.

The Novosure™ device uses bipolar radiofrequency ablation and a recent development includes a reduction in diameter, which promises to reduce the degree of cervical dilation needed. Thermachoice™ is a thermal balloon ablation device, which has the advantage of requiring less cervical dilation, but it has an 8 minute treatment time. The Thermachoice III™ model circulates hot water within the

balloon more evenly than previous models, which seems to make them more effective at ablation[64,92]. The Thermablate™ thermal balloon system was introduced in 2005 and has a treatment time of 2min 8seconds[189]. Future developments in thermal balloon procedure may look at further reducing the treatment time.

There are a number of other devices using different techniques that have entered or are coming to market. These include developments in technology that have previously gone out of favour, such as cryotherapy and microwave ablation.

Antibiotics

A recently completed double-blind, randomised, placebo controlled trial assessed the role of antibiotic administration during hysteroscopic procedures in the office setting[190]. A total of 1046 women who had operative hysteroscopy were given either 1g Cefazolin intramuscularly or 10mL of isotonic sodium chloride solution. There was no significant difference in the rates of postsurgical infection between the two groups. These results give credence to the current practice of not using antibiotics as standard for hysteroscopic procedures in the office setting.

Distension media and fluid management

The correct choice of distension media has been the subject of the many randomised controlled trials. The evidence from these trials has been synthesised in a recent systematic review and meta-analysis comparing carbon dioxide to normal saline[191]. The review combined 10 randomised controlled trials involving a

total of 1,839 women. There were problems with clinical heterogeneity and study quality, but the results showed normal saline to be superior to carbon dioxide in terms of procedural pain, side effects (mainly shoulder pain), speed of procedure, quality of view and patient satisfaction.

A double blind RCT looking at the effect of filling pressures on visibility and pain scores has recently been completed[192]. They found visibility was lower with 40 mmHg compared with 70 and 100 mmHg ($P < 0.05$). While there was no difference in mean pain scores between 40, 70 and 100 mmHg.

As operation times become shorter there should be less chance of fluid overload and the increased use of isotonic distension media should decrease the chances of electrolyte imbalances. Nevertheless, it is necessary for patient safety to keep a careful fluid balance in longer procedures and new developments should include more reliable and precise fluid management systems.

Summary

Chapter 1 provides an introduction and describes the scope of the subsequent studies in this thesis. Historically, dilation and curettage was used to investigate the uterine cavity. When it was realised that hysteroscopy was more accurate, diagnostic hysteroscopy with or without biopsy became the investigation of choice[193]. Advances in technology have minituarised hysteroscopes and provided novel energy systems and endoscopic therapeutic tools these innovations have increasingly allowed diagnostic and operative hysteroscopic procedures to be moved to the office setting, where they are performed without general anaesthesia.

Office investigation of post-menopausal bleeding

In **Chapter 2**, the role of hysteroscopy in recurrent postmenopausal bleeding is described. 106/1938 (5%) of consecutive women that presented to Birmingham Women's Hospital with postmenopausal bleeding had a recurrent episode after previously having normal investigations. The fact that most women with PMB do not have serious endometrial disease and that failure to address the underlying pathology once malignancy has been excluded results in high rates of representation[21] has largely been ignored. Our work presented in this thesis on recurrent PMB is reassuring because it appears to show that after previous normal investigation the likelihood of pre-malignant and malignant endometrial disease is decreased, although one in four women have benign endometrial polyps as the most likely cause of their PMB. First line investigation for women with recurrent

PMB should be with tests that have a high accuracy for diagnosing focal pathologies such as office hysteroscopy or saline infusion sonography.

Vaginoscopy for diagnostic office hysteroscopy

Vaginoscopy is a technique used to access the uterine cavity without the use of a vaginal speculum or cervical instrumentation. By avoiding instrumentation of the lower genital tract we hypothesised that vaginoscopy could lead to a better patient experience. **Chapter 3** compared vaginoscopy against standard hysteroscopy in the office setting. A total of 200 women were randomly allocated to a diagnostic hysteroscopy with either vaginoscopy or standard technique using a speculum. Vaginoscopy was found to be more successful than standard hysteroscopy where success was defined using a composite outcome of: a complete procedure, no complications, a level of pain acceptable to the patient and no sign of infection two weeks after the procedure. The choice of this aggregated outcome was based upon clinical outcomes deemed important to practitioners and likely to influence their current practice. Thus, based on the preliminary findings from this pilot RCT, vaginoscopy may be the preferred technique replacing standard approaches utilising vaginal speculum. However, large RCT's allowing analysis of important subgroups of where genital tract examination can be more challenging are needed to confirm and further elucidate these findings.

Office endometrial ablation for heavy menstrual bleeding

Endometrial ablation has become an established treatment for heavy menstrual bleeding. Nevertheless, many women go on to require further surgical treatment, usually in the form of hysterectomy. **Chapter 4** explores whether clinical factors can predict women that require further surgical intervention after endometrial ablation such that treatment choices can be better informal and the need for repeated surgical intervention minimised. 51/391 (13%) of consecutive women who had endometrial ablation in the office setting required further surgical intervention. Dysmenorrhoea before treatment (aOR 4.01; 95% CI 1.63 to 9.91) or a uterine cavity length >9cm (aOR 2.65; 95% CI 1.33 to 5.27) were associated with the need for further surgical interventions after office endometrial ablation. These findings should help inform more rational clinician and patient decision making when considering treatment options for heavy menstrual bleeding.

In **Chapter 5**, the five year follow-up data for a randomised controlled trial comparing bipolar radiofrequency to thermal balloon ablation in the office setting was presented. At five years follow-up, 59 (73%) of women responded to questionnaires, of which seven (11.9%) had undergone a further surgical intervention in the form of a hysterectomy. There was no significant difference in amenorrhoea rates, satisfaction rates, further intervention rates, condition specific or generic health related quality of life measures. Thus both approaches can be equally recommended from a clinical symptomatic outcome perspective.

Office uterine polypectomy for abnormal uterine bleeding

Chapter 6 presents a systematic review to assess the efficacy of uterine polypectomy in the treatment on abnormal uterine bleeding. 17 studies met our inclusion criteria enrolling a total of 1829 patients between 1989 and 2009. However, most of the evidence was derived from observational studies that reported high success rates, but in general the quality of the research was poor. The heterogeneity of available study designs, population, interventions and outcome assessments precluded meta-analysis. All the studies reported an improvement in symptoms from 60-100%. The evidence we aggregated supports the notion that removing uterine polyps is effective at improving symptoms of AUB.

Office endometrial polypectomy

A new technology known as hysteroscopic morcellation has recently become available in clinical practice. In **Chapter 7** we compared the hysteroscopic morcellator to bipolar resection for the treatment of endometrial polyps in the office setting. A total of 121 women were randomly allocated to polyp removal by one of the two methods. In comparison to electrosurgical resection during hysteroscopic polypectomy, morcellation was significantly quicker, less painful, more acceptable to women and more likely to completely remove endometrial polyps compared with electrosurgical resection. Thus hysteroscopic morcellation should be advocated above conventional electrosurgical resection in the office setting from a feasibility and patient experience perspective.

Conclusion

In **Chapter 8** the results of the studies described within this thesis are discussed and put into a broader context. In conclusion, an increasing number of hospitals are adopting office diagnostic and surgical procedures. However, further work is needed to optimise patient selection and techniques to achieve the best results and experience to women.

Recommendations for clinical practice

Based on the results of this thesis the following is recommended:

Diagnostic Hysteroscopy

- Women with recurrent PMB should be investigated with a treatment modality that can identify discrete pathology like hysteroscopy or saline infusion sonography.

- Vaginoscopy should probably be used in preference to other techniques to introduce the hysteroscope into the uterine cavity, because overall it is associated with better patient experience and outcomes.

Therapeutic office hysteroscopy

Endometrial ablation

- Women who have a uterine cavity >9cm or dysmenorrhoea should be warned they are more likely to require further intervention after endometrial ablation.

- Women should be informed that symptomatic alleviation of heavy menstrual bleeding with office endometrial ablation is high but 1:10 treated women will require further intervention, usually in the form of hysterectomy. They should

be aware that there appears to be no difference between the effectiveness of bipolar radiofrequency ablation and thermal balloon ablation at five years of follow up and choice of health technologies should be based on procedural factors, and patient experience and satisfaction.

Hysteroscopic endometrial polypectomy

- Women who present with abnormal uterine bleeding and an endometrial polyp should have it removed.

- The hysteroscopic morcellator should be used in preference to bipolar resection for endometrial polyp removal, because it is associated with quicker, less painful, more acceptable and more successful polyp treatment.

REFERENCES

1. Health and Social Care Information Centre. Hospital Episode Statistics 2012/2013 [Internet]. Department of Health (UK); [cited 2014 Nov 26]. Available from: http://www.hscic.gov.uk/

2. Clark TJ, Bakour SH, Gupta JK, Khan KS. Evaluation of outpatient hysteroscopy and ultrasonography in the diagnosis of endometrial disease. Obstet Gynecol. 2002 Jun;99(6):1001–7.

3. Clark TJ, Gupta JK. Handbook of outpatient hysteroscopy: a complete guide to diagnosis and therapy. CRC Press; 2005.

4. Clark TJ, Cooper NA, Kremer C. Best practice in outpatient hysteroscopy. RCOG Press Greentop Guideline No. 59;

5. Wortman M, Daggett A, Ball C. Operative hysteroscopy in an office-based surgical setting: review of patient safety and satisfaction in 414 cases. J Minim Invasive Gynecol. 2013 Feb;20(1):56–63.

6. Clark TJ, Samuels N, Malick S, Middleton L, Daniels J, Gupta J. Bipolar Radiofrequency Compared With Thermal Balloon Endometrial Ablation in the Office: A Randomized Controlled Trial. Obstet Gynecol. 2011 May;117(5):1228.

7. Sinha D, Kalathy V, Gupta JK, Clark TJ. The feasibility, success and patient satisfaction associated with outpatient hysteroscopic sterilisation. BJOG Int J Obstet Gynaecol. 2007 Jun;114(6):676–83.

8. Smith PP, Middleton LJ, Connor M, Clark TJ. Hysteroscopic morcellation compared with electrical resection of endometrial polyps: a randomized controlled trial. Obstet Gynecol. 2014 Apr;123(4):745–51.

9. Payment by Results Guidance for 2012-13 [Internet]. Department of Health (UK); 2013. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/214902/PbR-Guidance-2013-14.pdf

10. Cooper NAM, Clark TJ. Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): Systematic reviews, IPD meta-analysis and model based economic evaluation [Internet]. Health Technology Appraisal Programme; [cited 2013 Sep 27]. Available from: http://www.hta.ac.uk/2145

11. Astrup K, Olivarius N de F. Frequency of spontaneously occurring postmenopausal bleeding in the general population. Acta Obstet Gynecol Scand. 2004 Feb;83(2):203–7.

12. Key Health Statistics from General Practice: Analyses of morbidity and treatment data, including time trends, England and Wales [Internet]. London: National Statistics; 1998 [cited 2013 Oct 6]. Available from:

http://www.statistics.gov.uk/downloads/theme_health/Key_Health_Stats_1998.pdf

13. Bachmann LM, ter Riet G, Clark TJ, Gupta JK, Khan KS. Probability analysis for diagnosis of endometrial hyperplasia and cancer in postmenopausal bleeding: an approach for a rational diagnostic workup. Acta Obstet Gynecol Scand. 2003 Jun;82(6):564–9.

14. NVOG (Dutch Society of Obsterics and Gynaecology). NVOG Guideline: Abnormal Vaginal Bleeding During the Postmenopause. NVOG; 1997.

15. Scottish Intercollegiate Guidelines Network. Investigation of postmenopausal bleeding 1st edn [Internet]. SIGN, Royal College of Physicians; 2002. Available from: www.sign.ac.uk

16. Gupta JK, Chien PFW, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-analysis. Acta Obstet Gynecol Scand. 2002 Sep;81(9):799–816.

17. Smith-Bindman R, Kerlikowske K, Feldstein VA, Subak L, Scheidler J, Segal M, et al. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA J Am Med Assoc. 1998 Nov 4;280(17):1510–7.

18. Tabor A, Watt HC, Wald NJ. Endometrial thickness as a test for endometrial cancer in women with postmenopausal vaginal bleeding. Obstet Gynecol. 2002 Apr;99(4):663–70.

19. Spencer CP, Whitehead MI. Endometrial assessment re-visited. Br J Obstet Gynaecol. 1999 Jul;106(7):623–32.

20. Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. Am J Obstet Gynecol. 2003 Feb;188(2):401–8.

21. Timmermans A, van Doorn LC, Opmeer BC, Kroeks MVAM, Duk MJ, Bouwmeester AM, et al. Follow-up of women after a first episode of postmenopausal bleeding and endometrial thickness greater than 4 millimeters. Obstet Gynecol. 2008 Jan;111(1):137–43.

22. Feldman S, Shapter A, Welch WR, Berkowitz RS. Two-year follow-up of 263 patients with post/perimenopausal vaginal bleeding and negative initial biopsy. Gynecol Oncol. 1994 Oct;55(1):56–9.

23. Gimpelson RJ, Rappold HO. A comparative study between panoramic hysteroscopy with directed biopsies and dilatation and curettage. A review of 276 cases. Am J Obstet Gynecol. 1988 Mar;158(3 Pt 1):489–92.

24. Lacey JV Jr, Ioffe OB, Ronnett BM, Rush BB, Richesson DA, Chatterjee N, et al. Endometrial carcinoma risk among women diagnosed with endometrial hyperplasia: the 34-year experience in a large health plan. Br J Cancer. 2008 Jan 15;98(1):45–53.

25. Clark TJ, Neelakantan D, Gupta JK. The management of endometrial hyperplasia: an evaluation of current practice. Eur J Obstet Gynecol Reprod Biol. 2006 Apr 1;125(2):259–64.

26. Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK. Relapse of endometrial hyperplasia after conservative treatment: a cohort study with long-term follow-up. Hum Reprod Oxf Engl. 2013 May;28(5):1231–6.

27. Indraccolo U, Di Iorio R, Matteo M, Corona G, Greco P, Indraccolo SR. The pathogenesis of endometrial polyps: a systematic semi-quantitative review. Eur J Gynaecol Oncol. 2013;34(1):5–22.

28. Svirsky R, Smorgick N, Rozowski U, Sagiv R, Feingold M, Halperin R, et al. Can we rely on blind endometrial biopsy for detection of focal intrauterine pathology? Am J Obstet Gynecol. 2008;199(2):115–e1 – 3.

29. Van Dongen H, de Kroon CD, Jacobi CE, Trimbos JB, Jansen FW. Diagnostic hysteroscopy in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG Int J Obstet Gynaecol. 2007 Jun;114(6):664–75.

30. Clark TJ, Barton PM, Coomarasamy A, Gupta JK, Khan KS. Investigating postmenopausal bleeding for endometrial cancer: cost-effectiveness of initial diagnostic strategies. BJOG Int J Obstet Gynaecol. 2006 May;113(5):502–10.

31. Bakour SH, Khan KS, Gupta JK. The risk of premalignant and malignant pathology in endometrial polyps. Acta Obstet Gynecol Scand. 2000 Apr;79(4):317–20.

32. Lieng M, Istre O, Qvigstad E. Treatment of endometrial polyps: a systematic review. Acta Obstet Gynecol Scand. 2010 Aug;89(8):992–1002.

33. Nathani F, Clark TJ. Uterine polypectomy in the management of abnormal uterine bleeding: A systematic review. J Minim Invasive Gynecol. 2006 Aug;13(4):260–8.

34. De Kroon CD, de Bock GH, Dieben SWM, Jansen FW. Saline contrast hysterosonography in abnormal uterine bleeding: a systematic review and meta-analysis. BJOG Int J Obstet Gynaecol. 2003 Oct;110(10):938–47.

35. Timmermans A, Opmeer BC, Veersema S, Mol BWJ. Patients' preferences in the evaluation of postmenopausal bleeding. BJOG Int J Obstet Gynaecol. 2007 Sep;114(9):1146–9.

36. Fung Kee Fung M, Burnett M, Faught W. Does persistent postmenopausal bleeding justify hysterectomy? Eur J Gynaecol Oncol. 1997;18(1):26–8.

37. Van Doorn HC, Timmermans A, Opmeer BC, Kruitwagen RFMP, Dijkhuizen FPHLJ, Kooi GS, et al. What is the recurrence rate of postmenopausal bleeding in women who have a thin endometrium during a first episode of postmenopausal bleeding? Acta Obstet Gynecol Scand. 2008;87(1):89–93.

38. Ronghe R, Gaudoin M. Women with recurrent postmenopausal bleeding should be re-investigated but are not more likely to have endometrial cancer. Menopause Int. 2010 Mar;16(1):9–11.

39. Cooper NAM, Smith P, Khan KS, Clark TJ. Vaginoscopic approach to outpatient hysteroscopy: a systematic review of the effect on pain. BJOG Int J Obstet Gynaecol. 2010 Apr;117(5):532–9.

40. Busquets M, Lemus M. [Practicability of panoramic hysteroscopy with CO2. Clinical experience: 923 cases]. Rev Chil Obstet Ginecol. 1993;58(2):113–8.

41. Sharma M, Taylor A, di Spiezio Sardo A, Buck L, Mastrogamvrakis G, Kosmas I, et al. Outpatient hysteroscopy: traditional versus the “no-touch” technique. BJOG Int J Obstet Gynaecol. 2005 Jul;112(7):963–7.

42. Garbin O, Kutnahorsky R, Göllner JL, Vayssiere C. Vaginoscopic versus conventional approaches to outpatient diagnostic hysteroscopy: a two-centre randomized prospective study. Hum Reprod Oxf Engl. 2006 Nov;21(11):2996–3000.

43. Almeida ZMMC de, Pontes R, Costa H de LFF. [Evaluation of pain in diagnostic hysteroscopy by vaginoscopy using normal saline at body temperature as distension medium: a randomized controlled trial]. Rev Bras Ginecol E Obstetrícia Rev Fed Bras Soc Ginecol E Obstetrícia. 2008 Jan;30(1):25–30.

44. Sagiv R, Sadan O, Boaz M, Dishi M, Schechter E, Golan A. A new approach to office hysteroscopy compared with traditional hysteroscopy: a randomized controlled trial. Obstet Gynecol. 2006 Aug;108(2):387–92.

45. Guida M, Di Spiezio Sardo A, Acunzo G, Sparice S, Bramante S, Piccoli R, et al. Vaginoscopic versus traditional office hysteroscopy: a randomized controlled study. Hum Reprod Oxf Engl. 2006 Dec;21(12):3253–7.

46. Paschopoulos M, Paraskevaidis E, Stefanidis K, Kofinas G, Lolis D. Vaginoscopic approach to outpatient hysteroscopy. J Am Assoc Gynecol Laparosc. 1997 Aug;4(4):465–7.

47. Medical Research Council. Good Clinical Practice [Internet]. 1998. Available from: http://www.mrc.ac.uk/documents/pdf/good-clinical-practice-in-clinical-trials/

48. Di Spiezio Sardo A, Taylor A, Tsirkas P, Mastrogamvrakis G, Sharma M, Magos A. Hysteroscopy: a technique for all? Analysis of 5,000 outpatient hysteroscopies. Fertil Steril. 2008 Feb;89(2):438–43.

49. Kremer C, Duffy S, Moroney M. Patient satisfaction with outpatient hysteroscopy versus day case hysteroscopy: randomised controlled trial. BMJ. 2000 Jan 29;320(7230):279–82.

50. Brooks PG. Complications of operative hysteroscopy: how safe is it? Clin Obstet Gynecol. 1992 Jun;35(2):256–61.

51. Agostini A, Cravello L, Shojai R, Ronda I, Roger V, Blanc B. Postoperative infection and surgical hysteroscopy. Fertil Steril. 2002 Apr;77(4):766–8.

52. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869.

53. Côté I, Jacobs P, Cumming DC. Use of health services associated with increased menstrual loss in the United States. Am J Obstet Gynecol. 2003 Feb;188(2):343–8.

54. Coulter A, Bradlow J, Agass M, Martin-Bates C, Tulloch A. Outcomes of referrals to gynaecology outpatient clinics for menstrual problems: an audit of general practice records. Br J Obstet Gynaecol. 1991 Aug;98(8):789–96.

55. CG44 N. Heavy Menstrual Bleeding. Clinical Guideline No. 44. National Collaborating Centre for Women's and Children's Health Commissioned by the National Institute for Health and Clinical Excellence. RCOG Press; 2007.

56. Dickersin K, Munro MG, Clark M, Langenberg P, Scherer R, Frick K, et al. Hysterectomy compared with endometrial ablation for dysfunctional uterine bleeding: a randomized controlled trial. Obstet Gynecol. 2007 Dec;110(6):1279–89.

57. Fergusson RJ, Lethaby A, Shepperd S, Farquhar C. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. Cochrane Database Syst Rev. 2013;11:CD000329.

58. Lethaby A, Penninx J, Hickey M, Garry R, Marjoribanks J. Endometrial resection and ablation techniques for heavy menstrual bleeding. Cochrane Database Syst Rev. 2013;8:CD001501.

59. Daniels JP, Middleton LJ, Champaneria R, Khan KS, Cooper K, Mol BWJ, et al. Second generation endometrial ablation techniques for heavy menstrual bleeding: network meta-analysis. BMJ. 2012;344:e2564.

60. Kleijn JH, Engels R, Bourdrez P, Mol BWJ, Bongers MY. Five-year follow up of a randomised controlled trial comparing NovaSure and ThermaChoice endometrial ablation. BJOG Int J Obstet Gynaecol. 2008 Jan;115(2):193–8.

61. Peeters JAH, Penninx JPM, Mol BW, Bongers MY. Prognostic factors for the success of endometrial ablation in the treatment of menorrhagia with special reference to previous cesarean section. Eur J Obstet Gynecol Reprod Biol. 2013 Mar;167(1):100–3.

62. El-Nashar SA, Hopkins MR, Creedon DJ, St Sauver JL, Weaver AL, McGree ME, et al. Prediction of treatment outcomes after global endometrial ablation. Obstet Gynecol. 2009 Jan;113(1):97–106.

63. Middleton LJ, Champaneria R, Daniels JP, Bhattacharya S, Cooper KG, Hilken NH, et al. Hysterectomy, endometrial destruction, and levonorgestrel releasing intrauterine system (Mirena) for heavy menstrual bleeding: systematic review and meta-analysis of data from individual patients. BMJ. 2010;341:c3929.

64. Smith PP, Malick S, Clark TJ. Bipolar radiofrequency compared with thermal balloon ablation in the office: a randomized controlled trial. Obstet Gynecol. 2014 Aug;124(2 Pt 1):219–25.

65. Jack SA, Cooper KG, Seymour J, Graham W, Fitzmaurice A, Perez J. A randomised controlled trial of microwave endometrial ablation without endometrial preparation in the outpatient setting: patient acceptability, treatment outcome and costs. BJOG Int J Obstet Gynaecol. 2005 Aug;112(8):1109–16.

66. Tresserra F, Grases P, Ubeda A, Pascual MA, Grases PJ, Labastida R. Morphological changes in hysterectomies after endometrial ablation. Hum Reprod Oxf Engl. 1999 Jun;14(6):1473–7.

67. Longinotti MK, Jacobson GF, Hung Y-Y, Learman LA. Probability of hysterectomy after endometrial ablation. Obstet Gynecol. 2008 Dec;112(6):1214–20.

68. Bansi-Matharu L, Gurol-Urganci I, Mahmood TA, Templeton A, van der Meulen JH, Cromwell DA. Rates of subsequent surgery following endometrial ablation among English women with menorrhagia: population-based cohort study. BJOG Int J Obstet Gynaecol. 2013 Nov;120(12):1500–7.

69. Gemer O, Kruchkovich J, Huerta M, Kapustian V, Kroll D, Anteby E. Perioperative predictors of successful hysteroscopic endometrial ablation. Gynecol Obstet Invest. 2007;63(4):205–8.

70. Punnonen R, Grönroos M. Cathetron and radium in the treatment of functional uterine bleeding. Ann Chir Gynaecol Fenn. 1972;61(4):215–9.

71. Crosignani PG, Vercellini P, Apolone G, De Giorgi O, Cortesi I, Meschia M. Endometrial resection versus vaginal hysterectomy for menorrhagia: long-term clinical and quality-of-life outcomes. Am J Obstet Gynecol. 1997 Jul;177(1):95–101.

72. Dwyer N, Hutton J, Stirrat GM. Randomised controlled trial comparing endometrial resection with abdominal hysterectomy for the surgical treatment of menorrhagia. Br J Obstet Gynaecol. 1993 Mar;100(3):237–43.

73. Gannon MJ, Holt EM, Fairbank J, Fitzgerald M, Milne MA, Crystal AM, et al. A randomised trial comparing endometrial resection and abdominal hysterectomy for the treatment of menorrhagia. BMJ. 1991 Nov 30;303(6814):1362–4.

74. O'Connor H, Broadbent JA, Magos AL, McPherson K. Medical Research Council randomised trial of endometrial resection versus hysterectomy in management of menorrhagia. Lancet. 1997 Mar 29;349(9056):897–901.

75. Pinion SB, Parkin DE, Abramovich DR, Naji A, Alexander DA, Russell IT, et al. Randomised trial of hysterectomy, endometrial laser ablation, and transcervical endometrial resection for dysfunctional uterine bleeding. BMJ. 1994 Oct 15;309(6960):979–83.

76. Sculpher MJ, Bryan S, Dwyer N, Hutton J, Stirrat GM. An economic evaluation of transcervical endometrial resection versus abdominal hysterectomy for the treatment of menorrhagia. Br J Obstet Gynaecol. 1993 Mar;100(3):244–52.

77. Cooper KG, Parkin DE, Garratt AM, Grant AM. Two-year follow up of women randomised to medical management or transcervical resection of the endometrium for heavy menstrual loss: clinical and quality of life outcomes. Br J Obstet Gynaecol. 1999 Mar;106(3):258–65.

78. Overton C, Hargreaves J, Maresh M. A national survey of the complications of endometrial destruction for menstrual disorders: the MISTLETOE study. Minimally Invasive Surgical Techniques--Laser, EndoThermal or Endorescetion. Br J Obstet Gynaecol. 1997 Dec;104(12):1351–9.

79. A Scottish audit of hysteroscopic surgery for menorrhagia: complications and follow up. Scottish Hysteroscopy Audit Group. Br J Obstet Gynaecol. 1995 Mar;102(3):249–54.

80. Lethaby A, Hickey M, Garry R. Endometrial destruction techniques for heavy menstrual bleeding. Cochrane Database Syst Rev. 2005;(4):CD001501.

81. Herman MC, Penninx JPM, Mol BW, Bongers MY. Ten-year follow-up of a randomised controlled trial comparing bipolar endometrial ablation with balloon ablation for heavy menstrual bleeding. BJOG Int J Obstet Gynaecol. 2013 Jul;120(8):966–70.

82. Sambrook AM, Jack SA, Cooper KG. Outpatient microwave endometrial ablation: 5-year follow-up of a randomised controlled trial without endometrial preparation versus standard day surgery with endometrial preparation. BJOG Int J Obstet Gynaecol. 2010 Mar;117(4):493–6.

83. Penninx JPM, Herman MC, Mol BW, Bongers MY. Five-year follow-up after comparing bipolar endometrial ablation with hydrothermablation for menorrhagia. Obstet Gynecol. 2011 Dec;118(6):1287–92.

84. Hallberg L, Högdahl AM, Nilsson L, Rybo G. Menstrual blood loss--a population study. Variation at different ages and attempts to define normality. Acta Obstet Gynecol Scand. 1966;45(3):320–51.

85. Clark TJ, Khan KS, Foon R, Pattison H, Bryan S, Gupta JK. Quality of life instruments in studies of menorrhagia: a systematic review. Eur J Obstet Gynecol Reprod Biol. 2002 Sep 10;104(2):96–104.

86. Thirlaway K, Fallowfield L, Cuzick J. The Sexual Activity Questionnaire: a measure of women's sexual functioning. Qual Life Res Int J Qual Life Asp Treat Care Rehabil. 1996 Feb;5(1):81–90.

87. Stead ML, Crocombe WD, Fallowfield LJ, Selby P, Perren TJ, Garry R, et al. Sexual activity questionnaires in clinical trials: acceptability to patients with gynaecological disorders. Br J Obstet Gynaecol. 1999 Jan;106(1):50–4.

88. EuroQol Group. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy Amst Neth. 1990 Dec;16(3):199–208.

89. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med. 2001 Jul;33(5):337–43.

90. Shaw RW, Brickley MR, Evans L, Edwards MJ. Perceptions of women on the impact of menorrhagia on their health using multi-attribute utility assessment. Br J Obstet Gynaecol. 1998 Nov;105(11):1155–9.

91. Lamping DL, Rowe P, Clarke A, Black N, Lessof L. Development and validation of the Menorrhagia Outcomes Questionnaire. Br J Obstet Gynaecol. 1998 Jul;105(7):766–79.

92. Varma R, Soneja H, Samuel N, Sangha E, Clark TJ, Gupta JK. Outpatient Thermachoice endometrial balloon ablation: long-term, prognostic and quality-of-life measures. Gynecol Obstet Invest. 2010;70(3):145–8.

93. Abbott J, Hawe J, Hunter D, Garry R. A double-blind randomized trial comparing the Cavaterm and the NovaSure endometrial ablation systems for the treatment of dysfunctional uterine bleeding. Fertil Steril. 2003 Jul;80(1):203–8.

94. Bongers MY, Bourdrez P, Mol BWJ, Heintz APM, Brölmann HAM. Randomised controlled trial of bipolar radio-frequency endometrial ablation and balloon endometrial ablation. BJOG Int J Obstet Gynaecol. 2004 Oct;111(10):1095–102.

95. Kato I, Toniolo P, Akhmedkhanov A, Koenig KL, Shore R, Zeleniuch-Jacquotte A. Prospective study of factors influencing the onset of natural menopause. J Clin Epidemiol. 1998 Dec;51(12):1271–6.

96. fox H, Buckley H. Gynaecological and obstetric pathology for the MRCOG. London: RCOG press; 1998.

97. Kim K-R, Peng R, Ro JY, Robboy SJ. A diagnostically useful histopathologic feature of endometrial polyp: the long axis of endometrial glands arranged parallel to surface epithelium. Am J Surg Pathol. 2004 Aug;28(8):1057–62.

98. Lopes RGC, Baracat EC, de Albuquerque Neto LC, Ramos JFD, Yatabe S, Depesr DB, et al. Analysis of estrogen- and progesterone-receptor expression in endometrial polyps. J Minim Invasive Gynecol. 2007 Jun;14(3):300–3.

99. Dreisler E, Stampe Sorensen S, Ibsen PH, Lose G. Prevalence of endometrial polyps and abnormal uterine bleeding in a Danish population aged 20-74 years. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2009 Jan;33(1):102–8.

100. Fatemi HM, Kasius JC, Timmermans A, van Disseldorp J, Fauser BC, Devroey P, et al. Prevalence of unsuspected uterine cavity abnormalities diagnosed by office hysteroscopy prior to in vitro fertilization. Hum Reprod Oxf Engl. 2010 Aug;25(8):1959–65.

101. De Ziegler D. Contrast ultrasound: a simple-to-use phase-shifting medium offers saline infusion sonography-like images. Fertil Steril. 2009 Jul;92(1):369–73.

102. Fay TN, Khanem N, Hosking D. Out-patient hysteroscopy in asymptomatic postmenopausal women. Climacteric J Int Menopause Soc. 1999 Dec;2(4):263–7.

103. Reslová T, Tosner J, Resl M, Kugler R, Vávrová I. Endometrial polyps. A clinical study of 245 cases. Arch Gynecol Obstet. 1999;262(3-4):133–9.

104. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. Gynecol Oncol. 2004 Aug;94(2):256–66.

105. Chalas E, Costantino JP, Wickerham DL, Wolmark N, Lewis GC, Bergman C, et al. Benign gynecologic conditions among participants in the Breast Cancer Prevention Trial. Am J Obstet Gynecol. 2005 Apr;192(4):1230–7; discussion 1237–9.

106. Bakour SH, Khan KS, Gupta JK. The risk of premalignant and malignant pathology in endometrial polyps. Acta Obstet Gynecol Scand. 2002 Feb;81(2):182–3.

107. Perrone G, DeAngelis C, Critelli C, Capri O, Galoppi P, Santoro G, et al. Hysteroscopic findings in postmenopausal abnormal uterine bleeding: a

comparison between HRT users and non-users. Maturitas. 2002 Dec 10;43(4):251–5.

108. Clark TJ, Khan KS, Gupta JK. Current practice for the treatment of benign intrauterine polyps: a national questionnaire survey of consultant gynaecologists in UK. Eur J Obstet Gynecol Reprod Biol. 2002 Jun 10;103(1):65–7.

109. Orvieto R, Bar-Hava I, Dicker D, Bar J, Ben-Rafael Z, Neri A. Endometrial polyps during menopause: characterization and significance. Acta Obstet Gynecol Scand. 1999 Nov;78(10):883–6.

110. Savelli L, De Iaco P, Santini D, Rosati F, Ghi T, Pignotti E, et al. Histopathologic features and risk factors for benignity, hyperplasia, and cancer in endometrial polyps. Am J Obstet Gynecol. 2003 Apr;188(4):927–31.

111. Ben-Arie A, Goldchmit C, Laviv Y, Levy R, Caspi B, Huszar M, et al. The malignant potential of endometrial polyps. Eur J Obstet Gynecol Reprod Biol. 2004 Aug 10;115(2):206–10.

112. Anastasiadis PG, Koutlaki NG, Skaphida PG, Galazios GC, Tsikouras PN, Liberis VA. Endometrial polyps: prevalence, detection, and malignant potential in women with abnormal uterine bleeding. Eur J Gynaecol Oncol. 2000;21(2):180–3.

113. Shushan A, Revel A, Rojansky N. How often are endometrial polyps malignant? Gynecol Obstet Invest. 2004;58(4):212–5.

114. Antunes A Jr, Costa-Paiva L, Arthuso M, Costa JV, Pinto-Neto AM. Endometrial polyps in pre- and postmenopausal women: factors associated with malignancy. Maturitas. 2007 Aug 20;57(4):415–21.

115. Gregoriou O, Konidaris S, Vrachnis N, Bakalianou K, Salakos N, Papadias K, et al. Clinical parameters linked with malignancy in endometrial polyps. Climacteric J Int Menopause Soc. 2009 Oct;12(5):454–8.

116. Wang J-H, Zhao J, Lin J. Opportunities and risk factors for premalignant and malignant transformation of endometrial polyps: management strategies. J Minim Invasive Gynecol. 2010 Feb;17(1):53–8.

117. Clevenger-Hoeft M, Syrop CH, Stovall DW, Van Voorhis BJ. Sonohysterography in premenopausal women with and without abnormal bleeding. Obstet Gynecol. 1999 Oct;94(4):516–20.

118. Elfayomy AK, Habib FA, Alkabalawy MA. Role of hysteroscopy in the detection of endometrial pathologies in women presenting with postmenopausal bleeding and thickened endometrium. Arch Gynecol Obstet. 2012 Mar;285(3):839–43.

119. DeWaay DJ, Syrop CH, Nygaard IE, Davis WA, Van Voorhis BJ. Natural history of uterine polyps and leiomyomata. Obstet Gynecol. 2002 Jul;100(1):3–7.

120. Munro MG, Critchley HOD, Fraser IS. The FIGO systems for nomenclature and classification of causes of abnormal uterine bleeding in the reproductive years: who needs them? Am J Obstet Gynecol. 2012 Oct;207(4):259–65.

121. Hospital Episode Statistics - 2011/12. Ungrossed data. [Internet]. Departement of Health (England); [cited 2013 Aug 9]. Available from: http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=215

122. Lieng M, Istre O, Sandvik L, Engh V, Qvigstad E. Clinical effectiveness of transcervical polyp resection in women with endometrial polyps: randomized controlled trial. J Minim Invasive Gynecol. 2010 Jun;17(3):351–7.

123. Lee SC, Kaunitz AM, Sanchez-Ramos L, Rhatigan RM. The oncogenic potential of endometrial polyps: a systematic review and meta-analysis. Obstet Gynecol. 2010 Nov;116(5):1197–205.

124. Lieng M, Istre O, Sandvik L, Qvigstad E. Prevalence, 1-year regression rate, and clinical significance of asymptomatic endometrial polyps: cross-sectional study. J Minim Invasive Gynecol. 2009 Aug;16(4):465–71.

125. Timmermans A, Veersema S, van Kerkvoorde TC, van der Voet LF, Opmeer BC, Bongers MY, et al. Should endometrial polyps be removed in patients with postmenopausal bleeding?-an assessment of study designs and report of a failed randomised controlled trial (ISRCTN73825127). BJOG Int J Obstet Gynaecol. 2009 Sep;116(10):1391–5.

126. Vercellini P, Trespidi L, Bramante T, Panazza S, Mauro F, Crosignani PG. Gonadotropin releasing hormone agonist treatment before hysteroscopic endometrial resection. Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet. 1994 Jun;45(3):235–9.

127. Oguz S, Sargin A, Kelekci S, Aytan H, Tapisiz OL, Mollamahmutoglu L. The role of hormone replacement therapy in endometrial polyp formation. Maturitas. 2005 Mar 14;50(3):231–6.

128. Gardner FJE, Konje JC, Bell SC, Abrams KR, Brown LJR, Taylor DJ, et al. Prevention of tamoxifen induced endometrial polyps using a levonorgestrel releasing intrauterine system long-term follow-up of a randomised control trial. Gynecol Oncol. 2009 Sep;114(3):452–6.

129. Timmermans A, van Dongen H, Mol BW, Veersema S, Jansen FW. Hysteroscopy and removal of endometrial polyps: a Dutch survey. Eur J Obstet Gynecol Reprod Biol. 2008 May;138(1):76–9.

130. Van Dijk LJEW, Breijer MC, Veersema S, Mol BWJ, Timmermans A. Current practice in the removal of benign endometrial polyps: a Dutch survey. Gynecol Surg. 2012 May;9(2):163–8.

131. Grimes DA. Diagnostic dilation and curettage: a reappraisal. Am J Obstet Gynecol. 1982;142(1):1–6.

132. MacKenzie IZ, Bibby JG. Critical assessment of dilatation and curettage in 1029 women. Lancet. 1978 Sep 9;2(8089):566–8.

133. Bettocchi S, Ceci O, Vicino M, Marello F, Impedovo L, Selvaggi L. Diagnostic inadequacy of dilatation and curettage. Fertil Steril. 2001;75(4):803–5.

134. Loffer FD. Hysteroscopy with selective endometrial sampling compared with D&C for abnormal uterine bleeding: the value of a negative hysteroscopic view. Obstet Gynecol. 1989 Jan;73(1):16–20.

135. Moghal N. Diagnostic value of endometrial curettage in abnormal uterine bleeding--a histopathological study. JPMA J Pak Med Assoc. 1997 Dec;47(12):295–9.

136. Gebauer G, Hafner A, Siebzehnrübl E, Lang N. Role of hysteroscopy in detection and extraction of endometrial polyps: results of a prospective study. Am J Obstet Gynecol. 2001 Jan;184(2):59–63.

137. Bettocchi S, Ceci O, Nappi L, Di Venere R, Masciopinto V, Pansini V, et al. Operative office hysteroscopy without anesthesia: analysis of 4863 cases performed with mechanical instruments. J Am Assoc Gynecol Laparosc. 2004 Feb;11(1):59–61.

138. Timmermans A, Veersema S. Ambulatory transcervical resection of polyps with the Duckbill polyp snare: a modality for treatment of endometrial polyps. J Minim Invasive Gynecol. 2005 Feb;12(1):37–9.

139. Garuti G, Centinaio G, Luerti M. Outpatient hysteroscopic polypectomy in postmenopausal women: a comparison between mechanical and electrosurgical resection. J Minim Invasive Gynecol. 2008 Oct;15(5):595–600.

140. Magos AL, Baumann R, Lockwood GM, Turnbull AC. Experience with the first 250 endometrial resections for menorrhagia. Lancet. 1991 May 4;337(8749):1074–8.

141. Wamsteker K, Emanuel MH, de Kruif JH. Transcervical hysteroscopic resection of submucous fibroids for abnormal uterine bleeding: results regarding the degree of intramural extension. Obstet Gynecol. 1993 Nov;82(5):736–40.

142. Preutthipan S, Herabutya Y. Hysteroscopic polypectomy in 240 premenopausal and postmenopausal women. Fertil Steril. 2005 Mar;83(3):705–9.

143. Cravello L, de Montgolfier R, D'Ercole C, Boubli L, Blanc B. Hysteroscopic surgery in postmenopausal women. Acta Obstet Gynecol Scand. 1996 Jul;75(6):563–6.

144. Betjes HE, Hanstede MMF, Emanuel M-H, Stewart EA. Hysteroscopic myomectomy and case volume hysteroscopic myomectomy performed by high- and low-volume surgeons. J Reprod Med. 2009 Jul;54(7):425–8.

145. Batra N, Khunda A, O'Donovan PJ. Hysteroscopic myomectomy. Obstet Gynecol Clin North Am. 2004 Sep;31(3):669–85.

146. Kung RC, Vilos GA, Thomas B, Penkin P, Zaltz AP, Stabinsky SA. A new bipolar system for performing operative hysteroscopy in normal saline. J Am Assoc Gynecol Laparosc. 1999 Aug;6(3):331–6.

147. Clark TJ, Godwin J, Khan KS, Gupta JK. Ambulatory endoscopic treatment of symptomatic benign endometrial polyps: feasibility study. Gynaecol Endosc. 2002;11(2/3):91–7.

148. Vilos GA. Intrauterine surgery using a new coaxial bipolar electrode in normal saline solution (Versapoint): a pilot study. Fertil Steril. 1999 Oct;72(4):740–3.

149. Emanuel MH, Wamsteker K. The Intra Uterine Morcellator: a new hysteroscopic operating technique to remove intrauterine polyps and myomas. J Minim Invasive Gynecol. 2005 Feb;12(1):62–6.

150. Van Dongen H, Emanuel MH, Wolterbeek R, Trimbos J, Jansen FW. Hysteroscopic morcellator for removal of intrauterine polyps and myomas: a randomized controlled pilot study among residents in training. J Minim Invasive Gynecol. 2008;15(4):466–71.

151. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.1. 2008.

152. Akers J, Agular-Ibáñez R, Baba-Akbari Sari A, Benyon S, Booth A. Systematic Reviews: CRD's Guidance for Undertaking Reviews in Health Care. Univerisity of York: York UK: NHS Centre for Reviews and Dissemination; 2009.

153. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr;61(4):344–9.

154. AlHilli MM, Nixon KE, Hopkins MR, Weaver AL, Laughlin-Tommaso SK, Famuyide AO. Long-term outcomes after intrauterine morcellation vs hysteroscopic resection of endometrial polyps. J Minim Invasive Gynecol. 2013 Mar;20(2):215–21.

155. Barisic D, Strelec M, Velimir S. Operative Hysteroscopy in Patients with Abnormal Uterine Bleeding Caused by Benign Intrauterine Growths. Croat Med J. 36(4):275–7.

156. Brooks PG, Loffer FD, Serden SP. Resectoscopic removal of symptomatic intrauterine lesions. J Reprod Med. 1989 Jul;34(7):435–7.

157. Cravello L, Stolla V, Bretelle F, Roger V, Blanc B. Hysteroscopic resection of endometrial polyps: a study of 195 cases. Eur J Obstet Gynecol Reprod Biol. 2000 Dec;93(2):131–4.

158. Henriquez DDCA, van Dongen H, Wolterbeek R, Jansen FW. Polypectomy in premenopausal women with abnormal uterine bleeding: effectiveness of hysteroscopic removal. J Minim Invasive Gynecol. 2007 Feb;14(1):59–63.

159. Nagele F, Mane S, Chandrasekaran P. How successful is hysteroscopic polypectomy? Gynaecol Endosc. 1996;5(3):137–40.

160. Pace S. Transcervical resection of enign endocavitary lesions. Gynaecol Endosc. 1993;2(3):165–9.

161. Polena V, Mergui J-L, Zérat L, Daraï E, Barranger E, Uzan S. [Long-term results of hysteroscopic resection of endometrial polyps in 367 patients. Role of associated endometrial resection]. Gynécologie Obstétrique Fertil. 2005 Jun;33(6):382–8.

162. Stamatellos I, Apostolides A, Stamatopoulos P, Bontis J. Pregnancy rates after hysteroscopic polypectomy depending on the size or number of the polyps. Arch Gynecol Obstet. 2008 May;277(5):395–9.

163. Towbin NA, Gviazda IM, March CM. Office hysteroscopy versus transvaginal ultrasonography in the evaluation of patients with excessive uterine bleeding. Am J Obstet Gynecol. 1996 Jun;174(6):1678–82.

164. Van Dongen H, Janssen CAH, Smeets MJGH, Emanuel MH, Jansen FW. The clinical relevance of hysteroscopic polypectomy in premenopausal women with abnormal uterine bleeding. BJOG Int J Obstet Gynaecol. 2009 Sep;116(10):1387–90.

165. Clark TJ. Outpatient versus Inpatient Polypectomy Treatment: a Randomised Controlled Pilot Study. Grey Lit. 2013;

166. Tjarks M, Van Voorhis BJ. Treatment of endometrial polyps. Obstet Gynecol. 2000 Dec;96(6):886–9.

167. Hamerlynck TWO, Dietz V, Schoot BC. Clinical implementation of the hysteroscopic morcellator for removal of intrauterine myomas and polyps. A retrospective descriptive study. Gynecol Surg. 2011 May;8(2):193–6.

168. Marsh FA, Rogerson LJ, Duffy SRG. A randomised controlled trial comparing outpatient versus daycase endometrial polypectomy. BJOG Int J Obstet Gynaecol. 2006 Aug;113(8):896–901.

169. Cooper NAM, Clark TJ, Middleton L, Diwaker L, Smith P, Denny E, et al. A randomised trial of outpatient versus inpatient uterine polyp treatment for abnormal uterine bleeding. BMJ. 2015;In Print.

170. Bettocchi S, Ceci O, Di Venere R, Pansini MV, Pellegrino A, Marello F, et al. Advanced operative office hysteroscopy without anaesthesia: analysis of 501 cases treated with a 5 Fr. bipolar electrode. Hum Reprod Oxf Engl. 2002 Sep;17(9):2435–8.

171. AlHilli MM, Hopkins MR, Shannon LK, Famuyide AO. Histopathological Outcomes Following Operative Intrauterine Morcellation of Endometrial Polyps: A Cohort Study. J Minim Invasive Gynecol. 2010;17(6):S38.

172. Saridogan E, Tilden D, Sykes D, Davis N, Subramanian D. Cost-analysis comparison of outpatient see-and-treat hysteroscopy service with other hysteroscopy service models. J Minim Invasive Gynecol. 2010 Aug;17(4):518–25.

173. Hidlebaugh D. A comparison of clinical outcomes and cost of office versus hospital hysteroscopy. J Am Assoc Gynecol Laparosc. 1996 Nov;4(1):39–45.

174. Marsh F, Kremer C, Duffy S. Delivering an effective outpatient service in gynaecology. A randomised controlled trial analysing the cost of outpatient versus daycase hysteroscopy. BJOG Int J Obstet Gynaecol. 2004 Mar;111(3):243–8.

175. Cooper NAM, Smith P, Khan KS, Clark TJ. Does cervical preparation before outpatient hysteroscopy reduce women's pain experience? A systematic review. BJOG Int J Obstet Gynaecol. 2011 Oct;118(11):1292–301.

176. Cooper NAM, Khan KS, Clark TJ. Local anaesthesia for pain control during outpatient hysteroscopy: systematic review and meta-analysis. BMJ. 2010;340:c1130.

177. Cooper NAM, Smith P, Khan KS, Clark TJ. A systematic review of the effect of the distension medium on pain during outpatient hysteroscopy. Fertil Steril. 2011 Jan;95(1):264–71.

178. Celik C, Tasdemir N, Abali R, Bastu E, Akbaba E, Yucel SH, et al. The effect of uterine straightening by bladder distention before outpatient hysteroscopy: a randomised clinical trial. Eur J Obstet Gynecol Reprod Biol. 2014 Sep;180:89–92.

179. Issat T, Beta J, Nowicka MA, Maciejewski T, Jakimiuk AJ. A randomized, single blind, placebo-controlled trial for the pain reduction during the

outpatient hysteroscopy after ketoprofen or intravaginal misoprostol. J Minim Invasive Gynecol. 2014 Oct;21(5):921–7.

180. El-Mazny A, Abou-Salem N. A double-blind randomized controlled trial of vaginal misoprostol for cervical priming before outpatient hysteroscopy. Fertil Steril. 2011 Oct 1;96(4):962–5.

181. Hassa H, Aydin Y, Oge T, Cicek K. Effectiveness of vaginal misoprostol and rectal nonsteroidal anti-inflammatory drug in vaginoscopic diagnostic outpatient hysteroscopy in primarily infertile women: double-blind, randomized, controlled trial. J Minim Invasive Gynecol. 2013 Dec;20(6):880–5.

182. Isley MM, Jensen JT, Nichols MD, Lehman A, Bednarek P, Edelman A. Intrauterine lidocaine infusion for pain management during outpatient transcervical tubal sterilization: a randomized controlled trial. Contraception. 2012 Mar;85(3):275–81.

183. Lethaby AE, Cooke I, Rees M. Progesterone or progestogen-releasing intrauterine systems for heavy menstrual bleeding. Cochrane Database Syst Rev. 2005;(4):CD002126.

184. Campbell I. Uterine physiology. Anaesth Intensive Care Med. 2005;6(3):76.

185. Kumar V, Gupta JK. Hysteroscopic local anaesthetic intrauterine cornual “focal local” block before endometrial ablation with direct cervical block in an outpatient setting: a feasibility study. Eur J Obstet Gynecol Reprod Biol. 2013 Sep;170(1):222–4.

186. Madari S, Al-Shabibi N, Papalampros P, Papadimitriou A, Magos A. A randomised trial comparing the H Pipelle with the standard Pipelle for endometrial sampling at “no-touch” (vaginoscopic) hysteroscopy. BJOG Int J Obstet Gynaecol. 2009 Jan;116(1):32–7.

187. Duffy S, Marsh F, Rogerson L, Hudson H, Cooper K, Jack S, et al. Female sterilisation: a cohort controlled comparative study of ESSURE versus laparoscopic sterilisation. BJOG Int J Obstet Gynaecol. 2005 Nov;112(11):1522–8.

188. Levie MD, Chudnoff SG. Prospective analysis of office-based hysteroscopic sterilization. J Minim Invasive Gynecol. 2006 Apr;13(2):98–101.

189. Prasad P, Powell MC. Prospective observational study of Thermablate Endometrial Ablation System as an outpatient procedure. J Minim Invasive Gynecol. 2008 Aug;15(4):476–9.

190. Nappi L, Di Spiezio Sardo A, Spinelli M, Guida M, Mencaglia L, Greco P, et al. A multicenter, double-blind, randomized, placebo-controlled study to assess whether antibiotic administration should be recommended during office

operative hysteroscopy. Reprod Sci Thousand Oaks Calif. 2013 Jul;20(7):755–61.

191. Craciunas L, Sajid MS, Howell R. Carbon dioxide versus normal saline as distension medium for diagnostic hysteroscopy: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2013 Dec;100(6):1709–14.e1–4.

192. Shahid A, Pathak M, Gulumser C, Parker S, Palmer E, Saridogan E. Optimum uterine filling pressure for outpatient diagnostic hysteroscopy: a double-blind, randomized controlled trial. Reprod Biomed Online. 2014 Jan;28(1):86–91.

193. Birinyi L, Daragó P, Török P, Csiszár P, Major T, Borsos A, et al. Predictive value of hysteroscopic examination in intrauterine abnormalities. Eur J Obstet Gynecol Reprod Biol. 2004 Jul 15;115(1):75–9.

194. Clark J. Outpatient Polypectomy Trial Protocol [Internet]. The Univeristy of Birmingham; 2009. Available from: http://www.birmingham.ac.uk/Documents/college-mds/trials/bctu/opt/OPT-Pro-V22.pdf

APPENDIX

Appendix 1: Consent form for VAST

VAST

A randomised controlled trial of Vaginoscopy Against Standard Hysteroscopy

Participant Consent Form

	Please initial each box to confirm consent
I confirm that I have read and understand the information sheet for the above study (PIS v1.2 01.01.2014). I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily.	☐
I understand that my participation is voluntary and that if I take part, I am free to withdraw at any time, without giving a reason, and without my medical care or legal rights being affected.	☐
I accept that the study researchers will telephone or email me to check how I've been since the procedure.	☐
I understand that the personal information and details about my treatment will be used for medical research only. I will not be identified in any way in the analysis and reporting of the results. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Birmingham Women's Hospital or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my record.	☐
I agree to my GP being informed of my participation in the VAST Trial. I understand my GP may be contacted to obtain information about any complications or further gynaecology consultations.	☐
I understand what is involved in the trial, agree to participate and be randomised between trial treatments.	☐

……	……	……..
Name of Patient	Date	Signature
……	……	……..
Name of Person taking consent	Date	Signature

Trial Number ☐☐☐

Appendix 2: Patient information leaflet for VAST

Birmingham Women's NHS
NHS Foundation Trust

Birmingham Women's Hospital
Metchley Park Road
Edgbaston
Birmingham
B15 2TG

Switchboard: 0121 472 1377

VAST

A randomised controlled trial of Vaginoscopy Against Standard Technique for outpatient hysteroscopy

PARTICPANT INFORMATION SHEET

VAST information leaflet version 1.2 01/01/14

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

Invitation to participate a new technique study
You are invited to take part in a research study to find out which is the best technique to enter the womb. The study is entirely voluntary – you do not have to take part, nor give a reason why, if you decide not to. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it would involve if you do choose to take part. Please take your time to read this information carefully. Talk to others such as family, friends or your GP about the study if you wish. If there is anything that is not clear, or you would like more information you should ask your gynaecologist or clinic nurse for further advice.

What is hysteroscopy?
Hysteroscopy is an investigation in which a special telescope is inserted into the womb.

What is the purpose of the study?
The established technique for hysteroscopy involves using a speculum inserted into the vagina to visualise the opening of the womb. Pain during hysteroscopy can lead to poor patient experience and even failure. There is uncertainty whether an alternative technique, known as vaginoscopy, will minimise the pain experienced by the patient. Vaginoscopy is where the telescope is inserted directly into the vagina, and guided into womb avoiding the need for potentially painful introduction of other instruments. However, this technique may be more prone to failure due to an inability to cross the entrance to the womb and infection rates may be higher due to vaginal contamination.

Do I have to take part?
No. Taking part is entirely voluntary and it is up to you to decide. If you do not wish to take part your decision will not affect the standard of care you will receive.

If I take part will the hysteroscope be inserted using the standard technique or using vaginoscopy?
Women are allocated at random to either vaginoscopy or standard technique by the central study office. There is an equal chance of being allocated to the vaginoscopy or standard technique group. Neither you nor your gynaecologist will know which of the groups you will be in until after you have been entered into the study. This means that doctors can not choose which women will receive which treatment and this makes the results much more reliable. This is called a 'randomised clinical trial' and it is the standard medical research method for comparing treatment.

What will happen to me if I take part?
If you agree to take part you will be randomised to either standard technique or vaginoscopy. The process of randomisation will prolong the procedure by up to 2 minutes. You will then have the hysteroscopy, which takes 2-5 minutes. . After the procedure you will be able to rest and have a cup of tea in comfortable surroundings. While you are resting you will be asked to fill in a short, confidential, questionnaire on your experience. About 2 weeks after the procedure you will be contacted by email or phone to ask how you have been since the procedure.

How will I feel during and after outpatient hysteroscopy?
During the procedure you may get some crampy period type pains in your lower abdomen, which usually settle once treatment is completed. If it does not the nurse will give you some simple painkillers. A minority of women may feel a little faint following the procedure requiring them to lie down for a few minutes until the sensation passes. Light spotting or fresh blood loss is not uncommon but again should settle within a few hours of the procedure, although some women may experience light vaginal blood loss for a few days. After the procedure you will be able to rest and have a cup of tea in comfortable surroundings. It is advisable to have someone with you when you get home. You will need to rest for the remainder of the day. If you do require further pain relief, we suggest simple painkillers such as paracetamol every 6 hours.

What are the alternatives for diagnosis and treatment?
Pelvic ultrasound is the usual first line investigation to look at the womb. However, this has limited accuracy in

detecting problems. Another alternative is to be put to sleep to have the procedure.

What are the risks and disadvantages of taking part?
Outpatient hysteroscopy is widespread in the NHS and all doctors involved will have the relevant experience. Both vaginoscopy and the standard technique for hysteroscopy have been shown to be safe.

What happens when the research study stops?
When the results of the study are known they will be published in medical journals and the results circulated to medical staff and participants. The results will influence the way hysteroscopy is performed in the future.

What are the side effects of treatment received when taking part?
Minor side-effects of hysteroscopy include prolonged blood stained vaginal discharge, and infection of the womb lining or bladder (cystitis requiring a short course of antibiotics). Some women can experience severe, cramping period-like pain and some may feel faint for a few minutes immediately following the procedure. The only serious and rare complication specific to the procedure of hysteroscopy is making a hole in the wall of the womb ('perforation'), which normally heals naturally, but occasionally can cause bleeding or damage to other organs in the abdomen that requires immediate abdominal surgery to repair.

Are there any benefits for me from taking part in the study?
Participants may not gain any individual benefit. However, if one technique is shown to better, in the future women could benefit in terms of safety and acceptability.

What if there is a problem?
Any compliant about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. The study will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2

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

What if there is a problem?
You have the same legal rights whether or not you take part in this study. If you are not satisfied with any aspect of the way you have been approached or treated during the course of this study, you should speak to the researchers who will do their best to answer your questions. If you remain unhappy and wish to complain formally, the normal NHS complaints mechanisms are available and you should ask for the complaints manager at the hospital. Taking part in the trial should not affect any private medical insurance you may have, but you are advised to contact your medical insurance provider to confirm this.

Will information about me be kept confidential?
Yes, all information will be kept strictly confidential like your other medical records. If you agree to take part, your doctor will send basic information about you and your condition to Birmingham Women's Hospital. This information will be put into a computer and analysed by the study staff only. The questionnaires will not contain your name and will be identified using code number and not be seen by your GP or gynaecologist. No named information about you will be published in the study report. Occasionally, inspectors of clinical study data are undertaken to ensure that, for example, all participants have given consent to take part. But, apart from this, only the study organisers will have access to the data.

Involvement of the General Practitioner
With your consent we will inform your GP of your participation in the trial.

What will happen to the results of the research study?
It is expected that the results will be reported in a medical journal around 12months after recruitment is completed. Everyone who takes part will then be told the results in a newsletter that will be posted directly to them.

Who is funding and organising the research?
The doctors and researchers involved are not being paid for recruiting women into the study. Patients are not paid to take part either, but their help in finding out more about how best to treat polyps is much appreciated.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity.

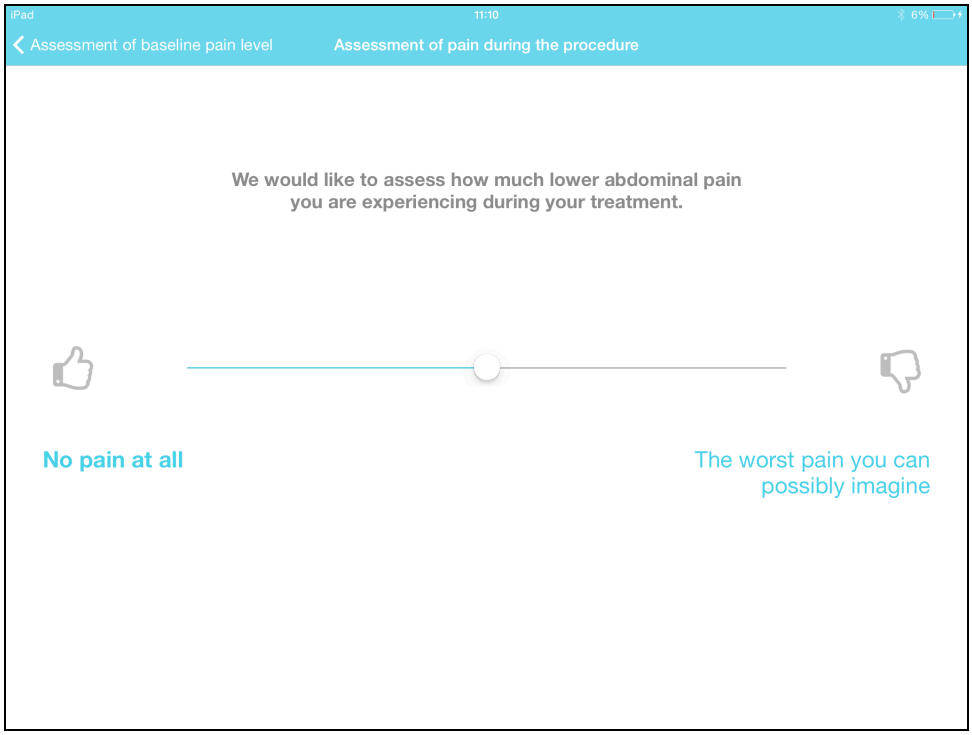
Do you have any further questions?
If you have any questions about the study now or later feel free to ask your gynaecologist or clinic nurse. Their names and telephone numbers are given below. Please take the time before your appointment to decide whether you wish to take part in the trial. You may like to discuss your decision with friends or relatives.

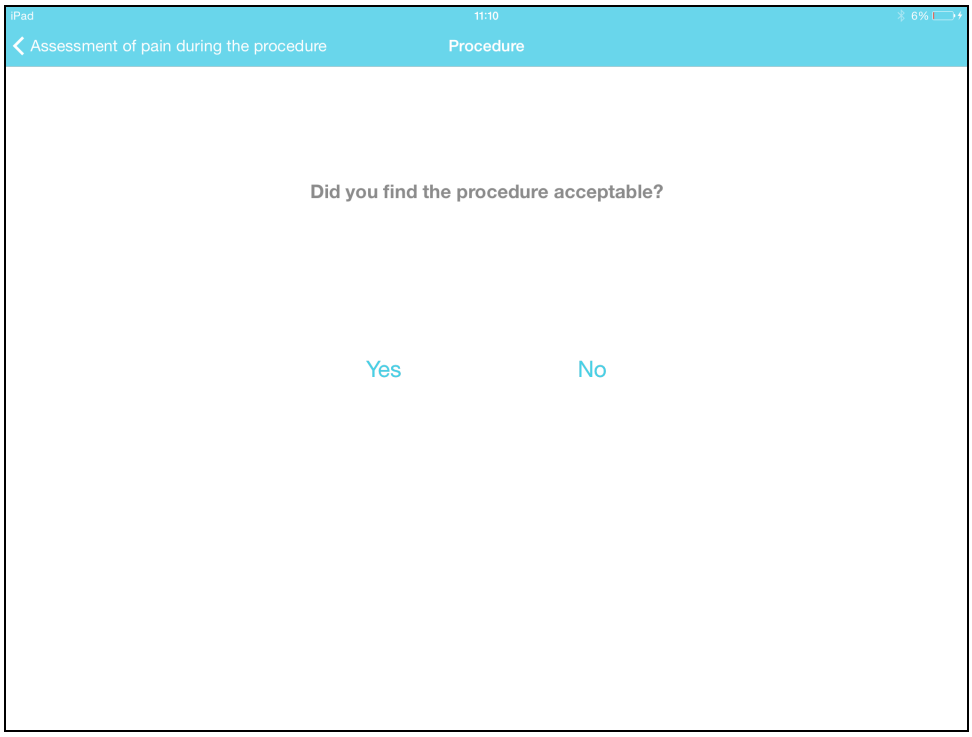
The UK Clinical Research Collaboration has produced a guide entitled, 'Understanding Clinical Trials'. This can be down loaded from their website: www.ukcrn.org.uk and maybe useful if you require general information about research. If you require specific information about the research project please contact any of the trial staff listed below.

Contact details
Study Organisers:
Mr Justin Clark, Chief investigator, Consultant Gynaecologist, Birmingham Women's Hospital, Metchley Park Road, Edgbaston, Birmingham B15 2TG Tel:

Patient Advice & Information Centre:
If your would like to speak to someone else, you can contact the Patient Advice and Liason Service
dhft.contactpals@nhs.net or freephone 0800 783 7691

Appendix 3: Screen shots for VAST ipad^{TM} application.





Appendix 4: Surgical treatment form for VAST.

A Randomised Controlled Trial of Vaginoscopy against Standard Technique

Patient details
Trial Number: ☐☐☐ Patient initials: ☐☐ Weight (kg): ☐☐☐

Date of birth (dd/mm/yyyy): ……../……./…… Height (cm): ☐☐☐

Parity: ☐☐ (Vaginal: ☐☐ C/S: ☐☐)

Indication for hysteroscopy: Bleeding ☐ Fertility ☐ Dysmenorrhoea ☐
Lost intrauterine device ☐ Thickened endometrium/polyp ☐

Menopausal status: Premenopausal ☐ Postmenopausal ☐

Vaginoscopy ☐ **Standard** ☐ Date of procedure: ……../……./……

Surgical technique:
Local anaesthetic: None ☐ Direct cervical ☐ Paracervical ☐

Tenaculum used: Yes ☐ No ☐

Cervical dilatation: Yes ☐ No ☐

Speculum ☐ No speculum (i.e. 'vaginoscopic' polyp removal) ☐

Endometrial biopsy performed: Yes ☐ No ☐

Any other surgical procedure performed: ……

If procedure failed please state why:
Patient discomfort ☐ Equipment failure ☐
Other ☐ (if Other, please state) ……..

Operative complications (attach separate sheet if necessary)
None ☐ Vaso-vagal episode ☐ Cervical trauma ☐ Uterine perforation ☐ Haemorrhage ☐ Other ☐ (if other please state)……

Time taken
From insertion to removal of vaginal instrumentation post randomisation
☐☐ (mins)

Name and grade of surgeon ……
Grade: Consultant ☐ Associate specialist ☐ Staff Grade ☐
Specialist registrar ☐ Other ☐ if other, please specify: ……
Signed: …… Date: ……/……/…… (dd/mm/yy)

Appendix 5: Serious adverse event form for VAST.

VAST

A randomised controlled trial of Vaginoscopy Against Standard Technique

SERIOUS ADVERSE EVENT FORM

Please report any serious and unexpected adverse events that are suspected to be due to treatments[1] given as part of the trial by sending or faxing the following details to the trial office (Fax: 0121 415 9135) within 2 days of the event.

Patient Identification:
Patient's full name: ……
Trial No: ……..
Date of birth: day/month/year …../…../…..
Centre Name: ……..
Responsible doctor: ……..

Associated Treatment:
Vaginoscopy ☐ Standard Technique ☐
Date of treatment: day/month/year …../…../…..

SAE description:
Category of event: Death ☐ Life threatening ☐
Hospitalisation (or prolongation of) ☐ Persistent or significant disability/incapacity ☐
Date SAE started: day/month/year …./…. /….
Date SAE ceased: day/month/year …./…. /….

Outcome:
Fatal ☐ Recovered Continuing ☐
Details of adverse event (please attach copies of relevant reports):
……
……
……
……
……

Did the event require or prolong hospitalisation? No ☐ Yes ☐ No. of days ☐
Please give reasons why you consider the event to be treatment related:
……
……
……
……
……

Name of person reporting (please print):……
Signed: ……
Tel No: …… Date: day/month/year …../…../…..

[1]For the purposes of this study, "**serious**" adverse events are those that are fatal, life-threatening, disabling or require hospitalisation. "**Unexpected**" adverse experiences are defined as those that would not be expected among patients given these treatments. It is not required to report in this way side-effects or adverse events that might reasonably be expected.

Appendix 6: Patient information leaflet for COAT.

COAT

PATIENT INFORMATION LEAFLET

Invitation to take part in the COAT research study

You will have decided to have an outpatient endometrial ablation for the treatment of your heavy menstrual periods (menorrhagia). Your consultant will have explained to you what this involves and you will have consented for treatment.

We would like to invite you to take part in a study comparing two of the most commonly used techniques for endometrial ablation, '*Thermachoice'* and '*NovaSure'*. We have called this study the COAT trial that stands for the Comparison of the effectiveness of Outpatient endometrial Ablation Techniques (*Novasure™ versus Thermachoice™*) in the treatment of menorrhagia. 80 women, who like you have had problematic heavy menstrual periods, will take part in the study. Half will be randomly allocated to have the *NovaSure™* technique for endometrial ablation and the other half will have the *Thermachoice™* endometrial ablation technique. Women in the study will not be told which group they are in because we don't want this to influence how they feel after the operation. This is called 'blinding' and allows us to trust the results we obtain from the study.

What is the purpose of the COAT study?

Endometrial ablation is an established surgical treatment for heavy menstrual bleeding and has shown to be very effective. Advances in technology have resulted in the production of several ablative devices that can be used in an outpatient setting without the need for general anaesthesia. However, we do not know which, if any, of the available devices are more acceptable to women and effective in terms of reducing the amount of bleeding a woman has during her period and improving her quality of life. Two of the most established devices used for outpatient endometrial ablation are called *Thermachoice™* and *Novasure™* . The COAT study aims to find out which outpatient ablation treatment:

- controls menstrual bleeding symptoms the best
- has the best overall effect on women's quality of life
- is easier to use
- is the more acceptable to women
- can avoid the future need for hysterectomy
- is the most cost-effective treatment

What is Outpatient Endometrial Ablation?

Endometrial ablation is a surgical technique to reduce the amount of bleeding that a woman experiences during her period. The technique involves removal of the lining of the uterus called the 'endometrium' by the use of controlled heat known as 'ablation'. Endometrial ablation can be done in a variety of ways, all of which do not require surgical incisions and are associated with minimal side effects and rapid recovery, usually within 48 hours. Two techniques, *Novasure™* and *Thermachoice™* can be performed with or without the need for general anaesthetic (i.e women can be awake or asleep for the procedure). If women choose to have the procedure without general anaesthetic then the procedure is termed an 'outpatient' endometrial ablation as admission to hospital is not usually required and the operation is performed in an outpatient treatment room rather than a formal operating theatre.

Women undergoing outpatient endometrial ablation do not need to fast prior to the procedure and are usually discharged from hospital within 2 to 6 hours of the procedure.

What are 'NovaSure' and 'Thermachoice'?

NovaSure™ and *Thermachoice™* are both techniques of endometrial ablation. They use specially designed, miniaturized equipment, which allow the procedures to be carried out safely without the need for general anaesthetic and require less than 10 minutes to complete. Both techniques involve the use of small devices that are placed inside the uterus (womb). These devices impart heat to the lining of the uterus (the 'endometrium') so that it is removed and subsequent menstrual periods either disappear or become much lighter. One technique involves the use of a hot water balloon device called '*Thermachoice*' and the other a fan-shaped electrical device called '*NovaSure'*.

Will 'NovaSure' or 'Thermachoice' Help Me?

Previous clinical studies have shown that most women with heavy menstrual bleeding undergoing endometrial ablation with *Thermachoice™ or Novasure™* are satisfied with their results because they get substantial improvement in their bleeding symptoms. This improvement can mean complete relief of bleeding (periods stop altogether or just monthly 'spotting' occurs) or partial relief of bleeding (reduction in amount of bleeding during a menstrual period) depending on the individual woman. By taking part in this trial, you will help us find out whether outpatient treatment by *Thermachoice™ or Novasure™* relieves bleeding more effectively. In addition we will be able to assess which outpatient treatment is the better tolerated and more acceptable to women so that women in the future obtain the best treatment for their condition.

What happens during Outpatient Endometrial Ablation?

Outpatient endometrial ablation is a simple technique that ***does not*** require you to be put to sleep under general anaesthetic in an operating theatre. For this reason you can eat and drink before arriving at the designated hospital ward for the procedure where you will be given simple pain killers and an anti-sickness tablet. You will asked to remove you're undergarments and wear a hospital gown. You will then be taken to a private outpatient treatment room where you will be required to lie flat on a special couch where your legs will be placed apart in leg rests. A speculum will be placed in the vagina (like when you have a cervical smear test), which enables a tiny telescope (called a hysteroscope) to be passed through the cervix (entrance to the womb) into the uterus (womb). The gynaecologist will examine your uterus to see if you have any obvious reason for your heavy bleeding and to confirm that you are suitable for outpatient endometrial ablative treatment. A local anaesthetic will then be injected into the cervix to 'freeze it' which enabled the *Thermachoice™* or *NovaSure™* device to be placed inside the uterus and the treatment cycle commenced according to which technique you have been randomly allocated to. It is not possible to anaesthetise or 'freeze' the entire uterus so you will experience some abdominal discomfort during the procedure which most women describe as cramping period-like pain (it should be noted that the uterus does not sense heat). The discomfort experienced varies from woman to woman but is usually described as mild to moderate although some women may experience more severe cramping pain. The time taken to complete either ablation procedure is under 10 minutes and you can request the treatment to be stopped at anytime if the discomfort is not tolerable, although this situation is unusual.

Following the procedure you will return to the hospital ward where you will be encouraged to drink and be given pain killers if required. Over the next 1-4 hours most women will continue to experience cramping period-like pain, which gradually settles, and the majority of women are discharged within 2-6

hours following the procedure but occasionally some patients may be required to stay in overnight. Any abdominal discomfort, should settle over the next 24 hours and you will be given simple pain killers to control this. It should be noted that the procedures do not require any cuts or stitches.

What else will I be asked to do?

Before you have the surgery, you will be asked to complete a questionnaire to assess you're menstrual bleeding (heavy periods) and how this bleeding affects you. After the procedure, but before discharge from hospital, you will be asked to rate the amount of discomfort associated with the procedure and comment upon your experience. The same questionnaire will be sent to you at home 3, 6,12 and 24 months after the surgery and then once more at 5 years after surgery. You will not need to make any special trips back to the hospital. There are four parts to the questionnaire - your assessment of your menstrual bleeding and related symptoms, what additional treatment you have taken for your bleeding, questions on how it affects your sexual relationships and some questions to determine your overall state of health and quality of life. The results of the trial will be reported once everyone in it has reached the six-month time point after surgery. We would, however, like you to complete the same questionnaires yearly until 5 years after the surgery to see if the effects of the treatment are long lasting.

What are my rights?

You have the right to be given all-important information about your condition, your treatment, the COAT study and what you will be asked to do if you decide to take part. You should only agree to take part if you feel happy that you know enough about all these things. You do not have to take part in the study if you do not want to. **If you decide not to take part in this research, your doctor will respect your decision and advise you of the current standard treatment options that are available.** If you do agree to take part, you are entitled to withdraw from the study at any time without having to give a reason. This will not affect your medical care in any way either.
Whether or not you take part in the study, you have the right to confidentiality of your medical records (although we will inform your GP that you are taking part in the COAT study, unless you object). If you agree to take part, your doctor will send basic information about you and your condition to the study's central organisers at the University of Birmingham Clinical Trials Unit to allow the results to be analysed. The information will be kept securely and in strict confidence. The questionnaires will be identified only by a code number and will not be seen by your doctor. No named information about you will be published in the trial report. If there are any further questions, you can ask your doctor or contact:

Mr T.J. Clark	**Jan Godwin**
Consultant Gynaecologist	**Charge Nurse**

Both are based at Birmingham Women's Hospital, Birmingham. B15 2TG

Appendix 7: Patient consent form for COAT

COAT

PATIENT CONSENT FORM

A RANDOMISED CONTROLLED TRIAL TO COMPARE THE EFFECTIVENESS OF OUTPATIENT ENDOMETRIAL ABLATION TECHNIQUES (NOVASURE VERSUS THERMACHOICE) IN THE TREATMENT OF MENORRHAGIA

I ..... agreed to take part in the COAT study, which has been explained to me by Dr.

The explanation included .....

- a patient information sheet which I have read, understood and accepted
- the purpose and length of the study
- What the study involves, if I take part

I understand that I am free to withdraw from this study at any time and that, if I do, this will not adversely affect my future treatment. I am aware and agree that information obtained during the study will be sent to the central study organisers for analysis, where it will be treated as strictly confidential and nothing identifying me personally will be made publicly available.

Signature of patient ..... Date .....

Signature of investigator ..... Date .....

Appendix 8: Letter to patient's general practitioner for COAT.

Doctors name

Ambulatory Gynaecology Department

Birmingham Women's Hospital

Edgbaston

Birmingham

B15 2TG

NAME
DATE OF BIRTH
HOSPITAL NUMBER
DATE RANDOMISED
TRIAL NUMBER

Dear Dr *gp*,
You will be aware that your patient named above has had heavy menstrual bleeding which has not responded to medical therapy and has been seen by Dr *consultant* at *hospital*. With her written consent, she is participating in a clinical trial named **COAT** to compare the effectiveness of two outpatient endometrial ablation techniques (Thermachoice™ and NovaSure™) for the treatment of heavy menstrual bleeding refractory to medical therapy.
If she fulfils all the surgical eligibility criteria she will have her operation on *date.* Treatment allocation will be Thermachoice™ or NovaSure™ ablation of the endometrium. The result of the randomisation cannot be disclosed until the end of the trial, which is anticipated to be December 2005. The patient will receive postal questionnaires, including questions on menstrual bleeding and related symptoms, quality of life, sexual function and demands on health care resources, at 3, 6, 12, 24 and 60 months post-operatively.
The patient should not need any additional treatment for her menstrual bleeding, but the trial does not preclude GP intervention. The investigators do not anticipate that there will any complications that would necessitate the unblinding of the treatment, but in exceptional circumstances the consultant has a record of the treatment, which is kept separate from her notes.

The local co-ordinator for the trial is Mr Clark, Consultant Gynaecologist, Birmingham Women's Hospital, Birmingham, B15 2TG. Ethical approval from the Local Research Ethics Board has been granted.

Please file this letter in the patient's notes. I would appreciate being notified if there are any errors or if she is no longer one of your patients.

Yours sincerely,

Justin Clark.
Trial Co-ordinator

Appendix 9: Randomisation form for COAT

COAT REGISTRATION AND RANDOMISATION FORM

Patient Surname: ..... **Forenames:** .....

Address: .....

..... **Postcode:** .....

Date of Birth: ____/____/____ ..... **Hospital Number:** .....

Hospital:

Referring Surgeon: ..... **Patient GP** .....

Patient GP Address: .....

PRE-ABLATION ELIGIBILITY CHECKLIST : Complete in clinic

- ❍ Women with heavy menstrual bleeding without organic pathology (DUB)
- ❍ Duration of symptoms over 6 months
- ❍ Age over 25
- ❍ No desire to preserve fertility
- ❍ Negative effect of symptoms on life quality
- ❍ Non-response to recommended medical treatment
- ❍ No previous open myomectomy or endometrial ablation / resection
- ❍ Uterine cavity length less then or equal to 11cm
- ❍ Premenopausal follicular follicle stimulating hormone (FSH) level less than 40 IU/L.
- ❍ Prepared to undergo endometrial ablation without general anaesthesia
- ❍ Written informed consent given.

Patient is <u>eligible</u> if all clinical questions are ticked 'yes'.

☎

Pre-Ablation Registration:

Fax: 0121 414 7602

Randomisation line: 0800 371969 Or 0800 731 7625

TREATMENT ALLOCATION

Thermachoice™ ☐

NovaSure™ ☐

Trial number ☐

Signed: ..... Date of Randomisation: / /

Appendix 10: Surgical treatment form for COAT

Patient Surname: ..... **Forenames:** .....

Address: .....

Date of Birth: ..... **Hospital Number:** .....

Hospital: ..... **Referring Surgeon:** .....

GENERAL INFORMATION

- Age: _____
- Parity: _____ (_____ vaginal _____ C/S)
- Occupation: _____ part-time ☐ full-time) ☐
- Partners occupation: _____
- Sexually active: Yes ☐ No ☐

CLINICAL INFORMATION

- Duration of symptoms: _____ years _____ months
- Flood or pass large clots: Yes ☐ No ☐
- Cycle regularity: Regular / Irregular (please circle)
- Past or present treatment for periods (you may tick more than one category):

None	☐	Mefanamic acid	☐	Tranexamic acid	☐
Combined oral contraceptive	☐	Oral progestin	☐	Depot / implant progestin	☐
Mirena	☐	Hysteroscopic myomectomy	☐		
Other	☐	(please state) _____			

- Period pain: Yes ☐ No ☐
- Pain killers: Yes ☐ No ☐
- Pre-menstrual symptoms: Yes ☐ No ☐
- Significant medical conditions: (please state) _____

ADDITIONAL INFORMATION *(Your doctor will complete this section)*

- Antiplatelet / coagulants: Yes ☐ No ☐
- Pre-treatment GnRH-a**:** Yes ☐ No ☐
- LMP: ____/____/____
- Phase of cycle: prolif / sec / mens / other (circle &confirm at hysteroscopy)
- BMI: _____
- Uterine axis: anteflexed / retroflexed / axial (please circle)
- Uterine length: _____ cm
- Operating surgeon: _____ Grade:_____
- Pre-treatment GnRH-a**:** Yes ☐ No ☐

Signed: ..... Date of completion: / /

Appendix 11: Search History for polypectomy systematic review

1. MEDLINE; exp POLYPS/; 26612 results.

2. MEDLINE; (endometri* OR uter*).ti,ab; 205911 results.

3. MEDLINE; (surgery OR currettage OR hysteroscopy OR polypectomy).ti,ab; 809885 results.

4. MEDLINE; 1 AND 2 AND 3; 408 results.

5. EMBASE; exp POLYP/; 50684 results.

6. EMBASE; (endometri* OR uter*).ti,ab; 229380 results.

7. EMBASE; (surgery OR currettage OR hysteroscopy OR polypectomy).ti,ab; 1012684 results.

8. EMBASE; 5 AND 6 AND 7; 1114 results.

9. CINAHL; exp POLYPS/; 1771 results.

10. CINAHL; (endometri* OR uter*).ti,ab; 8907 results.

11. CINAHL; (surgery OR currettage OR hysteroscopy OR polypectomy).ti,ab; 69959 results.

12. CINAHL; 9 AND 10 AND 11; 12 results.

Appendix 12. Patient information leaflet for MERT

Birmingham Women's NHS
NHS Foundation Trust

Birmingham Women's Hospital
Metchley Park Road
Edgbaston
Birmingham
B15 2TG

Switchboard: 0121 472 1377

MERT

A Randomised Controlled Trial of Mechanical versus Electrical Instrumentation for Outpatient Polypectomy

PARTICIPANT INFORMATION SHEET

MERT information leaflet version 1.0 11/11/11

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

Invitation to participate a new technology study
You are invited to take part in a research study to find out which is the best treatment to remove polyps in the outpatient setting. The study is entirely voluntary – you do not have to take part, nor give a reason why, if you decide not to. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it would involve if you do choose to take part. Please take your time to read this information carefully. Talk to others such as family, friends or your GP about the study if you wish. If there is anything that is not clear, or you would like more information you should ask your gynaecologist or clinic nurse for further advice.

What is the procedure that is being tested?
Outpatient polyp treatment with electrical operating instruments compared to mechanical operating instruments.

What is a polyp?
A polyp is an overgrowth of tissue that may be the cause of your bleeding or infertility. Polyps can be found at the cervix (neck of the womb) or inside the uterus (womb). Polyps require removal for examination under the microscope.

What is the purpose of the study?
Outpatient polyp treatment can be performed in a few different ways but generally involves passing a special type of hysteroscope (3-6 millimetre in diameter) into the womb through which specifically designed miniature operating instruments are passed to remove the polyp(s). At present the most commonly used instruments use an electrical cutting edge. However, a new instrument using a mechanical cutting edge has come to market. In patients having a general anaesthesia the mechanical cutting instrument has been shown to be easier to learn, more effective at completely removing polyps and quicker. However, the instrument is slightly larger, which could potentially cause more discomfort and prolong the procedure in the outpatient setting. Therefore, we want to compare the electrical and mechanical instruments for speed, completeness of polyp removal and patient acceptability.

Do I have to take part?
No. Taking part is entirely voluntary and it is up to you to decide. If you do not wish to take part your decision will not affect the standard of care you will receive.

If I take part will I be treated with the electrical or mechanical operating instruments?
Women are allocated at random to either electrical or mechanical operating instruments by the central study office. There is an equal chance of being allocated to the mechanical instrument or electrical instrument group. Neither you nor your gynaecologist will know which of the groups you will be in until after you have been entered into the study. This means that doctors can not choose which women will receive which treatment and this makes the results much more reliable. This is called a 'randomised clinical trial' and it is the standard medical research method for comparing treatment.

What will happen to me if I take part?
If a polyp is seen on diagnostic hysteroscopy you will be eligible to enter the trial. The diagnostic hysteroscopy usually takes 2-5 minutes and the process of randomisation will prolong the procedure by up to 2 minutes. Depending on the local circumstances you will then either have the polyp removed immediately or you will be listed on an outpatient operative list at a later date. The operative procedure usually takes 5-20 minutes on average. In some cases the procedure requires local anaesthetic to be applied to the neck of the womb to help make the procedure easier and more comfortable. After the procedure you will be given a short, confidential, questionnaire about your experience.

How will I feel during and after outpatient polyp treatment?
During the procedure you may get some crampy period type pains in your lower abdomen, which usually settle once treatment is completed. If it does not the nurse will give you some simple painkillers. A minority of women may feel a little faint following the procedure requiring them to lie down for a few minutes until the sensation passes. Light spotting or fresh blood loss is not uncommon but again should settle within a few hours of the procedure, although some women may experience light vaginal blood loss for a few days. After the procedure you will be able to rest and have a cup of tea in comfortable surroundings. It is advisable to have someone with you when you get home. You will need to rest for the remainder of the day. If you do require

further pain relief, we suggest simple painkillers such as paracetamol every 6 hours.

What are the alternatives for diagnosis and treatment?
The vast majority of doctors recommend removing polyps with the aim of improving symptoms and examining the removed specimen to make sure that they are not precancerous, which would require additional treatment. However, most polyps are not worrying and some may even disappear on their own naturally, but this is uncommon and generally applies to very small polyps only. Another alternative is to remove the polyp at a later date as a day-case procedure under a general anaesthetic

What are the risks and disadvantages of taking part?
Outpatient treatment of polyps is widespread in the NHS and all doctors involved will have the relevant experience. Both the electrical and mechanical instruments for polyp removal have been shown to be safe.

What happens when the research study stops?
When the results of the study are known they will be published in medical journals and the results circulated to medical staff and participants. The results will influence the way women with polyps are treated in the future.

What are the side effects of treatment received when taking part?
Minor side-effects of hysteroscopy include prolonged blood stained vaginal discharge, and infection of the womb lining or bladder (cystitis requiring a short course of antibiotics). Some women can experience severe, cramping period-like pain and some may feel faint for a few minutes immediately following the procedure. The only serious and rare complication specific to the procedure of polyp removal is making a hole in the wall of the womb ('perforation'), which normally heals naturally, but occasionally can cause bleeding or damage to other organs in the abdomen that requires immediate abdominal surgery to repair.

Are there any benefits for me from taking part in the study?
Participants may not gain any individual benefit. However, if the mechanical polyp removal instruments are better, in the future women could benefit in terms of speed, safety and acceptability.

What if there is a problem?
Any compliant about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information is given in Part 2.

Will my taking part in the study be kept confidential?
Yes. The study will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2

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

What if there is a problem?
You have the same legal rights whether or not you take part in this study. If you are not satisfied with any aspect of the way you have been approached or treated during the course of this study, you should speak to the researchers who will do their best to answer your questions (Mr Justin Clark, Chief investigator, Tel:0121 607 4712). If you remain unhappy and wish to complain formally, the normal NHS complaints mechanisms are available and you should ask for the complaints manager at the hospital. Taking part in the trial should not affect any private medical insurance you may have, but you are advised to contact your medical insurance provider to confirm this.

Will information about me be kept confidential?
Yes, all information will be kept strictly confidential like your other medical records. If you agree to take part, your doctor will send basic information about you and your condition to Birmingham Womens Hospital. This information will be put into a computer and analysed by the study staff only. The questionnaires will not contain your name and will be identified using code number and not be seen by your GP or gynaecologist. No named information about you will be published in the study report. Occasionally, inspectors of clinical study data are undertaken to ensure that, for example, all participants have given consent to take part. But, apart from this, only the study organisers will have access to the data.

Involvement of the General Practitioner
With your consent we will inform your GP of your participation in the trial.

What will happen to the results of the research study?
It is expected that the results will be reported in a medical journal around 12months after recruitment is completed. Everyone who takes part will then be told the results in a newsletter that will be posted directly to them.

Who is funding and organising the research?
The study researchers have received support from the instrument manufacturers.

The doctors and researchers involved are not being paid for recruiting women into the study. Patients are not paid to take part either, but their help in finding out more about how best to treat polyps is much appreciated.

Who has reviewed the study?
All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity.

Do you have any further questions?
Having read this leaflet, it is hoped that you will choose to take part in the trial. If you have any questions about the study now or later feel free to ask your gynaecologist or clinic nurse. Their names and telephone numbers are given below. Please take the time before your appointment to decide whether you wish to take part in the trial. You may like to discuss your decision with friends or relatives.

The UK Clinical Research Collaboration has produced a guide entitled, 'Understanding Clinical Trials'. This can be down loaded from their website: www.ukcrn.org.uk and maybe useful if you require general information about research. If you require specific information about the research project please contact any of the trial staff listed below.

Contact details
Local Study Organisers:
Doctor:……..
Nurse:……..
Central Study Organisers:
Mr Justin Clark, Chief investigator, Consultant Gynaecologist, Birmingham Women's Hospital, Metchley Park Road, Edgbaston, Birmingham B15 2TG

Appendix 13: Patient consent form for MERT.

MERT

A Randomised Controlled Trial of Morcellation versus Bipolar Resectoscopy

Participant Consent Form

	Please initial each box to confirm consent
I confirm that I have read and understand the information sheet for the above study. I have had the opportunity to consider the information, ask questions and these have been answered satisfactorily.	☐
I understand that my participation is voluntary and that if I take part, I am free to withdraw at any time, without giving a reason, and without my medical care or legal rights being affected.	☐
I accept that the study researchers may telephone or email me, if necessary, to remind me to complete questionnaires, or to ask the questions over the phone.	☐
I understand that the personal information and details about my treatment will be used for medical research only. I will not be identified in any way in the analysis and reporting of the results. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Birmingham Women's Hospital or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my record.	☐
I agree to my GP being informed of my participation in the MERT Trial. I understand my GP may be contacted to obtain information about any complications or further gynaecology consultations.	☐
I understand what is involved in the trial, agree to participate and be randomised between trial treatments.	☐

……	……	……..
Name of Patient	Date	Signature
……	……	……..
Name of Person taking consent	Date	Signature

Trial Number ☐☐☐

MERT consent form version 2 22/11/11

Appendix 14: Surgical treatment form for MERT.

MERT **MERT: Morcellation and Electrical Resection Trial**

TREATMENT FORM

Patient details

Trial Number: …….. Patient initials: …… Weight (kg): …….

Date of birth (dd/mm/yyyy): ……../……./…… Height (cm): ……

Parity: …… (Vaginal: ……. C/S: ……..)

Indication for surgery: Bleeding ☐ Fertility ☐ Incidental ☐

Menopausal status: Premenopausal ☐ Postmenopausal ☐

Morcellator ☐ **Versapoint** ☐ Date of procedure: ……../……./……

If Versapoint, please state make, size and angle of hysteroscope……..

……

Polyp(s):
Number: ……. Size (cm, to 1 decimal place): …… (largest if multiple)

Location(s): anterior ☐ posterior ☐ left lateral ☐ right lateral ☐
fundal ☐ isthmic ☐ left cornual ☐ right cornual ☐

Type: sessile ☐ pedunculated ☐ both ☐

Consistency: Glandulo-cystic ☐ Fibrous ☐

Surgical technique:
Local anaesthetic: None ☐ Direct cervical ☐ Paracervical ☐ Topical ☐

Cervical dilatation: Yes ☐ No ☐

Speculum ☐ No speculum (i.e. 'vaginoscopic' polyp removal) ☐

Complete polyp removal ☐ Partial removal ☐ Failed removal ☐
If failed or partial removal please state why:
Patient discomfort ☐ Inadequate visualisation ☐
Unable to locate 'blindly' ☐ Equipment failure ☐
Other ☐ (if Other, please state) ……..

Complications: (attach separate sheet if necessary)
None ☐ Vaso-vagal episode* ☐ Cervical trauma ☐ Uterine perforation ☐
Haemorrhage ☐ Other ☐ (if other please state)……

Prolonged post-operative stay (>1 hour stay due to a CLINICAL reason) Yes ☐ No ☐

MERT **MERT: Morcellation and Electrical Resection Trial**

TREATMENT FORM

Time taken
From insertion to removal of vaginal instrumentation post randomisation…… (mins)

From insertion of instrument for polypectomy (i.e. versapoint or Truclear) to removal of

vaginal instrumentation …….. (mins)

Analgesia
Pre-operative (ask patient) Yes ☐ No ☐ (If Yes please specify) ……..

Post-operative Yes ☐ No ☐ (If Yes please specify) ……

Name and grade of surgeon ……

Grade: Consultant ☐ Other ☐ if other, please specify: ……

Signed: …… Date: ……/……/…… (dd/mm/yy)

* Definition of vaso-vagal episode: unable to get off examination couch within 5 minutes due to dizziness, feeling faint or nausea.

Appendix 15: Pre-procedure patient questionnaire for MERT.

MERT

A Randomised Controlled Trial of Morcellation versus Bipolar Resectoscopy

Pre Procedure Questionnaire

Thank you very much for taking part in the MERT study

Before you have your treatment we would be grateful if you would complete this short questionnaire. The completed questionnaire should be handed into one of the nurses or ward staff. If you take it home with you could you return it as soon as possible to the FREEPOST address given below:

MERT Study Office, FREEPOST Minimal Access Research Team, Birmingham Womens Hospital, Birmingham B15 2TG

Thank you again for your participation in the MERT study, your time and interest are very much appreciated

The MERT study is organised by the University of Birmingham Clinical Trails Unit.

The MERT study staff will return this completed questionnaire in the pre-paid envelopes to:

MERT Study Office
FREEPOST
Minimal Access Research Team
Birmingham Womens Hospital
Birmingham
B15 2TG

MERT study staff, please complete at hysteroscopy clinic:

MERT Study No.

☐☐☐☐

Patient Initials

☐☐☐

Date form completed: ../../..

Date of procedure: ../../..

Centre name: .....

Assessment of baseline pain level

We would like to assess how much lower abdominal pain you experienced before your treatment. Please place a mark **(x)** on the lines shown below to indicate how much pain you had. One extreme of the line represents "no pain at all" while the other represents "as much pain as you can possibly imagine".

1. Pain before the procedure

No pain at all _____ Worst imaginable pain

2. We are also interested in knowing how much pain you have currently with your periods. Please tick the most appropriate box:

- I do not have periods ☐
- I get little or no period pain ☐
- I get a moderate amout of period pain ☐
- I get some severe period pain ☐
- I get very severe period pain ☐

Thank you for taking the time to complete this questionnaire

Please check that you have answered each question on this page.

Appendix 16: Post-procedure patient questionnaire for MERT.

MERT

A Randomised Controlled Trial of Morcellation versus Bipolar resectoscopy

Post Procedure Questionnaire

Thank you very much for taking part in the MERT study

You have now had your treatment and we would be grateful if you would complete this short questionnaire about your experience before you go home. The completed questionnaire should be handed into one of the nurses or ward staff. If you take it home with you could you return it as soon as possible to the FREEPOST address given below:

MERT Study Office, FREEPOST Minimal Access Research Team, Birmingham Womens Hospital, Birmingham B15 2TG

Thank you again for your participation in the MERT study, your time and interest are very much appreciated

The MERT study is organised by the University of Birmingham Clinical Trails Unit.

The MERT study staff will return this completed questionnaire in the pre-paid envelopes to:

MERT Study Office
FREEPOST
Minimal Access Research Team
Birmingham Womens Hospital
Birmingham
B15 2TG

MERT study staff, please complete at hysteroscopy clinic:

MERT Study No.

☐☐☐☐

Patient Initials

☐☐☐

Date form completed: ..../..../....

Date of procedure: ..../..../....

Centre name: .....

Assessment of polypectomy experience

We would like to assess how much abdominal pain you experienced during and after your treatment. Please place a mark **(x)** on the lines shown below to indicate how much pain you had. One extreme of the line represents "no pain at all" while the other represents "as much pain as you can possibly imagine".

1. Pain during the procedure

No pain at all _____ Worst imaginable pain

2. Pain at 15 minutes post-procedure/or at discharge if earlier

No pain at all _____ Worst imaginable pain

3. Would you describe the procedure as:

Totally acceptable	☐	Generally acceptable	☐
Fairly acceptable	☐	Unacceptable	☐

4. Please give any comments about your treatment experience: ……..

……...

Thank you for taking the time to complete this questionnaire

Please check that you have answered each question on this page.

Appendix 17: Toxicity and known side effects form for MERT.

Complications of uterine instrumentation (diagnostic hysteroscopy, 'blind' mechanicalpolypectomy, mechanical or electrosurgical polypectomy under direct hysteroscopic vision) are as follows:

- Genital tract infection
- Uterine trauma
- Haemorrhage
- Uterine perforation leading to exploratory laparoscopy / laparotomy to exclude or repair damage to internal abdominal structures (e.g. bowel, urinary tract) or stop internal bleeding

Side-effects specific to outpatient polypectomy:

- Intravascular injection of local anaesthetic resulting in depression of the central nervous system (dizziness, light-headedness, feeling of inebriation, nausea and vomiting, circumoral anaesthesia and feeling of numbness, auditory disturbance (tinnitus), visual disturbance (difficulty focusing, blurred vision), tingling ('pins and needles'), disorientation and nervousness, drowsiness and loss of consciousness, shivering and twitching, fitting) and cardiac toxicity (arrhythmias, bradycardia, hypotension, asystole (cardiac arrest))
- Vaso-vagal reaction (episode of hypotension, bradycardia, pallor and fainting associated with feelingcold, sweaty, shivery and vomiting. Usually self-limiting but may require medical intervention (e.g. intravenous line, blood pressure support, atropine reversal)

The information within this form was copied from the 'toxicity and known side effects form' developed for the outpatient polypectomy trial (OPT) [194].

Appendix 18: Serious adverse event form for MERT.

MERT

A Randomised Controlled Trial of Morcellation versus Bipolar Resectoscopy

SERIOUS ADVERSE EVENT FORM

Please report any serious and unexpected adverse events that are suspected to be due to treatments[1] given as part of the trial by sending or faxing the following details to the trial office (Fax: 0121 415 9135) within 2 days of the event.

Patient Identification:
Patient's full name: ……
Trial No: ……..
Date of birth: day/month/year …../…../…..
Centre Name: ……..
Responsible doctor: ……..

Associated Treatment:
Morcellation ☐ Bipolar resectoscopy ☐
Date of treatment: day/month/year …../…../…..

SAE description:
Category of event: Death ☐ Life threatening ☐
Hospitalisation (or prolongation of) ☐ Persistent or significant disability/incapacity ☐
Date SAE started: day/month/year …./…. /….
Date SAE ceased: day/month/year …./…. /….

Outcome:
Fatal ☐ Recovered Continuing ☐
Details of adverse event (please attach copies of relevant reports):
……
……
……
……
……

Did the event require or prolong hospitalisation? No ☐ Yes ☐ No. of days ☐
Please give reasons why you consider the event to be treatment related:
……
……
……
……
……

Name of person reporting (please print):……
Signed: ……
Tel No: …… Date: day/month/year …../….. /…..

[1]For the purposes of this study, "**serious**" adverse events are those that are fatal, life-threatening, disabling or require hospitalisation. "**Unexpected**" adverse experiences are defined as those that would not be expected among patients given these treatments. It is not required to report in this way side-effects or adverse events that might reasonably be expected.

Appendix 19: Letter to patient's general practitioner for MERT.

MERT

A Randomised Controlled Trial of Morcellation versus Bipolar Resectoscopy

GP INFORMATION SHEET

Dear Doctor *Name of Doctor*

Your patient ……

Date of Birth: date/month/year ……/……../…… MERT trial No: ……

Date randomised: date/month/year ……/……../……

was referred to the outpatient hysteroscopy clinic. With her written consent, she has agreed to participate in the Morcellation versus Electrical Resection Trial (MERT).

On finding a benign intrauterine polyp during diagnostic hysteroscopy, randomisation was carried out to decide whether the polyp should be removed using instruments with a mechanical cutting edge or those using electrical cutting point. There is no long term follow-up of the patient other than the routine care they would expect for the condition they were referred for.

The Chief Investigator for MERT is Dr Justin Clark, Consultant Obstetrician and Gynaecologist, Birmingham Women's Hospital, United Kingdom B15 2TG, . Please file this letter in the patient's notes. Please contact the MERT Trial Office Tel: 0121 627 4712 if there are any errors in the details above or if she is no longer one of your patients.

Yours sincerely

Name of Local Study Doctor