AMBULATORY GYNAECOLOGY: GUIDELINES AND ECONOMIC ANALYSIS

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ABSTRACT

The aim of this thesis was to investigate the role of outpatient hysteroscopy in modern gynaecological care by conducting a series of systematic reviews and meta-analyses to examine how the procedure can be optimised to reduce pain and by performing a cost effectiveness analysis.

The systematic reviews concluded that women undergoing outpatient hysteroscopy should take simple analgesia beforehand and that the hysteroscopist should adopt a vaginoscopic approach using a small diameter, rigid hysteroscope and normal saline as the distension medium. If dilatation of the cervix is required this should be done under a paracervical block. These findings were incorporated into a clinical guideline and the quality of the evidence that the reviews provided was assessed using the SIGN and GRADE methods. A comparison of the assessments found that they gave varying estimates of the quality of evidence and that neither offered a perfect solution to the assessment of evidence quality when writing clinical guidance.

The economic analysis found that initial testing with outpatient hysteroscopy was the most cost-effective testing strategy for investigation of heavy menstrual bleeding when compared to other diagnostic tests, regardless of a woman's wish for future fertility or prior treatment with a levonorgestrel intrauterine system.

DEDICATION

To my family

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LIST OF ABBREVIATIONS

AUB	Abnormal uterine bleeding
BMI	Body mass index
BSO	Bilateral salpingo-oophorectomy
BWH	Birmingham Women's Hospital
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CI	Confidence interval
D&C	Dilatation and curettage
DUB	Dysfunctional uterine bleeding
EA	Endometrial ablation
EBx	Endometrial biopsy
FIGO	International Federation of Gynaecology and Obstetrics
FPR	False positive rate
GnRH-a	Gonadatrophin releasing hormone antagonist
HMB	Heavy menstrual bleeding
HRG	Health resources group
HRQL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
LNG-IUS	Levonorgestrel intrauterine system
NICE	National institute for health and clinical excellence
NHS	National Health Service

NSAIDs	Non-steroidal anti-inflammatories
OPH	Outpatient hysteroscopy
QALY	Quality adjusted life years
RCT	Randomised controlled trial
SIS	Saline infusion sonography /scan
SR	Systematic review
TAH	Total abdominal hysterectomy
TPR	True positive rate
TVS	Transvaginal ultrasound scan
UAE	Uterine artery embolisation
WTP	Willingness to pay

CHAPTER 1

THESIS OVERVIEW AND OBJECTIVES

In recent years the 'classical' inpatient hysteroscopy, which allows gynaecologists to visualise the lining of the womb has evolved into a diagnostic and therapeutic outpatient procedure. The Royal College of Obstetricians and Gynaecologists (RCOG) has published standards of care stating that 'outpatient-based diagnostic services should be available in the community and hospital setting, including operative procedures for carefully selected cases'(1). For this to be possible, outpatient hysteroscopy (OPH) needs to be acceptable to patients and to be cost-effective when compared to alternative outpatient diagnostic testing strategies such as transvaginal ultrasound scan (TVS) and global endometrial biopsy (EBx).

The aim of this thesis was to investigate the role of outpatient hysteroscopy in modern gynaecological care. There are two themes within the thesis. The first examines how outpatient hysteroscopy can be optimised using systematic reviews. A clinical guideline was then produced to recommend 'best-practice' for outpatient hysteroscopy. The quality of the evidence behind the guideline was then graded and examined using two guideline methods.

The second theme within the thesis looks at the cost-effectiveness of outpatient hysteroscopy and other diagnostic tests in the investigation of heavy menstrual bleeding. The aim of this analysis is

to determine the most cost-effective diagnostic strategy for investigating women who present to secondary care with HMB.

Project objectives

The thesis objectives are as follows:

- to examine different aspects of outpatient hysteroscopy and perform systematic reviews to determine how best they can be adapted to make the procedure as tolerable as possible for patients.
- to use the data from the systematic reviews to write a ‘Green-top’ style guideline and a compare the evidence gradings produced with those allocated by the GRADE guideline process.
- to examine strategies for investigating HMB to see if outpatient hysteroscopy is a cost-effective option when compared to other outpatient diagnostic tests.

CHAPTER 2

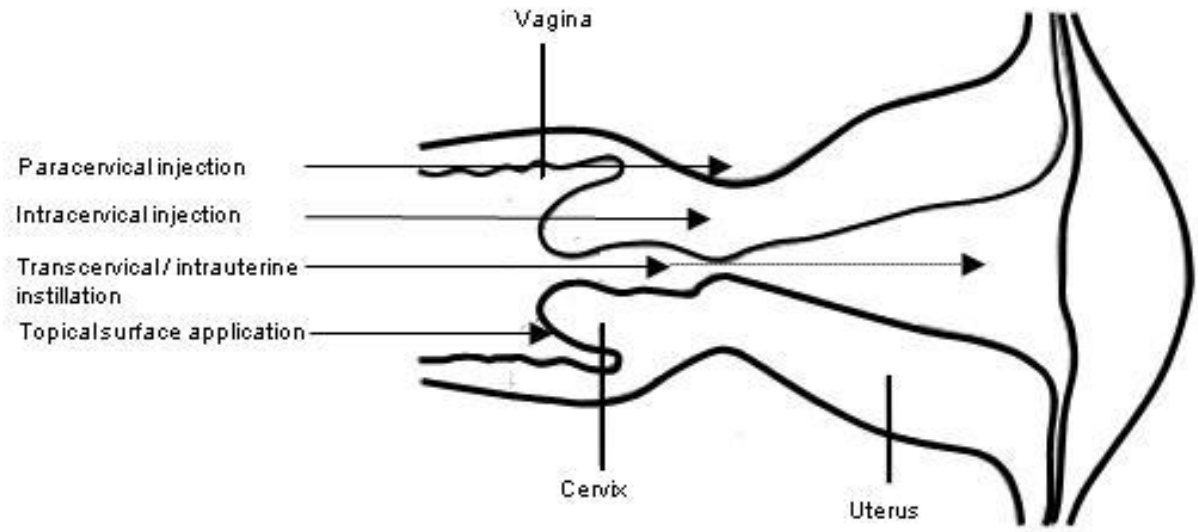
INTRODUCTION TO A SERIES OF SYSTEMATIC REVIEWS AND META-ANALYSES WHICH INVESTIGATE PAIN REDUCTION IN OUTPATIENT HYSTEROSCOPY

Diagnostic and operative outpatient hysteroscopy is feasible, safe and acceptable to women (2-5), however, the outpatient setting can present many challenges, with the conscious patient being less forgiving of induced discomfort (6). To examine how outpatient hysteroscopy can be optimised to reduce pain, different aspects of the procedure can be examined and the available alternative options evaluated. For example, is using normal saline as a distension medium less painful than using carbon dioxide? What method of anaesthetising the cervix is the least painful? Can the procedure be performed without passing a vaginal speculum?

The obvious method of controlling pain is to use pharmaceuticals, whether they are anaesthetics or analgesics. Pain from the body of the uterus is relayed by T12 to L2 nerve roots which are not accessible vaginally (7) and thus cannot be anaesthetised, however the splanchnic plexus nerves (S2-S4) (7) which sense pain from the cervix and lower uterus can be anaesthetised by administering local anaesthetic to the cervix. Vasovagal reactions during outpatient hysteroscopy are reported to occur in 20% of women in the general population (8). Nerve stimulation during passage of instruments through the cervical canal has been suggested as the cause of vasovagal

episodes. It has been theorised that blocking the nerves with local anaesthetic may reduce the incidence of attacks (9-11) but there is also a study which has shown conflicting results (12). Individual studies examining the effect of local anaesthetics are often imprecise and hence provide contradictory results (13). Local anaesthetic can be applied as an injection directly into the body of the cervix (intracervical or direct cervical block) or to the surrounding tissues (paracervical block), or topically to the uterine cavity (transcervical application) or the ectocervix (topical application), these methods are shown in Figure 2.1.

Figure 2.1 Diagram showing the different methods of local anaesthetic administration for outpatient hysteroscopy



A recent review (14) examined the use of paracervical injection for cervical dilatation and uterine interventions in a variety of obstetric and gynaecological procedures, however, there is no

comprehensive review evaluating comparative effectiveness of the whole range of local anaesthetic modalities for specific procedures.

Analgesics block pain receptors and prevent pain signals being relayed to the central nervous system. They can be administered before, during or after procedures to reduce pain. Opiate and non-steroidal inflammatory drugs (NSAID's) have been used to reduce pain during outpatient hysteroscopy as has conscious sedation (6), however no guidance exists on use of analgesics for outpatient hysteroscopy, resulting in eclectic practice.

A compromise between general anaesthesia and analgesics might be to use conscious sedation (i.e. depression of the central nervous system enabling treatment to be carried out, but during which verbal contact with the patient is maintained' (15)) which is widely used in endoscopic procedures of the gastrointestinal system and in dentistry to make unpleasant interventions more acceptable but it is less commonly employed in outpatient hysteroscopy. The Royal College of Anaesthetists has issued guidance on the safe use of conscious sedation by other medical specialties, recommending that a designated trained staff member be responsible for monitoring the patient throughout the sedation and that resuscitation facilities be available (15). This has obvious cost implications on staffing, equipment and recovery areas. To justify these costs there would need to be a large added benefit of using conscious sedation over less compromising medication.

A final group of drugs which may alleviate discomfort during outpatient hysteroscopy are those which can dilate the cervix and potentially aid the passage of the hysteroscope into the uterine

cavity. Hysteroscopy is traditionally an inpatient procedure that requires dilatation of the cervix so that large diameter instruments can be passed into the uterine cavity. Blind mechanical dilatation risks perforation of the uterus, especially where the cervical canal provides more resistance i.e. postmenopausal or nulliparous women or those who have had previous cervical surgery or caesarean section (16;17). Studies examining the use of pharmaceutical (antiprogestogens, prostaglandins) and mechanical (laminaria) dilatation of the cervix prior to inpatient hysteroscopy under general anaesthesia have produced conflicting results regarding their effect on dilatation and trauma during the procedure (18-22).

Prostaglandins are commonly used in gynaecology for inducing dilatation of the cervix for termination of pregnancy and for removing retained products of conception (23). The natural progression from this has been for clinicians to use prostaglandins in non-pregnant women to dilate the cervix and ease access to the uterine cavity for transcervical procedures (24). However, the evidence is unclear as to whether the dilatory effect is apparent in a non-pregnant cervix and prostaglandins have unpleasant side effects (nausea, vomiting and excessive bleeding) (25). Similarly antiprogestogens have also been used to soften the cervix (26) as well as dilatory materials which when inserted into the cervical canal absorb water and cause a mechanical dilatation (18;27;28). Again these methods have associated side effects .Thus any benefit may become outweighed by the associated adverse effects. The technological advances that have resulted in miniaturisation of endoscopic instruments have done away with the need for routine, painful cervical dilatation. However, a significant minority of women undergoing an outpatient procedure will require cervical dilatation with the risks of excessive pain and potential trauma to the genital tract.

As well as investigating pharmaceuticals that can play a role in pain there are technical aspects of the outpatient hysteroscopy procedure that can be adapted to be less painful. The first method explored is vaginoscopy, also known as the 'no-touch' technique which is an alternative method for performing hysteroscopy without the need for a vaginal speculum to view the cervix (29) or cervical instrumentation to grasp and steady it (6). The hysteroscope is inserted into the vagina which is distended with the selected medium, the external cervical os identified and the hysteroscope steered into the cervical canal so that the hysteroscopy can be performed. Distension of the vagina to aid identification of the cervix can be facilitated by a Trendelenburg tilt and manual closure of the labia minora. Individual papers have suggested that use of the vaginoscopic technique is feasible and may reduce the pain of outpatient hysteroscopy (30-33) but no clear, collated summaries of evidence exist.

Once the cervix is traversed and the cavity entered a distending medium needs to be instilled to visualise the uterine cavity. A variety of fluid (normal saline, water, sorbitol, dextran and glycine (34-37)) and gaseous (carbon dioxide (38;39)) media have been used. As with any hollow viscous, distension of the uterine cavity causes pain (irritation of T10 –L2 nerve roots). Moreover, spilling of distension medium into the abdominal cavity can be associated with phrenic (C3-5) nerve irritation and referred pain to the shoulder tip and cervical manipulation may cause vagal stimulation resulting in fainting episodes (6). Image quality is an important consideration and may vary according to medium used.

The final technical aspect of the procedure to explore is the type of hysteroscope used for the procedure. Flexible endoscopes are used to investigate the gastrointestinal and respiratory tracts

as they allow the operator to negotiate the convoluted anatomy. Flexible hysteroscopes are able to exploit this advantage when negotiating the cervical canal and viewing the cornuae (40). Studies have shown that outpatient flexible hysteroscopy is well tolerated (41;42) so this technique was compared to outpatient hysteroscopy using rigid hysteroscopes.

CHAPTER 3

METHODS FOR THE SEVEN SYSTEMATIC REVIEWS AND META-ANALYSES WHICH INVESTIGATE PAIN REDUCTION IN OUTPATIENT HYSTEROSCOPY

Topics for investigation

Seven different aspects of outpatient hysteroscopy were evaluated:

1. the use of local anaesthesia
2. the use of analgesics
3. the use of conscious sedation
4. the use of cervical preparation
5. the vaginoscopic approach
6. different distension media
7. the type of hysteroscope

All of the systematic reviews were conducted prospectively, devising a protocol based upon widely documented methods (43;44).

Data Sources, Searches and Study Selection

A comprehensive literature search was conducted for each of the seven topics to identify relevant studies. The databases searched included Medline (from 1950 to September 2008), EMBASE (from 1980 to September 2008), CINAHL (from 1981 to September 2008) and the Cochrane library. The search terms used are shown in Table 3.1 and the full search strategies are shown in Appendix 1. There were no limits or filters placed on the searches to ensure maximal sensitivity. The reference sections of selected original articles were checked for relevant papers that had not already been retrieved by the database searches. The contents lists from two specialist journals (Gynaecological Surgery and The Journal of Minimally Invasive Gynecology) from November 1993 until 2008 were scrutinised for relevant studies.

The titles and abstracts from the electronic literature searches were reviewed in duplicate (see acknowledgements). The citations were selected if they appeared to fulfil the selection criteria. The selection criteria for each systematic review are shown in Table 3.1.

The complete manuscripts of selected citations were then reviewed in full to reach the final decision on inclusion or exclusion. Studies were excluded if numerical data assessing pain were not presented explicitly (e.g. some papers displayed results graphically such that the mean pain scores could only be estimated from the graph and given this ambiguity were excluded from further analysis). An attempt was made to contact authors for missing data but in some instances this was not possible (11) and in others no reply was received (45-47). When duplicate data were

published, only the most up to date, larger series were included. Any disagreements about study eligibility were resolved by consensus. Inter-rater agreement for study selection was assessed using the kappa statistic (48)

Table 3.1. Search terms and selection criteria for the seven systematic reviews and meta-analyses which investigate pain reduction in outpatient hysteroscopy

Topic	Search terms		Study selection criteria			
	Medline, EMBASE, CINAHL	**Cochrane Library**	**Population**	**Intervention**	**Outcome**	**Study Design**
Local anaesthesia	'hysteroscopy', 'vaginoscopy', 'local anaesthetic' and associated Medical Subject Headings	'hysteroscopy', 'anaesthetic'	Women undergoing diagnostic or operative hysteroscopy in the outpatient setting i.e. without general anaesthesia	Use of local anaesthetic for pain relief during the procedure (e.g. intracervical block, paracervical block, local anaesthetic instilled into the cavity or applied to the ectocervix - see figure 2.1), compared to no intervention, placebo, oral analgesics or conscious sedation.	Assessment of pain (primary outcome) and vasovagal episodes (secondary outcome) associated with the procedure	Randomised controlled trials
Analgesia	'hysteroscopy', 'vaginoscopy', 'analges*and associated Medical Subject Headings	'hysteroscopy', 'analgesia'	As above.	Use of analgesics for pain relief during the procedure compared to no intervention or placebo.	Assessment of pain associated with the procedure (primary outcome) and medication side effects (secondary outcome).	Randomised controlled trials

Table 3.1 continued

Topic	Search terms		Study selection criteria			
	Medline, EMBASE, CINAHL	**Cochrane Library**	**Population**	**Intervention**	**Outcome**	**Study Design**
Conscious sedation	'hysteroscopy', 'vaginoscopy', 'conscious sedation', 'sedative', 'sedati*', 'pain' and associated Medical Subject Headings	'hysteroscopy', 'sedation'	As above	Use of conscious sedation for pain relief during the procedure compared to no intervention or placebo.	Assessment of pain associated with the procedure (primary outcome) and medication side effects (secondary outcome).	Randomised controlled trials
Cervical preparation	'hysteroscopy', 'vaginoscopy', 'cervical ripening', 'laminaria', 'progest*', 'prostaglandin', 'oestrogen' 'cervical preparation' and associated Medical Subject Headings	'hysteroscopy', 'cervical'	As above	Use of cervical preparation prior to the procedure, compared to no intervention, or placebo.	Assessment of pain associated with the procedure.	Randomised controlled trials
Vaginoscopic approach	'hysteroscopy', 'vaginoscopy', 'vaginoscop*', 'no-touch' and associated Medical Subject Headings	'hysteroscopy', 'vaginoscopy', 'vaginoscopic', 'no-touch'	As above	Comparison of the vaginoscopic technique versus hysteroscopy using a vaginal speculum.	Assessment of pain associated with the procedure and feasibility (secondary outcome).	Randomised controlled trials

* is used in the search terms to identify all possible suffixes e.g. analges* will identify analgesia, analgesic, and analgesics

Table 3.1 continued

Topic	Search terms		Study selection criteria			
	Medline, EMBASE, CINAHL	**Cochrane Library**	**Population**	**Intervention**	**Outcome**	**Study Design**
Distension media	'hysteroscopy', 'vaginoscopy', 'vaginoscop*', '(uter* AND disten*)', 'distension media', 'sodium chloride', 'normal saline', carbon dioxide', 'dextran', 'mannitol' and associated Medical Subject Headings	'hysteroscopy', 'distension'	As above	Comparison of the use of carbon dioxide versus another distending medium for the outpatient hysteroscopy.	Assessment of pain associated with the procedure.	Randomised controlled trials
Type of hysteroscope	'hysteroscopy', 'vaginoscopy', 'flexible', 'rigid', 'pain' and associated Medical Subject Headings	'hysteroscopy', 'flexible', 'rigid'	As above	Comparison of the use of flexible versus rigid hysteroscope	Assessment of pain associated with the procedure.	Randomised controlled trials

* is used in the search terms to identify all possible suffixes e.g. analges* will identify analgesia, analgesic, and analgesics

Data extraction

For each systematic review data were extracted from the selected studies using a piloted data extraction form (see Appendix 2 for an example). Data were extracted independently by two reviewers. Data were collected from each trial for study quality (the confidence that the trial design, conduct, and analysis has minimized or avoided biases in its treatment comparisons) (49), the intervention, technical aspects of the outpatient hysteroscopy, assessment of pain and for the relevant secondary outcomes (feasibility, vasovagal episodes, effectiveness, side-effects).

Jadad's scoring method (Appendix 3) which allowed a quality score on a 5-point scale to be calculated (50;51) was used to assess the quality of the selected studies in the systematic reviews of local anaesthetic, analgesia, conscious sedation and cervical preparation. Papers that scored more than three points were considered to be of high quality. For the systematic reviews of vaginoscopy, distension media and type of hysteroscope the scoring system was adapted to allow for the fact that blinding would not have been possible in the studies.

Further information regarding the seven different topics reviewed is detailed in the sections below**.**

Local anaesthetic

Table 3.2 shows the quality assessment of the studies selected for use in the systematic review of the use of local anaesthetic for outpatient hysteroscopy.

Table 3.2. Methodological quality assessment of the studies included in the systematic review of use of local anaesthetic for outpatient hysteroscopy

Study	Randomised	±1	Double blind?	±1	Withdrawals and dropouts	Total	Quality (>3 = high)
Al-sunaidi(52)	1	1	0	0	1	3	Low
Bellati(53)	1	0	0	0	1	2	Low
Broadbent(54)	1	1	1	1	1	5	High
Cicinelli 1997 (9)	1	1	1	1	1	5	High
Cicinelli 1998 (10)	1	1	1	1	1	5	High
Costello(55)	1	1	1	1	1	5	High
Davies (56)	1	1	1	1	1	5	High
Esteve (57)	1	0	1	1	1	4	High
Finikiotis (58)	1	-1	0	0	1	1	Low
Giorda (59)	1	1	0	0	1	3	Low
Guida (60)	1	1	0	0	1	3	Low
Kabli (61)	1	1	0	0	1	3	Low
Lau 1999(12)	1	1	1	1	1	5	High
Lau 2000 (62)	1	1	1	1	1	5	High
Makris (63)	1	0	0	0	1	2	Low
Sagiv (33)	1	1	0	0	1	3	Low
Shankar(64)	1	1	0	0	1	3	Low
Soriano(65)	1	1	1	1	1	5	High
Vercellini (66)	1	1	0	0	1	3	Low
Wong (67)	1	1	1	1	1	5	High

See Appendix 3 for explanation of scoring method.

Studies varied in how pain was assessed. Some studies gave an overall pain score for the procedure. Others scored each of the steps separately (i.e. tenaculum application, administration of anaesthetic or placebo, insertion of the scope, inspection of uterine cavity, during the biopsy and at intervals after the end of the procedure). When an overall pain score was given, this was used for the meta-analysis but when the individual steps were scored, and no overall score was given, the score relating to inspection of the uterine cavity was deemed most appropriate to use rather than the scores for other aspects of the procedure (e.g. cervical dilatation, endometrial biopsy). When scores were only given after the procedure, the most immediate score was used. Vasovagal reactions during outpatient hysteroscopy are reported to occur in 20% of women in the general population (8). Parasympathetic nerve stimulation during passage of instruments through the cervical canal has been suggested as the cause of vasovagal episodes. To examine the incidence of vasovagal episodes in relation to use of local anaesthetics, data were extracted as 2 x 2 contingency tables (occurrence versus non-occurrence).

Analgesia

Table 3.3 shows the quality assessment of studies that were selected for use in the systematic review of analgesia for pain control during outpatient hysteroscopy.

Table 3.3 Methodological quality assessment of the studies included in the systematic review analgesia for pain control during outpatient hysteroscopy

Study	Randomised	±1	Double blind?	±1	Withdrawals and dropouts	Total	Quality (>3 = high)
Bellati (53)	1	0	0	0	1	2	Low
Caligiani (68)	1	0	0	0	1	2	Low
Floris (45)	1	1	1	1	1	5	High
Lin (69)	1	1	0	0	1	3	Low
Nagele (46)	1	0	1	1	1	4	High
Tam (70)	1	1	1	1	1	5	High

See Appendix 3 for explanation of scoring method.

Again, studies varied in how pain was assessed so the same rules were applied to this review as for the local anaesthetic review (see page 17).

Side effects are an important consideration when administering drugs and it must be established whether the benefit of the medication outweighs any adverse effects experienced by the patient, hence the incidence of reported side effects was collected.

Conscious sedation

Only one study was selected from the abstracts of studies which looked at the use of conscious sedation for outpatient hysteroscopy. This was assessed as a low quality study (see Table 3.4).

Table 3.4 Methodological quality assessment of the studies included in the systematic review of conscious sedation for pain control during outpatient hysteroscopy

Study	Randomised	±1	Double blind?	±1	Withdrawals and dropouts	Total	Quality (>3 = high)
Guida (60)	1	1	0	0	1	3	Low

See Appendix 3 for explanation of scoring method.

Cervical preparation

The quality assessment of the studies selected for the systematic review of cervical preparation is detailed in .Table 3.5.

Table 3.5 Methodological quality assessment of the studies included in the systematic review of the effect of cervical preparation on pain during outpatient hysteroscopy

Study	Randomised	±1	Double blind?	±1	Withdrawals and dropouts	Total	Quality (>3 = high)
Atay (71)	1	0	0	0	1	2	Low
Ben-Chetrit (72)	1	1	1	1	1	5	High
Da Costa (73)	1	1	1	1	1	5	High
Singh (74)	1	1	0	0	1	3	Low
Valente (75)	1	1	1	1	1	5	High
Waddell (76)	1	1	1	1	1	5	High

See Appendix 3 for explanation of scoring method.

Data regarding pain were reported in an inconsistent manner so were collected for the most appropriate time point reported. When an overall pain score was given, this was used but when the individual steps were scored, and no overall score was given, the score relating to inspection of the uterine cavity was deemed most appropriate to use rather than the scores for other aspects of the procedure (e.g. cervical dilatation, endometrial biopsy). When scores were only given after the procedure, the most immediate score was used. The evidence is unclear as to whether the dilatory effect of prostaglandins is apparent in a non-pregnant cervix, moreover, any potential benefit has to be weighed against unpleasant side effects (nausea, vomiting, excessive bleeding) and the costs associated with prostaglandin use. Therefore data regarding the effect on dilatation and the presence of side effects were collected in 2 x 2 contingency tables.

Vaginoscopy

The quality assessment of the data for the systematic review of the vaginoscopic technique is shown in Table 3.6.

Table 3.6 Methodological quality assessment of the studies included in the systematic review of the effect on pain of the vaginoscopic approach to outpatient hysteroscopy

Study	Randomisation sequence[a]	Allocation Concealment[b]	Follow-up[c]	Total Adequate
Almeida (77)	Adequate	Inadequate	100%	2
Garbin (31)	Adequate	Inadequate	100%	2
Guida (78)	Adequate	Adequate	100%	3
Paschopoulos (79)	Not reported	Not reported	100%	1
Sagiv (33)	Adequate	Not reported	100%	2
Sharma (32)	Adequate	Inadequate	100%	2

[a]Randomisation adequate if computer generated random number sequence.
[b] Concealment considered adequate if third party e.g. nursing staff. Inadequate if sealed envelopes used.
[c] If the total number of patients entering the trial are accounted for in follow-up it was considered 100%. This is because if the patients have not had the procedure they would be unable to contribute to the results but the authors are able to explain why data are missing for these patients.

The rules regarding pain score data were applied as in the previous reviews. Data regarding feasibility of the procedure were extracted as 2 x 2 contingency tables (successful versus failed procedures).

Distension media

The quality assessment of the data for the systematic review of distension media is shown in Table 3.7

Table 3.7. Methodological quality assessment of the studies included in the systematic review of the effect of the distension medium used on pain during outpatient hysteroscopy.

Study	Randomisation sequence[a]	Allocation concealment[b]	Follow-up[c]	Total Adequate
Brusco (80)	Inadequate	Inadequate	100%	1
Lavitola (81)	Adequate	Adequate	100%	3
Litta (82)	Inadequate	Inadequate	100%	1
Nagele (83)	Inadequate	Inadequate	100%	1
Paschopoulos (35)	Inadequate	Inadequate	100%	1
Shankar (64)	Inadequate	Inadequate	100%	1

[a]Randomisation adequate if computer generated random number sequence.
[b] Concealment considered adequate if third party e.g. nursing staff. Inadequate if sealed envelopes used.
[c] If the total number of patients entering the trial are accounted for in follow-up it was considered 100%. This is because if the patients have not had the procedure they would be unable to contribute to the results but the authors are able to explain why data are missing for these patients.

The majority of studies gave an overall pain score for the procedure. One scored the steps separately (i.e. insertion of the endoscope, inspection of the uterine cavity, during endometrial biopsy and at intervals after the end of the procedure) so the score relating to inspection of the uterine cavity was used as it seemed the most appropriate.

Data were collected regarding image quality as this may be adversely affected by the type of distension medium used. Normal saline has a higher refractive index than air which causes magnification and reduces the visual field (35). Carbon dioxide does not create a lavage and so blood, mucus and bubbles may obscure the image. The different mechanisms of administration (insufflators for carbon dioxide and pressure bags for normal saline) may affect the length of the procedure which prompted the collection of data regarding procedural time. Data regarding shoulder tip pain (a common side effect of gas insufflations caused by gas leaking from the

fallopian tubes and irritating the phrenic nerve) and vasovagal episodes (a common side effect of hysteroscopy) were also extracted.

Type of hysteroscope

The quality assessment of the data for the systematic review of flexible versus rigid hysteroscopes is shown in Table 3.8.

Table 3.8. Methodological quality assessment of the studies included in the systematic review of the effect on pain of the type of hysteroscope used for outpatient hysteroscopy

Study	Randomisation sequence[a]	Allocation Concealment[b]	Blinding[c]	Follow-up[d]	Total Adequate
Baxter (84)	Adequate	Not reported	Single blind	100%	3
Unfried (85)	Adequate	Not reported	Not reported	100%	2

[a]Randomisation adequate if computer generated random number sequence.
[b] Concealment considered adequate if third party e.g. nursing staff. Inadequate if sealed envelopes used.
[c] If the total number of patients entering the trial are accounted for in follow-up it was considered 100%. This is because if the patients have not had the procedure they would be unable to contribute to the results but the authors are able to explain why data are missing for these patients.

Pain data were collected and data regarding failed procedures were collected in 2x2 contingency tables.

Data Synthesis

Meta-analysis of pain data was conducted in the systematic reviews of local anaesthetic, distension media and use of the vaginoscopic approach. The standardised mean difference (SMD) was used because it allowed comparison of outcome data from studies using different scales to quantify pain (43). Heterogeneity was assessed by examining forest plots and the I^2 statistic, which if greater than 75% suggests considerable heterogeneity (43). Studies were weighted by the inverse of the variance and random effects models were used as standard as they give conservative estimates of effect (43). This method was also used to assess the secondary outcome of procedure time in the systematic review of distension media. Data assessing pain with the use of analgesics, conscious sedation, cervical preparation and type of hysteroscope were not suitable for meta-analysis.

Meta-analysis was possible for secondary outcomes in the systematic reviews of local anaesthetic, cervical preparation, vaginoscopy and distension media. For dichotomous outcomes the Peto method was used due to a low incidence of outcome events in the studies (86). Analyses were performed using RevMan software (87).

In the systematic review of local anaesthesia, subgroup meta-analysis was performed for data grouped according to method of local anaesthetic administration (intracervical, paracervical, transcervical and topical) because it was felt that the different methods were not directly

comparable. Meta-regression analysis (88) was then used to explore if one of the four types of local anaesthetic techniques was superior. Meta-regression was performed using Stata (89).

Subgroup analysis was not performed in the six other systematic reviews.

CHAPTER 4

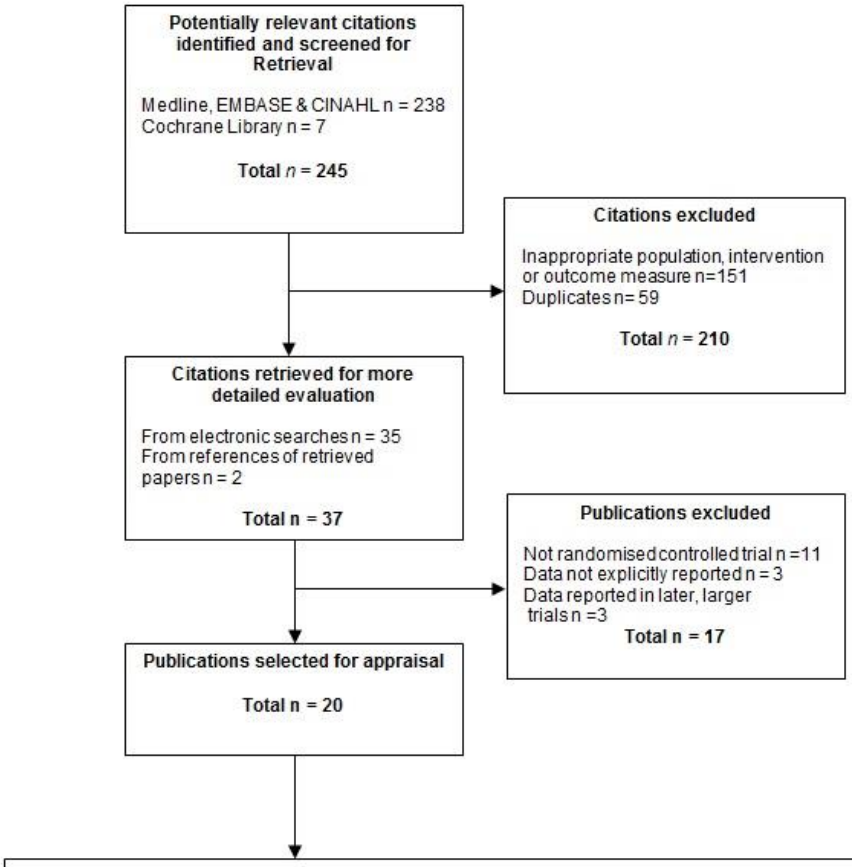
RESULTS OF THE SEVEN SYSTEMATIC REVIEWS AND META-ANALYSES WHICH INVESTIGATE PAIN REDUCTION IN OUTPATIENT HYSTEROSCOPY

Results of the systematic review and meta-analysis of local anaesthesia for pain control during outpatient hysteroscopy

Study Selection, Details and Quality

The literature search yielded 245 citations. Reviewing the reference lists yielded two further citations. Of these, 20 studies were considered eligible for inclusion in the review (Figure 4.1). The inter-rater reliability for the study selection was very good (kappa=0.9). Details of the study populations, intervention, outcome assessment and data reporting are shown in Tables 4.1a- 4.1c. The quality of the studies varied with deficiencies in randomisation and blinding (Figure 4.2).

Figure 4.1 Study selection process for systematic review of local anaesthetic for pain relief during outpatient hysteroscopy



Subgroups	Included in Systematic Review (n)	Included in meta-analysis of pain (n)	Included in meta-analysis of vasovagal episodes (n)
Intracervical			
versus normal saline	1	0	1
versus nil	3	2	0
versus normal saline and versus i.m. tramadol	1	1	0
Paracervical			
versus normal saline	2	2	2
versus nil	3	3	1
versus uterosacral block	1	0	0
versus conscious sedation	1	0	1
Transcervical			
versus normal saline	3	3	2
versus normal saline containing local anaesthesia	2	2	1
Topical			
versus placebo	3	2	1
Total	**20**	**15**	**9**

Of the 20 selected studies, 18 reported data comparing local anaesthetic to placebo or nothing. One of these studies also reported data for a third randomised group of patients who received opiate analgesia (tramadol) (53). Of the remaining two studies, one compared use of local anaesthetic to conscious sedation (midazolam) (60) and the other compared different local anaesthetic regimens (paracervical injection versus uterosacral ligament injection) (58).

Of the 18 papers reporting data for pain relief, three were excluded from meta-analysis; two because data were reported as the median value (56) or the mean but without standard deviation or standard error (63) precluding calculation of the SMD and another because of differences in intervention between the groups in addition to the use of local anaesthetic (33). The majority of the papers used continuous visual analogue scales (VAS) to assess pain, other studies used ordinal numerical or descriptive scales (Tables 4.1a-4.1c).

Tables 4.1a-c Characteristics of the studies included in the systematic review of use of local anaesthetic during outpatient hysteroscopy, subgrouped according to distension media.

Table 4.1a Studies using carbon dioxide as the distension medium

Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Bellati (53) *(Study written in Italian, abstract in English also)*	Women undergoing diagnostic out-patient hysteroscopy and endometrial biopsy.	Intracervical injection of 4ml 2% mepivicaine, 5 minutes before the procedure. N=40	2 groups: 1. Tramadol 100mg i.m. 50 mins pre-procedure. N=40 2. Nil. N=40	Ordinal score 0-20 during the hysteroscopy.	Mean and Standard deviation calculated from raw data.
Broadbent (54)	Women undergoing diagnostic out-patient hysteroscopy for abnormal uterine bleeding. Exclusions: patients who were unable to tolerate the procedure.	Intracervical injection of 10ml 1% lignocaine with 1:200,000 adrenaline, at least 5 minutes before the procedure. N=49	Intracervical injection with 10ml 0.9% saline, at least 5 minutes before the procedure. N=48	Pain defined by selecting a category from none, mild, moderate and severe. Graded before, during, immediately and 30min after the procedure.	Mean and Standard deviation calculated by assigning a numerical value to the groups.
Cicinelli 1997 (9)	Post-menopausal women undergoing diagnostic hysteroscopy and endometrial biopsy because of endometrial bleeding.	2ml 2% mepivicaine injected transcervically through the os into the uterine cavity 5 minutes before the procedure. N=40	2ml 0.9% saline injected transcervically through the os into the uterine cavity 5 minutes before the procedure. N=40	VAS 0-20 completed before, during and 15 minutes after the procedure and during the endometrial biopsy.	Mean and standard deviation reported.
Cicinelli 1998 (10)	Post-menopausal women undergoing diagnostic hysteroscopy and endometrial biopsy because of endometrial bleeding.	Paracervical block of 10ml 1.5% mepivicaine 10minutes before the procedure. N=36	Paracervical injection of 10ml 0.9% saline 10minutes before the procedure. N=36	VAS 0-20 completed before, during and 15 minutes after the procedure and during the endometrial biopsy.	Mean and standard deviation reported.

Table 4.1a continued

Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Costello (55)	Women referred for out-patient hysteroscopy	Scope passed into cervical os until 'snug'. 5ml 2% lignocaine was then injected through the operating channel of the scope. 2 minutes then passed before the procedure continued. N=49	Scope passed into cervical os until 'snug'. 5ml 0.9% saline was then injected through the operating channel of the scope. 2 minutes then passed before the procedure continued. N=50	VAS 0-10cm to score pain during the procedure.	Mean and standard deviation reported.
Davies (56)	Women requiring out-patient hysteroscopy. Exclusions: known sensitivity to lignocaine, epilepsy, significantly impaired respiratory or cardiac function, liver disease, treatment with tricyclic antidepressants or monoamine oxidase inhibitors.	10% lignocaine sprayed onto the endocervix and through the cervical os into the uterine cavity, 10 sprays in total. N=60	Placebo sprayed onto the endocervix and through the cervical os into the uterine cavity, 10 sprays in total. N=60	VAS 10cm to score pain as the tenaculum was applied, the nozzle of the spray inserted into the canal, insertion of the scope, during the procedure, during the biopsy and 5 minutes after the end of the procedure.	Median VAS and interquartile ranges reported.
Esteve (57)	Women attending for out-patient hysteroscopy.	Intracervical injection of 8ml 2% lignocaine. N=34	Intracervical injection of 8ml 0.9% saline. N=28	VAS 0-10 cm to score pain during the hysteroscopy, during the biopsy, at the end of the procedure and 30 minutes after the end of the procedure.	Mean and standard deviation reported.

Table 4.1a continued

Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Giorda (59)	All post-menopausal women referred for diagnostic out-patient hysteroscopy. Exclusions: patient refused to partake, allergy to anaesthesia, previous hysteroscopy, and previous severe vagal reaction to a blind endometrial biopsy.	Paracervical injection of 20ml 1% mepivicaine at least 5 minutes before the procedure. Hysteroscopy performed with a 5mm diameter scope. N=121	2 groups: 1. No paracervical injection. Hysteroscopy performed with a 5mm scope. 2. No paracervical injection. Hysteroscopy performed with a 3.5mm diameter scope. N=119	Visual numerical rating scale ranging from 0 to 10 to score pain during the procedure only (patients who received a paracervical block were asked to discount the pain from the injection from their assessment.)	Mean reported. Standard deviation calculated from standard error.
Lau 1999 (12)	Women undergoing diagnostic outpatient hysteroscopy for abnormal uterine bleeding.	Paracervical injection of 10ml 2% lignocaine 5 minutes before the procedure. N=49	Paracervical injection of 10ml 0.9% saline 5 minutes before the procedure. N=50	VAS 10cm used to score the pain when the tenaculum was applied, after the paracervical injection, at hysteroscopy insertion, during hysteroscopy, after endometrial biopsy and 30 minutes after the procedure.	Mean and standard deviation reported.
Lau 2000 (62)	Women scheduled for diagnostic outpatient hysteroscopy.	5ml 2% lignocaine instilled transcervically into the uterine cavity. N=45	5ml 0.9% saline instilled transcervically into the uterine cavity. N=44	VAS 10cm used to score the pain when the tenaculum was applied, after the paracervical injection, at hysteroscopy insertion, during hysteroscopy, after endometrial biopsy and 30 minutes after the procedure.	Mean and standard deviation reported.

Table 4.1a continued

Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Makris (63)	Women undergoing diagnostic outpatient hysteroscopy ± endometrial biopsy.	Intracervical injection of 1-3ml 3% mepivicaine, 3 minutes before the procedure. N=100	Intracervical injection of 1-3ml 0.9% saline, 3 minutes before the procedure. N=100	Ordinal scale 0-10. Patients asked to rate pain experienced during hysteroscopy and at 30 and 60 minutes after the procedure by circling one of the numbers.	Mean reported. Unable to calculate standard deviation.
Wong (67)	Women referred for investigation of abnormal uterine bleeding or suspected endometrial pathology. Exclusions: women who spoke a dialect (study carried out in China) or had other communication problems.	4ml of 2% lignocaine rubbed over the cervix for 20 seconds immediately before the hysteroscopy. N=250	4ml of KY Jelly (Johnson and Johnson Medical, UK) rubbed over the cervix for 20 seconds immediately before the hysteroscopy. N=250	Patients asked to grade the severity of pain at 1 minute intervals using the PPI scale. The mean pain score, peak pain score and overall pain score were all calculated as were mean pain scores for each of the individual steps of the procedure.	Mean and standard deviation reported.

Table 4.1b. Studies using normal saline as the distension medium

Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Al-sunaidi (52)	Women undergoing diagnostic out-patient hysteroscopy for evaluation of uterine cavity. Exclusions: women needing operative hysteroscopy under GA, positive Chlamydia culture, pregnancy or allergy to local anaesthetic.	Intracervical injection of 2ml 0.5% bupivacaine and paracervical injection of 8ml 0.5% bupivacaine, 5 minutes before the procedure. N=42	Intracervical injection of 2ml 0.5% bupivacaine, 5 minutes before the procedure. N=42	VAS 0-10, completed during the procedure and at 10, 30 and 60 minutes post procedure.	Mean and standard deviation reported.
Guida (60)	Women undergoing operative out-patient hysteroscopy for surgically treatable lesions associated with infertility or abnormal uterine bleeding.	Paracervical injection of 10ml 1% mepivicaine. N=82	Conscious sedation with o.5mg atropine i.v., 0.25mg fentanyl i.v. and 2mg midazolam i.v. N=84	5cm VAS used during, immediately after, 15 and 60 minutes after and 24 and 72 hours after the procedure.	Mean and standard deviation reported.
Kabli (61)	Infertile women undergoing outpatient hysteroscopy. Exclusions: women needing operative hysteroscopy under GA, positive Chlamydia culture, pregnancy or allergy to local anaesthetic.	Intracervical injection of 2ml 1% lignocaine and distension media with 18ml lignocaine per 250ml saline. N=42	Intracervical injection of 2ml 1% lignocaine. N=36	VAS 0-10 used to score pain after the hysteroscopy, after endometrial biopsy and at 10, 30 and 60 minutes after the procedure.	Mean and standard deviation reported.
Sagiv (33)	Women undergoing diagnostic outpatient hysteroscopy.	Intracervical injection of 10ml 3% mepivicaine. N=47	Vaginoscopy (procedure performed without a speculum or anaesthesia). N=83	VAS 0-10cm used to score the pain immediately and 15 minutes after the hysteroscopy.	Mean and standard deviation reported.
Shankar (64)	Women with abnormal uterine bleeding referred by their general practitioner for diagnostic outpatient hysteroscopy. Exclusions: unable to visualize the cervix or severe cervical stenosis.	Distension media containing 40ml 2% lignocaine per 500ml 0.9% saline. N=100	Distension media of 0.9% saline only. N=100	Pain scored with VAS 0-10, and PPI.	Mean and standard deviation reported.

Table 4.1b continued

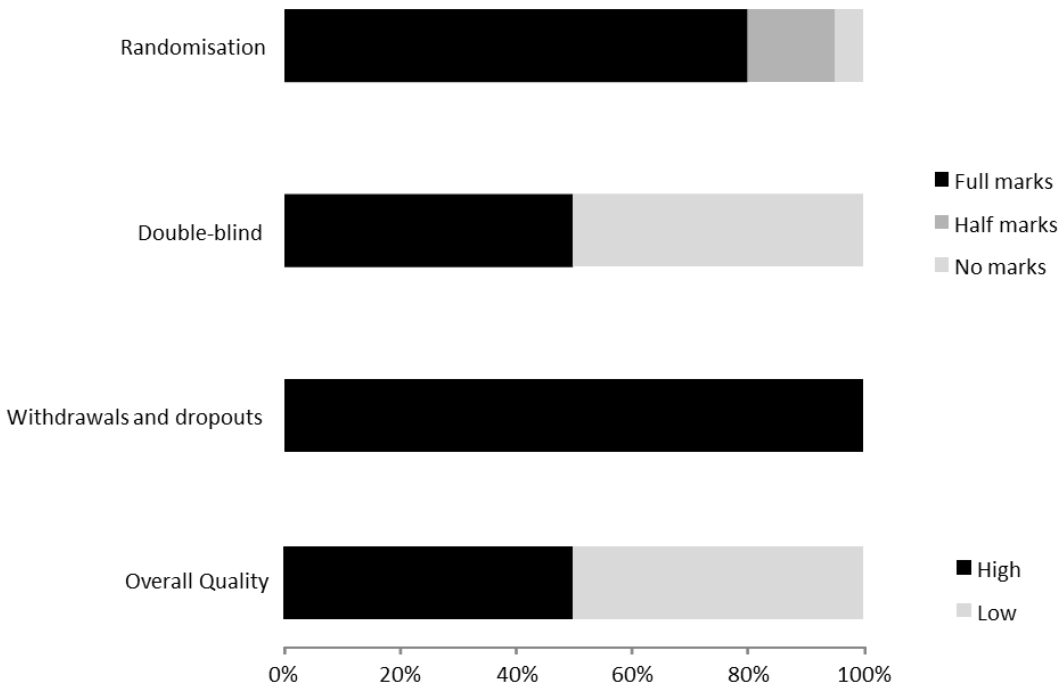
Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Soriano (65)	Women undergoing diagnostic hysteroscopy for abnormal uterine bleeding or infertility. Exclusions: menorrhagia at the time of the procedure, sensitivity to lignocaine, epilepsy, significantly impaired respiratory or cardiac function and active liver disease.	5% lignocaine sprayed onto the endocervix and into the cervical canal, (3 sprays in total) 5 minutes before the procedure. N=62	Placebo sprayed on the endocervix and into the cervical canal, (3 sprays in total) 5 minutes before the procedure. N=56	VAS 0-10cm to score pain experienced during the procedure.	Mean and standard deviation reported.

Table 4.1c Studies using other distension media

Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Studies using 1.5% glycine as the distension medium					
Vercellini (66)	Premenopausal (FSH <30mIU/ml) non-pregnant (negative β-hCG test) women referred for investigation of excessive uterine bleeding of ≥ 3 months duration. Exclusion: genital infection, previous cervical surgery or hysteroscopy, severe cardiac disease and known sensitivity to local anaesthetics.	Paracervical injection of 1% mepivicaine more than 5 minutes before the procedure. N=87	No anaesthesia. N=90	10 point visual analogue scale used to score pain during the hysteroscopy and the endometrial biopsy.	Mean and standard deviation reported.
Distension medium not stated					
Finikiotis (58)	Patients referred from general practitioners and from other gynaecologists for the investigation of a variety of gynaecological complaints.	Paracervical injection of 16-20ml 1% lignocaine. N=60	Uterosacral injection of 2ml 2% lignocaine with 1:80,000 adrenaline. N=60	VAS 0-10cm to score pain during the procedure. Reported as the number of patient selecting VAS between 0 and 3.3, 3.4 and 6.3 and 6.4 to 10.0.	Mean and standard deviation calculated using the mean value of each category.

NB. For consistency the group receiving local anaesthetic (or a combination of anaesthetics) are considered as the intervention group even if that was not the case in the original study.
GA= general anaesthetic, VAS= visual analogue scale, i.m.= intra muscular, i.v.= intra vascular, HR= heart rate, BP= blood pressure, PPI= Present pain intensity scale (verbal descriptors of pain ranked from 0-5 on a numeric scale).

Figure 4.2 Jadad Quality Assessment of Studies Using Local Anaesthetic for Out-patient Hysteroscopy



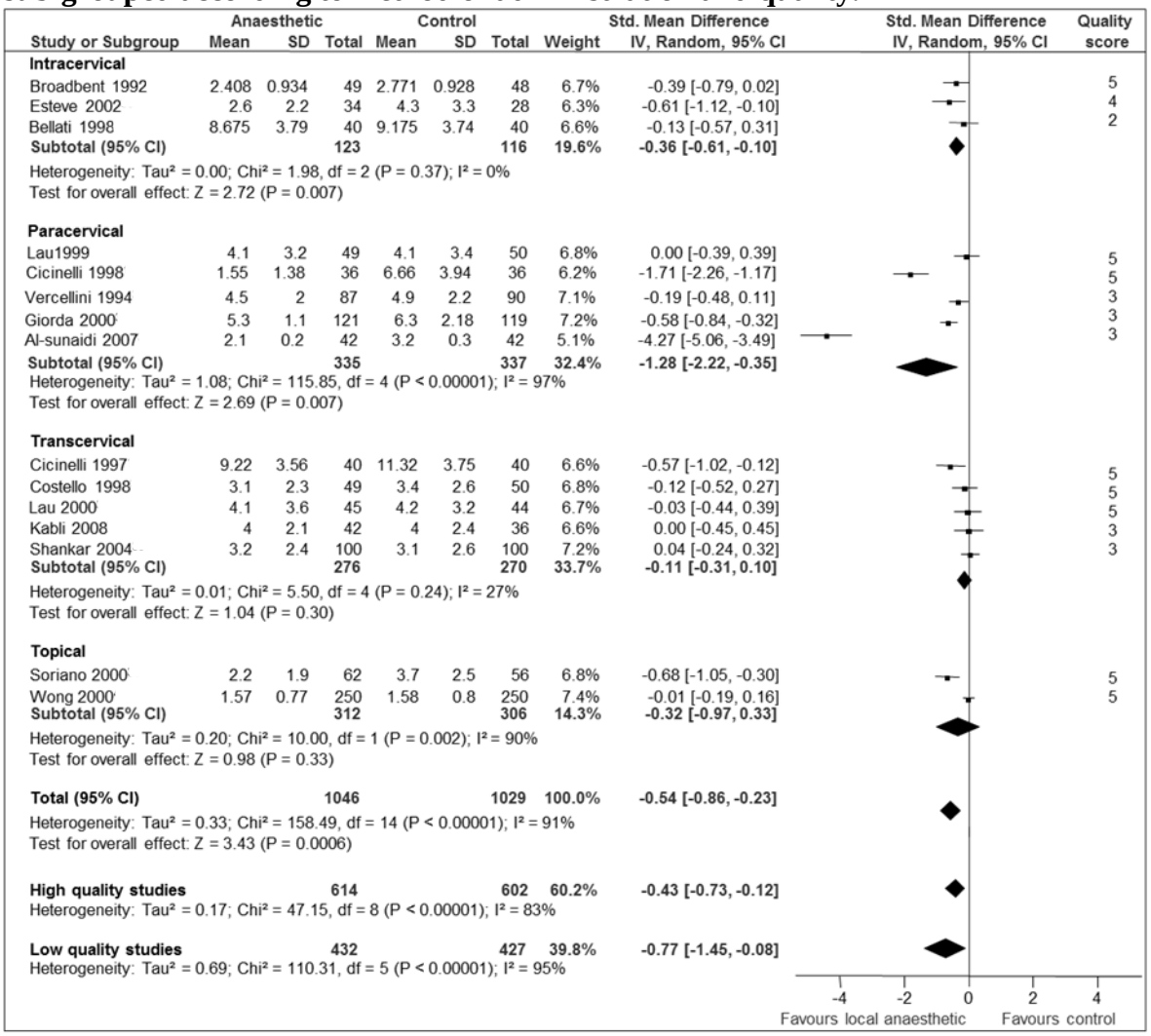
Results were reported as mean or median pain scores, but for the one study using a descriptive scale (54), numerical values were applied to each category (none=1, mild=2, moderate=3 and severe=4) and used to calculate the mean scores and standard deviations (90). One study reported raw patient data (53) from which the mean and standard deviation were calculated (90). The populations in the two studies (53;54) for which the mean and standard deviation were calculated were sufficiently large for them to be approximated to a normal distribution according to central limit theorem (91). Another study reported the standard error (59) which was converted into the standard deviation (92).

Nine of the selected studies had data on vasovagal episodes. Four of the studies reported vasovagal attacks according to a strict definition based upon heart rate, blood pressure and symptoms (9;10;12;62), four of them reported vasovagal symptoms (e.g. faintness, nausea, pallor) (59;60;63;64) and one reported a vasovagal attack in the complications but did not give any *a-priori* definition of symptoms or signs (65).

Effect of local anaesthetic on pain

Meta-analysis of 15 studies showed that the use of local anaesthetic reduced the amount of pain experienced during outpatient hysteroscopy (SMD = -0.54, 95%CI -0.86 to -0.23, I^2 = 91%) (Figure 4.3). Meta-analysis of the studies sub-grouped according to quality found that both the poor and the high quality studies demonstrated a significant benefit of using local anaesthetic for outpatient hysteroscopy (SMD = -0.77, 95%CI -1.45 to -0.08, I^2 = 95% and SMD = -0.43, 95%CI -0.73 to- 0.12, I^2 = 83% respectively) (Figure 4.3).

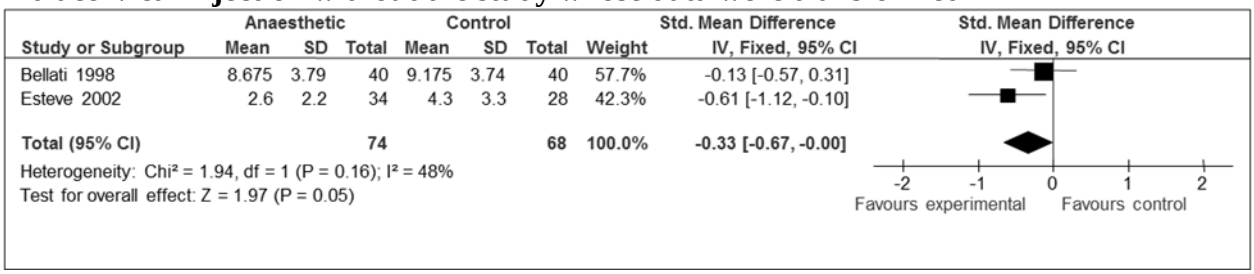
Figure 4.3 Forest plot showing the results of meta-analysis of studies that examine the use of local anaesthetic for reducing pain during out-patient hysteroscopy. Results overall and sub-grouped according to method of administration and quality.



When divided into subgroups there were three studies examining intracervical injection (53;54;57), five which used paracervical injection, (10;12;52;59;66), five that used transcervical application (topical into the uterine cavity) (9;55;61;62;64) and two that applied the anaesthetic topically (topical to the cervix only) (65;67).

The use of an intracervical injection of local anaesthetic significantly reduced pain during out-patient hysteroscopy (SMD = -0.36, 95%CI -0.61 to -0.10, I^2 = 0%) (Figure 4.3). This finding however, contrasted with a single study included in the review but not in the meta-analysis because of insufficient data (63), which found no significant effect of intracervical local anaesthetic on pain relief for out-patient hysteroscopy. To examine this conflicting result, a sensitivity analysis was performed excluding from the meta-analysis the study where categorical data had been transformed (54). No significant reduction in pain was observed with intracervical injection (SMD =-0.35, 95% CI -0.82 to 0.12, I^2 =48%) (Figure 4.4).

Figure 4.4 Forest plot showing the results of meta-analysis of studies that examine the use of intracervical injection without the study whose data were transformed



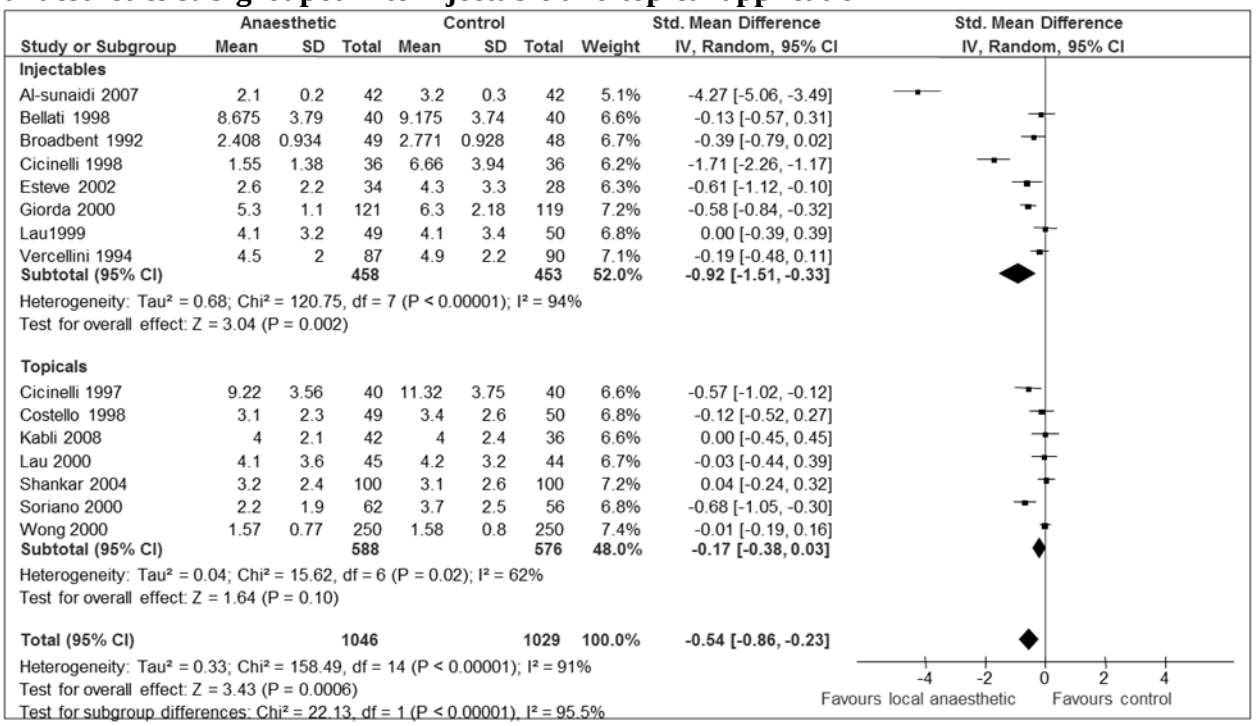
The use of paracervical injection was associated with a significant reduction of pain during out-patient hysteroscopy (SMD = -1.28, 95%CI -2.22 to -0.38, I^2 =97%) (Figure 4.3).

The use of topically administered local anaesthetic did not ameliorate pain during outpatient hysteroscopy. Specifically, transcervical local anaesthetic was not found to significantly reduce the amount of pain experienced during hysteroscopy (SMD= -0.11, 95%CI -0.31 to 0.10, I^2 =27%) (Figure 4.3). Similarly, there was no significant alleviation of pain when local anaesthetic

was applied topically to the cervix (SMD = -0.32, 95%CI -0.97 to 0.33, I^2 = 90%) (Figure 4.3), although meta-analysis demonstrated substantial heterogeneity. A further study included in the review that could not be used for the meta-analysis because it reported median VAS scores, showed no significant difference between topical cervical local anaesthetic and placebo for the hysteroscopy, but it did show a significant reduction in pain in the local anaesthetic group during application of a cervical tenaculum (p=0.005) (56).

A further meta-analysis was performed to compare injectable administration of local anaesthetic (intracervical and paracervical) against topical application (transcervical to uterine cavity and topical to the cervix). This showed a benefit of using injectable local anaesthetics (SMD = -0.92, 95% CI -1.51 to -0.33, I^2 = 94%) but not topical ones (SMD =-0.17, 95%CI -0.38 to 0.03, I^2 = 62%). (Figure 4.5). Meta-regression analysis showed that paracervical injection was significantly more effective than the other anaesthetic modalities in reducing the pain of diagnostic outpatient hysteroscopy (p = 0.048).

Figure 4.5 Forest plot showing the results of meta-analysis of studies that examine the use anaesthetics sub-grouped into injectable and topical application

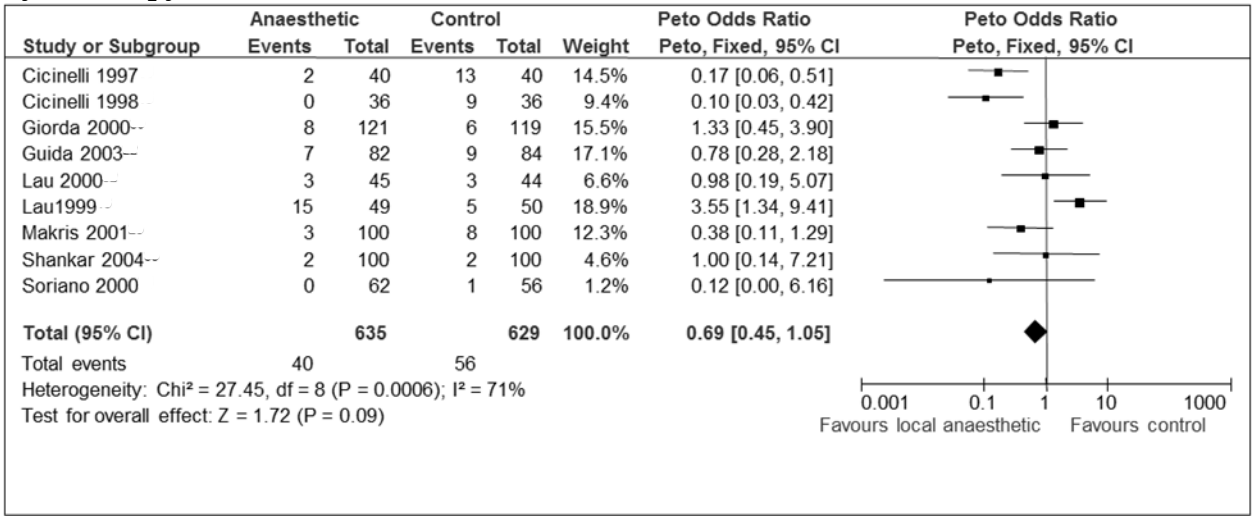


A single study compared two methods of cervical block (58) and found no significant difference in pain between a paracervical and an uterosacral ligament local block p<0.65. Two studies compared local anaesthetic to other medication (53;60). The first compared intracervical local anaesthetic to a control group (data used in meta-analysis) and to intramuscular injection of 100mg tramadol. Tramadol was significantly better at reducing the amount of pain experienced during hysteroscopy (p=0.001) compared to intracervical block (53). The second study compared paracervical injection of local anaesthetic to the use of conscious sedation for operative hysteroscopy and found no significant difference in the pain experienced between the two groups (60).

Effect on vasovagal episodes

There was no significant difference in the incidence of vasovagal episodes between local anaesthetic and control (nil, normal saline, placebo, conscious sedation) groups p=0.09 (Figure 4.6), regardless of how a vasovagal reaction was defined.

Figure 4.6 Forest plot showing the results of meta-analysis examining the incidence of vasovagal episodes in studies examining the use of local anaesthetic for out-patient hysteroscopy

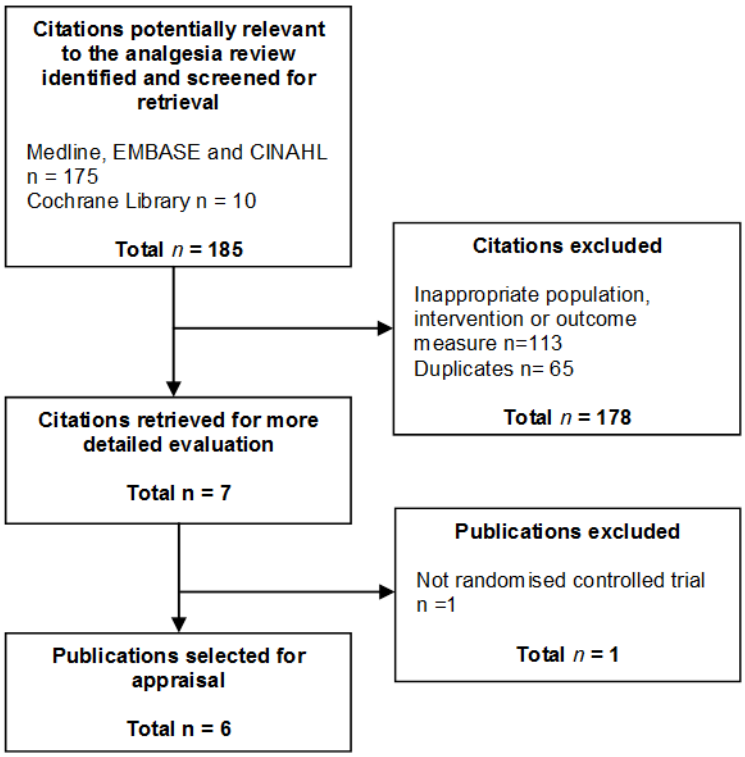


Results of the systematic review of analgesia for pain control during outpatient hysteroscopy

Study Selection, Details and Quality

The analgesia literature search yielded 185 citations. Of these, 6 studies were considered eligible for inclusion in the review (Figure 4.7). The inter-rater reliability for the study selection was good (kappa 0.67).

Figure 4.7 Study selection process for the systematic reviews of the effect of analgesia on pain during outpatient hysteroscopy.



Details of the study populations, intervention, outcome assessment and data reporting are shown in Table 4.2.

Table 4.2. Characteristics of the selected studies included in the systematic reviews of analgesia for pain control during outpatient hysteroscopy

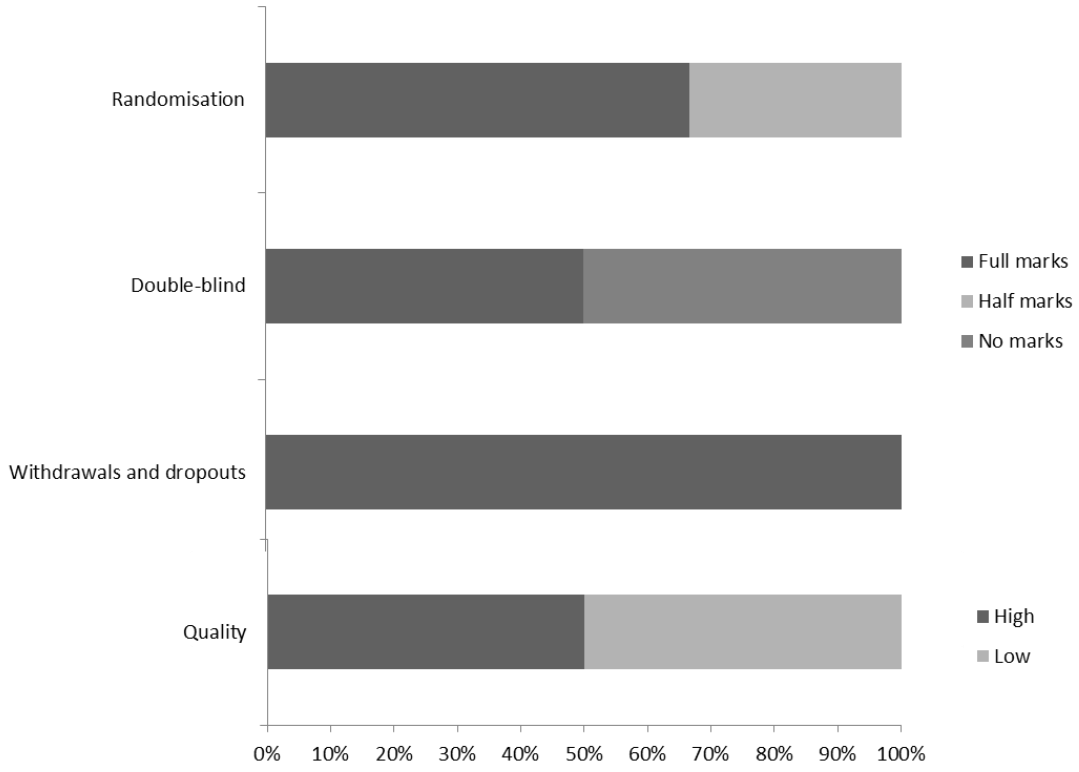
Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Bellati (53) *(Study written in Italian, abstract in English also)*	Women undergoing diagnostic out-patient hysteroscopy and endometrial biopsy.	2 groups: 1. Tramadol 100mg i.m. 50 mins pre-procedure. N= 40 2. Nil. N=40. Rigid 5mm hysteroscope and carbon dioxide for distension.	Intracervical injection of 4ml 2% mepivicaine, 5 minutes before hysteroscopy with a rigid 5mm hysteroscope and carbon dioxide for distension. N=40 Rigid 5mm hysteroscope and carbon dioxide for distension.	Ordinal score 0-20 during the hysteroscopy.	Mean and Standard deviation calculated from raw data.
Caligiani (68) *(Study written in Italian, abstract in English also)*	Women undergoing diagnostic out-patient hysteroscopy and endometrial biopsy to investigate post-menopausal bleeding.	Intracervical injection of 4ml 3% mepivicaine, 5 minutes before the procedure and ketorolac 30mg i.m. and atropine 0.5mg i.m. 45 minutes before the procedure. Hysteroscopy not described. N=12.	Intracervical injection of 4ml 3% mepivicaine, 5 minutes before the procedure and atropine 0.5mg i.m. 45 minutes before the procedure. Hysteroscopy not described. N=12.	VAS 0-10cm to score pain at insertion of the speculum, during the hysteroscopy, during endometrial biopsy and 5 minutes after the end of the procedure.	Mean and standard error.
Floris (45)	Perimenopausal women undergoing outpatient diagnostic hysteroscopy and endometrial biopsy. Exclusions: known uterine malformation, previous uterine surgery.	Tramadol 100mg i.v. over 20 minutes, followed 30 minutes later by the outpatient hysteroscopy with a 2.9mm, rigid, 30 degree fore-oblique hysteroscope using carbon dioxide as the distension medium. N = 25.	Placebo infusion i.v. over 20 minutes, followed 30 minutes later by the outpatient hysteroscopy with a 2.9mm, rigid, 30 degree fore-oblique hysteroscope using carbon dioxide as the distension medium. N = 25.	VAS 0-10cm to score pain during and 15 minutes after the end of the procedure. ACTH and cortisol levels were also assayed from blood samples pre and post procedure.	Mean reported graphically, no values given.

Table 4.2 continued

Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Lin (69)	Pre- and post-menopausal women undergoing outpatient hysteroscopy to investigate abnormal bleeding, infertility and suspected intracavity lesion.	Buprenorphine 0.2mg sublingually, 40 minutes before the hysteroscopy, which was performed a 3.1mm flexible hysteroscope, using 5% dextrose as the distension medium. N= 80.	Placebo tablet, sublingually, 40 minutes before the hysteroscopy, which was performed with a 3.1mm flexible hysteroscope, using 5% dextrose as the distension medium. N=84.	VAS 0-10cm to score the worst pain experienced during the procedure.	Mean and standard deviation.
Nagele (46)	Pre- and post-menopausal women undergoing outpatient hysteroscopy. Exclusions: sensitivity to NSAID's and prostaglandin synthesis inhibitors, medication that interacts with NSAID's, inflammatory bowel disease, porphyria and those unable to consent.	Mefenamic acid 500mg orally, 1 hour pre-procedure. Hysteroscopy with 4mm, rigid, 30 degree fore-oblique hysteroscope with a 5mm sheath using carbon dioxide as the distension medium. N= 49.	Placebo orally, 1 hour pre-procedure. Hysteroscopy with 4mm, rigid, 30 degree fore-oblique hysteroscope with a 5mm sheath using carbon dioxide as the distension medium. N- 46.	Women asked to score the worst pain experienced during the hysteroscopy and at 30 and 60 minutes after the procedure using a 4 point ordinal scale (0=none, 1=mild, 2=moderate, 3=severe).	No values given for pain during the procedure, results expressed graphically. Pain after the procedure reported as medians with interquartile ranges
Tam (70)	Pre- and post-menopausal women undergoing outpatient diagnostic hysteroscopy.	Diclofenac 50mg, orally, 1-2 hours pre-procedure. Hysteroscopy with 2.7mm, rigid, 25 degree fore-oblique hysteroscope with a 5mm sheath and carbon dioxide for distension. N=92.	Placebo tablet, orally, 1-2 hours pre-procedure. Hysteroscopy with 2.7mm, rigid, 25 degree fore-oblique hysteroscope with a 5mm sheath and carbon dioxide for distension. N=89.	VAS (length not stated) to score pain before the procedure, when tenaculum applied, insertion of hysteroscope, examination of the uterine cavity, after biopsy and 30 minutes post procedure.	Mean and standard deviation.

The quality of the studies varied with deficiencies in randomisation and blinding (Figure 4.8).

Figure 4.8. Methodological quality assessment of studies using analgesia for outpatient hysteroscopy



Of the 6 selected analgesia studies, three examined the use of opiate drugs (45;53;69) and three examined non-steroidal anti-inflammatory drugs (NSAIDs) (46;68;70). All six studies examined diagnostic outpatient hysteroscopy. Four studies reported data comparing analgesia to placebo (45;46;69;70), one compared ketorolac and intracervical block to intracervical block alone (68) and the final study compared tramadol to intracervical block (53). Two of the selected studies reported their data graphically without any specific numerical values (45;46); the authors were contacted to try and obtain the values but no replies were received. Four of the papers used

continuous visual analogue scales (VAS) to assess pain, and two used ordinal numerical or descriptive scales (Table 4.2).

Effect of analgesics on pain

Meta-analysis was not performed as the studies used different drugs, in different doses, making them non-comparable. When divided into medication subgroups, there were three studies examining the use of opiate analgesics (45;53;69) and three which studied NSAID's (46;68;70). Two of the opiate studies examined the use of 100mg tramadol administered approximately 50 minutes before the outpatient hysteroscopy, one study giving it intramuscularly (53) and the second giving it as an intravenous infusion (45). The first study found that the women who had received tramadol had significantly less pain at the end of the procedure than women in the intracervical block group and the women who received no medication ($p = 0.001$ and $p < 0.001$ respectively) (53). Although this was a low quality study the result was supported by those from the second, high quality study that reported significantly lower pain scores in the tramadol group when compared to placebo both during ($p < 0.012$) and 15 minutes after ($p < 0.008$) the procedure (45). The third opiate study examined the use of sublingual buprenorphine 0.2mg, 40 minutes before the procedure, versus placebo. There was no significant pain reduction with the use of buprenorphine overall and when stratified for menopausal status and parity (69).

The three NSAID studies all examined different drugs. The first, high quality study compared the use of 500mg of oral mefenamic acid, one hour prior to the procedure, to placebo. It found that mefenamic acid did not significantly reduce the pain of the hysteroscopy, however it did significantly reduce the pain experienced at 30 minutes ($p < 0.01$) and 60 minutes ($p < 0.05$) post-

procedure. The second high quality study examined oral diclofenac 50mg, given one to two hours before the procedure (70). Pain was assessed at a number of points during the procedure (see Table 4.2) but no significant difference between the intervention and control groups was found (p values not reported) (70). The final NSAID study was low quality. It assessed the use of oral ketorolac 30mg with an intracervical block compared to intracervical block alone and found that the addition of ketorolac significantly reduced pain at all stages of the procedure (no p values reported) (68).

Side effects

Two of the opiate studies reported side effects (45;70). The tramadol study found no significant difference between the groups in incidence of nausea, vomiting or bradycardia (45). Conversely, in the buprenorphine study there was a high incidence of adverse effects (nausea, vomiting, drowsiness) in the intervention group (38.8%) and none in the control group (69).

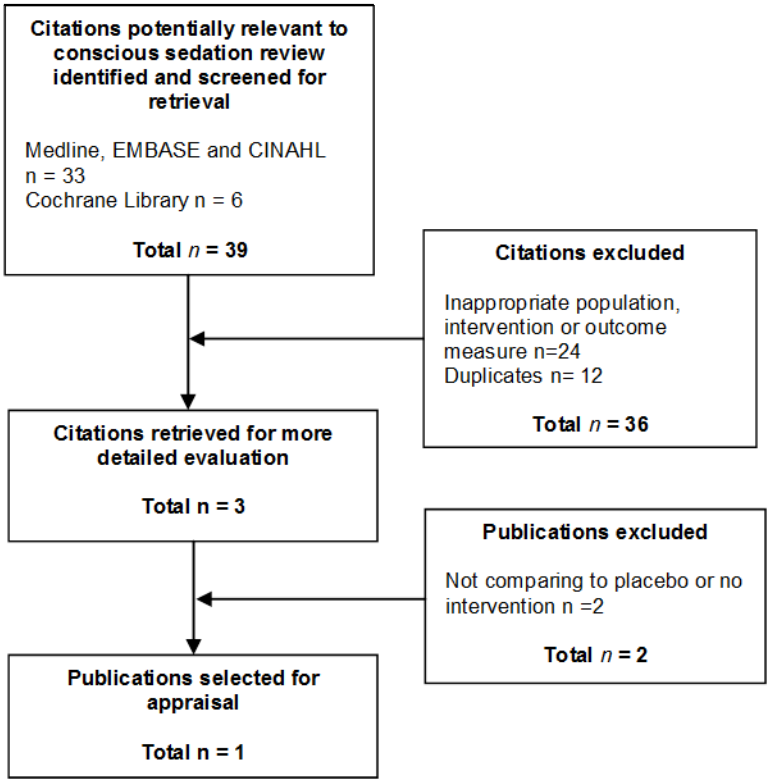
The diclofenac study was the only NSAID study to report side effects (70). Two patients (2.2%) in the diclofenac group reported side effects (one reported epigastric pain and one reported a rash) which were mild and self-limiting (70).

Results of the systematic review of conscious sedation for pain control during outpatient hysteroscopy

Study Selection, Details and Quality

The conscious sedation literature review yielded 39 citations with just one being eligible for inclusion in the review (Figure 4.9).

Figure 4.9 Study selection process for the systematic reviews of the effect of conscious sedation on pain during outpatient hysteroscopy



There was complete agreement between the reviewers and so the kappa score was 1. According to the Jadad quality assessment this paper was of low quality, however this was due to the study not scoring any points for blinding. It would be very difficult to blind conscious sedation versus intracervical injection and so blinding was removed as a quality consideration. The paper received full marks for randomisation and follow-up of withdrawals and dropouts, thus was ultimately deemed to be of high quality.

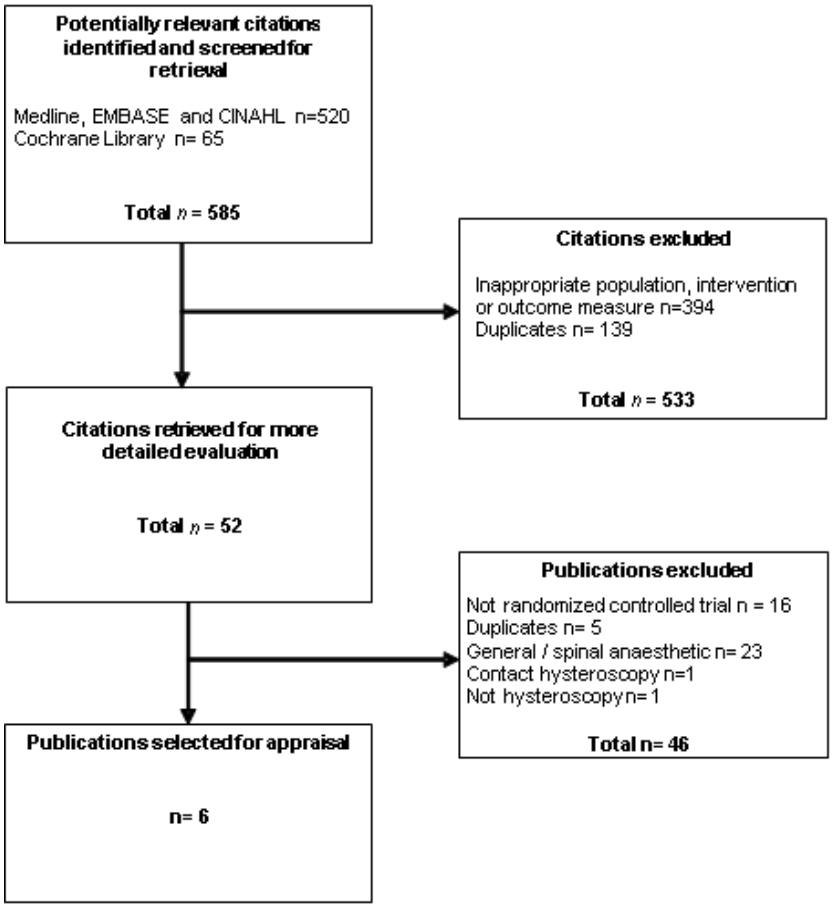
The conscious sedation study (60) compared midazolam to a paracervical anaesthetic block for operative outpatient hysteroscopy using a bipolar electrode. A VAS marked with pain descriptions was used to evaluate the pain experienced and the results were reported as means and standard deviations. The trial examined the use of conscious sedation immediately before operative outpatient hysteroscopy (polypectomy, myomectomy, septoplasty and adhesiolysis) using the Versapoint™ bipolar electrosurgical system (Gynecare, Ethicon Inc. Menlo Park, CA, USA). It compared 0.25 mg of fentanyl i.v., 0.5 mg of atropine and 2mg of midazolam, to paracervical anaesthesia with 10mL 1% mepivicaine hydrochloride without sedation. There were no significant differences between local anaesthesia and conscious sedation in terms of pain control during the procedure, postoperative pain, side effects or patient satisfaction (60).

Results of the systematic review of the effect of cervical preparation on pain during outpatient hysteroscopy

Study Selection, Details and Quality

The literature search yielded 585 citations. Of these, six studies were considered eligible for inclusion in the review (Figure 4.10) (71-76). The inter-rater reliability for the study selection was very good (kappa=0.86).

Figure 4.10 Study selection process for the systematic review of the effect of cervical preparation on pain during outpatient hysteroscopy



Four of the six papers were deemed to be of high quality (72;73;75;76) (Table 4.3). Details of the study populations, intervention, outcome assessment and data reporting are shown in Table 4.3. A single study (72) examined the use of oral mifepristone for cervical dilatation in premenopausal women given 30 hours pre-procedure. The five remaining studies examined the use of vaginal misoprostol administered between four and 24 hours before the hysteroscopy. The dose used was 400µg in all but one study (73) which used 200µg. Two studies used only premenopausal women (71;75), one, only postmenopausal women (73) and the remaining two a combination of both (74;76) . All studies reported results for pain and five (71-74;76) reported results for cervical dilatation. One paper used an ordinal scale from zero to ten to assess pain (71) whilst the other studies all used continuous visual analogue scales (VAS).

Results were reported in a variety of ways (see Table 4.3) that could not be compared, making meta-analysis impossible. Cervical dilatation was assessed in different ways (adequate if scope passes into os, need for dilatation, force needed to dilate) and so the results were once again unsuitable for meta-analysis. Gastrointestinal side effects were reported by two studies (75;76), bleeding by four studies (71;74-76), cervical lacerations by three studies (71;73;76) and failed procedures by three studies (72;73;75). These results were meta-analysed.

Table 4.3. Methods, interventions and results for the studies included in the systematic review of the effect of cervical preparation on pain during outpatient hysteroscopy

	Antiprogestogen	**Prostaglandins**				
	Premenopausal	**Premenopausal**		**Postmenopausal**	**Pre and postmenopausal**	
	Ben Chetrit (72)	**Atay (71)**	**Valente (75)**	**Da Costa (73)**	**Singh (74)**	**Waddell (76)**
Intervention	Mifepristone 200mg PO 30 hours pre hysteroscopy	Misoprostol 400µg PV 4 hours pre hysteroscopy	Misoprostol 400µg PV 6 hours pre hysteroscopy	Misoprostol 200µg PV 8 hours pre hysteroscopy	Misoprostol 400µg PV 4-6 hours pre hysteroscopy	Misoprostol 400µg PV 12-24 hours pre hysteroscopy
Control method	Placebo	Placebo	Placebo	Placebo	Nil	Placebo
Number in intervention group vs. control group	28 vs. 30	22 vs. 21	20 vs. 24	60 vs. 60	50 vs. 50 (only 8 postmenopausal women in the intervention group and 1 in the control group).	50 vs. 51
Routine use of cervical dilatation	No	If 7mm resectoscope sheath or 6 Hegar not easily passed into the cervical canal.	No	No	No	Yes
Hysteroscope size	2.9mm rigid hysteroscope	4mm rigid hysteroscope with 30° fore oblique lens for diagnostic and 7mm resectoscope for operative	4mm hysteroscope with 30° fore oblique lens	4mm rigid hysteroscope with 30° fore oblique lens and 5mm sheath	4mm rigid hysteroscope with 30° fore oblique lens	4mm rigid hysteroscope with 30° fore oblique lens and 5.5mm sheath

Table 4.3 continued

	Ben Chetrit (72)	Atay (71)	Valente (75)	Da Costa (73)	Singh (74)	Waddell (76)
Quality	High	Low	High	High	Low	High
Operative or Diagnostic	Diagnostic	Suggests all operative but not clear.	Diagnostic	Diagnostic	Diagnostic	Diagnostic
Method of assessing cervical dilatation	Dilatation measured using Hegar dilators before administration of mifepristone and when patient returned for hysteroscopy. The change in Hegar is reported as mean (standard deviation).	Adequate if 7mm hysteroscope sheath or Hegar 6 dilator passes into cervical canal. Number assessed adequate in each group.	Not reported.	Need for dilatation. Percentages.	Need for dilatation. Number (percentage).	Force needed to dilate at 3, 4, 5 and 6mm measured with dilators attached to a tonometer. Mean (standard deviation).
Dilatation in intervention group vs. control group	1.28 (1.4) Hegar vs. 1.06 (1.4) Hegar p=0.50	20 vs. 6 adequate p<0.001		17.2 vs. 20.3% p=0.66	15 (30%) vs. 11 (22%) p=0.36	3mm= 1.7 (1.7)vs. 1.8 (2.1) p=0.82 4mm= 2.6 (3.5) vs. 3.0 (4.5) p= 0.86 5mm= 4.3 (6.0) vs. 4.0 (3.1) p= 0.21 6mm= 5.0 (4.2) vs. 7.5 (5.9) p= 0.02 Scores separated into pre and postmenopausal are all non-significant (p>0.05)

Table 4.3 continued

	Ben Chetrit (72)	Atay (71)	Valente (75)	Da Costa (73)	Singh (74)	Waddell (76)
Method of pain assessment	100mm VAS	Score from 0-10 (0= no pain, 10= worst menstrual pain).	0-10cm VAS with faces symbolising the amount of pain.	VAS (length not reported but assumed to be 10cm).	10cm VAS	Sliding visual analogue scale of 1 to 100.
Timing of pain assessment	Pain as hysteroscope passes through the cervical os. Mean (standard deviation).	Pain during cervical dilatation. Mean (range).	Pain during the hysteroscopy, biopsy and after the hysteroscopy. Number (percentage), selecting between 0-5 and 6-10	Pain as scope passes through internal cervical os, as the cervix is clamped and the biopsy is taken. Median.	Pain at the end of the procedure. Median (standard deviation).	Pain assessed during assessment of cervical dilatation at baseline (before administration of misoprostol) and after cervix dilated to 6mm before hysteroscopy. Mean (standard deviation).
Pain score in intervention group vs. control group	33.4mm (23.5)vs. 37.0mm (30.0) p=0.60	5.1 (4-10) vs. 9.3 (6-10) p<0.05	Selecting 0-5: 7 (53.8%) vs. 11 (47.8%) Selecting 6-10: 6 (46.2%) vs. 12 (52.2%) p=0.72	During procedure medians: 5 vs. 7, p=0.02 Comparing number in group selecting Vas>6 : Clamping p = 0.507 Hysteroscopy p=0.0132 Endometrial biopsy p= 0.5919 Presence of pain: Clamping p = 0.74 Hysteroscopy p=0.32 Endometrial biopsy p= 0.19	4.5cm (2.0) vs. 5.0cm (1.8) p=0.03	42.1 (23.1) vs. 57.2 (24.9), p= 0.004 If adjusted for baseline pain: 43.2 (3.7) vs. 55.5 (3.4), p= 0.01 Premenopausal: Overall p = 0.56 or if adjusted for baseline pain p= 0.77 Postmenopausal: Overall p=0.004 or if adjusted for baseline pain p= 0.006

Effect of cervical preparation on pain

Premenopausal women

Mifepristone given 30 hours before hysteroscopy did not reduce the pain of the outpatient procedure for pre-menopausal women (p=0.60) (72) (Table 4.3).

Two studies examined the use of misoprostol 400µg given vaginally before the hysteroscopy to premenopausal women. The drugs were administered 4 hours before in one of the studies (71) and 6 hours before in the other (75). The low quality study (71) found that pain during cervical dilatation was significantly reduced after the use of prostaglandin compared to placebo ($p<0.05$) however the other study which, was considered to be high quality (75), found no significant reduction in pain during the hysteroscopy with the use of misoprostol (p= 0.72) (Table 4.3).

Postmenopausal women

One study (73) examined the use of misoprostol 200µg given vaginally 8 hours before the hysteroscopy to postmenopausal women. The median pain scores as the hysteroscope passed through the cervical os were five in the intervention group and seven in the placebo group (p=0.02). When the pain severity was assessed by comparing the number of patients scoring more than six on the VAS (i.e. considerable pain) there were significantly fewer in the intervention group (p=0.0132). However no significant difference between the groups was identified when assessing the presence of pain during clamping of the cervix (p= 0.74), during the examination (p= 0.32) or during the endometrial biopsy (p=0.19) (Table 4.3).

Pre- and postmenopausal women

Two studies included pre- and post-menopausal women in their study populations (74;76). One of these studies gave misoprostol 400µg vaginally four to six hours before the

hysteroscopy (74) and found that pain at the end of the procedure was significantly less in the intervention group when compared to no medication (p=0.03). This was judged to be a low quality study due to the lack of blinding. The second study gave the same dose of misoprostol twelve to twenty-four hours before the procedure and assessed pain after the cervix was dilated to 6mm (76). Pain was found to be significantly less in the misoprostol group (p=0.004 and when adjusted for baseline pain score p=0.01). This study subgrouped the patients according to menopausal status and found that there was a significant reduction in pain for postmenopausal women given misoprostol (p= 0.004 and when adjusted for baseline scores p=0.006) but not for premenopausal women (p=0.56, and when adjusted for baseline scores p=0.77). This was a high quality study (Table 4.3).

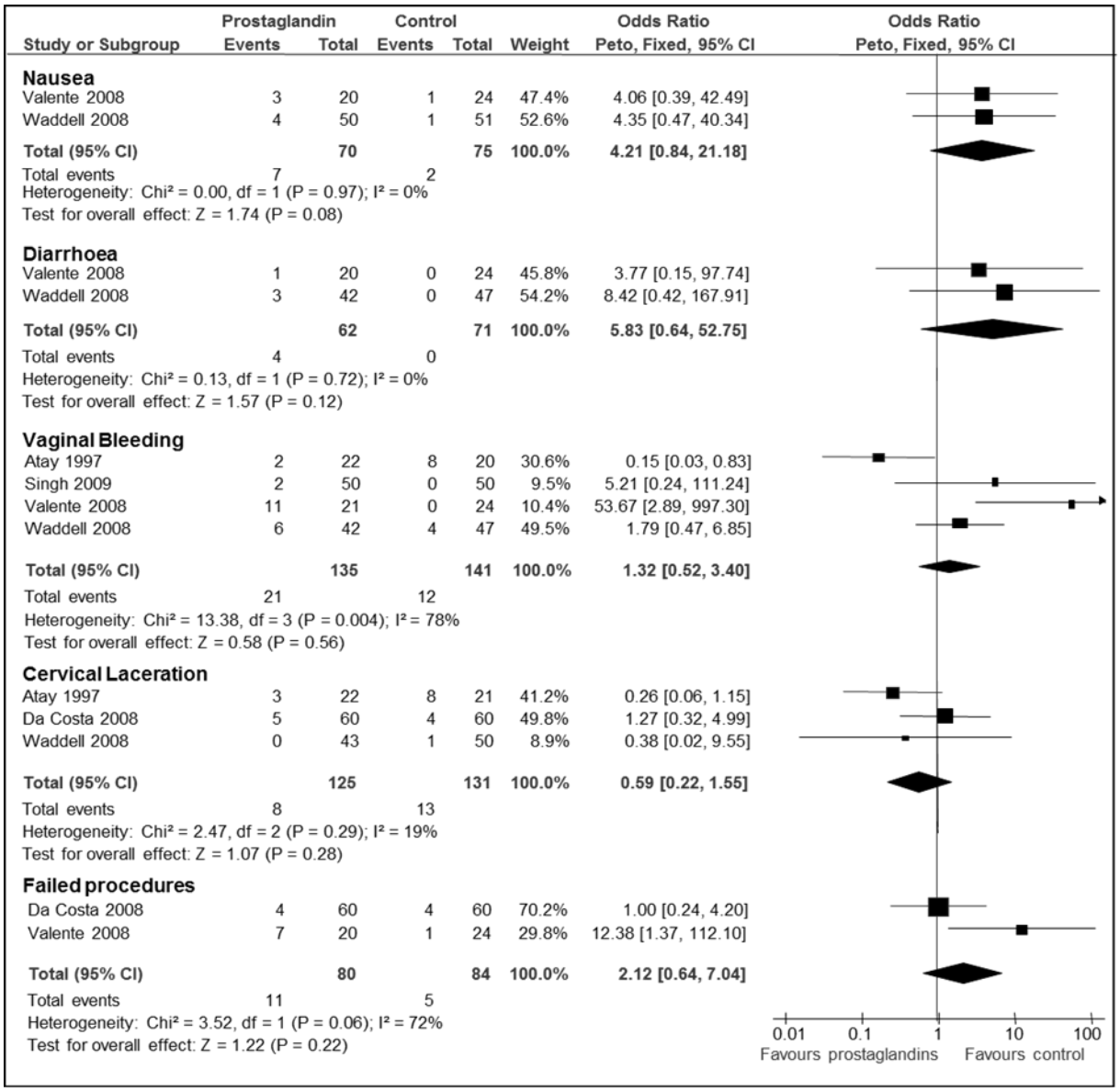
Effect of cervical preparation on dilatation of the cervix

Five studies evaluated the effect of cervical priming with antiprogestogens or prostaglandins on cervical dilatation. No significant differences were seen between priming and placebo as regards the need for or degree of cervical dilatation. The only significant results were for the amount of force required to dilate the cervix above 6mm in a mixed pre and postmenopausal population (76) and the number of premenopausal women requiring dilatation above 6mm (p=0.001) (71) (Table 4.3).

Side effects

No significant differences in the prevalence of gastrointestinal side effects, unscheduled vaginal bleeding, cervical laceration or failed procedures were found (Figure 4.11).

Figure 4.11 Forest plots showing the results of meta-analysis of adverse effects and failed procedures when prostaglandins are given prior to outpatient hysteroscopy

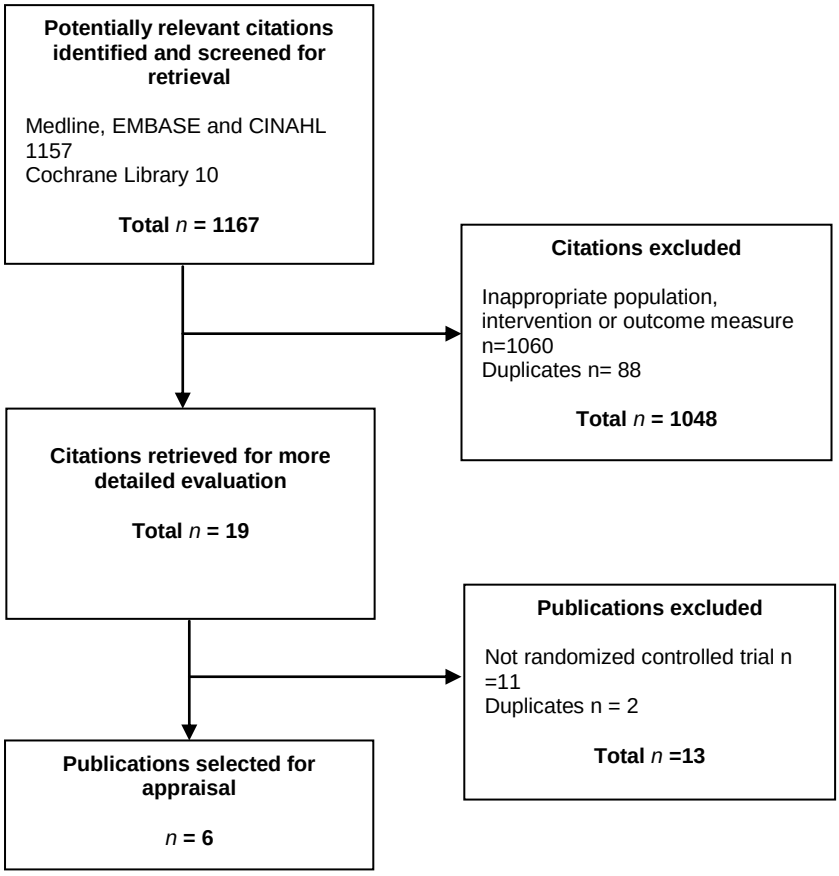


Results of the systematic review of the effect on pain of the vaginoscopic approach to outpatient hysteroscopy

Study Selection, Details and Quality

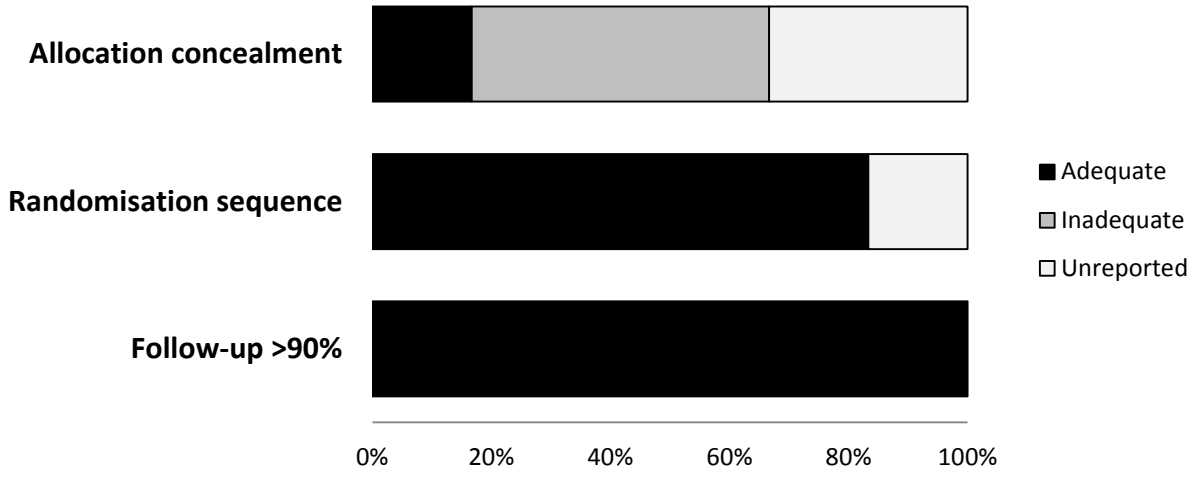
The literature search yielded 1167 citations. Of these, 6 studies (31-33;77-79) were considered eligible for inclusion in the review (Figure 4.12). The inter-rater reliability for the study selection was very good (K=0.81).

Figure 4.12 Study selection process for systematic review of the effect on pain of the vaginoscopic approach to outpatient hysteroscopy.



Details of the study populations, intervention, outcome assessment and data reporting are shown in Table 4.4. The quality of the studies was high but with deficiencies in allocation concealment (Figure 4.13).

Figure 4.13 Methodological Quality Assessment of Studies Examining the effect of the vaginoscopic approach on pain during outpatient hysteroscopy



All six papers (31-33;77-79) used a visual analogue scale (VAS) to assess the patients' level of pain. Of the six papers reporting data for pain experience three reported means and standard deviations (31;33;77), two reported medians (32;78) and one reported the pain in categories (79). The data reported as median pain scores could not be used to calculate the SMD, so were excluded from the analysis. For data reported categorically, the midpoint of each category and the number of people selecting that category were used to calculate the mean and standard deviation.

Table 4.4. Characteristics of the selected studies included in the systematic review of the effect of the vaginoscopic approach on pain during outpatient hysteroscopy

Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Almeida (77)	Pre- and post-menopausal women undergoing diagnostic outpatient hysteroscopy. Exclusions: pelvic inflammatory disease, pregnancy, uterine perforation within the last 30 days, active uterine bleeding and use of hormonal vaginal cream.	Patients positioned in lithotomy, vagina cleaned and the rigid, 2.7mm (3.7mm with the sheath) hysteroscope introduced into the vagina. Holding the labia minora together the vagina was distended with normal saline and the hysteroscope steered into the external cervical os and along the canal into the uterine cavity. The hysteroscopy then continued as normal. Endometrial biopsies were also taken without the use of a speculum. N =91.	Patients positioned in lithotomy, Collins speculum inserted, vagina and cervix cleaned and the cervix grasped with a tenaculum. The rigid, 2.7mm (3.7mm with sheath) hysteroscope was then inserted into the external cervical canal and advanced into the uterine cavity which was then distended with carbon dioxide. The hysteroscopy then continued as normal and endometrial biopsies were taken. N=93.	VAS 0-10 with five faces drawn above the line indicating the amount of pain. Scored during the procedure and 5, 10, 15 and 20 minutes afterwards.	Mean and standard deviation reported.
Garbin (31)	Pre- and post-menopausal women undergoing diagnostic outpatient hysteroscopy. Exclusions: age < 18 years, current genital infection, refusal to participate.	Vagina cleaned and the rigid, 2.7mm (3.5mm with the sheath) hysteroscope introduced into the vagina, which was distended with normal saline so that the hysteroscope could be steered into the external cervical os and along the canal into the uterine cavity. The hysteroscopy then continued as normal. N =200.	Speculum inserted, vagina and cervix cleaned and the cervix grasped with a tenaculum. The rigid, 2.7mm (3.5mm with sheath) hysteroscope was then inserted into the external cervical canal and advanced into the uterine cavity, using normal saline as the distension medium. The hysteroscopy then continued as normal. N=200.	VAS 0-10cm, pain rated immediately after the procedure.	Mean and standard deviation and median and range reported.

Table 4.4 continued

Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Guida (78)	Pre- and post-menopausal women undergoing diagnostic outpatient hysteroscopy. Exclusions: active genital tract infection, cervical cancer, heavy bleeding, severe cardiovascular disease and suspected pregnancy.	Rigid, 3.5mm minihysteroscope introduced into the vagina, which was distended with normal saline so that the hysteroscope could be steered into the external cervical os and along the canal into the uterine cavity. The hysteroscopy then continued as normal. Endometrial biopsies were taken when indicated. N =145.	Speculum inserted in to the vagina and if necessary the cervix was grasped with a tenaculum. The 3.5mm minihysteroscope was then inserted into the external cervical canal and advanced into the uterine cavity, using normal saline as the distension medium. The hysteroscopy then continued as normal. Endometrial biopsies were taken when indicated. N=145.	VAS 0-5cm marked no, slight, tolerable, severe and intolerable pain. Asked to rate pain at introduction of the hysteroscope or speculum into the vagina, progression through the cervical canal, inspection of the cavity and during the endometrial biopsy.	Median and 95% confidence intervals.
Paschopoulos (79)	Pre- and post-menopausal women undergoing diagnostic outpatient hysteroscopy.	Rigid, 3.5mm hysteroscope introduced into the vagina. Holding the labia minora together the vagina was distended with normal saline and the hysteroscope steered into the external cervical os and along the canal into the uterine cavity. The hysteroscopy then continued as normal. N=98.	Conventional hysteroscopy. N=99.	VAS 0-10cm	Divided into groups scoring <3, 3 – 5, >5.

Table 4.4 continued

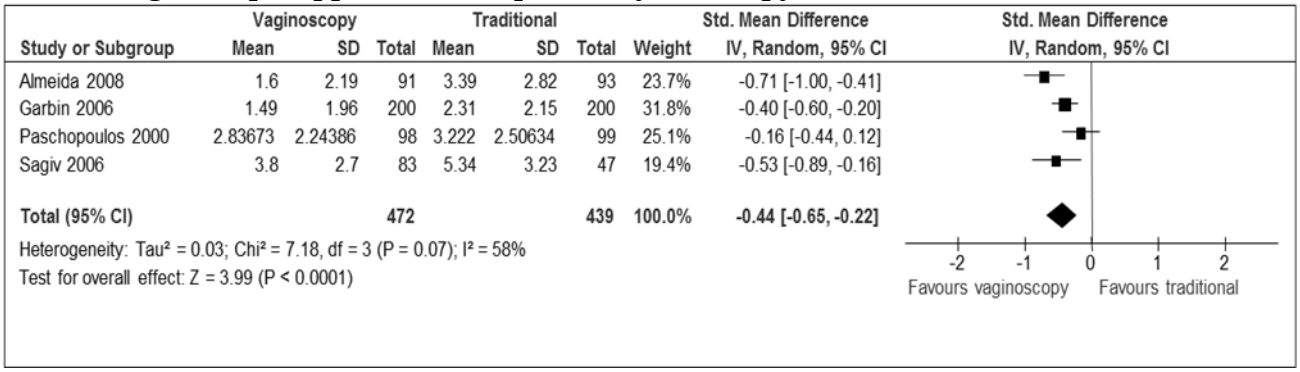
Study	Participants	Intervention	Comparison	Outcome measure	Data reported
Sagiv (33)	Pre- and post-menopausal women undergoing diagnostic outpatient hysteroscopy.	Patients positioned in lithotomy, vagina cleaned and the rigid, 3.7mm hysteroscope introduced into the vagina which was then distended with normal saline and the hysteroscope steered into the external cervical os and along the canal into the uterine cavity. The hysteroscopy then continued as normal. Endometrial biopsies were performed as necessary. N=83.	Traditional hysteroscopy using a rigid, 3.7mm hysteroscope and normal saline, with an intracervical injection of local anaesthetic. N=47.	VAS 0-10cm used to score the pain immediately and 15 minutes after the hysteroscopy.	Mean and standard deviation reported.
Sharma (32)	Pre- and post-menopausal women undergoing diagnostic outpatient hysteroscopy.	Rigid, 3.5mm or 5mm hysteroscope introduced into the vagina, which was distended with normal saline so that the hysteroscope could be steered into the external cervical os and along the canal into the uterine cavity. The hysteroscopy then continued as normal. Endometrial biopsies were taken when indicated. N =60.	Speculum inserted in to the vagina and the cervix was grasped with forceps. Cervical canal dilated if necessary and local anaesthetic given if requested by the patient. Either a 3.5mm or 5mm rigid hysteroscope was then inserted into the external cervical canal and advanced into the uterine cavity, using normal saline as the distension medium. The hysteroscopy then continued as normal. Endometrial biopsies were taken when indicated N=60.	VAS 0-10cm, rated at insertion of hysteroscope, inspection of cavity, insertion of speculum, administration of local anaesthetic, endometrial biopsy, at the end of the procedure and 30mins after the procedure.	Medians and ranges.

Five papers reported data on the feasibility of the vaginoscopic procedure versus the traditional hysteroscopy (31-33;77;78). Feasibility was assessed using the number of failed procedures (i.e. failure to adequately visualise the uterine cavity) in each of the study arms.

Effect of vaginoscopy on pain

Meta-analysis of four studies showed that in the outpatient setting, the use of the vaginoscopic approach to hysteroscopy was less painful than using the traditional technique with a vaginal speculum (SMD -0.44, 95%CI -0.65 to -0.22, $I^2 = 58\%$) (Figure 4.14).

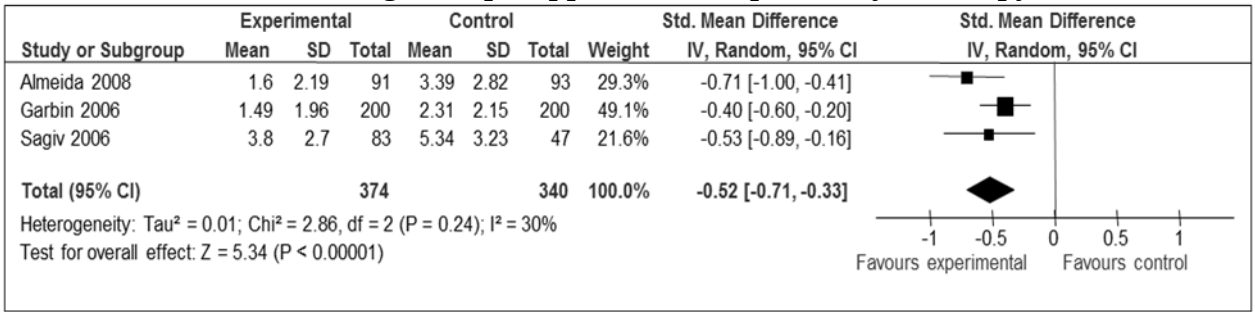
Figure 4.14 Forest plot showing the results of meta-analysis of studies that examine the use of a vaginoscopic approach to outpatient hysteroscopy



One of these studies was considered 'poor' quality (79) as it only met one of the three quality criteria. When this study was excluded from meta-analysis, the magnitude of reduction in pain favouring vaginoscopy was not significantly altered and results were more homogenous (SMD -0.52, 95%CI -0.71 to -0.33, $I^2 = 30\%$) (Figure 4.15). Neither of the two papers included in the systematic review that could not be included in the meta-analysis (32;78) reported any significant differences in the mean pain scores between the vaginoscopic and the traditional hysteroscopy groups. However one of the studies (78) found that the 95%

confidence interval in the vaginoscopic group was significantly lower than in the traditional hysteroscopy group ($p<0.05$).

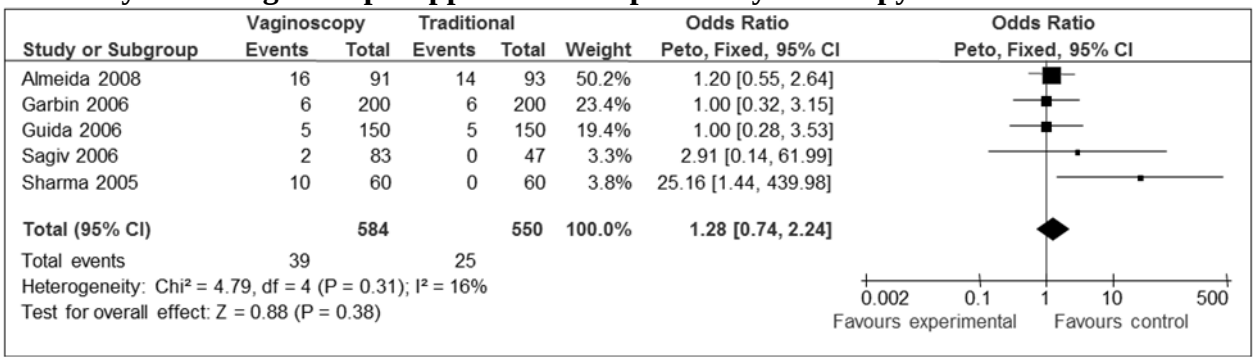
Figure 4.15 Forest plot showing the results of meta-analysis of the high quality studies that examine the use of a vaginoscopic approach to outpatient hysteroscopy



Feasibility

There was no significant difference in the number of failed procedures between the vaginoscopic and traditional approaches to hysteroscopy p=0.38 (Figure 4.16).

Figure 4.16 Forest plot showing the results of meta-analysis of the studies that report feasibility of the vaginoscopic approach to outpatient hysteroscopy



Results of the systematic review of the effect of distension media on pain during outpatient hysteroscopy

Study Selection, Details and Quality

The literature search yielded 703 citations; twenty were retrieved for further evaluation. Eleven studies were rejected because they did not meet the inclusion criteria (34;36-38;60;93-98) and two were rejected as duplicates (64;93). The seven remaining studies were selected as eligible for inclusion in the review (35;60;64;80-83); however it became apparent that two of these papers may have reported the same study (81;99). The authors were contacted to confirm this, however no answer was received. To prevent probable duplication of data only the earliest published paper was used (81) resulting in six papers being eligible for the review (Figure 4.17). The inter-rater reliability for the study selection was very good (kappa=0.85).

Details of the study populations, interventions, outcome assessment and data reporting are shown in Table 4.5. The quality of the studies was poor with only one considered to have adequate randomisation and concealment (81) this study was randomised by computer and so it was assumed that it was also concealed.

Figure 4.17 Study selection process for systematic review of the effect of distension media on pain during outpatient hysteroscopy

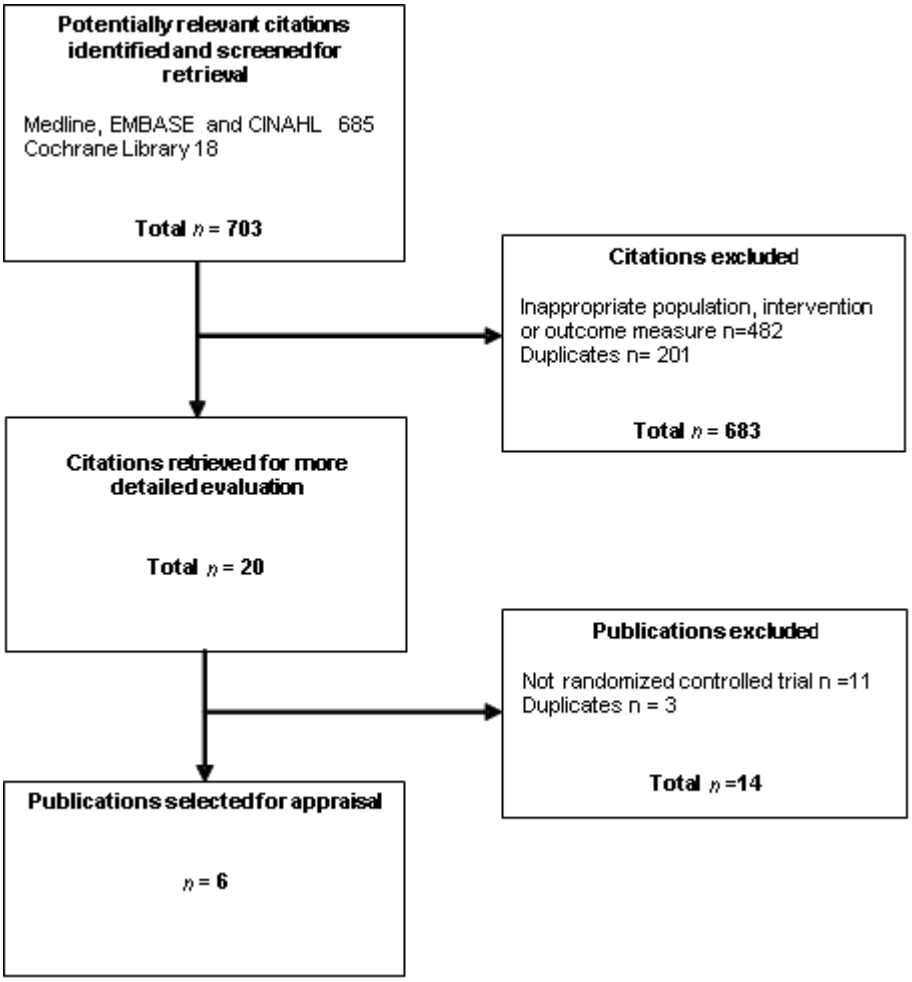


Table 4.5 Characteristics of the selected studies included in the systematic review of the effect of the distension medium used on pain during outpatient hysteroscopy.

Study	Participants	Intervention	Comparison	Outcome measures	Data reported
Brusco (80)	Women attending for hysteroscopy at an artificial insemination and sterility clinic.	External genitalia cleaned with disinfectant. Outpatient hysteroscopy performed with a 4mm rigid hysteroscope and a 7mm operative sheath by a vaginoscopic approach. Normal saline delivered by a pressure bag (at 50mmHg) used to distend the uterine cavity. A paracervical block was used when necessary. N =45.	External genitalia cleaned with disinfectant. Outpatient hysteroscopy performed with a 4mm rigid hysteroscope and a 7mm operative sheath by a traditional approach using a speculum and tenaculum. Carbon dioxide delivered by a uterine insufflator at 40ml/min used to distend the uterine cavity. A paracervical block was used when necessary. N =29.	Scale of 0-5 to score pain during the procedure. Also, presence of shoulder pain was recorded. Operators graded the quality of the image on a scale from 0-5 (5= good image quality). Time from introduction of the hysteroscope until the removal at the end of the procedure.	Pain and procedure time reported as mean and standard deviation. Number and percentage of women experiencing shoulder tip pain reported. Image quality reported as percentages.
Lavitola (81)	Infertile women undergoing diagnostic outpatient hysteroscopy.	Vaginoscopic hysteroscopy with a 30 degree continuous flow hysteroscope, using normal saline as the distension medium introduced by a pressure bag at 50-120mmHg measured by a manometer. An endometrial biopsy was taken when indicated. N =97.	Vaginoscopic hysteroscopy with a 30 degree continuous flow hysteroscope, using carbon dioxide as the distension medium introduced by uterine insufflator at a pressure of 100mmHg. An endometrial biopsy was taken when indicated. N =92.	VAS 0-10 used to score pain during progression of the scope through the canal, during inspection of the cavity, and the intensity of any shoulder pain. The image quality was scored by the operator on a scale of 0-5 (5 = excellent). The incidence of vasovagal episodes.	Mean and standard deviation for pain and procedural time. Number and percentage of women experiencing vasovagal episodes and having examinations with mediocre image quality.

Table 4.5 continued

Study	Participants	Intervention	Comparison	Outcome measures	Data reported
Litta (82)	Pre- and post-menopausal women undergoing diagnostic outpatient hysteroscopy.	Speculum inserted in to the vagina to visualise the cervix. Rigid, 2.9mm, 30 degree hysteroscope, introduced into the cervical os and along the canal into the uterine cavity which was distended with normal saline infused by a 100mmHg pressure bag. Endometrial biopsies were taken when indicated. N =214.	Speculum inserted in to the vagina to visualise the cervix. Rigid, 2.9mm, 30 degree hysteroscope, introduced into the cervical os and along the canal into the uterine cavity which was distended with carbon dioxide administered by a hysterosufflator with a pressure of 100mmHg and flow rate of 40ml/min. Endometrial biopsies were taken when indicated. N =201.	VAS 0-10 completed approximately 10 minutes after the end of the procedure to rate the pain experienced. Procedure duration. Presence of shoulder tip pain.	Mean and standard deviation for pain and procedural time. Number and percentage of women experiencing shoulder tip pain.
Nagele (83)	Pre- and post-menopausal women undergoing diagnostic outpatient hysteroscopy.	Speculum inserted in to the vagina. Os probed and if thought to be tight ,dilated under local anaesthesia. Rigid, 5.5mm , 30 degree hysteroscopy with normal saline infused by a 150-250mmHg pressure bag. Targeted endometrial biopsies and minor surgical procedures were performed when indicated using a 7mm operative sheath. N =78.	Speculum inserted in to the vagina. Os probed and if thought to be tight ,dilated under local anaesthesia .Rigid, 5.5mm , 30 degree hysteroscopy with carbon dioxide distension media administered by a hysterosufflator at 100mmHg. Targeted endometrial biopsies and minor surgical procedures were performed when indicated using a 7mm operative sheath. N =79.	Abdominal pain and shoulder tip pain ranked on a scale of 0-4. (0= no pain, , 4= very severe pain). Image quality was graded on a scale of 0-4 (0= none, 1= good, 2 = adequate, 3= poor, 4= very poor). Incidence of vasovagal episodes. Procedure duration.	Abdominal pain, shoulder pain, hysteroscopic vision and procedural time were all reported as means and standard deviations. The number of women experiencing shoulder pain and vasovagal episodes were also reported as numbers. The number of poor or very poor image examinations was reported.

Table 4.5 continued

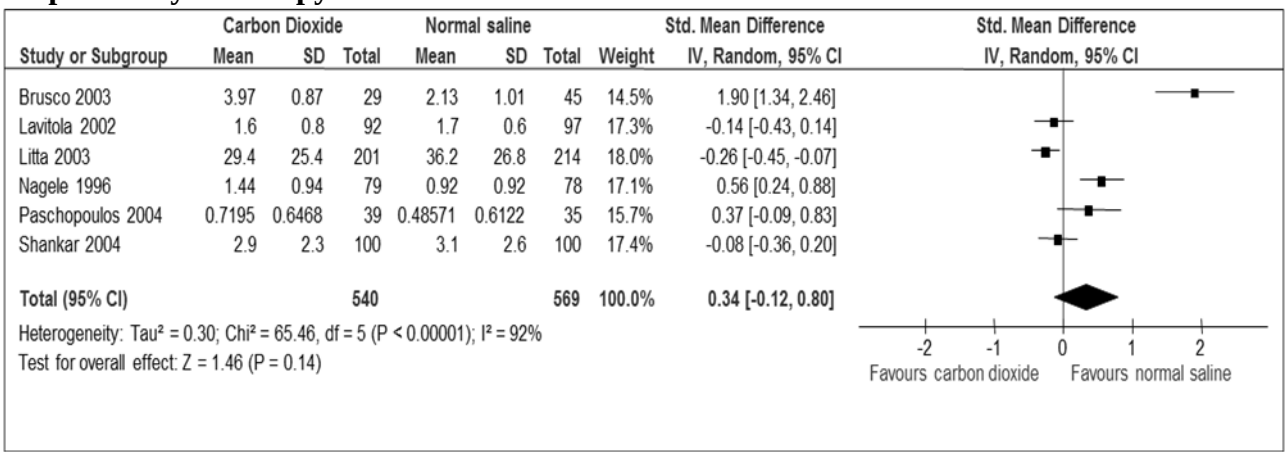
Study	Participants	Intervention	Comparison	Outcome measures	Data reported
Paschopoulos (35)	Women admitted for total abdominal hysterectomy who agreed to undergo outpatient diagnostic hysteroscopy 12-24 hours prior to surgery. Exclusions: suspicion of endometrial cancer	Hysteroscopy performed with a 2.8mm, 30 degree, rigid hysteroscope by a vaginoscopic approach. Normal saline delivered by a pressure bag (40-80mmHg) used to distend the uterine cavity. N =35.	Hysteroscopy performed with a 2.8mm, 30 degree, rigid hysteroscope by a vaginoscopic approach. Carbon dioxide was delivered by a microhysteroflator with a maximum pressure of 200mmHg and a flow rate of 25ml/min to distend the uterine cavity. N =39.	Completed a questionnaire after the hysteroscopy which asked patients to rate shoulder pain and pelvic pain on a 4 point scale (0= none, 1= mild, 2=severe, 3= pain which did not allow the procedure to continue).	Number and percentage of women in each group selecting each of the four categories. Values were allocated to the categories i.e. 0, 1, 2, 3 and calculated the mean and standard deviation.
Shankar (64)	Pre- and post-menopausal women undergoing diagnostic outpatient hysteroscopy for abnormal uterine bleeding. Exclusions: procedure not feasible as unable to visualise the cervix or severe cervical stenosis.	Speculum inserted in to the vagina to visualise the cervix. Vulsellum applied. Cervix dilated if necessary. Rigid, 5.5mm (with sheath), 30 degree hysteroscope, introduced into the uterine cavity which was distended with normal saline infused by a 150-250mmHg pressure bag. Endometrial biopsies were taken from all patients. N= 100. Another saline group had lignocaine added to the distension medium. This group was not used in the analysis. N=100	Speculum inserted in to the vagina to visualise the cervix. Vulsellum applied. Cervix dilated if necessary. Rigid, 5.5mm (with sheath), 30 degree hysteroscope, introduced uterine cavity which was distended with carbon dioxide, delivered by a hysteron-insufflator at a maximum pressure of 100mmHg with a variable flow rate of up to 100ml/min. Endometrial biopsies were taken from all patients. N= 100.	Pelvic pain was scored with VAS 0-10, and PPI. Shoulder tip pain scored with VAS 0-10. The image quality was ranked as very satisfactory, satisfactory or unsatisfactory.	Pelvic pain reported as mean and standard deviation. Shoulder tip pain reported as percentages with 95% confidence intervals. Percentages were converted to numbers. Image quality reported as number of examinations falling into each category.

PPI= Present pain intensity scale (verbal descriptors of pain ranked from 0-5 on a numeric scale). VAS= visual analogue scale

Effect of distension media on pain

All six studies reported data for pain when comparing normal saline versus carbon dioxide as the distension media for the procedure. Five studies used scales to collect the data (64;80-83) and reported them as means and standard deviations. One study reported the number of people selecting each of four numbered categories (0= none, 1= mild, 2=severe, 3= pain which did not allow the procedure to continue) (35). The category number was used as a value and the mean and standard deviation were calculated (90) for the pain experienced during the procedure. Meta-analysis showed that there was no significant difference in pain scores when carbon dioxide or normal saline were used as the distension medium for outpatient hysteroscopy (SMD= -0.05, 95% CI -0.17 to 0.07, I^2 = 92%) (Figure 4.18).

Figure 4.18 Forest plot showing the effect of distension media on procedural pain during outpatient hysteroscopy

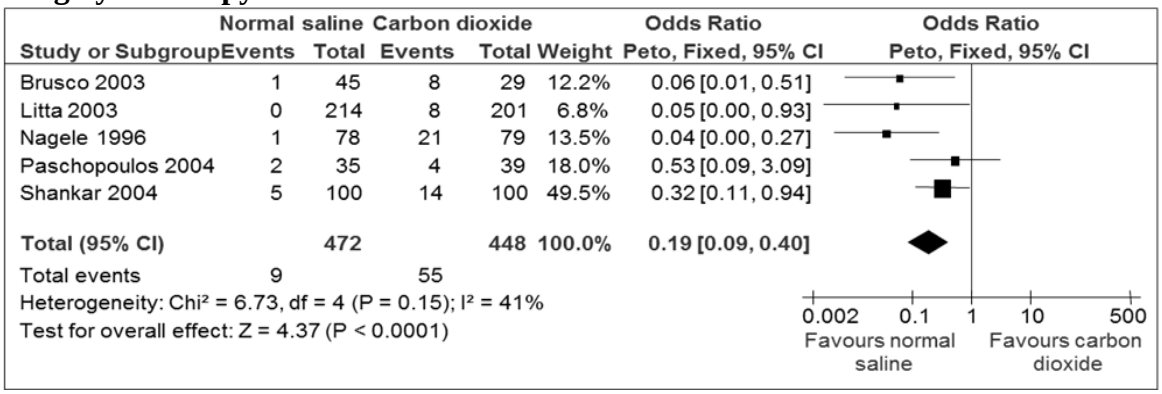


Effect of distension media on shoulder tip pain

Shoulder tip pain was reported by all six studies. One study used a visual analogue scale to assess the severity of the pain and reported a mean and standard deviation (81). The remaining five studies (35;64;80;82;83) reported the number of events or the percentage of women that experienced shoulder tip pain. If the number of events were not reported (64;82)

the value was calculated from the percentage. Meta-analysis of five studies found that shoulder tip pain was significantly reduced when using normal saline as compared to carbon dioxide as the distension medium (OR = 0.19, 95% CI 0.09 to 0.40, I^2= 41%) (Figure 4.19).

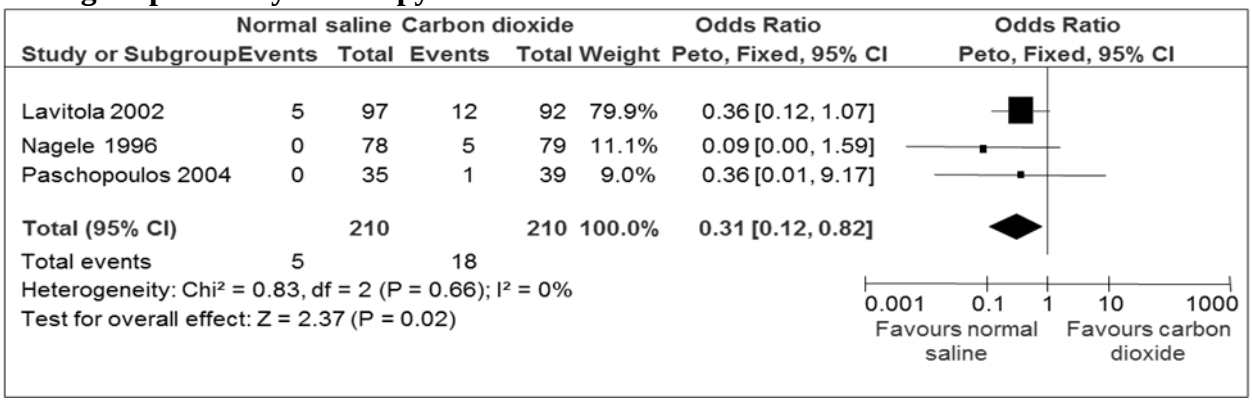
Figure 4.19 Forest plot showing the effect of distension media on shoulder tip pain during hysteroscopy



Effect on vasovagal episodes

Vasovagal reactions were specifically reported by four studies (35;81-83), one of which reported no vasovagal episodes (82). The two studies that didn't report vasovagal episodes did report symptoms that may be attributed to vasovagal episodes (nausea, dizziness, hypotension) (64;80) but did not specifically state them to be vasovagal reactions. The number of events from the three studies (35;81;83) that stated the patients had suffered vasovagal episodes were used for meta-analysis and it was found that there were significantly fewer vasovagal episodes when using normal saline as the distension medium (OR = 0.31, 95% CI 0.12 to 0.82, I^2= 0%) (Figure 4.20).

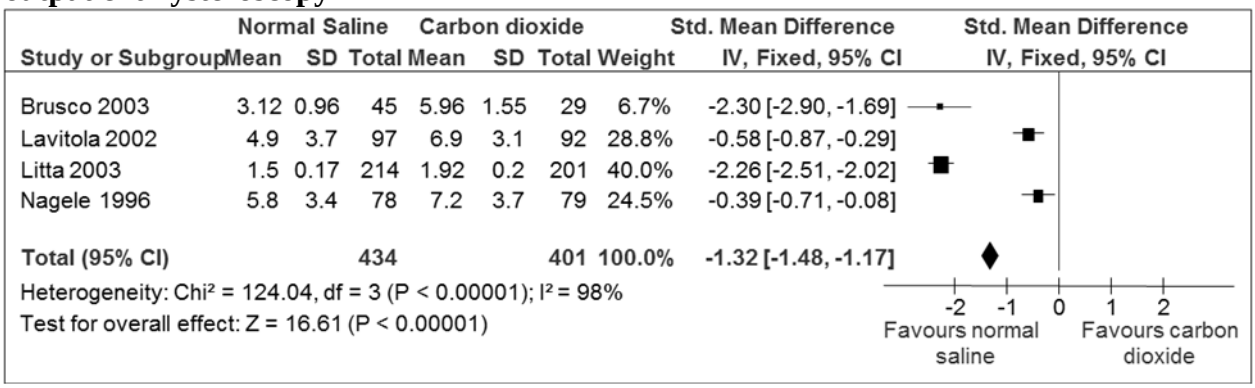
Figure 4.20 Forest plot showing the effect of distension media on vasovagal episodes during outpatient hysteroscopy



Effect on duration of the procedure

Procedural time was reported by four studies (80-83) as means and standard deviations. Meta-analysis found that outpatient hysteroscopy using normal saline was significantly shorter than when using carbon dioxide (SMD=-1.32, 95% CI -1.48 to -1.17, I^2 =98%) (Figure 4.21).

Figure 4.21 Forest plot showing the effect of distension media on procedural time for outpatient hysteroscopy



Effect of distension media on image quality

Image quality was reported by four studies (64;80;81;83). Three studies used scales with categories (e.g. 0= no view, 1= poor view etc.) (80;81;83) and asked the operators to select the appropriate number. One study used this data to calculate a mean and standard deviation

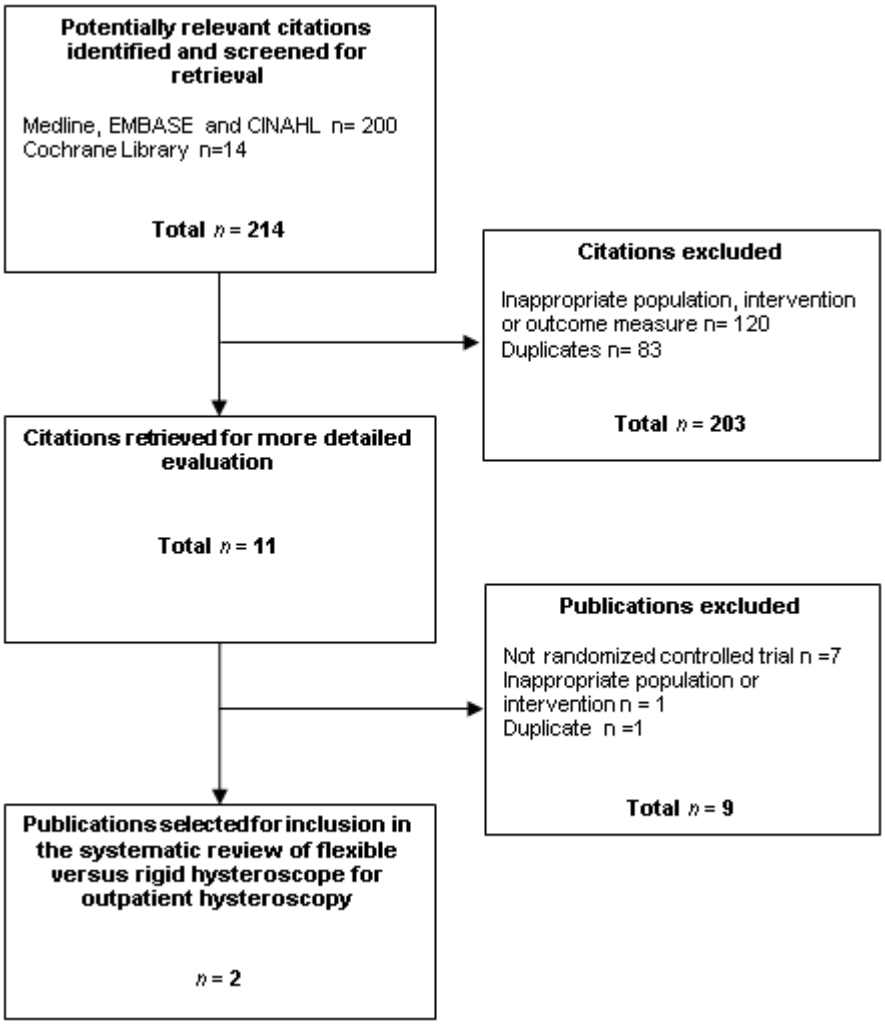
(83). The remaining two studies (80;81) reported the number of operators selecting from certain categories but did not give data for all of the categories. The final study (64) used unnumbered categories (very satisfactory, satisfactory, unsatisfactory) and asked the operators to select an appropriate one. Data for the 'very satisfactory' category were reported in the text and for the 'unsatisfactory' category in a table, thus allowing calculation of the number of operators selecting the 'satisfactory' category. Data from the studies could not be meta-analysed as they were not adequately reported and outcome assessments were not comparable. Three studies reported no significant difference in image quality between carbon dioxide and normal saline (80;81;83), however one of these studies (83) reported changing the distension media from carbon dioxide to normal saline in 8 (10.1%) patients. One study found a statistically significant increased risk of unsatisfactory view with the use of carbon dioxide (Relative risk (RR) =4.75, 95% CI 1.61, 16.4) attributing it to bubbles, and bleeding (64). Of the 19 patients who had an unsatisfactory view at hysteroscopy using carbon dioxide, 17 were changed to normal saline and an improved view reported in 11 (64.7%).

Results of the systematic review of the effect on pain of the type of hysteroscope used for outpatient hysteroscopy

Study Selection, Details and Quality

From 214 citations, 212 were rejected on methodological grounds or because they were duplicates. That left just two studies (84;85) which were selected for review (Figure 4.22).

Figure 4.22 Study selection process for systematic review of the effect on pain of the type of hysteroscope used for outpatient hysteroscopy



Both selected studies were randomised controlled trials that compared flexible with rigid hysteroscopes, using normal saline as the distension medium. The inter-rater reliability for the study selection was very good (kappa=0.84). Pain scores were assessed on 10cm visual analogue scales in both studies. Both studies assessed pain immediately after the procedure (84;85) and one assessed pain during the procedure (85). The study characteristics and results are shown in Table 4.6.

Pain during the procedure was found to be significantly less when the flexible hysteroscope was used (flexible median pain score 1.2, rigid median pain scores 3.1, p = 0.0001 (85)). Immediately after the hysteroscopy the studies reported different results, with one finding a significantly lower pain score when a flexible hysteroscope was used (flexible pain scores mean 1.8, median 1.2 versus rigid pain scores mean 4.0, median 3.6, p= 0.0001) (84) and the second finding no difference between pain scores (median 0 in flexible and rigid groups) (85).

No vasovagal episodes occurred in the single study reporting this outcome (84). Image quality was assessed by the hysteroscopists and reported in both studies. One study (84) reported that the view was good to excellent in all examinations whereas the other study (85) reported a significantly better view with the use of the rigid hysteroscope (p< 0.001). There were no failures in the rigid hysteroscopy groups, however one of the studies (85) reported five failures in the flexible hysteroscopy group. This is reported as '(5/40) 12.5%' in the paper, however there were 70 rather than 40 patients in the group which results in a 7.2% failure rate. One of the studies found use of a rigid hysteroscope to be significantly quicker than using a flexible scope (p = 0.003) (85) in contrast to the second paper which reported similar procedure times in both groups (flexible 5.9 minutes, rigid 6.1 minutes) (84).

Table 4.6 Overview of the studies included in the systematic review of the effect on pain of the type of hysteroscope used for outpatient hysteroscopy including interventions and results

	Baxter (84)	**Unfried (85)**
Design	Randomised controlled trial	Randomised controlled trial
Randomisation	Computer generated random number sequence	Computer generated random permutation list with 36 blocks of length four
Blinding	Single blinded	Not reported
Follow-up	100%	100%
No. in flexible group	40	70
No. in rigid group	43	72
Intervention	After a vaginal examination to assess uterine size and position, a Cusco's speculum was inserted and the cervix was visualized and cleaned. When necessary, the anterior lip of the cervix was grasped gently with a tenaculum. Occasionally a local anaesthetic block was used. Hysteroscopy was then performed with either a 3mm flexible hysteroscope (Olympus Keymed, Southend-on Sea, UK) or a 3.3mm rigid scope, including sheath (Storz, Slough, UK). The distension medium was warmed normal saline at a pressure of up to 100 mmHg.	The procedure was performed according to a standard protocol which is not described in the paper. Lignocaine spray was applied to the cervix before the hysteroscopy and occasionally an additional local anaesthetic block was used. Hysteroscopy was then performed with either a 3.6mm flexible hysteroscope with 100° bending section (Olympus HYF type P, Hamburg, Germany) or a 3.7mm rigid hysteroscope with a 30° fore oblique lens (WISAP, Munich, Germany). The distension medium was normal saline at a pressure of 120-200 mmHg.

Table 4.6 continued

	Baxter (84)	Unfried (85)
Method of scoring pain	Analogue pain scale measuring 10 cm long, with a score of 0 at one end corresponding to having 'no pain at all' and 10 at the other being 'the worst pain they have ever had'. Completed immediately and 30 minutes after the hysteroscopy.	A 10cm visual analogue scale completed before the test, at insertion of the hysteroscope, during and immediately after the hysteroscopy and at endometrial biopsy.
Pain score in flexible group	During hysteroscopy- not reported Immediately after- mean 1.8, median 1.2	During hysteroscopy- Median 1.2 Immediately after – 0
Pain score in rigid group	During hysteroscopy- not reported Immediately after- mean 4.0, median 3.6	During hysteroscopy- Median 3.1 Immediately after – 0
P value of pain score difference	During hysteroscopy- not reported Immediately after p= 0.0001	During hysteroscopy- p<0.001 Immediately after- p= NS
Vasovagal episodes in flexible group	0	Not reported
Vasovagal episodes in rigid group	0	Not reported
Failures in flexible group	0	5 (7.2%) –reported as 12.5% in the paper.
Failures in rigid group	0	0
Quality of image in flexible group	Excellent to good	66% excellent to good
Quality of image in rigid group	Excellent to good	100% excellent to good

CHAPTER 5

DISCUSSION REGARDING THE RESULTS OF THE SYSTEMATIC REVIEWS AND META-ANALYSES WHICH INVESTIGATE PAIN REDUCTION IN OUTPATIENT HYSTEROSCOPY

Principal findings of the reviews

The systematic review of local anaesthetic found that pain is reduced during outpatient hysteroscopy with paracervical and intracervical injections of anaesthetic but not with transcervical and topical application. Paracervical injection appears to be the most effective method of administering local anaesthetic for the procedure. Local anaesthetic did not significantly reduce the incidence of vasovagal attacks during outpatient hysteroscopy but there was a beneficial trend.

The analgesia systematic review found that opiates may reduce the pain of outpatient hysteroscopy during the procedure but not without significant side effects, although some of the symptoms experienced (nausea, vomiting, dizziness) could be attributed to the procedure. In one study the side effects attributed to buprenorphine caused high rates of patient dissatisfaction, demonstrating the importance of considering whether the benefit of pain relief outweighs medication side effects. A study, examining mefenamic acid found a significant reduction in post-operative pain at 30 and 60 minutes.

Conscious sedation with midazolam was found to be as effective as intracervical local anaesthetic for reducing pain during outpatient hysteroscopy. Sedation requires regular monitoring and may be associated with inadvertent overdose, requiring reversal. Hysteroscopists will be experienced in administering an intracervical block but will have far less experience in the use of conscious sedation and are unlikely to feel confident to manage the sedation without an anaesthetist or a second clinician. Additionally, ambulatory gynaecologists who perform colposcopy are already familiar with techniques for anesthetising the cervix when taking biopsies. Thus to ensure patient safety and reduce the number of trained staff required, alternatives to conscious sedation should be used for outpatient hysteroscopy.

The studies used in the systematic review of cervical preparation examined different drug doses and administration times and assessed pain at different time points. Similarly, effectiveness of cervical priming was assessed in a variety of ways. This heterogeneity made meta-analysis unfeasible and interpretation of the results problematic. However the following conclusions were drawn from the results. Mifepristone given before hysteroscopy does not have any significant effect on the pain experienced during the procedure or dilatation of the cervix in premenopausal women. Cervical priming with prostaglandins is beneficial in reducing pain when dilating the cervix beyond 6mm but this is likely to be greater in postmenopausal women. Pain on inserting the hysteroscope and during the hysteroscopy is reduced when using large diameter hysteroscopic systems (4mm endoscopes with 5.5mm sheath) but miniaturisation of the instruments used in the outpatient setting means that there is rarely any need to dilate the cervix above six millimetres thus these findings are, in the most, clinically irrelevant. It was demonstrated that prostaglandins do not have significant adverse

effects when compared to placebo and do not increase the number of failed procedures, however the negligible benefit means that the routine use of cervical priming prior to outpatient hysteroscopy cannot be recommend.

The review of vaginoscopy for outpatient hysteroscopy found that the vaginoscopic approach to hysteroscopy significantly reduces the pain experienced by patients during the procedure. The vaginoscopic technique is successful as demonstrated by the majority of hysteroscopies being completed successfully (83-98%) and there being no significant difference in the number of failed procedures between groups of patients undergoing a vaginoscopic hysteroscopy and a traditional outpatient hysteroscopy using a vaginal speculum. However whilst a reduction in pain is clearly advantageous in outpatient procedures to optimise acceptability to patients, the review did not demonstrate any improvement in procedural feasibility (i.e. successful completion of hysteroscopy) as a consequence of minimising discomfort.

There is no significant difference in pain experienced between carbon dioxide and normal saline when used as the distension medium for outpatient hysteroscopy. However, meta-analysis found that vasovagal episodes, shoulder tip pain and procedural time were all significantly reduced when using normal saline. Image quality may be better with normal saline as it causes a *lavage* and so prevents blood and bubbles obscuring the view.

Flexible hysteroscopy causes less pain than rigid hysteroscopy in the outpatient setting. Rigid hysteroscopy may provide a better image, resulting in fewer failed procedures and be quicker to perform although these results were not consistently reported. Mean pain scores were low

with both types of hysteroscope (≤4) and so without further qualitative assessment it is difficult to assess the clinical relevance of the lower pain score associated with flexible hysteroscopy, especially when procedure times may be more prolonged (85) and more likely to fail (85) with a non-rigid endoscope. Whilst the current review did not evaluate test accuracy, the superior image quality with rigid hysteroscopy reported in one study (85) may further offset any clinical advantage of a less painful procedure using a flexible instrument.

Strengths and limitations of the reviews

Many aspects of the reviews support their results being valid. Firstly, clinically focused questions were formulated. Comprehensive searches were then performed which encompassed multiple online databases as well as searching of the reference sections of relevant studies. The searches were not restricted to the English language and broad search terms were used to avoid making the question too specific to be adequately sensitive. Unpublished data were not sought and therefore there is a risk of publication bias. Data were restricted by the study design to randomised controlled trials to minimise selection bias. Excepting the review of local anaesthesia, all of the reviews contained small numbers of studies which limits the conclusions. However, although there was paucity of studies the reviews did contain the totality of published, randomised data. Meta-analysis was not always possible making it difficult to draw conclusions for the examined elements of hysteroscopy in some of the reviews.

For the systematic review of local anaesthetic the studies were sub-grouped according to quality to examine for the overall heterogeneity. Heterogeneity was reduced in the high

quality sub-group, but I^2 was still 83%. Meta-analysis of the high quality studies found a significant reduction in pain with the use of local anaesthetic, a finding which was consistent with and thus supportive of the overall findings. Intracervical injection of local anaesthetic was associated with a significant reduction in pain during outpatient hysteroscopy, but the strength of this finding is limited. This is because a sensitivity analysis excluding a study in which categorical data had been transformed, demonstrated no beneficial effect of intracervical injection, although this finding was associated with increased heterogeneity. Reasons for heterogeneity could not be examined in the method of administration sub-groups due to the paucity of studies.

Out-patient hysteroscopy is a multi-faceted procedure and so there are many factors that contribute towards pain. These can be categorised into patient factors (e.g. menopausal status, reason for hysteroscopy) and procedural factors (e.g. the type of distension media, use of a speculum, use of a rigid or flexible hysteroscope). The small number of studies in the review of local anaesthesia meant that there were not enough data to sub-group the patients according to menopausal status and indication for hysteroscopy. Confounding due to procedural factors should be eradicated on the basis of the study designs being restricted to randomised controlled trials in this review.

There were further limitations in the study of the cervical preparation, mainly due to the heterogeneity of the studies. Although the majority of studies gave 400µg misoprostol (71;74-76) the administration times varied between the studies from four, to twenty-four hours before the procedure. One study used mifepristone as a priming agent (72) and so was incomparable with the other five studies The studies varied in the timing of pain assessment with some

assessing pain during cervical dilatation whilst others assessed pain during or after the procedure. Similarly, cervical dilatation was assessed in a non-uniform manner, some studies assessing the force needed to dilate and others assessing change in dilatation from baseline or dilatation pre-procedure. The study populations differed so that conclusions regarding menopausal status and the use of cervical priming agents were limited.

Only the abstract was available for one of the studies included in the vaginoscopy systematic review (79) and only limited information about the study method was available hence it was graded as low quality. However, the five remaining RCT's were all considered to be of high quality. All of the studies used a tenaculum in the 'traditional' hysteroscopy arm and thus it was not assessed whether there was a significant pain reduction when there is no cervical instrumentation. Whilst all studies included in the review compared vaginoscopy with a traditional approach to hysteroscopy utilising a vaginal speculum, there were some minor procedural differences between the studies (e.g. use of intracervical local anaesthetic (33), varying distension media between the arms of the study (77)), however heterogeneity was low in all analyses, showing consistency of findings across studies in favour of vaginoscopy. Effectiveness of the procedure in sub-groups of patients (e.g. pre- versus post-menopausal, nulliparous versus parous) could not be assessed as all of the studies included mixed populations. There were no studies which used flexible hysteroscopes for vaginoscopy or that compared vaginoscopy to flexible hysteroscopy.

There was considerable heterogeneity (I^2 =92%) in the meta-analysis of procedural pain when comparing distension media for outpatient hysteroscopy. Because the random effects model gives more weight to small studies, one small study (80) with an outlying result was excluded

to explore heterogeneity. As well as being small this study used a vaginoscopic approach (without a speculum and tenaculum) in the normal saline group and a traditional approach with a speculum in the carbon dioxide group and so had more than one variable. Analysis without this study reduced the heterogeneity to 82% but still produced a non-significant result overall (SMD = 0.06, 95% CI -0.24 to 0.37). No causes for heterogeneity were identified but may be attributable to the small number of studies used for the meta-analysis.

Heterogeneity was also high in the meta-analysis of procedural time (I^2 =98%), again this was difficult to explain. All of the studies in this analysis found individual significant results in favour of the use of normal saline, which were in keeping with the meta-analysis result. In contrast, heterogeneity was low in the meta-analyses exploring vasovagal episodes and shoulder tip pain. A weakness of this distension media review is that it only contains six studies, five of which were assessed to be of low quality due to inadequate randomisation and concealment and two of which have small populations. However, as already mentioned, these data reflect the totality of the published trials in this area. Although statistically significant results were found it was not possible to assess whether they were clinically significant.

Comparison with other studies

The systematic reviews that examine local anaesthetic, vaginoscopy, cervical preparation and distension media have been published in peer reviewed journals (100-103) since this thesis was undertaken. Prior to that there were no published systematic reviews that addressed methods to relieve pain during outpatient or office hysteroscopy. The conclusions of these reviews were unique in having been drawn from the available primary studies.

A Cochrane review had assessed the use of paracervical injection for a variety of obstetric and gynaecological procedures including hysteroscopy, endometrial biopsy, fractional curettage, vacuum aspiration, suction termination of pregnancy or evacuation of retained products of conception and bimanual removal of retained placenta (14). Only three studies involving hysteroscopy were included in the review and only two in the meta-analysis so their conclusion that the use of paracervical injection does not reduce the pain of 'uterine intervention' cannot be applied specifically to hysteroscopy. The meta-analysis of paracervical injection in this systematic review contains five studies assessing paracervical anaesthesia in hysteroscopy and so has greater power, adding weight to the findings. Moreover, intracervical and topical administration of local anaesthesia is more commonly practised in ambulatory hysteroscopy than paracervical approaches (6). The systematic review of local anaesthesia described in this dissertation assesses all routes of local anaesthetic administration thereby providing relevant guidance to clinicians for one of the most commonly practised interventions in gynaecology. Similarly, a Cochrane review published in 2012 examined analgesics and local anaesthetics (104) but did not separate the anaesthetics according to method of administration. This review agreed that local anaesthetics were successful at reducing pain during outpatient hysteroscopy but by failing to look at method of administration it is difficult to make clinical inferences and decide how to administer the anaesthetic for maximum effect. In fact, the review of local anaesthetic in this thesis was able to demonstrate that the topical methods of administration do not have any benefit in pain reduction and thus provide clinically useful information.

The Cochrane review of local anaesthetics and analgesia (104) concluded that there was insufficient evidence for the use of analgesics prior to outpatient hysteroscopy which is in keeping with the review conducted for this thesis. A review that assessed the use of analgesia for hysterosalpingogram (HSG) found that when using analgesia versus placebo there was no benefit of using the analgesia during the procedure, however there was a benefit 30 minutes post-procedure (105). This is in keeping with the results of the outpatient analgesia review and although it refers to a different procedure, HSG is an outpatient test which also involves distension of the uterus in a similar way to hysteroscopy.

A systematic review of the use of paracervical local anaesthesia for cervical dilatation and uterine intervention (14) assessed conscious sedation versus cervical block for hysteroscopy and bimanual removal of placenta and found there to be no difference in pain between the sedated patients and those receiving local anaesthetic. This is in keeping with the findings of the only study retrieved in the review of conscious sedation.

A review that examined the use of misoprostol prior to hysteroscopy (studies examining procedures under general anaesthetic and in the office) (24) found that misoprostol given to premenopausal women reduced the need for cervical dilatation as well as the incidence of cervical laceration. However, vaginal bleeding, abdominal cramping and fever were significantly increased in the misoprostol groups. No significant difference was found between the control and intervention groups in postmenopausal women. These results conflict with the findings of the review of cervical preparation for outpatient hysteroscopy, mainly because the majority of the studies examined were assessing the use of misoprostol for inpatient hysteroscopy which routinely requires cervical dilatation because of the use of larger

instruments. Secondly as most of the patients were anaesthetised the review was unable to assess pain during the procedure. The systematic review of cervical dilatation for outpatient hysteroscopy was only able to meta-analyse a small number of studies to assess the adverse effect of prostaglandins and thus the result may underestimate their true incidence.

Two recent systematic reviews have examined the use of misoprostol given prior to hysteroscopy (106;107). The first examined the benefits and harms of misoprostol given prior to operative hysteroscopy with hysteroscopes of greater than 9mm in diameter. These procedures were not carried out in the outpatient setting but despite the use of much larger hysteroscopes, there was still no benefit of using misoprostol for dilatation of the cervix or in reducing complications. Similarly to the review by Crane et al. (24), side effects were significantly increased in the group of women who had taken misoprostol. This is not in keeping with the results found in this thesis as discussed above. The second review (107) investigated the feasibility of using misoprostol to facilitate the passage of the hysteroscope and the side effects associated with the medication. Pain during the hysteroscopy was not assessed. Studies that included inpatient and outpatient procedures were included, resulting in 17 studies being eligible. However, this will have caused heterogeneity as the size of hysteroscopes used will vary. The authors do not discuss this. This review found that misoprostol significantly reduced the need for cervical dilatation in the total population but when the women were analysed according to menopausal status there was no significant difference for either pre or postmenopausal women. The difference found for women overall may have been driven by the studies which used large hysteroscopes and although the differences were statistically significant they may not be clinically significant. Once again, the presence of side effects was significantly increased in the misoprostol group. The authors

concluded that there was not enough evidence to recommend routine use of misoprostol prior to hysteroscopy.

A large case series of five thousand patients found that carbon dioxide and normal saline were both feasible distending media, with no difference in success rate but that there were significantly more vasovagal episodes and shoulder tip pain when carbon dioxide was used (93). This is in keeping with the findings of the distension media review.

Clinical implications of the reviews

Injectable, preferably paracervical, administration of local anaesthetic should be used for out-patient hysteroscopy to reduce the amount of pain that women experience. Topical application of local anaesthetic does not reduce the pain of the hysteroscopy but should be used when applying a tenaculum to the cervix. Only one study examined the use of local anaesthetic for operative hysteroscopy (60) and therefore the results do not adequately address the benefit of local anaesthetic in this variation of the procedure.

Although these conclusions show a benefit of using local anaesthetic, data reviewing the harms could not be reviewed. This is because harms were not explicitly reported by the majority of studies except when referring to symptoms caused by vagal stimulation (hypotension, bradycardia, nausea, vomiting etc.) although it is possible that similar symptoms may arise from intravasation of injected local anaesthetic. Therefore side effects resulting from the use of local anaesthetic for outpatient hysteroscopy are likely to be underestimated. For example, the time taken to perform the block prolongs the procedure and

the pain scores may not take into account the pain experienced during injection of local anaesthetic, in itself a painful procedure. In fact it was found in one study that a vaginoscopic approach to hysteroscopy was significantly less painful than having the procedure done traditionally using a vaginal speculum and a local anaesthetic block (33).

Good pain control is important to ensure an efficient outpatient 'ambulatory' hysteroscopy service with rapid discharge and high levels of patient satisfaction (6;108). When prescribing analgesia non-steroidal anti-inflammatories should be preferred to opioids as they have fewer side effects but should be avoided in certain patient groups (asthmatics, history of peptic ulceration, allergy).

For investigation of the gastrointestinal tract, which cannot be anaesthetised and may require quashing of the gag reflex, conscious sedation is an invaluable resource. However, conscious sedation requires an experienced clinician to monitor the degree of sedation and possibly reverse the medication (15) and this is an unfamiliar entity to the gynaecologist. As there is no benefit of conscious sedation over paracervical block (a technique familiar to the hysteroscopist and administrable by them) it would seem that conscious sedation should be avoided for outpatient hysteroscopy.

The review of cervical preparation suggests that routine use of prostaglandins prior to outpatient hysteroscopy would not provide a clinically significant change in dilatation or pain and although no significant adverse effects were found, other systematic reviews of their use suggest that this may have been underestimated. A further clinical consideration is the added cost of using cervical preparations. As well as the cost of the drugs there may be increased

costs related to the added intervention, such as extra clinic appointments and management of adverse effects. There may need to be a facility for administering the vaginal drugs, especially in elderly women. Whether they are admitted for the prostaglandin and stay until the procedure or they go home between, there will be significant inconvenience for the patient and a possible impact on hospital beds. The final consideration is patient acceptability. Patients may prefer to have a short period of discomfort during the procedure, rather than abdominal cramping and vaginal bleeding for hours beforehand.

The findings that vaginoscopy is associated with significantly reduced procedural pain and comparable feasibility, compared with traditional speculum assisted and cervical instrumentation approaches to office hysteroscopy have clinical implications for clinical practice. Outpatient hysteroscopy is a common diagnostic and increasingly therapeutic intervention (e.g. polypectomy, sterilisation) and vaginoscopy is not widely taught or practised (6). The findings of this review however, strongly support vaginoscopic outpatient hysteroscopy as the technique of choice. Although it was not examined by this review, it is proposed that the vaginoscopic approach allows greater intracavity manoeuvrability of the hysteroscope as there is no restriction on external movement caused by the presence of a vaginal speculum. This is particularly advantageous in certain patient groups (e.g. restricted hip abduction / flexion, inability to lie supine due to respiratory disease, obesity, enlarged or acutely flexed uteri) and when access to the tubal ostia is required, for example, during hysteroscopic sterilisation (109). In addition, nulliparous women, those who have not been sexually active, have atrophy of the genital tract or who find intimate examinations distressing are likely to find the vaginoscopic approach more acceptable as it obviates the need for stretching the vagina by a bivalve speculum. Traditional hysteroscopy, with a vaginal

speculum and possibly cervical instrumentation, will still be necessary in the minority of cases where visualisation of the cervical canal is difficult (e.g. deficient intravaginal cervix, previous cone biopsy) or cervical stenosis is encountered. A vaginal speculum is also required when a global endometrial biopsy is indicated although there are new developments in global hysteroscopic endometrial sampling (110). Adopting a first-line approach of vaginoscopy allows visualisation of the uterine cavity with a subsequent recourse to either directed hysteroscopic biopsy or global 'blind' office sampling of the endometrium.

Normal saline and carbon dioxide are both suitable for outpatient hysteroscopy, as pain experienced during the diagnostic procedure is comparable between media. However, normal saline is the distension medium of choice in the office setting because it is associated with significantly fewer vasovagal episodes and incidences of shoulder tip pain. Furthermore, distension of the uterine cavity with normal saline as opposed to carbon dioxide results in a quicker hysteroscopic procedure, which is especially advantageous in conscious patients undergoing an invasive test. Although image quality could not adequately be assessed two of the studies reported changing from carbon dioxide to normal saline when the image was poor or obscured by blood (64;83) thus suggesting that normal saline is a more practical medium and can cause an improvement in view over carbon dioxide. A further consideration is the specialist equipment that is required to use carbon dioxide to distend the uterus. A hysterosufflator is required to control insufflation of carbon dioxide into the uterus however normal saline can be administered simply with a giving set and gravity or a pressure bag, although this can result in leakage of fluid and a more 'messy' procedure, compared with carbon dioxide. This review did not examine cost-effectiveness of the distension media but the increased duration of the procedure and capital outlay for specialist equipment associated

with the use of carbon dioxide, for no apparent benefit over normal saline, may not support the routine use of carbon dioxide in an outpatient setting from an economic perspective. A final, important consideration when choosing distension medium refers to the increasing use of therapeutic procedures in outpatient hysteroscopy. These procedures include the use of bipolar electrosurgery (6;111) for removing fibroids, polyps, synechiae (112) and septae (113;114) which require a conducting liquid medium (i.e. normal saline). Moreover, other office interventional procedures using mechanical equipment (115) or where there is a likelihood of endometrial fragmentation, necessitate the use of a liquid distension medium to maintain visualisation by clearing both blood and debris. Thus performing a diagnostic hysteroscopy with normal saline will negate the need to change distending medium should a subsequent operative procedure be required (i.e. the 'see and treat' ethos).

The review of hysteroscope type was not able to address the differences between the types of scope with regards to cost and maintenance. It has been reported that flexible hysteroscopes are approximately twice as expensive to purchase (40;116) as rigid hysteroscopes and more expensive to sterilise and maintain (116). The clinical implications of this review are that when purchasing hysteroscopes, clinicians should consider the advantage of flexible hysteroscopy as regards to reduced procedural pain against the potential disadvantages of procedure duration, feasibility and cost.

Unanswered questions and future research

These reviews have implications for future research. They highlight the need for large trials comparing how the different hysteroscopic techniques (e.g. vaginoscopy versus a traditional

hysteroscopy with or without local anaesthesia, type of distension media, use of a flexible or rigid scope, cervical preparation etc.) affect pain, feasibility and the incidence of vasovagal episodes during outpatient hysteroscopy. Such trials should explicitly define and standardise the procedure and systematically examine acceptability and quality of life, in addition to alleviation of pain. These qualitative outcomes can then be correlated with pain scores to see if any reported reduction in pain during outpatient hysteroscopy is actually clinically meaningful. Is the pain that women feel during a hysteroscopy enough to warrant the use of anaesthetic? It may cause a significant reduction in the amount of pain experienced, however in the majority of studies the mean pain scores felt in the intervention and control groups showed little variation and tended to be low anyway. Then it must be considered that case selection is important when assessing who will benefit the most from the use of local anaesthetic. Parous, pre-menopausal women are less likely to benefit as it is presumed that they have less narrowing of the cervical canal, whereas nulliparous post-menopausal women who will almost certainly have a degree of cervical stenosis may benefit greatly. The results from these reviews cannot quantify this benefit. It may be that altering different aspects of the procedure (e.g. vaginoscopy, warming liquid distension media, distension pressures etc.) can reduce the pain significantly without having to use local anaesthetic injection. There are obvious cost implications (for equipment and medication, as well as reducing the number of people seen in clinic) of using local anaesthetic for every patient who undergoes an outpatient hysteroscopy.

Research trials should also evaluate administration of local anaesthetic, analgesics and hysteroscopic technique in operative outpatient hysteroscopic surgery, which is becoming increasingly prevalent with technological advances in endoscopic instrumentation

(6;117;118). The timing of administration needs to be assessed as well as the different available drugs and doses and the incidence of adverse effects. It would be prudent to assess the benefit of simple analgesics regimens (e.g. paracetamol or ibuprofen) self-administered by the patient prior to attending for their examination. The use of 'rescue analgesia' once the patient has left the hospital may be indicative of the medium term benefit of analgesics and this information could also be collected along with qualitative data referring to the patient experience and rates of satisfaction. Additionally, the role of simply administered, short acting inhalational sedation (e.g. Entonox^{TM} - nitrous oxide with oxygen) should be examined with randomised studies, particularly for therapeutic outpatient hysteroscopic procedures.

It is during blind dilatation of the cervix that perforation of the uterus is most likely to occur. There are subgroups of women (previous caesarean section, nulliparous, postmenopausal, previous loop biopsy) who more often need dilatation of the cervix to facilitate passage of the hysteroscope. A well designed clinical trial should concentrate on these subgroups to assess whether the use of prostaglandins provides a clinically significant reduction in pain, reduces the need for dilatation and incidence of genital tract trauma and whether these benefits outweigh the potential harms (bleeding, laceration, abdominal cramping, fever). As well as focussing on certain populations the study should use miniature hysteroscopes to make the results clinically relevant to modern practice. If positive results were found, further research would be needed to determine optimum dose and timing of administration of the prostaglandins.

Large trials are needed to compare vaginoscopy to traditional hysteroscopy using both rigid and flexible hysteroscopes. Such trials should explicitly define and standardise the procedure

and systematically examine acceptability and quality of life, in addition to alleviation of pain, the risk of ascending infection and the incidence of vasovagal episodes. In addition, studies need to look *a priori* at patient factors, such as parity, menopausal status, previous cervical biopsy or caesarean section and body mass index to identify patient sub-groups in whom the vaginoscopic procedure is less likely to succeed.

An economic analysis should be performed to analyse whether there is any true discrepancy regarding cost when different distension media or flexible or rigid hysteroscopes are used for outpatient hysteroscopy. Personal experience is that the majority of clinicians within the UK are using normal saline and rigid hysteroscopes and it would be interesting to examine the reasons for this with qualitative research.

Summary

The ideal outpatient hysteroscopy would be pain free. However this is impossible and so the utmost should be done to minimise pain. The seven systematic reviews conducted suggest that in order to optimise success and minimise pain, women undergoing outpatient hysteroscopy should take simple analgesia a short time prior to the procedure and the hysteroscopist should adopt a vaginoscopic approach using a small diameter, rigid hysteroscope and normal saline as the distension medium. If dilatation of the cervix is required, this should be done under a paracervical block. The use of cervical preparation and conscious sedation should not be routinely used.

CHAPTER 6

EVIDENCE QUALITY IN CLINICAL GUIDELINES: A COMPARISON OF TWO METHODS

In the 21st century we no longer practice medicine based on our own experience and prejudices but try to find real evidence that our practice is not only beneficial but that it does not harm and is cost-effective. This process is called evidence based medicine and should be the foundation of modern medical care.

Guidelines and protocols are developed using evidence relevant to their topics and this should be critically appraised during development. The Royal College of Obstetricians and Gynaecologists use the SIGN methodology (119;120) for their clinical, Green-top guidelines, which are used to inform practice in Obstetrics and Gynaecology throughout the UK and internationally.

'Quality of evidence' has been defined as 'reflecting the extent to which confidence in the estimate of an effect is adequate to support recommendations' (121). Guidelines report the quality of the evidence used when formulating recommendations so that clinicians can decide how reliable the recommendation might be. Unfortunately, different organisations use different methods of grading the quality of evidence which can make interpretation difficult (122), particularly if multiple guidelines are being considered. In view of this, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group have

developed the GRADE system which is intended as a common, sensible and transparent approach to grading the quality of evidence (123) for use in clinical guidelines. The GRADE format (122) claims to make it easier for users to assess the judgments behind recommendations by tabulating the evidence.

Using the systematic reviews of outpatient hysteroscopy presented in this thesis, a guideline was written for the British Society of Gynaecological Endoscopists (BSGE) in the format of an RCOG Green-top guideline, entitled 'Best Practice in Outpatient Hysteroscopy'. This guideline has since been published by the RCOG as a formal Green-top guideline (124) and is available to clinicians in the UK and abroad (Appendix 4). To investigate how the evidence quality would have been graded if the GRADE method was used, evidence profiles were created for the outcomes from the outpatient hysteroscopy reviews and compared to the gradings in the original guideline.

This chapter examines how assessment of the quality of evidence differs between the GRADE and SIGN guideline methods and discusses whether the GRADE method offers significant advantages that might benefit the RCOG Green-top guidance.

Methods for comparing SIGN and GRADE for assessing quality of evidence

Using the seven systematic reviews of outpatient hysteroscopy (described in previous chapters), a guideline was written entitled 'Best Practice in Outpatient Hysteroscopy' on behalf of the British Society of Gynaecological Endoscopists (BSGE). The guideline was developed with two NHS consultants and used the RCOG methods of guideline development

(119) which grades the quality of evidence and recommendations using the Scottish Intercollegiate Guideline Network (SIGN) model (125) (Table 6.1). The final guideline was published as a greentop guideline by the RCOG in association with the BSGE. The full guideline can be reviewed in Appendix 4

Table 6.1 SIGN method for classification of evidence for clinical guidelines (120)

Classification of evidence levels	
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1-	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion
Grades of Recommendation	
A	At least one meta-analysis, systematic reviews or RCT rated as 1++, and directly applicable to the target population; or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+
✓	Recommended best practice based on the clinical experience of the guideline development group

On reviewing Table 6.1 it is clear that by using the SIGN classification method, even the most poorly conducted randomised controlled trial (RCT) can at worst be classified as 1- and any recommendations that arise from this evidence will be graded as an A or B. Similarly, a rigorous observational study can at best be judged as 2++ and recommendations arising from it classified as C level evidence. This system puts the emphasis on trial design and not on trial quality.

The GRADE guideline method examines eight determinants of quality; five which can lead to downgrading of evidence (limitations of the study design, inconsistency, indirectness, imprecision and publication bias) and three which can lead to upgrading of the evidence (strong association, evidence of a dose-response gradient and possible dilution due to confounding). Randomised controlled trials start as high quality and are downgraded as appropriate and observational studies start as low quality and are upgraded as appropriate. The results of this evaluation are then tabulated as GRADE evidence profiles. The studies within the meta-analysis or the individual study that provides the evidence for recommendations must be evaluated for each of the outcomes and a decision made whether there is enough concern to downgrade the quality of the evidence. The hysteroscopy guideline only used randomised controlled trials and so in this evaluation the emphasis was on downgrading.

'Limitations of the study design' relates to the methodology of the studies and downgrades the quality if there are concerns about randomisation method, allocation concealment, blinding, reporting of pre-stated outcomes and loss to follow-up or inappropriate analysis (e.g. not analysed as intention to treat). When 'inconsistency' is considered, studies are

downgraded if there is heterogeneity that cannot be explained or if the point estimates vary widely with little overlap of the confidence intervals. When the systematic review or studies assess a different population, use surrogate outcomes or comparisons are not head-to-head, the evidence should be downgraded for 'indirectness'. 'Imprecision' considers the size of the study population to assess whether it is adequate to answer the point in question and examines the width of confidence intervals to assess if the clinical action would differ if the true point estimate lies at the upper or lower limit of the confidence interval. The final criterion for downgrading is 'publication bias 'which is likely if there are only a few small studies, duplicate publications or the studies are unrepresentative (all in English, all find a significant effect). Studies can be upgraded if there is a strong association (relative risk greater than 2 or less than 0.5), if there is evidence of a dose-response gradient or if the presence of confounding factors may have diluted the perceived result. However, it is recommended that studies with limitations are not upgraded.

To examine how the quality of evidence in the hysteroscopy guideline would be graded if the GRADE system was used evidence profiles were drawn for each of the recommendations in the hysteroscopy guideline, that had been directly drawn from the systematic reviews (chapters 2-5) using GradeProfiler (126). The GRADE tables are displayed in Appendix 5 with the recommendations and quality gradings from the original guideline. Each profile was made up of a number of elements which addressed different aspects of the clinical question e.g. when asking which type of distension media to use, five elements were investigated, (i) pain, (ii) shoulder tip pain, (iii) vasovagal episodes, (iv) procedure time and (v) unsatisfactory view. This GRADE table is displayed below as an example (Table 6.2)

Table 6.2 GRADE evidence table examining the evidence for using different types of distension medium for outpatient hysteroscopy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Normal saline	Carbon dioxide	Relative (95% CI)	Absolute		
Pain score (Better indicated by lower values)												
6	randomised trials	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	540	569	-	SMD 0.34 higher (0.12 lower to 0.8 higher)	⊕OOO VERY LOW	CRITICAL
Shoulder tip pain												
5	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/472 (1.9%)	55/448 (12.3%)	OR 0.19 (0.09 to 0.4)	97 fewer per 1000 (from 70 fewer to 110 fewer)	⊕⊕OO LOW	CRITICAL
Vasovagal episodes												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	5/210 (2.4%)	18/210 (8.6%)	OR 0.31 (0.12 to 0.82)	57 fewer per 1000 (from 14 fewer to 75 fewer)	⊕OOO VERY LOW	IMPORTANT
Procedure time (Better indicated by lower values)												
4	randomised trials	very serious[1]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	434	401	-	SMD 1.32 lower (1.48 to 1.17 lower)	⊕⊕OO LOW	IMPORTANT
Unsatisfactory hysteroscopic view												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[6]	4/100 (4%)	19/100 (19%)	RR 4.75 (1.61 to 16.4)	712 more per 1000 (from 116 more to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] Poor randomisation methods (quasi-randomised in some cases) and lack of allocation concealment in most studies. Neither patient nor operator was blinded but this would not be possible.
[2] High heterogeneity that cannot be explained by differences in technique.
[3] Outcome reported in just three of the six identified trials.
[4] High heterogeneity but all studies in favour of normal saline and heterogeneity can be explained by the two studies that don't using a speculum showing the largest effect size.
[5] Single study therefore imprecise.
[6] This is the only study that reports a difference.

The importance of each aspect was determined by clinicians and not patients; however this judgment does not contribute to the assessment of evidence quality and therefore was not felt to be a significant omission. A score was then allocated to the quality assessment in its GRADE and SIGN forms, with the highest quality rating awarded four points and the lowest (see Table 6.3), one point. The difference between the two methods could then be quantified.

Table 6.3 Score allocated to the quality of evidence gradings as determined by SIGN and GRADE

Score	SIGN	GRADE
4	A	High
3	B	Moderate
2	C	Low
1	D	Very low

To investigate which of the five aspects of the GRADE method (study limitations, indirectness, inconsistency, imprecision and publication bias) were most often chosen as reasons to downgrade the quality of the evidence, points were allocated to each aspect in the GRADE evidence profiles as detailed in Table 6.4. When there was 'no risk' of bias the score allocated was '0', When there was 'serious risk' of bias a score of '1' was allocated and if there was 'very serious' risk of bias a score of '2' was given. The aspect 'publication bias' can only be downgraded to 'serious' and so in this category a score of '2' was not possible. There were 37 elements examined using evidence profiles and so the maximum point allocation for each aspect was 74 (37 x 2), except for 'publication bias', which was just 37.

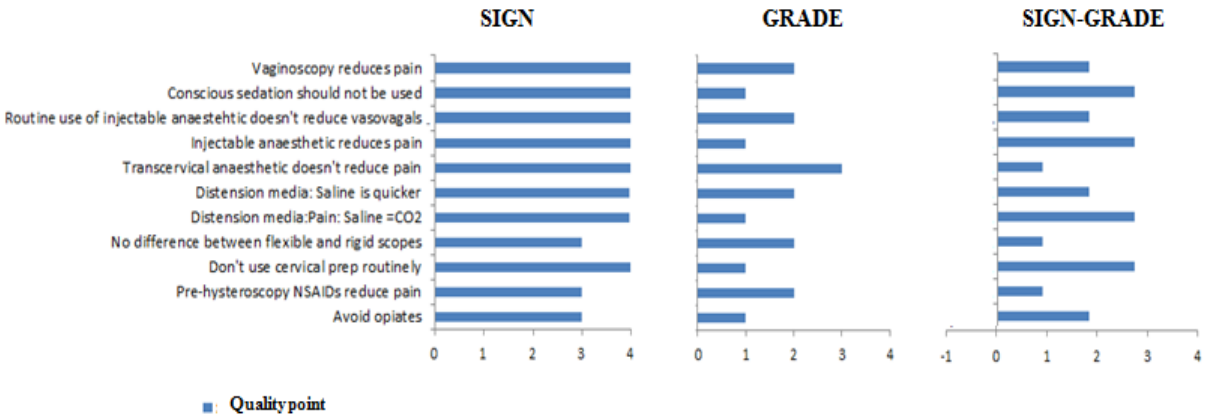
Table 6.4 Scores applied to the downgrading aspects of the GRADE profile elements

GRADE aspect	Risk	Score
Study limitations	No serious risk	0
	Serious	1
	Very serious	2
Inconsistency	As for 'study limitations'	
Indirectness	As for 'study limitations'	
Imprecision	As for 'study limitations'	
Publication bias	Undetected	0
	Strongly suspected	1

Results of the comparison of SIGN and GRADE for assessing quality of evidence

The differences between the allocated quality scores for the evidence behind each recommendation were plotted graphically (Figure 6.1).

Figure 6.1. Quality rating according to SIGN and GRADE methodology and the difference between the two scores.



Eleven of the recommendations from the SIGN guideline were converted into GRADE evidence profile tables with 37 elements. Figure 6.1 above shows the points allocated to each recommendation by SIGN and GRADE. It then shows the value when the GRADE rating is subtracted from the SIGN rating to show the difference between the two methods. A positive results shows that SIGN estimates the quality as higher than GRADE, a result of zero shows that the assessment was the same in both systems and a negative result shows that GRADE assessed the evidence quality as higher than SIGN. The figure illustrates that SIGN has a tendency to grade evidence as higher quality than GRADE because all of the recommendations were allocated a positive results when the scores were subtracted. None of the recommendations were assessed as being the same level of quality by both of the guidelines. The points difference ranged from one to three points.

Figure 6.2. Reasons for downgrading the quality of evidence for guideline recommendations when using the GRADE system.

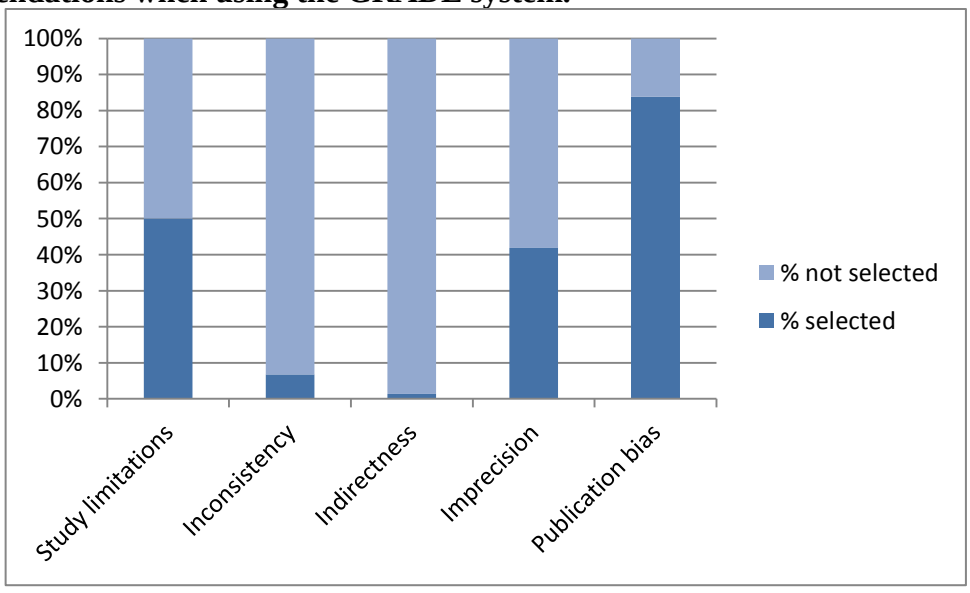


Figure 6.2 shows the contribution of each quality aspect to downgrading of the evidence. It gives an overview of the quality of the evidence used throughout the guideline. It is clear that

the most common reasons for downgrading evidence were ‘study limitations’,’ imprecision’ and ‘publication bias’. This is consistent with studies which have small populations and are poorly conducted and also reflects the paucity of data available. However, Figure 6.2 also suggests that the studies addressed the right questions and were reasonably homogenous as ‘indirectness’ and ‘inconsistency’ were rarely selected as reasons to downgrade the evidence. Evidence for all recommendations was downgraded and so upgrading was not appropriate.

Discussion of the comparison of SIGN and GRADE for assessing quality of evidence

Guidelines need to make clear recommendations. If the recommendations are open to interpretation they become unfit for purpose and rather than guiding practice can cause confusion and hesitancy. However, these recommendations can only be based upon the available evidence and it is important that the quality of the evidence is taken into account when making recommendations about health care. This evaluation of two different systems of assessing available evidence to formulate guideline recommendations showed that the GRADE and SIGN methods produced varying estimates of the quality of evidence. This may not be surprising given that the systems adopt different methodologies. The GRADE approach aims to demonstrate the available evidence in a transparent fashion that allows the users of the guideline to understand why recommendations are afforded their weight. In contrast the SIGN guideline system uses an alternative method of grading the quality of recommendations which is based on the hierarchy of published data, with systematic reviews and meta-analysis at the top, followed by randomised controlled trials and then observational studies.

Guideline developers have focused upon the quality of available evidence to inform recommendations but other considerations need to be taken into account especially as often the evidence available is of poor quality. These factors include the potential for an intervention to cause harm and its cost. For example, if we have an intervention that is cheap and unlikely to be harmful, we may recommend its use (if there is no better alternative) even if the quality of the studies showing benefit are of poor quality. However, if the intervention had the potential to cause significant harm or was prohibitively expensive we would be unlikely to recommend it. Thus, it is clear that when formulating recommendations from the available evidence, the benefits and harms of the intervention need to be taken into account in addition to the quality of the evidence.

The GRADE method considers these additional aspects when making recommendations but they do not form part of the quality of evidence judgment. SIGN rates quality according to study design with little consideration of the outcomes or publication bias. This is a simple system in which the user identifies the trial design and decides if there is any risk of bias. Although this method is subjective the classifications system dictates that all recommendations from RCT's or meta-analysis of RCT's will receive a high quality grading of A or B even if there is a high risk of bias. Conversely, GRADE focuses less on study type and considers multiple aspects of the available data when assessing quality. It is designed to be standardised and systematic (121;127;128) implying that if different people were presented with the same body of evidence and asked to produce GRADE evidence tables they would all come to the same conclusions regarding quality. However, a Spanish group examined the introduction of the GRADE system into oncology guidelines and looked at how different

groups of clinicians rated the same evidence. For the same aspect of care, three groups rated the body of evidence as ‘low’ quality, nine as ‘moderate’ quality and three as ‘high’ quality (129). This casts doubt about the reproducibility of the GRADE system and is likely to be due to factors inherent to the process.

The GRADE system is complicated (130) and time-consuming (128) because users must consider multiple aspects during their quality assessment, each of which is open to some degree of subjectivity. How does one decide whether the limitation identified is downgraded to ‘serious’ or ‘very serious’? This is probably based on the individual’s prior knowledge and experience of working with clinical studies. Users need to have some academic training to understand the concepts behind each of the quality categories. Whilst most clinicians understand different methods of randomisation and what is meant by ‘allocation concealment’, when it comes to the more complicated criteria which require assessment of the statistics or indicators of heterogeneity it is understandable that many would feel out of their depth. Secondly, these judgments are also affected by the user’s expectations of trial design and quality. Whilst an academic would prefer that the most rigorous methods are used at all times, a clinician might recognises that the practicalities of running a study dictate that the ideal methods cannot always be used if they are not pragmatic and would have jeopardised trial recruitment. In these cases the clinician may feel that the best methods for the studies in question were selected and that downgrading is not warranted, whilst the academic may decide to downgrade to ‘very serious’ risks of bias. In the SIGN method this subjectivity will only downgrade the quality of the recommendations to a B at worst but in the GRADE system, if this subjectivity is present in multiple aspects of the quality assessment the data could easily be assessed as high / moderate quality by one assessor and low / very by another.

Thus a criticism that could be justifiably levelled at the GRADE system is that it appears to have been developed by academics for academics. If the increased complexity of GRADE compared to other methods results in clinical guideline developers failing to understand the process clearly (131) then this will limit GRADE from achieving the objective of being standardised. One potential solution is to produce alternative methods of data display to make guidelines more user friendly for clinicians, who are ultimately the end users. Clinicians may find the guidance less confusing and easier to assimilate if only the outcome of the quality assessment was presented to them but they understood that this judgment was made after a rigorous assessment, using the GRADE methodology. Thus, the intimidating GRADE evidence profile tables, displaying cumbersome volumes of data (132) along with the rationale for upgrading or downgrading evidence quality could be dispensed with.. This would be reminiscent of the SIGN guidelines which display the result of quality assessment but don't explain the reasoning for reducing (-) or increasing (++) the quality within the text. However, as already discussed, the SIGN classification, which uses numbers and letters, does not reliably convey the quality of evidence. Graphical representation of the GRADE evidence profiles may prove more useful than the tables as it allows clinicians to quickly interpret the data and make a judgment at a glance, without having to read lots of text (133). In addition graphical display enables quick and easy comparison of the data quality for competing strategies. Graphical display of GRADE data using radar charts and traffic light systems have been suggested (132;134) although they are yet to be validated.

The current study is a comparison of two methods for assessing evidence quality for just one guideline. Future research should assess other guidelines in a similar way to evaluate whether

GRADE is indeed associated with more conservative grading of evidence quality and whether the magnitude of differences are similar to the current study . If this is the case, then research addressing the clinical significance of using the GRADE system upon existing recommendations would be needed. In addition further research should examine how clinicians interpret quality gradings when they are displayed in different formats, including tables, diagrams and codes.

In summary, when comparing the GRADE and SIGN methods for grading the quality of the evidence used in the guideline for 'Best Practice in Outpatient Hysteroscopy' the two different systems produced varying estimates of the quality of evidence. Furthermore, GRADE appeared to rate the evidence less highly than SIGN. It is evident from this assessment that neither GRADE nor SIGN offer a perfect solution to the assessment of evidence quality when it comes to writing clinical guidance. Whilst SIGN may be too simplistic and under or overestimate quality, GRADE is too complex which results in it being used incorrectly and the judgments not being reproducible. The GRADE system in its current form may need to be adapted so that results are displayed in a more user-friendly style, possibly by the incorporation of diagrams to present the evidence quality. A hybrid system which uses GRADE to assess the quality but displays only the result of the quality assessment in the guideline may prove to be the most manageable form of guidance for clinicians. Furthermore, high quality evidence is far from ubiquitous, and so the benefits, harms and costs of interventions should also have an influence upon the degree of evidence quality required in order to make a particular recommendation.

CHAPTER 7

INTRODUCTION TO THE ECONOMIC ANALYSIS OF DIAGNOSTIC STRATEGIES FOR THE INVESTIGATION OF HEAVY MENSTRUAL BLEEDING

The following economic analysis forms a small part of a report that was written for the National Institute for Health Research, Health Technology Assessment programme. The report investigated the cost-effectiveness of diagnostic tests in the management of all types of abnormal uterine bleeding. It is due to be published in late 2013.

Heavy Menstrual Bleeding

HMB affects 1 in 5 women of reproductive age, with 5% of women aged 30-49 consulting their General Practitioner each year because of the condition and accounting for a third of all gynaecology referrals (135). The overall prevalence of HMB in England and Wales has been estimated at 1.5 million women (136). The number and cost of consultations and treatments impose substantial demands on health service resources (137;138). Moreover, HMB can cause significant distress to women by affecting their performance at work as well as their social activities, and imposes a substantial adverse impact upon health-related quality of life (HRQL) (139-141). The National Institute for Clinical Excellence in their 2007 guideline into the management of heavy menstrual bleeding (HMB) recommended the condition be defined as "*excessive menstrual blood loss which interferes with the woman's physical, emotional,*

social and material quality of life, and which can occur alone or in combination with other symptoms" (142). This clinical definition is the most useful one as using objective measurement, with loss of > 80 ml of blood per cycle considered definitive of HMB (143), is impractical. More applicable semi-objective measurement, using pictorial blood loss assessment of sanitary ware (144;145) as a surrogate for objective measurement, has been tried but the correlation between objective and semi-objective quantification has been questioned (144). In any case, objective quantification of menstrual loss does not correlate in many cases with a woman's subjective complaint of HMB (146-148).

Causes of heavy menstrual bleeding

Heavy menstrual bleeding has been reported to be caused by a variety of underlying pathologies (142). However, whilst many conditions have been linked to HMB, in practice most cases are attributed to fibroids, endometrial pathology or dysfunctional uterine bleeding (DUB) and subsequent treatment is dictated by the presence or absence of these conditions (Table 7.1).

Table 7.1 Causes of heavy menstrual bleeding

Cause	Definition
Dysfunctional uterine bleeding	The occurrence of irregular or excessive uterine bleeding in the absence of identifiable organic pathology (142).
Uterine fibroids	Smooth-muscle tumours of the uterus, generally benign (>99%). They vary in size from millimetres to tens of centimetres, and are associated with heavy periods, pressure symptoms and occasionally pain. They are responsive to oestrogen and progesterone, so tend to shrink after the menopause (142).
Endometrial pathology:	
• Polyps	Focal outgrowths within the uterine cavity, containing a variable amount of glands, stroma and blood vessels which influence their macroscopic appearance. Usually benign with less than 1% frankly malignant (6).
• Hyperplasia	Endometrial hyperplasia is a proliferation of endometrial glands with structural abnormalities and crowding. If the nuclei exhibit cytological atypia the hyperplasia is classified as atypical (149) and is considered pre-malignant.
• Cancer	Well-differentiated carcinoma is distinguished from atypical hyperplasia by the presence of endometrial stromal invasion (149). Both conditions are rare in premenopausal women.

Diagnosis of heavy menstrual bleeding

The current National Institute for Health and Clinical Excellence (NICE) guideline advocates full gynaecological examination and taking a full blood count to exclude anaemia (142). This guideline (142) recognises the need for diagnostic tests to evaluate the uterus, namely endometrial biopsy, ultrasound scan and hysteroscopy in specific cases. These tests are described in Table 7.2.

Table 7.2 Description of currently used tests for the diagnosis of uterine pathology

Test	Description (adapted from CG44 NICE Heavy Menstrual Bleeding Guideline 2007 (142))	Capability
Tests primarily for detecting structural abnormalities		
Transvaginal Ultrasound (TVS)	A method of imaging the genital tract in women using high-frequency sound waves that bounce off body structures to create a picture on a screen. The ultrasound transducer is inserted directly into the vagina so that it closer to pelvic structures than with the conventional transabdominal technique.	Diagnoses endometrial, focal intracavity (polyps, submucous fibroids) myometrial and adnexal pathology
Saline infusion ultrasound	This is an extension of transvaginal ultrasound. Prior to the ultrasound, saline is injected into the uterine cavity to distend it and provide better visualisation of the anatomic structures within it by providing a liquid-solid interface.	As for TVS but with enhanced diagnosis of focal intracavity pathology
Outpatient hysteroscopy	A hysteroscopy is an examination of the inside of the uterus using an endoscope. The hysteroscope is carefully passed through the vagina and cervix and into the uterine cavity to allow direct visualisation. During the procedure a biopsy may be taken for examination.	Diagnoses endometrial and focal intracavity pathology
Tests primarily for detecting histological abnormalities		
Endometrial biopsy	A sample of endometrial tissue is obtained blindly using a sampler which is passed through the cervix and uses suction to obtain the tissue. This can then be histologically examined	Diagnoses endometrial pathology at a histological level.
Dilatation and curettage	A procedure performed under general anaesthetic in which the cervix is mechanically dilated and a curette is introduced into the uterine cavity to scrape away a sample of endometrial tissue.	As for endometrial biopsy

Current diagnostic pathways for heavy menstrual bleeding

It is only in the last 25 or so years, that evaluation of the uterine cavity in women with HMB symptoms has moved on from dilatation of the cervix and curettage of the endometrium lining from the uterine cavity (D&C). This test is now used only in exceptional circumstances as it requires general anaesthesia and has been superseded by outpatient endometrial biopsy, which obtains endometrial tissue samples for histological analysis in a convenient outpatient setting without the need for anaesthesia (150;151). Moreover, the development of high resolution transvaginal ultrasound (TVS) has allowed female pelvic structures, including the uterus, to be visualised. The 'inside' of the uterus i.e. the uterine cavity, cannot normally be seen without effecting distension using a fluid or gaseous medium to separate the opposing walls of the uterus. This potential limitation of TVS has been overcome by the advent of saline infusion sonography (SIS) (152-154) and outpatient hysteroscopy. These tests, described in Table 7.2, provide different, albeit overlapping information and diagnostic accuracy varies according to the particular pathology under scrutiny. NICE guidance from 2007 recognised that "…*particular investigative methods were better for identifying certain types of pathology than others*."

Thus, the availability of different, easy to use, miniature and increasingly portable 'bed side' tests has created uncertainty as to how best to employ them. This is particularly true in HMB where different aetiologies need to be considered and the preceding clinical history, and more often than not the examination too, are unable to predict causation with accuracy. As a result current testing is eclectic, depending upon the preferences of individual clinicians and the availability of services locally.

Literature review of cost-effectiveness studies for the diagnostic work up of heavy menstrual bleeding

A systematic search was performed of Medline and Embase electronic bibliographic databases using the terms ‘heavy menstrual bleeding’ and ‘cost-effectiveness’ along with their MeSH terms. 350 articles were identified once duplicates had been removed. Three relevant economic evaluations of diagnostic tests used for evaluating HMB were identified. One evaluation took place alongside an RCT (155) and the other two were economic modelling studies (142;156).

Cost-effectiveness was examined in a RCT conducted between 1999-2001 in Scotland comparing three outpatient diagnostic tests (outpatient biopsy, ultrasound and hysteroscopy) for the evaluation of abnormal uterine bleeding (AUB) in certain test combinations (155). Women were split into high, moderate and low risk groups for endometrial cancer. Resource use tended to be higher in the moderate- and low-risk women, because of the need to manage their persistent abnormal bleeding symptoms. Minimal difference in cost-effectiveness was found between investigation options in the high-risk group (postmenopausal), with the option involving hysteroscopy being marginally better than ultrasound (£88/woman, compared with the other options). The most cost-effective investigation in the moderate-risk group was biopsy alone (saving £128–212/ woman better) and in the low-risk group ultrasound (£74–452/woman better).

The mixed population of women with AUB, i.e. women of reproductive age with HMB and postmenopausal women with unexpected vaginal bleeding, limits clinical inferences because

the aim of investigation of women with PMB is to exclude endometrial cancer whereas in pre-menopausal women it is to optimise management of benign pathology. The authors of this RCT (155) highlight this themselves by stating "…*in future research into the evaluation and management of AUB, postmenopausal women should be studied separately from premenopausal women with menstrual bleeding problems*". Furthermore, the primary end-point defining 'effectiveness' was based upon the premise that a satisfactory diagnosis must have been reached once no further investigation had been carried out, as identified by retrospective case note review. Clearly such an indirect assumption of effective diagnosis, whilst expedient, is unlikely to be a reliable or valid measure of effectiveness and does not take account of patient-centred outcomes (e.g. satisfaction, reduction in bleeding, survival etc.).

As well as economic data from effectiveness studies, an alternative approach to assessment of cost-effectiveness of diagnostic testing is to employ decision-analytic modelling. Two economic evaluations of diagnostic testing in HMB using decision analytic modelling have been published (142;156). The first of these analyses was conducted from the perspective of the Dutch Health Care system and compared the percentage of patients treated successfully and the cost of six strategies for the evaluation of HMB: (0) hormonal treatment, (I) treatment of all patients with balloon ablation, (II) TVS and therapeutic hysteroscopy, (III) TVS, SIS and therapeutic hysteroscopy, (IV) SIS and therapeutic hysteroscopy, and (V) diagnostic hysteroscopy and therapeutic hysteroscopy. Hormonal treatment was considered to be the reference strategy to which the five strategies were compared. The study found that the strategy starting with SIS (IV) and the strategy with diagnostic hysteroscopy (V) revealed the highest number of patients treated successfully for HMB. However, the diagnostic strategy

based upon initial evaluation with SIS was the most cost-effective strategy for successful treatment of HMB, especially when the prevalence of intracavity pathology (polyps, submucous fibroids) was high. Study weaknesses limit to some degree the validity and stability of these findings. These included problems with construction of the decision model (limited pathologies were taken into account e.g. diagnosis of intramural fibroids and endometrial disease were not considered), the use of outmoded treatments (e.g. use of long term systemic progestogen) and overlooked ambulatory outpatient based treatment. Failure rates of testing were unaccounted for, the precision and quality of data sources used for estimating test accuracy were questionable and the definition of therapeutic effectiveness was unclear. The findings of the analysis were sensitive to changes in the key assumptions and so the robustness of the results is questionable.

The other decision-analytic model was developed to examine the cost- effectiveness of three imaging techniques; TVS, SIS and hysteroscopy from an NHS perspective (142). The model showed that TVS was more accurate and less costly than either SIS or hysteroscopy. For a cohort of 1000 women examined for the presence of structural abnormalities, ultrasound generated 810 correct diagnoses at a cost of £107,490 compared with 735 correct diagnoses at a cost of £145,110 using saline infusion sonography and 696 correct diagnoses at a cost of £209,720 using hysteroscopy. Although the economic analysis was conducted from an NHS perspective, the general applicability of the model is limited due to its simplistic construction. Women were assumed to have one of two health states: ‘no intrauterine pathology’, or ‘any intrauterine pathology’ and the outcome measure chosen was ‘correct diagnosis’. This was a pragmatic choice given the scope of the guideline (142) such that it was not possible to construct a model designed to take into account the range of pathologies under consideration

for HMB, and the associated range of treatment pathways. The impact on cost-effectiveness of women falsely diagnosed was not considered (the model did not follow women beyond an initial diagnosis) so that the model does not reflect the true longer term costs and outcomes associated with each diagnostic method. Moreover, diagnosis was restricted to one test, whereas this does not reflect contemporary practice where multiple testing is likely, either conducted simultaneously or conditional on previous test results.

The relative dearth of comprehensive diagnostic cost-effectiveness data in women with HMB reflects the complexity of care pathways (i.e. the varied outpatient tests available, the range of uterine pathologies) and the relatively recent introduction of minimally invasive, 'ambulatory' or 'outpatient' treatments.

Current treatment of heavy menstrual bleeding

Medical therapy

According to the recent NICE guideline on HMB, medical treatments should be considered where (i) structural and histological abnormalities of the uterus have been excluded; (ii) for fibroids < 3 cm in diameter which do not appear to distort the cavity of the uterus or (iii) where future fertility is required (142). The first line recommended medical treatment by NICE is the levonorgestrel-releasing intrauterine system (LNG-IUS or Mirena®, Bayer Healthcare Pharmaceuticals, Pittsburg, PA, USA) which is an effective non-surgical treatment for HMB, is reversible, contraceptive and fertility sparing. In the majority of cases, the device is fitted easily within a few minutes in the outpatient setting. Endometrial proliferation is suppressed as a result of local release of the synthetic progestogen levonorgestrel (LNG) and

this leads to a reduction in estimated menstrual blood loss of up to 96% by 12 months, with up to 44% of users reporting amenorrhoea, (157;158) at a cost which is a third of that for hysterectomy (159). However, the LNG-IUS can lead to troublesome break through bleeding and vaginal discharge in some women, causing early discontinuation of the device. The LNG-IUS works effectively in a relatively normal sized uterus (<11cm sound length) without distortion by focal pathology (160) i.e. in DUB or the presence of small uterine fibroids (<12 week uterine size) which do not encroach into the uterine cavity (161). Local release of progestogen can also reverse endometrial hyperplasia without atypia (162;163). Thus the LNG-IUS is applicable for most aetiologies of HMB with the exception of focal pathologies distorting the uterine cavity, large uterine fibroids (>12 weeks size) or in the presence of atypical hyperplasia or endometrial cancer.

Surgical treatment

Long-term medical treatment with the LNG-IUS is unsuccessful or unacceptable in many cases and surgical alternatives may be required (164). Traditional surgical treatment of HMB refractory to medical intervention has been with hysterectomy, but now removal of the uterus is generally restricted to women where conservative, uterine sparing surgical procedures have been unsuccessful or in the presence of large fibroids, atypical hyperplasia and endometrial cancer. Endometrial ablation is a technique where a semi-automated device is placed in the uterine cavity and thermal energy is applied to the endometrium and superficial myometrium to achieve a uniform, global and permanent destruction of the endometrial lining, thereby inducing amenorrhea or substantially reducing menstrual blood loss (6). Various modalities are available including fluid filled thermal balloons, free circulating warmed saline, bipolar radiofrequency ablative systems and cryotherapy. Prior to the automated techniques,

endometrial ablation was performed with a resectoscope, however this technique is now used in rare circumstances, having been replaced by the safer and cheaper (165) second generation methods. Endometrial ablation is recommended as a second line treatment when fertility is not desired and medical treatment has failed in DUB but can also be used in the presence of uterine fibroids when there is a relatively normal sized and shaped uterine cavity.

Hysteroscopic resection of focal intracavity lesions including polyps (166;167) and submucous fibroids (111;168-171) has been shown to improve HMB symptoms found in association with these pathologies. Hysteroscopic removal is standard practice in the UK (172) and in the case of polyps can usually be achieved in the outpatient setting (173-176). The procedures involve the use of electrosurgical cutting electrodes placed down a small operative working channel in the hysteroscope or a formal hysteroscopic resectoscope using a larger loop electrode.

In the presence of significant fibroids associated with an estimated uterine size of >12 weeks, and when retention of fertility is not required, hysterectomy is usually recommended. Uterine artery embolisation (UAE), is a less invasive, uterine sparing, interventional radiological intervention (177). This procedure is normally restricted to women with medical or surgical risk factors for open surgery. Myomectomy (removal of fibroids with conservation of the uterus) is sometimes offered but as it is as invasive as hysterectomy but less effective (178), the technique is generally reserved for women wanting to retain their fertility or to improve fecundity in those women with subfertility associated with a large fibroid uterus.

Defining treatment success in heavy menstrual bleeding

Menstruation is normal for women of reproductive age and so defining 'successful treatment' can be problematic. The primary aim of treating HMB is not to eradicate bleeding altogether, although some interventions do induce amenorrhoea, but to ameliorate bleeding symptoms to a tolerable level. As already discussed, objective measurement of reduction in menstrual bleeding is impractical and lacks relevance. Many studies have tried to measure the impact of interventions upon patient's quality of life and / or satisfaction with treatment outcome.

Health related quality of life

Generic health related quality of life measures have been used, but many have not been validated for use in HMB and fail to capture the cyclical nature of the symptom (179;180). In addition, they lack sensitivity as most women suffering with HMB are otherwise healthy and can continue to function in most generic health domains during menstruation (140;141). Condition-specific measures have been developed for HMB but either only assess surgical interventions (181) (as opposed to medical ones) or have been infrequently used which has limited a full assessment of their inherent psychometric qualities (182).

Satisfaction

Patient satisfaction is widely used as a primary outcome measure in studies of treatments for HMB and guidelines (136;142;183;184). Satisfaction is a subjective concept and represents the extent to which a service meets the users' expectations. A variety of questions and scales have been used to elicit satisfaction with treatment in HMB studies but this lack of uniformity has precluded meta-analysis of data across studies (136;166). Furthermore, the validity of

current patient satisfaction measures is questionable in light of the lack of published studies examining their development and application in HMB.

CHAPTER 8

METHODS FOR THE ECONOMIC ANALYSIS OF DIAGNOSTIC STRATEGIES FOR THE INVESTIGATION OF HEAVY MENSTRUAL BLEEDING

Construction of the decision model

A clinically informed cost effectiveness model was drawn as a decision tree using Treeage software (185) to reflect current service provision for the diagnostic work up of women presenting with heavy menstrual bleeding. The tree was constructed to examine the effectiveness of different diagnostic testing strategies for women referred to secondary care by their general practitioner. The tests evaluated were transvaginal ultrasound (TVS), saline infusion sonography (SIS), global endometrial biopsy (EBx) and outpatient hysteroscopy (OPH). The tree structure was informed by clinical input. As there is no consensus regarding how best to investigate women with HMB, initial investigation utilising all tests either alone or in combination were included in the model. Therefore the tree consisted of the four tests available deployed in isolation or in various clinically relevant combinations following initial presentation. The need for any additional subsequent tests was conditional upon the preceding test result(s). This resulted in the formation of eleven clinically relevant, alternative testing strategies. In addition, two scenarios were developed where testing was dispensed with and treatment of HMB instituted immediately regardless of diagnosis. The treatments chosen were the most effective medical treatment (the levonorgestrel intrauterine system (LNG-IUS)) and

surgical treatment (hysterectomy). This allowed comparison of the various approaches to diagnostic work up with the option of 'no investigation'. In view of the fact that NICE guidance (142) recommends the use of the LNG-IUS as first line treatment in HMB, this arm was used as the base-case scenario to compare all other strategies against. An incremental approach was used for reporting the results. Thus, in total there were 13 different scenarios evaluated in the decision model (eleven testing and two treatment alone strategies) which are listed below:

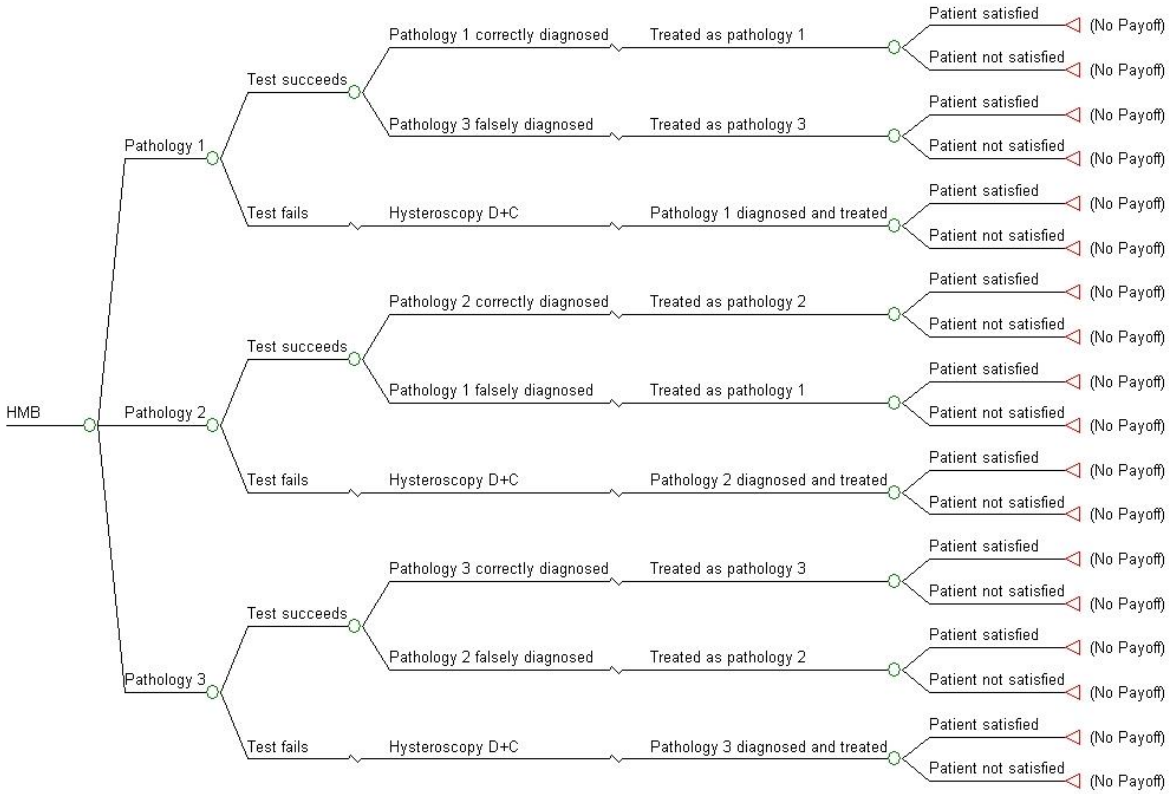
1. LNG-IUS alone
2. Hysterectomy alone
3. Outpatient hysteroscopy
4. Transvaginal scan
5. Endometrial biopsy
6. Saline infusion sonography
7. Outpatient hysteroscopy and endometrial biopsy
8. Transvaginal scan and endometrial biopsy
9. Saline infusion sonography and endometrial biopsy
10. Outpatient hysteroscopy and saline infusion sonography
11. Outpatient hysteroscopy and transvaginal scan
12. Saline infusion sonography, outpatient hysteroscopy and endometrial biopsy
13. Transvaginal scan, outpatient hysteroscopy and endometrial biopsy

Structure of the model

A series of decision trees evaluating various testing strategies for HMB were developed to represent alternative decision options and their possible consequences. The trees explicitly illustrate the patient pathway from suspected pathology underlying the clinical presentation through to the outcome of testing, distinguishing between correct and incorrect diagnosis. Then, conditional on the accuracy of the diagnostic testing strategy, the outcome of treatment for HMB was analysed at one year post initial presentation. Disease prevalence, diagnostic test accuracy, treatment effectiveness along with associated costs was used to populate the relevant branches of the decision tree. The basic tree structure is illustrated in (Figure 8.1). The thirteen trees representing the diagnostic testing options for HMB are detailed in Appendix 6, however the trees themselves are too large to display completely so a branch of one tree has been expanded as an example and a table has been included which details the data from the remaining branches of the tree.

Deterministic results were obtained using point estimates of the parameters to estimate the expected cost, outcome (satisfaction) and incremental cost-effectiveness (additional cost per extra patient satisfied). The stability of the results was then tested through sensitivity analysis.

Figure 8.1 Example decision tree for evaluating the cost-effectiveness of diagnostic testing in heavy menstrual bleeding



Clinical assumptions

The following section details the main clinical assumptions required to develop the economic model. Senior gynaecologists (see Acknowledgments) who were selected based upon their reputation and experience, were surveyed to ensure that the model structure and clinical inputs reflected contemporary practice. The clinicians were contacted by email, as well as telephone and face-to face interview. Initial correspondence concerned the structure of the model and clinical management. The size of the model precluded it from being presented as a whole, so only scenarios which appeared contentious were presented to the clinicians, asking how they would manage the patients. When starting to populate the tree with data it became clear that not all values could be identified from the literature. This was particularly true for 'satisfaction' values after inappropriate treatments (for example, women with large fibroid

uteri being treated with the levonorgestrel intrauterine system or endometrial ablation) because these scenarios only arise when women are unknowingly treated with unsuitable medications or procedures, hence the numbers are small and the data are not collected. In the absence of a consensus view, the opinion of the majority was adopted or when data were concerned the median values were used. Inevitably not all clinicians responded to all questions.

Demographics, pathologies and treatments

It was assumed that women presenting with HMB had a mean age of 45 years and no wish for future fertility. Forty-five years was selected for two reasons. Firstly, NICE recommends that endometrial biopsy should not be performed routinely for women with HMB before this age (142) as prevalence of endometrial premalignant or malignant disease is low. Secondly because HMB is most prevalent in parous women over 40 years, most of whom have completed their families (186) and are then eligible for all potential treatment options (the desire for current or future fertility restricts treatment options in HMB i.e. avoidance of hormonal contraceptive medical treatments or the surgical interventions endometrial ablation or hysterectomy).

All women were assumed to have been referred from primary care and to have not previously been seen for testing or treatment in secondary care. A single underlying aetiology was assumed to be causative and concurrent pathologies were not considered. This assumption is in keeping with the majority of HMB cases (142) and prevented unnecessary model complexity.

The premise was that optimal treatment of HMB is dependent upon correctly diagnosing the underlying cause so that appropriate, tailored treatment is arranged. The model was constructed based upon the true underlying diagnosis. The true diagnosis was assumed to fall within one of the following categories;

Intrauterine resectable pathology (endometrial polyps, submucous fibroids)

Fibroid uterus <12 weeks size (intramural and subserosal fibroids only)

Fibroid uterus >12 weeks size (intramural and subserosal fibroids only)

Endometrial disease (complex endometrial hyperplasia or endometrial hyperplasia with atypia or cancer)

Dysfunctional uterine bleeding

When choosing the pathology categories, it was decided that endometrial polyps and submucous fibroids should be grouped together as they are treated in the same way i.e. hysteroscopic resection of focal lesions. The majority of polyps were assumed to be treated in the outpatient setting (174;187;188) whereas the majority of submucous (intracavity) fibroids were assumed to be treated under general anaesthesia (169;170), 70% of which also required pharmaceutical endometrial down regulation with gonadatrophin releasing analogues (GnRH-a) for three months prior to surgery following outpatient diagnosis. Only 70% were pre-treated with GnRH-a because not all women would require or tolerate pre-treatment and not all gynaecologists use it. A minority of women would undergo hysteroscopy and D&C under general anaesthesia because the planned outpatient testing was unsuccessful. In these circumstances, where a polyp or submucous fibroid was detected at hysteroscopy and D&C, it was assumed that the focal lesion would be treated simultaneously; in the case of a

submucous fibroid this meant that GnRH-a pre-preparation of the endometrium would not have been used.

Intramural (confined to the myometrium) and subserosal (extending beyond the myometrium to distort the serosal surface of the uterus) fibroids were grouped according to size. This was because smaller fibroids, which do not substantially distort the shape of the uterine cavity or increase the uterine size beyond the equivalent size of a 12 week gravid uterus (the size at which the uterus becomes palpable abdominally), do not contraindicate the use of LNG-IUS or endometrial ablation (EA) (189-191); treatments which are successful in the majority of women (184;192-194). Thus the presence of small fibroids without cavity encroachment is, in practice, treated the same way as those women diagnosed with DUB (i.e. no identified structural uterine pathology).

In contrast, large fibroids increasing the uterine size beyond 12 weeks size, tend to be treated with invasive surgical interventions (abdominal hysterectomy or laparotomic myomectomy) as the LNG-IUS and minimally invasive surgery (EA or hysteroscopic resection of focal lesions) are either contra-indicated due to cavity size or ineffective (189;190). An alternative, less invasive radiological intervention for large uterine fibroids is uterine artery embolisation (UAE) but a randomised controlled trial of UAE and hysterectomy (195) has found no statistically significant differences between them in terms of satisfaction and effectiveness. Furthermore, hysterectomy is the gold standard definitive treatment and is more widely available than UAE therefore it was chosen as the treatment for fibroid uteri beyond 12 weeks size.

The majority of women with HMB have a benign, functional endometrium. However, over proliferation of the endometrium can lead to endometrial hyperplasia, which in the minority of cases (<5%) if left untreated, can result in the development of endometrial cancer (149). Endometrial cancer is rare in pre-menopausal women, but hyperplasia is not infrequently encountered as the result of anovulation and a relative excess of unopposed oestrogen stimulating the endometrium. Histological assessment of the endometrium is the only way to reliably diagnose endometrial hyperplasia and cancer and so EBx is mandatory where suspected. Endometrial hyperplasia is treated hormonally with progestogens either delivered systemically or more often now locally by fitting a LNG-IUS. Hysterectomy is recommended where the hyperplastic process does not respond to progestogen treatment or in the presence of cytological atypia. This is because the likelihood of developing malignant disease is increased to around 25% in the presence of atypia (149). Endometrial cancer is generally treated with hysterectomy with or without radiotherapy depending upon the stage and type of cancer. Over 70% of endometrial cancers are diagnosed early and are confined to the uterus so can be cured by timely hysterectomy (196). Given the rarity of malignant endometrial disease in pre-menopausal women it was assumed that when endometrial cancer was encountered it would be a well differentiated FIGO stage 1a endometrioid cancer, treated by hysterectomy alone.

Dysfunctional uterine bleeding, although not a distinct pathology, is a diagnosis of exclusion and the recommended first line medical treatment is the LNG-IUS (142). This was therefore the chosen treatment in the model for DUB.

Setting and decision making

The clinical setting was assumed to be an efficient, contemporary 'one-stop or 'see and treat' service run by a consultant gynaecologist. This setting meant that the expertise and infrastructure were available to perform all stipulated tests at the same visit and that therapeutic management could be implemented without unnecessary delay. When outpatient treatment was indicated, such as fitting of a LNG-IUS or hysteroscopic removal of a uterine polyp, then this was done at that visit. Interventions that required a general anaesthetic in a formal theatre setting (e.g. hysterectomy, endometrial ablations) were scheduled for a later date.

The results of all imaging tests would be available in real time to the senior clinician performing the test. However, in the case of EBx, the result would be delayed whilst the tissue sample was prepared, analysed and reported by the pathologist. Therefore when an EBx was performed because endometrial disease was suspected, any treatment or treatment plan could not be instigated immediately. However, when a testing strategy involved the initial use of endometrial biopsy in combination with OPH which showed a probable benign cause for HMB (normal appearance i.e. DUB or a focal lesions seen i.e. polyp or submucous fibroid), treatment would be initiated at that first appointment. If endometrial disease was then unexpectedly diagnosed once the biopsy result became available, an alternative treatment would be instigated at a further appointment if it was felt to be more a more appropriate treatment option.

Imaging tests (OPH, TVS and SIS) (197-199) can discriminate to some degree between normal and abnormal endometria, but are unable to accurately differentiate between histological subtypes of abnormal endometria; complex hyperplasia, complex hyperplasia

with cytological atypia or cancer (198;200). In keeping with clinical practice (opinion of expert panel), when imaging tests diagnose an abnormal endometrium it was felt by the panel of gynaecologists that no clinician would treat these suspected endometrial conditions without a histological tissue diagnosis. Therefore, a confirmatory histopathological test was performed if abnormal endometria were suspected by imaging; EBx will provide a result in 91% (151) of women but the remaining 9% would need to undergo formal D&C under a general anaesthetic as a day case because of failed procedures, non-diagnostic samples or patient preference. Therefore the cost for a confirmatory test was a composite value calculated as 91% of the cost of EBx plus 9% of the cost of D&C.

Formal hysteroscopy D&C under general anaesthesia, was considered a second line diagnostic test and was restricted, for consistency, to the minority of women where initial diagnostic testing was unsuccessful i.e. failure to complete the test.

Combination testing strategies and discordant results

When combinations of tests were used, the overall testing strategy was considered successful only if all tests were completed successfully. Failure of one or both tests was considered a failure of the testing strategy. This assumption seemed reasonable on clinical grounds and from a modelling point of view because success of one test in a dual testing strategy would simply replicate the analysis for the respective single test strategy in the model, rendering it redundant.

When a testing strategy involved more than one test applied simultaneously, the decision trees for each test were combined (appearing in series within the trees) to provide the additional information associated with combined testing. The final diagnoses were based upon the

results from the combination of tests. Tests in agreement presented no uncertainty, but where test results were modelled as being discordant, the panel of gynaecologists were asked to recommend the favoured diagnosis.

False diagnoses

Table 8.1 lists the false negative diagnoses which were considered plausible for true pathologies according to testing modality. The rationale underpinning the assumptions is also described.

Treatment failure

Following diagnosis, the most suitable treatment was arranged (Table 8.2). Only one treatment was considered for each diagnosis. As HMB is cyclical and patients would expect a delay in symptom relief with the LNG-IUS and EA, outcomes could not be assessed for at least six months. It was assumed that dissatisfied women would attend their general practitioner (GP) and be referred back to secondary care to be reviewed by a gynaecologist, who would undertake a further specific, second-line treatment (Table 8.2). The exception to this strategy was dissatisfaction after initial treatment with hysterectomy because no further treatment is possible in the absence of a uterus. These women were assumed to attend their GP for a consultation only. Women that remained dissatisfied following a second treatment were assumed to receive 'rescue treatment' consisting of a GP visit, a further hospital gynaecology outpatient appointment and a total abdominal hysterectomy (unless hysterectomy had been performed already in which case they were assumed to attend their GP for a consultation only). Patients were assumed to undergo the first two treatments within a 12 month period.

Table 8.1 False diagnoses according to testing modality

True pathology	False diagnoses	Rationale (Clinical consensus)
Transvaginal ultrasound		
Intrauterine polyp or submucous fibroid	Fibroids < 12 weeks Endometrial Disease DUB	Focal pathology can be easily missed by 2D imaging without cavity distension. Endometrial polyps can appear cystic and thus be mistaken for endometrial disease. A small fibroid encroaching into the endometrial cavity (submucous fibroid) could be erroneously considered intramural forming part of a small fibroid uterus.
Fibroid uterus <12 weeks size	Polyp / SMF Endometrial Disease DUB	Intramural fibroids may be wrongly diagnosed as submucosal. Small fibroids could be missed and a thickened, functional endometrium could appear hyperplastic.
Fibroid uterus >12 weeks size	Polyp / SMF Fibroids < 12 weeks	Large fibroids would be rarely overlooked entirely, but it is possible to underestimate their size or incorrectly classify fibroid location
Endometrial disease	Polyp / SMF Fibroids < 12 weeks DUB	A thickened hyperplastic or cancerous endometrium could be misdiagnosed as containing a polyp. Small fibroids may be incorrectly identified within the myometrium. The endometrium may appear to be normal.
Dysfunctional uterine bleeding	Polyp / SMF Fibroids < 12 weeks Endometrial disease	A normal, thickened endometrium could be considered falsely to be some form of endometrial disease (hyperplasia or cancer) or focal lesion (e.g. folds of normal endometrium mistaken for a polyp). Small fibroids may be incorrectly identified within the myometrium.

Table 8.1 continued

True pathology	False diagnoses	Rationale (Clinical consensus)
Saline infusion sonography		
Intrauterine polyp or submucous fibroid	Fibroids < 12 weeks Endometrial disease DUB	Focal pathologies could be missed on imaging, but this will occur less compared to TVS because of cavity distension with fluid. A small fibroid encroaching into the endometrial cavity (submucous fibroid) could be erroneously considered intramural forming part of a small fibroid uterus. Cystic looking polyps may be mistaken for endometrial hyperplasia.
Fibroid uterus <12 weeks size	Polyp / SMF Endometrial Disease DUB	As for transvaginal ultrasound...
Fibroid uterus >12 weeks size	Polyp / SMF Fibroids < 12 weeks	As for transvaginal ultrasound...
Endometrial disease	Polyp / SMF Fibroids < 12 weeks DUB	As for transvaginal ultrasound..
Dysfunctional uterine bleeding	Polyp / SMF Fibroids <12 weeks Endometrial disease	As for transvaginal ultrasound..
Outpatient hysteroscopy		
Intrauterine polyp or submucous fibroid	Endometrial disease DUB	Focal pathologies could be missed on imaging, but this will occur less compared to TVS because of cavity distension with fluid. OPH cannot visualise the myometrium and so, in contrast to TVS and SIS, presence of fibroids cannot be falsely diagnosed. Polyps may be mistakenly diagnosed as endometrial disease.

Table 8.1 continued

True pathology	False diagnoses	Rationale (Clinical consensus)
Fibroid uterus <12 weeks size	Polyp / SMF Endometrial disease	The myometrium is not visualised by OPH and preceding clinical examination is not sensitive enough to identify small fibroids. Thus, at OPH a normal cavity would be found in the presence of the true pathology (small intramural fibroids). Possible false diagnoses would be when normal, functional thickened endometrium is considered falsely to be some form of endometrial disease (hyperplasia or cancer) or focal lesion (e.g. folds of normal endometrium mistaken for a polyp).
Fibroid uterus >12 weeks size	Polyps / SMF Endometrial disease	Large fibroids would be missed at OPH because the myometrium is not visualised, although the majority would be detected on preceding clinical examination*. At OPH a normal cavity would be found in the presence of the true pathology (large intramural fibroids). Possible false diagnoses would be when normal, functional thickened endometrium is considered falsely to be endometrial disease (hyperplasia or cancer) or a focal lesion (e.g. folds of normal endometrium mistaken for a polyp).
Endometrial disease	Polyp / SMF DUB	A thickened hyperplastic or cancerous endometrium could appear normal or as a polyp.
Dysfunctional uterine bleeding	Polyp / SMF Endometrial disease	A normal, thickened endometrium could be considered falsely to be endometrial disease (hyperplasia or cancer) or a focal lesion (e.g. folds of normal endometrium mistaken for a polyp especially in the secretory phase of the menstrual cycle).

Table 8.1 continued

True pathology	False diagnoses	Rationale (Clinical consensus)
Endometrial biopsy		
Intrauterine polyp or submucous fibroid	Endometrial disease (hyperplasia but not cancer) DUB	Endometrial polyp tissue could be mistaken for normal or complex endometrial hyperplasia but it would be extremely unlikely to erroneously diagnose a polyp as endometrial cancer. The focal lesion may be missed by the biopsy.
Fibroid uterus <12 weeks size	Polyp / SMF Endometrial disease (hyperplasia not cancer)	Cystic pieces of endometrium could be mistaken for endometrial polyps. Fibroids can distort the uterine cavity and compact areas of endometrium. If these areas are sampled they can be mistaken for complex endometrial hyperplasia
Fibroid uterus >12 weeks size	Polyps / SMF Endometrial disease (hyperplasia not cancer)	As for small fibroids above
Endometrial disease	Polyp / SMF DUB	Polyp or DUB were considered the only plausible false diagnoses
Dysfunctional uterine bleeding	Polyp / SMF	An endometrial polyp or submucous fibroid were considered the only possible false diagnoses. It was felt to be extremely unlikely to mistakenly diagnose any endometrial disease from a normal sample.

*Note that it was assumed that a bimanual gynaecological examination took place in all women with HMB immediately pre-testing. Expert consensus was that this examination would allow the detection of a large fibroid uterus >12 week. A competent gynaecological examination would normally detect a large fibroid pelvic mass, but in some instances (e.g. poor patient tolerance, obesity) clinical examination would be less reliable so that the examination would be a false negative. This was assumed to occur in 20% of cases. In the absence of large fibroids, clinical examination was considered unable to discriminate between any of the other potential pathologies and so examination outcomes were dichotomous; i.e. either large fibroids > 12 weeks or 'normal'. As regards false positive diagnosis, it was felt that a small fibroid uterus < 12 weeks could be mistaken for large fibroid uterus > 12 weeks, OPH= outpatient hysteroscopy; TVS = transvaginal scan; SIS= saline infusion sonography; SMF= submucous fibroid; DUB= dysfunctional uterine bleeding.

Table 8.2 First and second line treatments for heavy menstrual bleeding according to underlying diagnosis in women with no desire to retain fertility

Diagnosis	Treatment 1	Treatment 2 (only performed if patient 'not satisfied' with treatment 1)
Endometrial polyp	Outpatient polypectomy	Levonorgestrel intrauterine system
Submucous fibroid	Transcervical resection of fibroid	Levonorgestrel intrauterine system
Fibroids <12 weeks size	Levonorgestrel intrauterine system	Endometrial ablation
Fibroids >12 weeks size	Total abdominal hysterectomy	GP visit
Complex hyperplasia	Levonorgestrel intrauterine system	Total abdominal hysterectomy
Complex hyperplasia with atypia / Endometrial Cancer	Total abdominal hysterectomy	GP visit
Dysfunctional uterine bleeding	Levonorgestrel intrauterine system	Endometrial ablation

GP= general practitioner

Adaptations of the base case tree to assess alternative clinical scenarios

Women being managed during multiple clinic visits

The base case tree was designed to reflect a contemporary 'one-stop' clinic to ensure that the results remain relevant and do not quickly become outdated as services evolve. However, this approach has not yet been widely adopted across the UK. Traditionally women referred to a gynaecologist would be reviewed in a general outpatient clinic before any investigation or treatment was instigated. The patient would have their history taken and be examined and then the clinician would plan appropriate tests and send the patient away to have these done at a later date. Weeks or even months later the patient would be seen again in clinic with the

results of those investigations and then the clinician would initiate treatment. The model was adapted to represent the 'traditional' multi-stop care model.

In this analysis all tests were performed at separate appointments except for endometrial biopsy which would be taken at the initial consultant appointment. Transvaginal scan and saline infusion sonography were assumed to be performed in the ultrasound department at a later date with the patients having a follow-up appointment to review the results. Outpatient hysteroscopy required a further consultant appointment for the hysteroscopic assessment. If polyps were diagnosed, whether by scan or hysteroscopy, patients required a further hysteroscopy appointment for removal. Submucous fibroids were removed under general anaesthesia and treatment with the LNG-IUS, hysterectomy and endometrial ablation were performed as in the base case tree.

Women refractory to LNG-IUS treatment

Alternative analysis was performed by adapting the model to fit with the scenario that all women referred to secondary care had already received treatment with a LNG-IUS in primary care but whose symptoms had not resolved. This was to reflect current NICE guidance which recommends that women receive a LNG-IUS in a primary care setting as first-line treatment for HMB (142) and only attend secondary care if their symptoms are refractory or structural abnormality is expected. The prevalence of disease changed within this tree as it was assumed that patients treated appropriately with the LNG-IUS (DUB, endometrial hyperplasia, fibroids <12 weeks size) would be less likely to be referred to secondary care than women who were being treated inappropriately (fibroids > 12 weeks size, polyps, SMF's, endometrial cancer) because their symptoms would be more likely to have resolved. Satisfaction rates for

treatment of each of the pathologies were used to re-calculate the disease prevalence. LNG-IUS was no longer a possible treatment within this tree as women had previously failed to respond to it. The exception to this rule was for women who were dissatisfied following removal of a polyp or SMF as they now had a 'normal' uterine cavity, where as previously there had been a structural abnormality compromising the effectiveness of the LNG-IUS. These women received a LNG-IUS as their second treatment following removal of focal pathology. Endometrial ablation became the first treatment to be offered to women who were thought to have a 'normal' uterine cavity and if this failed, hysterectomy was offered as the next treatment option. Given that patients already have a LNG-IUS in situ when they attend secondary care in this scenario the tree was adjusted so that the comparative strategy was 'no further treatment' to represent patients coming to clinic but not having any further treatment i.e. woman attending the clinic but ultimately deciding to continue with the LNG-IUS.

Women wishing to retain their fertility

The base case analysis was revised to reflect a population who wished to maintain their future fertility. This meant that endometrial ablation and hysterectomy were no longer possible treatments, except in the case of endometrial cancer when hysterectomy was still selected as the treatment of choice. Myomectomy and uterine artery embolisation (UAE) were introduced as possible treatments in this tree as they are far more likely to be offered to women who wish to have children than women who have completed their families. Myomectomy was assumed to be selected over UAE by 80% of women as it is thought to improve fertility to a greater extent than UAE (201). Following UAE or myomectomy patients who were 'not satisfied' with their treatment were offered the other treatment. Hysterectomy was not offered as a treatment for any benign cause of HMB and women who remained 'not satisfied' after two

treatments, or after one if no fertility preserving treatment could be offered, received a GP visit and a new gynaecology outpatient appointment as ‘rescue treatment’.

Clinical data collection

All literature derived data were obtained following systematic searches.

Accuracy data came from published systematic reviews and meta-analyses when possible, followed by data derived from primary, well conducted test accuracy studies.
For treatment data, systematic quantitative reviews using individual patient data (IPD) were considered as the highest level of data, followed by systematic reviews of study level data. Randomised controlled trials were acknowledged as the third step down the hierarchy, followed by large comparative cohort studies and then uncontrolled observational series. Prospectively collected data from studies with large populations were considered superior to small studies and those with retrospectively collected data. When possible data from a purely premenopausal population were used, however occasionally data came from studies of AUB incorporating both pre- and postmenopausal women. When possible these data were stratified by menopausal status.

Disease prevalence

For prevalence of disease underlying HMB symptoms a gold standard test was selected for confirmation of diagnosis (Table 8.3) A systematic literature review was then performed to estimate the prevalence of pathologies as estimated by the gold standard confirmatory test.

Table 8.3 Gold standard diagnostic tests for uterine pathology

Pathology	Confirmatory test
Polyps	Outpatient hysteroscopy
Submucous fibroids	Outpatient hysteroscopy
Uterine fibroids < 12 weeks	Pelvic ultrasound
Uterine fibroids > 12 weeks	Pelvic ultrasound
Endometrial disease	Histological sampling
Dysfunctional uterine bleeding	Diagnosis of exclusion

The searches for prevalence are reported in Appendix 7.1-7.4. As dysfunctional uterine bleeding is a diagnosis of exclusion a diagnostic test was not used as one of the search terms. The prevalence of each diagnosis was determined from published studies, using systematic reviews when possible. Seven quality criteria were used to assess the quality of identified studies (see Table 8.4) with a score from one to three being awarded for each criterion giving a maximum score of 21.Data from the highest scoring papers were used to populate the decision model.

Table 8.4 Quality criteria for disease prevalence studies

Criterion	Points awarded		
	3	2	1
Data collection	Prospective	Retrospective	Not clear
Consecutive patients	Yes	No	Not reported
Population size	>500	100-500	<100
Menopausal status	Premenopausal	Mixed but >50% premenopausal	Postmenopausal
Data collection	All have the gold standard test	Selection prior to gold standard test	Inferior test
Proportion having the gold standard test	>90%		<90%
Pathology clearly defined	Clear definition	Unclear definition	No definition

Data regarding the prevalence of fibroids (intramural and subserosal) were taken from a database of 473 women with HMB, held at Birmingham Women's Hospital (BWH) in the absence of a better quality published data set.

Data regarding the prevalence of DUB were often not specified within studies in contrast to organic pathologies. As the overall prevalence of disease must add up to 1 (100%) in the economic model it was decided that the prevalence of DUB (which is a diagnosis of exclusion) would be altered to become the remaining proportion once the prevalence of other pathologies had been estimated. The impact of this manipulation was tested with sensitivity analyses.

Test success and accuracy

To identify diagnostic data regarding the feasibility and accuracy of the tests under evaluation broad search terms were used for the literature searches to ensure a high level of sensitivity. If searches retrieved a large number of studies they were restricted to review articles only. In the case of searches for SIS, the search was qualified by the population under scrutiny because preliminary, broad searches were retrieving a large number of articles which evaluated the test in postmenopausal women and women with infertility. Duplicate articles were removed, the abstracts of all remaining articles were read and the full text of relevant papers retrieved based upon the following selection criteria:

Population	Heavy menstrual bleeding
Intervention	Outpatient test to evaluate the uterus (TVS, SIS, EBx, OPH)
Outcome	Feasibility (success rate) or test accuracy for uterine pathology
Study design	Restricted to systematic reviews if available

Although systematic reviews report high quality aggregated data of feasibility and/or test accuracy, the data reported did not always give the relevant accuracy data for all of the pathologies. In these circumstances restriction on study design was removed and in the absence of relevant primary study data, additional searches to look for data regarding the accuracy of the test without regard for population characteristics (heavy menstrual bleeding) were undertaken as were searches using specific pathologies as the population of interest. The quality of the studies was assessed using the criteria in Table 8.5. The highest scoring studies were selected. If studies were of equal quality the largest was selected and if this did not discriminate, blinding and interval between tests were taken into consideration.

Table 8.5 Quality criteria for assessing test accuracy studies

Criterion	**Explanation**
Population size	>100 women
Type of bleeding	>75% with heavy menstrual bleeding
Menopausal status	>70% premenopausal
Data collection	Prospective
Reference test	Appropriate 'gold' standard test applied (see Table 8.3)
Blinding	Present (diagnostic test and the gold standard test are performed by different, blinded clinicians).
Interval between tests	Within the same menstrual cycle
Cross tabulation	Data presented in a 2x2 table
Total	**8 points max** (one point awarded for each criteria present)

Details of searches are given in Appendix 7.5-7.8. An unsuccessful test was defined as failure of the test to provide a diagnosis. This may arise for a number of reasons such as an inability to pass the ultrasound probe (TVS, SIS) into the vagina, instrument the uterine cavity (SIS,

EBx, OPH) or because of inadequate visualisation (TVS,SIS, OPH). In the case of EBx, failure also included a successfully completed test but the subsequent finding of a tissue sample insufficient for diagnosis.

Accuracy data tended to be reported as sensitivity and specificity along with their respective 95% confidence intervals. These true positive and true negative rates were then used to calculate the false positive and negative rates (see Table 8.6).

Table 8.6 Accuracy value calculation using sensitivity and specificity

Accuracy value	Calculation
True positive rate	Sensitivity
True negative rate	Specificity
False positive rate	1 – specificity
False negative rate	1 – sensitivity

When data were reported as likelihood ratios, sensitivity and specificity values were derived. Sensitivity and specificity along with their 95% confidence intervals were calculated from raw data when necessary. In order to simplify the decision model, underlying pathologies were grouped when appropriate i.e. similar aetiologies and/or commonly associated treatments (see assumptions section). One problem with this approach was that accuracy data for these categories were often reported separately for each respective pathology. Therefore the figures were combined, weighting them according to the proportion of the pathology category they made up.

Taking EBx as an example test:

Endometrial hyperplasia = 60% of the endometrial disease category

Atypical endometrial hyperplasia / cancer = 40% of the endometrial disease category

The sensitivity value for endometrial biopsy for hyperplasia is 0.81

The sensitivity value for endometrial biopsy for atypia/cancer is 0.86

Combined sensitivity is (0.6 x 0.81) + (0.4 x 0.86)

Sensitivity = 0.83

A final data manipulation was needed when tests were reported in the literature as having a sensitivity or specificity of 1. These perfect accuracy data were rounded down to 0.99 as although tests can have high predictive values, no test can be reported as completely accurate.

Treatment satisfaction data

Systematic searches of the literature were conducted to identify patient satisfaction data at one year post-treatment. The electronic bibliographic databases EMBASE and Medline were searched using search terms for the relevant treatment, combined with menorrhagia or HMB, and satisfaction along with their alternatives. Searches and outputs are detailed in Appendix 7.9-7.13.

For the purpose of the model, effectiveness data in terms of patient satisfaction were needed according to underlying pathology. Whilst treatment outcome data are reported for women with HMB, in some cases the underlying diagnoses were not ascertained or treatments were not utilised when contraindicated. However, the diagnostic model required data for treatment outcomes not only used appropriately but also for when false diagnoses were made on testing

and so suboptimal or inappropriate treatments would be applied. When this data could not be identified in the published literature, the panel of gynaecologists were surveyed for their opinions regarding the likely treatment efficacy. The median values obtained in this way were used as the satisfaction rate and the range of values were used for sensitivity analysis.

Systematic reviews with meta-analysis were considered the highest quality data, followed by randomised controlled trials. When 12 month data weren't available the data reported closest to twelve months were used. If the time of reporting was not stated within the study the data were only used when no other appropriate data had been identified. For endometrial ablation, data were used that exclusively examined second generation techniques (6) as first generation methods are now seldom used.

Results of clinical data collection

Disease prevalence

Uterine polyps

The searches for prevalence of endometrial polyps identified 845 studies (Appendix 7.1). Seven studies were selected and the manuscripts obtained for further analysis. The majority of studies were rejected because they did not report prevalence or referred to postmenopausal or infertile populations. The highest quality study (score 20/21) reported a uterine polyp prevalence of 18% (202). The range in prevalence was wide however, with the next two best studies reporting a prevalence of 3.7% (203) and 33.9% (204).

Submucous fibroids

Searches for the prevalence of fibroids in women with heavy menstrual bleeding (Appendix 7.2) identified 134 papers, 3 of which were selected and assessed for quality and the prevalence data were extracted. Papers were discarded if they did not report prevalence of submucous fibroids in premenopausal women and if the reference test used was not the selected gold standard. The two highest scoring papers reported differing values of 21.9% and 7.4% for the prevalence of submucous fibroids (202;204) with 21.9% coming from the best paper (202) (quality score 18/21).

The prevalence of polyps and submucous fibroids reported in the highest quality studies were intended for use in the decision tree. However, whilst examining papers that reported the accuracy of hysteroscopy a systematic review of diagnostic hysteroscopy was identified which reported the prevalence of polyps and submucous fibroids (205). This systematic review meta-analysed over 3000 procedures. The prevalence of polyps was reported as 21% and that of submucous fibroids as 25%. However, polyps and submucous fibroids are estimated to co-exist in approximately one third of women (206) and so the value for submucous fibroids was reduced by one third to 17% to account for this. Thus the derived prevalence rate used for the pathology category 'endometrial polyps/SMF' was 38% (0.38).

Fibroids

Two studies were identified that looked at the prevalence of intramural or subserosal fibroids out of 134 studies identified from the original search (Appendix 7.2). One study only contained 80 participants (206) and the second was a study of women being scanned for a variety of symptoms (pain, worry, AUB, suspected fibroids) and not just heavy menstrual bleeding (207). The prevalence values reported by the two studies were 57.7% and 23.5%

respectively. Neither study specified whether submucosal fibroids were excluded and the patient populations were heterogeneous, preventing meta-analysis. Both studies scored 17 for quality but in view of the small size of the first study (80 patients), the poorly defined population in the second study and the large discrepancy in the reported values, a database of 473 women held at the BWH was consulted. This database showed that 19% (88/473) women had intramural fibroids less than 12 weeks size and that 6% (28/473) had fibroids greater than 12 weeks size, thus these data were used as the prevalence values within the decision tree.

Endometrial disease

The searches for prevalence of endometrial hyperplasia (Appendix 7.3) diagnosed by histology samples identified 86 studies of which five were chosen for review. Two studies were high quality (both scoring 20/21) and reported similar values for the prevalence of endometrial hyperplasia without atypia (3.0% and 2.4%). One study was a retrospective review of histology samples (208) and the second a retrospective audit of hysteroscopy findings (202). The same two studies were also identified as the best from the searches for studies reporting the prevalence of endometrial cancer (374 studies identified, 4 assessed further) (Appendix 7.4). Both studies were large and contained only premenopausal women. Meta-analysis of these two studies was performed to calculate the prevalence data more precisely. Data for endometrial hyperplasia without atypia were analysed separately from data for endometrial hyperplasia with atypia and endometrial cancer because the clinical implications of diagnosis and optimal therapeutic interventions differ. Meta-analysis was performed by converting the values from the studies to log odds and standard errors using Excel (Microsoft) this data was then copied across to RevMan (Cochrane Library) and analysed as the generic inverse variance using random effects analysis. The output from RevMan is the odds, so these were copied back into Excel and converted to values to give

prevalence rates with 95% confidence intervals. The value calculated for prevalence of endometrial hyperplasia without atypia was 3% and that for endometrial hyperplasia with atypia or endometrial cancer as 2%. Therefore the value for 'endometrial disease' was the sum of the two, 5%.

Dysfunctional Uterine Bleeding

In all decision trees the sum of all the branches from a common stem must add to 1. It was inevitable that the prevalences for the five pathology groups would not add up to one as the data came from a variety of sources and so dysfunctional bleeding was used as the 'buffer' to make the prevalences add to one (given DUB is a diagnosis assigned after exclusion of other identifiable 'organic' pathologies). This resulted in the prevalence of DUB being set at 32%. A summary of the derived disease prevalences is given in Table 8.7.

Table 8.7 Estimated prevalence of pathologies in heavy menstrual bleeding: Base case

Disease	Prevalence	Sensitivity analysis (range)	Source
Polyps/Submucous fibroids	0.38	0.2-0.5 (EP estimate)	SR (205)
Fibroids <12/40	0.19	0.15-0.22†	BWH database
Fibroids >12/40	0.06	0.04-0.08†	BWH database
Complex endometrial hyperplasia	0.03	0.02-0.03†	Meta-analysis of two studies (202;208)
Atypical hyperplasia / cancer	0.02	0.01-0.02†	Meta-analysis of two studies (202;208)
Endometrial disease (all hyperplasias and cancer)	0.05	0.03-0.05†	Meta-analysis of two studies (202;208)
Dysfunctional uterine bleeding	0.32	Remaining proportion	Remaining proportion used so that total sums to 1

SR= systematic review; †= 95% confidence interval; EP= expert panel

To calculate the prevalence of disease within the decision tree for women already treated with a LNG-IUS in primary care, the data were weighted by taking the proportion of women who would not be satisfied with a LNG-IUS for each pathology (see rates later on in this chapter) and dividing each by the total, so that the sum of them all came to one and became the new prevalences for the decision tree (Table 8.8).

Table 8.8 Recalculated disease prevalence for HMB in women refractory to treatment with a LNG-IUS

Disease	**Original prevalence (a)**	**Proportion dissatisfied with LNG-IUS (b)**	**Proportion coming to gynaecology (a x b) (c)**	**New prevalence (c / total c)**
Polyps/Submucous fibroid	0.38	0.60	0.228	0.592
Fibroids <12/40	0.19	0.17	0.032	0.083
Fibroids >12/40	0.06	0.71	0.043	0.111
Endometrial disease	0.05	0.56	0.028	0.073
Dysfunctional uterine bleeding	0.32	0.17	0.054	0.141
Total			**0.3853**	**1.0**

LNG-IUS= levonorgestrel intrauterine system

Test success

Success data for each of the four separate tests came from systematic reviews and meta-analysis (see Table 8.9).

Outpatient hysteroscopy

The search strategy for outpatient hysteroscopy identified three systematic reviews (198;199;205) from 1095 studies. Two studies reported test success (205) (198). The outpatient hysteroscopy value came from one of the systematic reviews (205) of diagnostic

hysteroscopy. This quantitative systematic review reported success data separately for all women having outpatient hysteroscopy and also for premenopausal women. However, the data for OPH included some postmenopausal women and the data for premenopausal women contained some women undergoing hysteroscopy as an inpatient under general anaesthesia. In total 2643/3158 (84%) procedures were done as outpatient hysteroscopies and only 306 women were specified as being postmenopausal, therefore it was decided to use the success rate value for outpatient hysteroscopy (0.97). This value was supported by the second review of predominantly pre-menopausal women (71%) but included both inpatient and outpatient hysteroscopy. The reported success rate in this meta-analysis was similar at 95.8% (CI 95.5-96.1%). (198).

Transvaginal ultrasound

There were no systematic reviews of premenopausal women undergoing transvaginal ultrasound that reported test success rate. Only one small study of 43 women reported the success rate of TVS and this was 100% (209). A previously used systematic review of women with postmenopausal bleeding reported a mean success rate of 100% with a standard deviation of 2% when data from 16 studies were meta-analysed (210). The value 0.99 was used because no test is 100% successful; women do occasionally refuse to have the test, cannot tolerate it or the visualisation on imaging is too poor to make a diagnosis.

Saline infusion sonography

Searches for reviews of saline infusion sonography identified 257 studies, two of which were systematic reviews (197;199) which were selected for data extraction. The first systematic review included meta-analysis of the accuracy of saline infusion sonography in a population of women with abnormal uterine bleeding (>50% premenopausal) and reported that the

success rate of the test in premenopausal women was 94.8% with confidence intervals of 93.5 -96.1% (197). A similar success rate of 95% reported by the second review examining SIS in premenopausal women supported this value (199).

Endometrial biopsy

Searches for reviews of endometrial biopsy identified two systematic reviews, one for the diagnosis of endometrial hyperplasia (150) and one for the diagnosis of endometrial cancer (151). The latter review of endometrial biopsy for diagnosis of endometrial cancer had a mainly postmenopausal population. Therefore the study looking at endometrial hyperplasia where the majority of women were premenopausal (50% were known to be premenopausal, 25% were known to be postmenopausal and 25% unknown) was used. This study found that 76/881 (8.6%) tests failed or were insufficient for histological diagnosis (150) and so a failure rate of 9% (0.09) was used. The raw data were used to calculate confidence intervals.

Test combinations

When combinations of tests were performed, the success rates of the individual tests were multiplied within the tree to calculate the success rate. The success rates of combined tests will always be worse than tests performed individually which is reflected by this manipulation. However it does not take into account whether the failure of one test is dependent upon the next, for example, if a hysteroscopy fails because of a stenosed cervical canal, an endometrial biopsy would be very likely to also fail.

Table 8.9 Diagnostic test success rate data

Test	Success rate	Sensitivity analysis (range)	Source
Outpatient hysteroscopy	0.97		SR(205)
Transvaginal ultrasound scan	0.99*		SR (210)
Endometrial pipelle biopsy	0.91	0.89- 0.93†	SR (150)
Saline infusion sonogram	0.95	0.94-0.96†	SR(197)

*reported as 0 but reduced to 0.99 as unlikely. †= 95% confidence interval, SR= systematic review

Test accuracy

Outpatient hysteroscopy

The accuracy data for hysteroscopy came from the two systematic reviews (see search in Appendix 7.5) used for test success and were identified by the outpatient hysteroscopy database searches (198;205). The first review looked at the accuracy of hysteroscopy for diagnosing intrauterine abnormalities in women presenting with abnormal uterine bleeding (pre and postmenopausal) using histopathology specimens as the reference standard. This study provided the data for polyps, submucous fibroids and dysfunctional uterine bleeding. This study has limitations as it has a mixed population and only 84% of procedures are specified as outpatient hysteroscopies. However, no other large data sets reporting accuracy exist. Data for the sensitivity and specificity of polyps (0.94 and 0.92) and submucous fibroids (0.87 and 0.95) are clearly reported in the paper and were combined to values for the combination group of polyps/submucous fibroids. Studies included in this large, systematic quantitative review of hysteroscopy report the accuracy of a test for diagnosing pathology rather than a normal cavity. Thus data for the accuracy of outpatient hysteroscopy in diagnosing dysfunctional uterine bleeding could not be identified, a reflection of the fact that DUB is considered a diagnosis of exclusion. Therefore the data values from the review were reversed i.e. used the proportion not diagnosed as abnormal and assigned these women as

DUB. In practice this results in the sensitivity and specificity being reversed. The sensitivity and specificity reported for diagnosing abnormalities were 0.94 and 0.89 respectively, so for diagnosing 'no' abnormality the values reverse and the sensitivity becomes 0.89 and specificity 0.94.

The data regarding the accuracy of outpatient hysteroscopy for diagnosis of endometrial disease comes from the second identified review (198) which specifically looks at this question in a mixed population with 29% of the women specified as postmenopausal. This large systematic review meta-analysed data from 65 studies (26,346 women) that compared outpatient hysteroscopy to endometrial histology results and reported that the sensitivity for diagnosis of endometrial disease (cancer and hyperplasia) was 0.78 and that specificity was 0.96, hence these values were used in the decision tree.

Transvaginal ultrasound

The search for transvaginal ultrasound accuracy data included terms for abnormal uterine bleeding and yielded 420 studies once duplicates had been removed (Appendix 7.6). Thirty-seven studies were selected for further assessment regarding accuracy of transvaginal scan. Only one of the selected papers was a systematic review (199) but as the studies included were heterogeneous, no meta-analysis was performed and no useful data could be extracted. The thirty-seven studies identified were assessed for quality and accuracy data were extracted for the different pathologies.

A prospective comparative study was selected as the highest quality paper reporting the accuracy of TVS for diagnosing polyps and submucous fibroids (211). The study compared the TVS diagnosis to hysteroscopic diagnosis. The tests were performed by different

clinicians and each one was blinded to the other result. The tests were performed within 24 hours of each other and the majority of women included in the study were premenopausal. The sensitivity and specificity of TVS for diagnosing polyps and submucous fibroids were reported as 0.45 (95% CI 0.32-0.58) and 0.78 (0.62-0.89), and these data were used to populate the decision tree. Data from the same study were used for accuracy of TVS for diagnosing endometrial disease reported as sensitivity 0.57 (95% CI 0.19-0.90) and specificity 0.66 (0.55-0.76).

Only one study was identified which reported the accuracy of TVS for diagnosing intramural or subserosal fibroids. The study aimed to assess the accuracy of TVS for diagnosing adenomyomas and fibroids and its ability to distinguish between the two pathologies by comparing the scan results to hysterectomy specimens (212). The mean age of women included in the study was 46.7 (range 35.7-51.8) years and 172 of the 206 women had menorrhagia or dysmenorrhoea. The sensitivity and specificity of TVS for diagnosing fibroids were reported as 95.1% and of 82.0% and were used as the accuracy values for TVS diagnosis of fibroids.

As with outpatient hysteroscopy, no studies reported the accuracy of TVS for diagnosing a normal uterus, so this had to be derived indirectly. The largest high quality study (7 points) that reported the accuracy of TVS for diagnosing abnormality (213) was selected and the sensitivity and specificity were reversed. This study evaluated 770 women with HMB to establish the accuracy of TVS for diagnosing a composite of all pathologies labelled ‘intrauterine disease’ by comparing the scan results to the results of hysteroscopy. As the reported sensitivity and specificity for abnormality were 0.96 (95% CI 0.934 to 0.972) and

0.86 (95% CI 0.823 to 0.898) they were reversed and 0.86 (95% CI 0.823 to 0.898) was used as the sensitivity and 0.96 (95% CI 0.934 to 0.972) as the specificity.

Saline infusion sonography

Searches for the accuracy of saline infusion scan identified 157 studies of saline scan for menorrhagia (Appendix 7.7). Forty-one papers were selected and assessed for quality and any reported accuracy data were extracted. Two systematic reviews were identified (199) (197), one of which was the study with no meta-analysis (199) identified during the TVS searches. The second was a systematic review and meta-analysis of diagnostic studies that compared SIS to either hysteroscopy or histopathology obtained at hysteroscopy or hysterectomy and reported the accuracy of the test for diagnosing intrauterine abnormalities (197). The analysis included twenty-four studies and more than 50% of the population were premenopausal. The accuracy of saline infusion sonography for diagnosing endometrial polyps and submucous fibroids was reported as a secondary outcome after meta-analysis of fifteen homogenous studies. These values were combined and weighted to calculate a value for the two pathologies combined. Once again data for a normal cavity were not available and so the sensitivity and specificity data for abnormalities were reversed.

The accuracy of SIS for diagnosing endometrial disease was not reported in the systematic reviews. Of the thirty-nine remaining studies, four reported the accuracy of SIS for diagnosis of endometrial disease (hyperplasia and or cancer). When the quality was assessed, two of the studies scored 6 points (211;214) but the values that they reported for sensitivity were very different with one reporting a sensitivity for endometrial hyperplasia as 0.94 (214) and the second reporting sensitivity for endometrial hyperplasia and cancer as 0.29 (211). The study sizes were very similar, as were the proportions of premenopausal women, however one of

the studies had a much higher prevalence of endometrial disease (17%) than would be expected in a mainly premenopausal population (214) and the interval between the SIS and the reference test was up to fourteen days when in the second study it was just 24 hours (211). The first study (214) used a cut-off threshold for women of reproductive age of 8mm for diagnosing abnormality. Using an endometrial thickness cut-off level is crude and more applicable to a postmenopausal population where endometrial thickness is constant rather than changeable according to the menstrual cycle In contrast, the second study diagnosed abnormalities based upon clinical features seen at SIS rather than defining abnormalities (211). The culmination of these factors resulted in the decision to use data from the second study (211) to populate the decision tree.

Endometrial biopsy

Searches for accuracy data of endometrial biopsy identified four studies with data regarding accuracy of the test. One of the studies was an RCT which looked at the use of three diagnostic tests, including endometrial biopsy, in groups of women at a specified risk of endometrial cancer (155). The population included pre and postmenopausal women and only reported the accuracy of pipelle for diagnosing endometrial cancer. Two of the remaining selected studies were systematic reviews one of which looked at diagnosis of endometrial hyperplasia (150) and a second which looked at endometrial cancer (151). Both studies used histopathology samples as the reference standard. These studies were limited in that they had mixed populations of pre and postmenopausal women. As postmenopausal women have an atrophic endometrium, focal lesion are more likely to be sampled and thus the effect of the postmenopausal women within these three studies may increase the sensitivity of the test above what may be expected in a purely premenopausal population. As systematic reviews with meta-analysis were rated as higher quality evidence than RCT data the values from the

systematic reviews (150;151) were used for accuracy of diagnosing endometrial disease. In these papers, likelihood ratios were reported, but in order to populate the model, the sensitivities and specificities were used which had been reported in the thesis from which the papers were taken (Clark TJ 2004; PERSONAL COMMUNICATION).

The fourth study reported the accuracy of endometrial biopsy for diagnosis of endometrial polyps (215). One hundred and seventy-six consecutive patients (77% premenopausal) who were scheduled for dilatation and curettage underwent transvaginal ultrasound and endometrial pipelle® biopsy prior to their surgery. The biopsy samples and the curettings were examined by different pathologists who were blinded to the other result. The paper reports these results in a cross-tabulated fashion enabling calculation of the sensitivity and specificity of endometrial biopsy for the diagnosis of endometrial polyps (216) as 0.997 (95% CI 0.973-1) and 0.003 (95% CI 0-0.027) respectively. These values were converted to the true positive and false positive values which were used in the decision tree. The some cross tabulation data were used to calculate the accuracy for diagnosis of dysfunctional uterine bleeding by looking at the accuracy for benign endometrium (excluding endometrial polyps and hyperplasia). The sensitivity was calculated as 0.953 (95% CI 0.895 to 0.98) and specificity as 0.971 (95% CI 0.902 to 0.992) and the corresponding true and false positive values used accordingly.

No studies reported the use of endometrial biopsy for diagnosis of submucous fibroids so further searches were performed that did not include ‘heavy menstrual bleeding‘ or its associated terms. One study of 330 postmenopausal women was identified that reported the accuracy of endometrial biopsy for diagnosis of submucous fibroids. This prospective study

compared Novak catheter samples to histopathology samples obtained during surgery to establish accuracy of the blind biopsy. The reported sensitivity and specificity of the Novak catheter were 13% and 100%. The specificity was reduced to 99% (no 'perfect' values were deemed to be plausible) and the values were converted accordingly for use in the decision tree.

The accuracy estimates, along with ranges for use in sensitivity analyses and data sources are summarised in Table 8.10.

Table 8.10 Test sensitivity for specific pathologies

Variable	Baseline sensitivity	Sensitivity analysis (range)	Source
OPH polyps	0.94	0.92-0.96†	SR (205)
OPH submucous fibroids	0.87	0.81-0.92†	SR (205)
OPH polyps / SMF	0.91	0.87-0.94†	Composite of polyp and SMF values
OPH endometrial disease	0.78	0.76-0.80†	SR (198)
OPH DUB	0.89	0.87-0.90†	SR (205) values reversed so for no pathology
TVS polyps / SMF	0.45	0.32-0.58†	Prospective comparative study(211)
TVS intramural fibroids	0.95		Prospective observational(212)
TVS endometrial disease	0.57	0.19-0.90†	Prospective comparative study (211)
TVS DUB	0.86	0.82- 0.90†	Prospective observational study (213)values reversed so for no pathology

Table 8.10 continued

Variable	Baseline sensitivity	Sensitivity analysis (range)	Source
EBx polyps	0.41	0.14-0.76†	Observational prospective cohort (215)
EBx SMF	0.13	-	Prospective comparative study (217) NB PMB
EBx polyp / SMF	0.27	0.14-0.76 †	Composite of polyp and SMF values
EBx endometrial hyperplasia	0.66	0.47-0.81†	SR (150)
EBx cancer / atypia	0.94	0.84-0.99†	SR (151)
EBx endometrial disease	0.78	0.62-0.88†	Composite of hyperplasia and cancer / atypia values
EBx DUB	0.95	0.90-0.98†	Observational prospective cohort (215) 2x2 created and benign data used to calculate
SIS polyps	0.86	0.81-0.91†	SR (197)
SIS SMF	0.87	0.79-0.92†	SR (197)
SIS polyps / SMF	0.87	0.80-0.92†	Composite of polyp and SMF values
SIS endometrial disease	0.29	0.05–0.71†	Prospective comparative study(211)
SIS DUB	0.88	0.85-0.92†	SR (197) values reversed so for no pathology

OPH= outpatient hysteroscopy; TVS = transvaginal scan; EBx= endometrial biopsy; SIS= saline infusion sonography; SMF= submucous fibroid; DUB= dysfunctional uterine bleeding; SR= systematic review; † = 95% confidence interval

False positive rates

Although the false positive rates were calculated from the specificity data (1-specificity = false positive rate) the derived values could not always be used in their pure form within the

decision model. This is because where a false diagnosis is made there are several possible erroneous options. However, the branches from one stem in the tree have to sum to one. This meant that all of the possible false diagnoses needed false positive rates which added up to one. To overcome this, if one of the erroneous diagnoses was DUB (i.e. normal) the FPR's for the other pathologies would be used and the value remaining would become the FPR for DUB. When DUB was not a possible false diagnosis each FPR was divided by the sum of them together to weight the respective values appropriately:

> Example 1:- 1.If it is assumed that for TVS the possible false diagnoses were polyp/SMF (FPR=0.22), endometrial disease (FPR=0.34) and normal (FPR = 0.04). The only value which changes is the value for normal (i.e. DUB) which becomes 1-(0.34+0.22) = 1-0.56 = 0.44.

> Example 2:- If it is assumed that for TVS the possible false diagnoses are polyp/SMF (FPR= 0.22) or fibroids <12 weeks size (FPR= 0.18). Both values are then divided by the combined FPRs [(0.22+0.18) = 0.40] to weight them so that the sum of the two values equals one e.g. 0.22/0.40= 0.55 and 0.18/0.40= 0.45.

This rule was used consistently throughout the decision tree. Weighting the values meant that the reported confidence intervals could not be used in subsequent sensitivity analyses so beta distributions were used to calculate appropriate confidence intervals. Table 8.11 details the false positive rates that were used within the tree as well as explanations as to how they were derived.

Table 8.11 Manipulation of false positive rates and their use within the decision tree

Test	True diagnosis	False diagnosis	Value	Why
TVS	Polyp/SMF	Fibroids <12wk	0.18	TVS FPR for intramural fibroids
		Endometrial disease	0.34	TVS FPR for endometrial disease
		Normal	0.48	Remaining
	Fibroids <12wk	Polyp/SMF	0.22	TVS FPR for polyp / SMF
		Endometrial disease	0.34	TVS FPR for endometrial disease
		Normal	0.44	Remaining
	Fibroids >12wk	Polyp/SMF	0.55	Unconditional FPR s weighted to add to 1
		Fibroids <12wk	0.45	
	Endometrial disease	Polyp/ SMF	0.22	TVS FPR for polyp / SMF
		Fibroids <12wk	0.18	TVS FPR for Intramural fibroids
		Normal	0.60	Remaining
	DUB	Polyp /SMF	0.30	Unconditional FPR s weighted to add to 1
		Fibroids <12wk	0.24	
		Endometrial disease	0.46	
OPH	Polyp / SMF	Endometrial disease	0.04	OPH FPR for endometrial disease
		Normal	0.96	Remaining
	Fibroids <12wk	Polyp/SMF	0.6	Unconditional FPR s weighted to add to 1*
		Endometrial disease	0.4	
	Fibroids >12wk	Polyp/SMF	0.6	Unconditional FPR s weighted to add to 1
		Endometrial disease	0.4	
	Endometrial disease	Polyp/SMF	0.06	OPH FPR for polyp/SMF
		Normal	0.94	Remaining
	DUB	Polyp/SMF	0.6	FPR s weighted*
		Endometrial disease	0.4	

Table 8.11 continued

Test	True diagnosis	False diagnosis	Value	Why
EBx	Polyp/SMF	Normal	0.95	Remaining
		Comp hyp	0.05	EBx FPR comp hyp
	Fibroids <12wk	Polyp/SMF	0.038	Unconditional FPR s weighted to add to 1
		Comp hyp	0.962	
	Fibroids >12wk	Polyp/SMF	0.038	Unconditional FPR s weighted to add to 1
		Comp hyp	0.962	
	Endometrial disease	Polyp/SMF	0.002	EBx FPR for polyp/SMF
		Normal	0.998	Remaining
	DUB	Polyp	1	As no alternative disease
SIS	Polyp/SMF	Fibroids <12wk	0.18	TVS FPR for intramural fibroids
		Endometrial disease	0.02	SIS FPR for endometrial disease
		Normal	0.80	Remaining
	Fibroids <12wk	Polyp/SMF	0.13	SIS FPR for polyp/SMF
		Endometrial disease	0.02	SIS FPR for endometrial disease
		Normal	0.85	Remaining
	Fibroids >12wk	Polyp/SMF	0.42	Unconditional FPR s weighted to add to 1
		Fibroids <12wk	0.58	
	Endometrial disease	Polyp/SMF	0.13	SIS FPR for polyp/SMF
		Fibroids <12wk	0.18	TVS FPR for intra fib
		Normal	0.69	Remaining
	DUB	Polyp/SMF	0.39	Unconditional FPR s weighted to add to 1
		Fibroids <12wk	0.55	
		Endometrial disease	0.06	

OPH= outpatient hysteroscopy; TVS = transvaginal scan; EBx= endometrial biopsy; SIS= saline infusion sonography; SMF= submucous fibroid; DUB= dysfunctional uterine bleeding; SR= systematic review; FPR= false positive rate

Test combinations

As the test combination trees display tests in series, no new values needed to be calculated for data accuracy for the combination trees.

Treatment satisfaction data

Levonorgestrel intrauterine device

The medical database searches identified 2987 studies using the terms 'levonorgestrel intrauterine device', 'heavy menstrual bleeding' and their associated phrases. Eighty-two studies reported data regarding the effectiveness of the LNG-IUS. They were selected based on whether they reported effectiveness data for the LNG-IUS in any form for any pathology. The highest quality data for each pathology were then selected and used within the analysis (Appendix 7.9). The LNG-IUS works optimally when used to treat DUB and so data that reported patient satisfaction when used in women with DUB as their underlying pathology were identified and used as a reference. One of the selected studies was a systematic review with individual patient data (IPD) meta-analysis which looked at the relative effectiveness of hysterectomy, endometrial destruction and levonorgestrel intrauterine devices (LNG-IUS) (184). The review used 12 month follow up data to report rates of dissatisfaction when comparing the different treatments. The dissatisfaction reported for LNG-IUS overall at 12 months was 17% (22/128). This was converted to a satisfaction rate of 83% and confidence intervals were calculated from the data so that the values used for satisfaction with LNG-IUS when used to treat DUB were 0.83 (95% CI 0.76-0.89).

No suitable studies were identified that reported the satisfaction level of premenopausal women with polyps, fibroids, endometrial hyperplasia or cancer if they were treated with an LNG-IUS. Any studies reporting this outcome were either very small (< 50 patients) or had a

mainly postmenopausal population. One study reported predictors of outcome for LNG-IUS and stated that small fibroids were not predictive of outcome (161), therefore an extrapolation was made from this and the same date were used for fibroids less than twelve weeks size as was used for DUB from the IPD study(184). For polyps / SMFs and for fibroids greater than twelve weeks size no studies were identified that reported patient satisfaction associated with the use of the LNG-IUS so the panel of gynaecologists were asked to estimate how effective the device would be in women with theses pathologies. The values of presumed treatment satisfaction for polyps/SMFs were inconsistent ranging from 20% to 85% with a median value of 40%. For fibroids > 12 weeks size the range was similarly imprecise varying from 10% to 75% with a median value of 29%. The median values formed the point estimates and the ranges were used in the sensitivity analysis.

One study was identified that reported the regression of endometrial disease with the use of the LNG-IUS (162), however only 37 of the women were premenopausal. The study reported that at 12 months 69/80 (86%) with complex hyperplasia had regressed and that 6/9 (66%) with atypical hyperplasia had regressed. This study was reported from data collected at BWH in 2008, however the database continued to be updated and so up-to-date data were used to produce values for endometrial hyperplasia and cancer. The database records follow-up data for women who have been diagnosed with endometrial hyperplasia with and without atypia, who are being treated with systemic or local progestogens. Women who were being treated with a LNG-IUS for endometrial disease were identified and their 6 and 12 month follow-up data examined. If they were still using the LNG-IUS at 12 months it was assumed that they were satisfied with it. If they had undergone hysterectomy or had the IUS removed they were counted as unsatisfied. One-hundred and one premenopausal women, 95 with complex

hyperplasia and 6 with complex hyperplasia with atypia were identified in the database. Thirteen of the women with complex hyperplasia had undergone a hysterectomy before 12 months so 82/95 (86%) women were considered satisfied. This value is consistent with the original study (162). However this treatment success rate is greater than the aforementioned literature derived estimates for successful treatment outcomes in women without uterine pathology (DUB). This was considered highly unlikely so the value for the satisfaction rate of treatment with LNG-IUS in women with endometrial hyperplasia was reduced to 83% to make it the same value as for the DUB population. Confidence intervals were calculated for the original data but they were varied around a point estimate of 0.83 instead of 0.86. Of the six women who were treated for complex endometrial hyperplasia with atypia, three had undergone hysterectomy by twelve months, giving a satisfaction rate of 50%.

It was assumed that the patients whose underlying disease was endometrial cancer would not be satisfied with the LNG-IUS treatment as the inappropriate treatment would mean persistence or worsening of their symptoms. In the database the ratio of pre-menopausal women with atypical endometrial hyperplasia to premenopausal women with endometrial cancer was 0.59: 0.41 so each was multiplied by the satisfaction value to produce a composite 'satisfaction' value for the group 'atypia/cancer':

Atypical hyperplasia	satisfaction rate= 0.50	prevalence= 0.59
Endometrial cancer	satisfaction rate= 0.00	prevalence= 0.41

Overall composite satisfaction rate is (0.50 x 0.59) + (0 x 0.41) = 0.295

Value used for treatment satisfaction = 0.3

Similarly, the value for complex hyperplasia was used proportionally with the value for 'atypia/cancer' to produce an overall satisfaction value for 'endometrial disease'.

Complex hyperplasia	satisfaction rate= 0.83	prevalence= 0.60
Atypia/cancer	satisfaction rate= 0.30	prevalence= 0.40

Overall composite satisfaction rate (0.60 x 0.83) + (0.30 x 0.40) = 0.44

Value used for treatment satisfaction = 0.44

Endometrial ablation

To populate the decision tree, values were needed for satisfaction after endometrial ablation for DUB and for fibroid uteri. As endometrial ablation requires women to undergo an endometrial biopsy and either a TVS, SIS or OPH prior to the procedure it was assumed that any intrauterine pathology would be picked up by one of these pre-ablation tests and then treated appropriately. Thus outcome data for polyps/SMF and endometrial disease were not required. Searches for endometrial ablation identified 319 relevant studies, 8 of which were systematic reviews, with 4 containing meta-analysis (184;193;194;218) (Appendix 7.10a-7.10b). Three of these studies appeared to be updated versions of the same Cochrane review and the fourth study was the IPD meta-analysis used for satisfaction with LNG-IUS (184). The most recent Cochrane review (193) and the IPD meta-analysis (184) were evaluated further. The IPD study was found to include 12 month satisfaction data from a larger overall population of women. It also had the benefit of using IPD data, so was selected as the preferable study. The reported dissatisfaction rates for second generation endometrial ablation 110/1034 were converted to satisfaction rates which were then used to calculate confidence

intervals (0.893, 95% CI 0.874-0.912). These values were used in the economic analysis for satisfaction after endometrial ablation for DUB.

An electronic database search was performed (Appendix 7.10c-7.10d) to identify studies that reported outcome after endometrial ablation in the presence of fibroids. Once duplicates had been removed 315 studies were identified of which 17 were selected for further evaluation because they reported the use of endometrial ablation in the presence of fibroids. None of the studies reported satisfaction after second generation endometrial ablation in the presence of intramural or subserosal fibroids, however one study reported that the presence of a small fibroid uterus did not increase the hysterectomy rate (219). Once again this was extrapolated and the same data were used for small fibroid uteri as for satisfaction after second generation endometrial ablation for DUB. In the absence of published data for large fibroid uteri, the gynaecologist panel were asked for their estimation of satisfaction rates, 1 year post endometrial ablation. The median value of 0.575 was used as the point estimate and the range of values as the data for sensitivity analysis (0.075-0.85)

Hysterectomy

The IPD meta-analysis for treatment satisfaction data following the use of a LNG-IUS and after an endometrial ablation also reported data for hysterectomy so these values were used for satisfaction after hysterectomy for DUB (184). The rates reported were 409/432 patients satisfied which equates to a value of 0.95 and confidence intervals of 0.93 to 0.97. The studies included in this IPD looked at heavy menstrual bleeding and included women with polyps and fibroids. Only three studies supplied data regarding treatment outcome in the presence of focal uterine pathology. The presence of endometrial polyps and fibroids were found not to be statistically significant indicators of outcome. Thus it was assumed that satisfaction would be

the same whether hysterectomy was performed for DUB, polyps/SMFs or fibroids less than 12 weeks size.

For large fibroids (> 12 weeks uterine size), database searches were performed to identify studies reporting satisfaction after hysterectomy for fibroids. No systematic reviews were identified that examined this outcome directly. However a study of 397 women, that retrospectively followed up women who had either had hysterectomy or uterine artery embolisation reported that 88% of women who had undergone hysterectomy felt that their symptoms were better and that 70% would recommend their treatment to a friend (220). A disadvantage of this study was that the mean follow up time was 8.6 years. By scrutinising the reference list of this study, two similar studies (195;221) were identified. The first was a randomised trial of uterine artery embolisation (UAE) versus hysterectomy, with 51 women in the hysterectomy arm (195). Women were included if they had fibroids of at least 2cm in diameter (no upper limit), which caused symptoms and which a clinician thought justified surgical treatment. At 12 months 93% of women would recommend their treatment to a friend. The second study randomly allocated women with uterine fibroids up to 10cm in size and menorrhagia, to two groups. The women in group 1 were offered UAE as an alternative to hysterectomy for their fibroids and the women in group 2 were not offered the alternative and all had hysterectomy (221). In total 17 women underwent hysterectomy and at 6 months 88% reported that they would have the same treatment again, suggesting that they were satisfied with the surgery (221). After evaluating the data from these studies 0.88 was chosen as the satisfaction level as this was reported in the large retrospective study (220) and supported by the smaller randomised study (221). For the sensitivity analysis, the proportion of women

who would recommend their treatment to a friend from the two separate studies was used (0.70 and 0.93) (195;220).

No studies were identified that reported satisfaction rates after hysterectomy for endometrial disease in premenopausal women. It was assumed that women having hysterectomy for atypical hyperplasia or cancer would be 100% satisfied because they would be prevented from developing cancer or treated for their cancer. For sensitivity analysis the lowest hysterectomy satisfaction value (i.e. 0.88 for fibroids) and the highest satisfaction value (1.0 for cancer) were used. For complex endometrial hyperplasia the same values as for DUB was used because complex hyperplasia is a benign condition so can be grouped with other benign causes of HMB without organic pathology i.e. DUB. Secondly, treatment satisfaction after LNG-IUS was the same for complex hyperplasia as for DUB and so this extrapolation regarding hysterectomy does not seem unreasonable. For endometrial disease overall, a composite value of the atypia/cancer value and the hyperplasia value was calculated as 0.97. For sensitivity analysis the lowest and highest satisfaction rates from the two categories were used i.e. 0.95 for hyperplasia to 1.0 for cancer.

Polyp/SMF removal

Satisfaction after removal of endometrial polyps and submucous fibroids was calculated as a composite of values for the two pathologies. For endometrial polyps two systematic reviews were selected (166;167) from the 216 studies identified by database searches. Neither systematic review included any meta-analysis because of the heterogeneity of the studies. The more recent review (167) identified all of the studies used in the older one (166) as well as more recently conducted studies. Satisfaction with polyp removal for abnormal uterine bleeding was reported as 75-100% so he high quality studies were examined for the most

appropriate data. Three studies were prospectively conducted (117;222;223). The first study was a cohort-controlled study comparing the effectiveness of outpatient and day case endometrial polypectomy which included 58 women, predominantly postmenopausal. At 6 months, 34 women responded to a follow-up questionnaire that asked them about satisfaction with the treatment. 78% of women in the outpatient group and 88% women from the inpatient group were satisfied with their treatment, which equates to an 82% satisfaction rate overall (117). The second trial was a cohort study which looked at 21 women with abnormal menstrual bleeding and evaluated the change in their symptoms following endometrial polypectomy (222). At 6 months there was a statistically significant reduction in menstrual blood loss ($p<0.001$). Thirteen of the women had HMB, which persisted in 10 (77%) of them at 6 months although they had a statistically significant reduction in pictorial blood loss assessment chart (PBAC) scores ($p=0.001$). Overall, 86% of the women felt that they were cured or that their symptoms had been relieved by endometrial polypectomy (222). The third study randomised 150 premenopausal women with abnormal uterine bleeding to polypectomy or conservative management and found no difference in PBAC scores at 6 months. There was a significant difference between the groups for some of the secondary outcome measures including mean periodic blood loss measured by visual analogue scale ($p=0.02$) and occurrence of gynaecological symptoms (intermenstrual bleeding, pain), however, satisfaction was not reported and so could not be used (223). As the two comparative studies reporting satisfaction were small, the populations were combined and meta-analysed using Excel and RevMan to calculate a satisfaction value of 0.86.

For satisfaction with transcervical resection of submucous fibroids (TCRF), 32 studies were identified by medical database searches. Nine studies reported satisfaction after transcervical

myomectomy but seven were rejected because they had fewer than forty patients (5;224) or reported satisfaction data from more than 3 years after treatment (170;225-228). The two remaining studies (168;171) were both prospectively conducted and had populations of over 100 women, with more than 90% being premenopausal. The first study examined resection of submucous fibroids using a resectoscope under general anaesthesia (90%) or local anaesthesia with sedation. The average follow-up period was 2.3 years. Satisfaction with treatment was reported as 71.4% (168). The second study examined removal of fibroids using a bipolar intrauterine operating system and performed 38% of them under local anaesthesia. The average follow-up period was 2.6 years. Satisfaction with treatment was reported as 86% (171). In the decision tree resection as day-case surgery, under general anaesthesia was used for submucosal fibroid removal as it is the gold standard. Therefore the satisfaction rate from the first study was chosen as it appeared to be most appropriate for the analysis (168).

The data from the polypectomy meta-analysis and the selected submucous fibroid resection study were used to create a value for the combined diagnostic group 'polyps/SMF' weighting the data according to the disease prevalence within the group (50% polyps, 50% SMFs). The value calculated was 0.79 and was used as the satisfaction value for removal of polyps and submucosal fibroids.

To account for removal of erroneously diagnosed focal pathology (i.e. when no intrauterine pathology was present so normal endometrium is being resected) a satisfaction rate for dilatation and curettage was sought as the patients will essentially be having normal endometrial tissue removed. 274 studies were identified form database searches but none reported patient satisfaction following the procedure. One study was identified which

reported relief of HMB after D&C and stated that the menstrual blood loss was reduced for the first month but returned to pre-operative levels after that (229). This does seem plausible as D&C is primarily a diagnostic procedure and removing the superficial endometrium will only be therapeutic until it grows back. As no additional data were available this value was used and allocated a satisfaction score of zero for satisfaction following 'virtual removal' when no intrauterine lesion was present.

Myomectomy and uterine artery embolisation

The alternative analysis which looked at treating women who wished to preserve their fertility included UAE and myomectomy as treatment options. Searches were performed to look at patient satisfaction after both treatments at 1 year (Appendix 7.14-7.15). For myomectomy one systematic review (230) was identified and selected from 120 studies and for UAE one systematic review (231) was identified and selected from 169 studies. Both systematic reviews compared UAE to surgical treatments (hysterectomy and myomectomy) (230;231) and both found no difference in patient satisfaction or quality of life between UAE, hysterectomy and myomectomy. Therefore the same value for satisfaction after hysterectomy was used for UAE and myomectomy (0.88).

Costs

Cost values were mainly taken from Healthcare Resource Group (HRG) codes for 2009 - 2010. The 'national average unit cost' was used as the cost for each intervention. The diagnostic and treatment codes for hysteroscopy include the cost of the consultation as well as any diagnostic or therapeutic procedures but the other diagnostic test codes equated to just the cost of the test. Within the decision tree patients could undergo multiple diagnostic tests and

treatments at one appointment. However, if the relevant HRG code costs were then used for each aspect the cost of the consultation would be included multiple times. In order to give an accurate reflection of the additional costs of multiple tests including hysteroscopic treatment, cost of consultation was removed from the diagnostic hysteroscopy costs and also from the therapeutic hysteroscopy codes. The cost of consultation and diagnostic hysteroscopy were subtracted so that the value remaining was the additional cost of performing the therapeutic hysteroscopic procedure alone. The relevant costs could then be added up depending upon the tests and treatments that the patients had undergone. For example,

Cost of new gynaecology consultation	£ 139
Cost of outpatient hysteroscopy (consultation+ diagnostic OPH)	£ 216
Cost of outpatient hysteroscopic polypectomy (consultation+ diagnostic OPH+ polypectomy)	£ 263
Cost of transcervical resection of fibroid	£1344
Cost of transvaginal ultrasound (test only)	£ 55
Cost of GnRH analogues	£ 226

So the cost of the diagnostic hysteroscopy is actually	£216 - £139 = £ 77
And the additional cost of hysteroscopic polypectomy is	£263 - £216 = £ 47

If a woman (assigned to the TVS diagnostic pathway) comes to clinic and has a diagnosis of ‘polyp/SMF’ made by TVS and then goes on to have removal of the lesion, the costs will equate to all the women having a consultation and a scan, half of them having an outpatient hysteroscopic polypectomy (ratio of polyps to submucous fibroids 50:50) and half of them

returning at a later date for a scheduled transcervical resection of fibroid (with 70% of these women having endometrial pre-treatment with GnRH analogues.

cGynaeNew + cTVS + (0.5*cOPH) + (0.5*cPolypectomy) + (0.5*cTCRF) + (0.35*cGnRH)

= £139 + £55 + (0.5 x £77) + (0.5 x £47) + (0.5 x £1344) + (0.35 x £226)

= £139 + £55 + £38.50 + £23.50 + £672 + £79.10

= £1007.10

However, if the HRG code was used for hysteroscopic polypectomy alone the cost would be considered as £263 or if the code for TCRF was used it would be £1344. For the cost of LNG-IUS and GnRH-a costs were taken from the British National Formulary (BNF) (25) The cost of uterine artery embolisation could not be identified in the HRG codes so the value used in the decision tree came from the REST study (195) as reported and used by NICE in an economic analysis for treatment of fibroids in their HMB guideline (142). Although this cost was published in 2007, the cost stated for hysterectomy was comparable to the cost stated in the HRG codes 2009-2010 (£2,566 vs. £2961) which are used in this economic analysis therefore no adjustment was made for inflation. For the cost of a GP appointment, data were taken from the Personal Social Services Research Unit (PSSRU (232)). Table 8.12 details all of the costs, ranges and sources of data.

Table 8.12 Costs for investigation and treatment of women presenting with HMB

Variable	Decision tree name	Cost (£)	Lower quartile	Upper quartile	Explanation
Consultations					
GP visit	cGP_visit	36			Personal Social Services Research Unit. (PSSRU) http://www.pssru.ac.uk/uc/uc2010contents.htm 11min appt. Inc direct staff
New gynaecology outpatient appointment	cGynaeNew	139	111	161	502 HRG consultant service code
Follow-up gynaecology outpatient appointment	cGynaeFU	97	73	109	502 HRG consultant service code
Diagnostic tests					
Diagnostic outpatient hysteroscopy	cOPH	77	43	111	MA10Z HRG less cost of new gynaecology outpatient appointment
Transvaginal ultrasound	cTVS	55	40	66	HRG code RA23Z
Endometrial biopsy	cEBx	34	16	34	HRG code DAP824
Saline infusion scan	cSIS	71	54	83	HRG code RA24Z
Confirmatory test	cConfirmatory_test	115.72	77.56	130.66	(0.91*cEBx)+(0.09*cDandC)
Treatments					
LNG-IUS fitting	cLngIUS_fitted	85.66			
Endometrial polypectomy	cPolypectomy	47	0	120	MA12Z HRG less the cost of diagnostic hysteroscopy MA10Z.
Transcervical resection of fibroid with D+C cost	cTCRF	1344	981	1541	HRG code MA09Z

Table 8.12continued

Variable	Decision tree name	Cost (£)	Lower quartile	Upper quartile	Explanation
Transcervical resection of fibroid without D+C cost	cTCRF_noDandC	401	281	433	HRG code MA09Z less the cost of D&C MA10Z
Use of GnRH-a analogue	cGnRHanalogue	225.73			BNF(25)
Hysterectomy for benign disease	cHysterectomy	2961	2346	3406	HRG code MA07D
Hysterectomy for malignant disease	cHysterectomy_malignant	3898	3052	4464	HRG code MA06Z
Second laparotomy after cancer diagnosis to remove ovaries, lymph nodes etc.	cReturn_for_BSO	3898	3052	4464	HRG code MA06Z
Endometrial ablation	cEndoAblation	896	697	1024	HRG code MA12Z
Dilatation and curettage	cDandC	942	700	1108	HRG code MA10Z
Rescue treatment	cRescue_Treatment	3136	2493	3606	cGP_visit + cGynaeNew + cHysterectomy
Myomectomy	cMyomectomy	2961	2346	3406	HRG code MA07D
UAE	cUAE	1685	1465	1905	REST study (195)

MA09Z Upper Genital Tract Laparoscopic / Endoscopic Intermediate Procedures
MA10Z Upper Genital Tract Laparoscopic / Endoscopic Minor Procedures
MA11Z Upper Genital Tract Intermediate Procedures
MA12Z Resection and ablation procedures for intra-uterine lesions
MA06Z Open Major Upper and Lower Genital Tract Procedures with malignancy
MA07D Upper Genital Tract Major Procedures without Major CC
RA 23Z Ultrasound Scan less than 20 minutes
RA 24Z Ultrasound Scan more than 20 minutes
DAP824 Histology / Histopathology
502 Face to face, non-admission gynaecology consultant appointment

OPH= outpatient hysteroscopy; TVS = transvaginal scan; EBx= endometrial biopsy; SIS= saline infusion sonography; SMF= submucous fibroid; DUB= dysfunctional uterine bleeding; LNG-IUS= levonorgestrel intrauterine system; TCRF= transcervical resection of fibroid; D&C= dilatation and curettage; BSO= bilateral salpingo-oophorectomy; UAE= uterine artery embolisation; GnRH-a= Gonadatrophin releasing hormone analogue; BNF= British National Formulary; GP= general practitioner; SR= systematic review; CI= confidence interval; HRG= health resource group.

Methods for the cost-effectiveness analysis

(The following explanation of the methods for the economic analysis was written with Dr P. Barton, Reader in Health Economics. This section is essential for understanding the figures displayed in the results section and therefore is included within this thesis.)

A decision tree was constructed using TreeAge Pro 2009. Model inputs included probabilities and costs. Effectiveness was measured in terms of patient satisfaction. Therefore each branch of the tree had an effectiveness outcome of 1 for a positive outcome and 0 if otherwise. Costs were unit costs for the various tests and treatments and were therefore treated as known with certainty, while probabilities depended on data and were treated as uncertain, to be varied in probabilistic sensitivity analysis. Note that the uncertainty in overall effectiveness for a given strategy is fully accounted for in the uncertainty in the probabilities, so there is no need to vary the outcome parameters.

The model was first run using the point estimates of the branch probabilities. The results, known as "base case" results, are shown in terms of mean costs and effectiveness (overall proportion of positive outcomes) for each strategy modelled. These are tabulated and shown in a cost-effectiveness plane, with the mean cost shown on the vertical axis and the mean effectiveness shown on the horizontal axis. In some cases, a further plot was made of selected strategies to show more clearly the relationship between points that were close together on the first graph.

Any strategy which has greater cost and worse effectiveness than some other strategy is said to be *simply dominated*. Such a strategy can be excluded from consideration. An incremental cost-effectiveness ratio (ICER) can be calculated between any two non-dominated strategies. The ICER is calculated by dividing the difference in cost by the difference in effectiveness. If

the ICER is less than the maximum willingness to pay for an additional positive outcome, then the more effective strategy can be said to be cost-effective relative to the other strategy.

There is a further reason for excluding strategies known as *extended dominance*. This can only apply when there are three or more non-dominated strategies. In this case, two different strategies (incorporating a cheaper but less effective strategy and a more effective, more costly strategy relative to a third strategy) can be mixed together, with a proportion of patients getting one or other of the strategies such that the third strategy now becomes dominated (i.e. is more expensive and less effective) than the blended strategies Suppose that A, B and C are non-dominated strategies in order of increasing cost. Since they are non-dominated, they must also be in order of increasing effectiveness. Now suppose that the ICER of B over A is higher than the ICER of C over A. Then, if B is cost-effective compared to A, so also must C be cost-effective compared to A and B. In such a case, there is no value of willingness to pay per positive outcome at which B will be the preferred strategy, and the strategy B can be excluded by extended dominance. Extended dominance can be seen on a cost-effectiveness plane. The point for strategy B will be above the straight line joining the points for strategies A and C.

Once all dominated strategies have been excluded, whether for simple or extended dominance, the remaining strategies are potentially cost-effective. Which will be preferred depends on the willingness to pay for an additional positive outcome.

To test for the effect of uncertainty in the model inputs, two types of sensitivity analysis were used: probabilistic and deterministic.

In *probabilistic* sensitivity analysis, probability distributions are placed around the point estimate for each model parameter. If there is correlation between the uncertainties, joint or conditional distributions may be used. Beta distributions were used to represent the uncertainty around the branch probabilities in this model. The beta distribution is the standard distribution for a proportion. It has two parameters a and b, with mean $a/(a+b)$ and variance essentially decreasing as a and b increase.

For individual parameters of the models, the information available was in the form of a point estimate and a 95% confidence interval. In all cases, the beta distribution was selected with mean equal to the point estimate. Usually the distribution also matched the width of the confidence interval, but there were two main exceptions to this:

- If the point estimate is either 0 or 1, then it is not possible to find a beta distribution with that mean. While it can be argued that the true mean estimate of the probability should be strictly between 0 and 1, taking any actual numerical value would risk overcompensating. Accordingly, it was decided to treat such probabilities as fixed, thereby preserving the mean but slightly underestimating the uncertainty in the model.
- If either parameter a or b is less than 2, the beta distribution gives an unreasonably high proportion of values very close to the extreme values 0 or 1. To avoid this, in such cases the values of a and b were increased to preserve the mean of the distribution but ensure that both values were at least 2. Again, this slightly underestimates the overall uncertainty.

In some cases, only a point estimate was available. In such cases, it is not appropriate to assume that the value is fixed. Instead the widest possible uncertainty was modelled subject to

the constraint that both parameters *a* and *b* should be at least 2, for the reasons given in the previous paragraph.

In the analysis of SIS for detecting fibroids, point estimates of TPR and FPR were assumed to be the same as for TVS. In these cases, independent samples were taken from Beta distributions with the same parameters *a* and *b*.

Since the costs in the model are all unit costs of specific procedures, these were treated as fixed, and the only parameters to be varied were the probabilities in the tree, which are proportions of patients expected to follow each branch.

When the model was run for probabilistic sensitivity analysis (PSA), 1000 replications were made, sampling from distributions for all branch probabilities simultaneously. It is generally accepted that 1000 replications are sufficient to give a clear picture of the uncertainty.
The parameters for this Beta distribution used for the probabilistic sensitivity analysis of the HMB tree are shown in Table 8.13.

Table 8.13 Beta distribution parameters for analysis of the base case decision tree for investigating women with heavy menstrual bleeding

Parameter	a*	b*	Low	High
Prevalence of disease				
EndometrialDisease	5	95	0.02	0.10
FibroidLarge	6	94	0.02	0.11
FibroidSmall	19	81	0.12	0.27
PolyporSMF	38	62	0.29	0.48
Success rates				
EBx	728	72	0.89	0.93
OPH	67.9	2.1	0.92	1.00
SIS	1520	80	0.94	0.96
TVS	198	2	0.97	1.00
True Positive Rates				
ED_EBx	28.86	8.14	0.64	0.90
ED_OPH	1248	352	0.76	0.80
ED_SIS	2.03	4.97	0.05	0.65
ED_TVS	3.249	2.451	0.19	0.90
Fibroids_SIS	38	2	0.87	0.99
Fibroids_TVS	38	2	0.87	0.99
Normal_EBx	95	5	0.90	0.98
Normal_OPH	1424	176	0.87	0.90
Normal_SIS	264	36	0.84	0.91
Normal_TVS	258	42	0.82	0.90
PolyporSMF_EBx	2.16	5.84	0.04	0.60
PolypsorSMF_OPH	227.5	22.5	0.87	0.94
PolypsorSMF_SIS	104.4	15.6	0.80	0.92
PolypsorSMF_TVS	22.5	27.5	0.32	0.59
False Positive Rates				
CompHyp_EBx	7.5	142.5	0.02	0.09
ED_OPH	1000	24000	0.04	0.04
ED_SIS	2	98	0.00	0.05
ED_TVS	27.2	52.8	0.24	0.45
Fibroids_SIS	2.16	9.84	0.03	0.43
Fibroids_TVS	2.16	9.84	0.03	0.43
PolypSMF_EBx	2	998	0.00	0.01
PolypSMF_OPH	33	517	0.04	0.08
PolypSMF_SIS	3.9	26.1	0.04	0.27
PolypSMF_TVS	7.7	27.3	0.10	0.37
pExDetectsFibroids	8	2	0.52	0.97
pHyperplasia	3	2	0.19	0.93

Table 8.13 continued

Parameter	a*	b*	Low	High
Probability of being satisfied				
EA_DUB	924	110	0.87	0.91
EA_Fibroids	2.76	2.04	0.17	0.92
Hysterectomy_AtypCa	parameter fixed at value 1			
Hysterectomy_ED	164.9	5.1	0.94	0.99
Hysterectomy_Fibroids	24.64	3.36	0.74	0.97
Hysterectomy_HMB	380	20	0.93	0.97
Hysterectomy_Hyperpl	380	20	0.93	0.97
LngIUS_DUB	107.9	22.1	0.76	0.89
LngIUS_ED	9.68	12.32	0.24	0.65
LngIUS_Fibroids	2.03	4.97	0.05	0.65
LngIUS_Hyperplasia	91.3	18.7	0.75	0.89
LngIUS_PolypSMF	420	580	0.39	0.45
Removal	11	3	0.55	0.95
Removal_CavityNormal	parameter fixed at value 0			

a, *b*: Parameters of Beta distribution. Low, High: 2.5 and 97.5 percentiles respectively of fitted distribution, corresponding to lower and higher limits of 95% confidence interval. All parameters sampled independently except for the prevalence parameters, which were sampled together from a Dirichlet distribution (see text). OPH= outpatient hysteroscopy; TVS = transvaginal scan; EBx= endometrial biopsy; SIS= saline infusion sonography; SMF= submucous fibroid; DUB= dysfunctional uterine bleeding
*Please read 'Methods for the cost-effectiveness analysis', for explanation regarding the parameters a and b

For models (such as Markov models) in which there is a non-linear relationship between model inputs and outputs it is appropriate to give a table of mean results from the probabilistic sensitivity analysis, as the Bayesian viewpoint is that the mean results from the PSA are the appropriate basis for decision making. However, in the case of the models presented here, these results would be statistically equivalent to the base case results and therefore there is no need to produce such a table. Results that have been shown are as follows:

A cost-effectiveness scattergraph: This shows, on a single graph, the uncertainty in the absolute expected cost and effectiveness for each option separately. For each option, the results of the 1000 replications of the model were shown each as a single point. In practice, the printed symbols used merge to form a "cloud" giving the general range of uncertainty in the results. The vertical spread of this cloud reflects the uncertainty in the overall cost and the

horizontal spread the uncertainty in overall effectiveness, while the centre of the cloud, where the points are most densely packed, indicates the most likely cost and effectiveness.

A cost-effectiveness acceptability frontier (CEAF): At any given willingness to pay, the preferred option is determined by the mean outcomes, which in the case of the models here are the same as the base case results described earlier. The CEAF shows the proportion of model replications for which this option remained the preferred strategy, as a function of the willingness to pay for an additional positive outcome.

While the graphs described above are the only convenient ways of showing results comparing all the modelled options, they are applicable only to a decision in which exactly those options are included. For other purposes, it is helpful to look at pairwise comparisons between strategies. The results shown from a pairwise comparison are helpful to any decision problem in which both those strategies are included. Pairwise comparisons were made between successive non-dominated options (in order of increasing cost or effectiveness), and others where a dominated option was close to another option.

For pairwise comparisons, the incremental cost-effectiveness scattergraph was shown. In this type of graph, there is a single point for each of the 1000 replications of the model, showing the difference in cost and effectiveness between the two strategies. If the "clouds" shown in the cost-effectiveness scattergraph for the two strategies overlap, it may be for two possible reasons. First, it may be because there is genuine uncertainty as to which is the more costly and/or more effective strategy. Second, it may be that one strategy is consistently more costly and/or more effective than the other, but this consistent difference is small compared to the

uncertainty in the absolute costs and/or effectiveness. The incremental cost-effectiveness scattergraph distinguishes between these two cases and shows the relevant uncertainty for a decision maker.

The other graph plotted for the pairwise comparisons was the cost-effectiveness acceptability curve (CEAC). This shows the proportion of model replications in which one of the strategies is cost-effective compared to the other, across a range of values of willingness to pay per additional positive outcome.

In *deterministic* sensitivity analysis, one or more model inputs are varied systematically and the effect on the model outcomes is noted. This was used to test the effect of reducing the prevalence of polyps and submucous fibroids and increasing the prevalence of dysfunctional uterine bleeding and also to examine the effect when the unit cost of saline infusion sonography was reduced. For prevalence of the various pathologies, a Dirichlet distribution was used. This is the generalisation of the Beta distribution for more than two options. Given that the prevalence data came from different sources, it was necessary to take a compromise between the effective sample sizes indicated by those sources. An effective sample size of 100 was assumed. The distribution of any prevalence parameter on its own then follows a Beta distribution

CHAPTER 9

RESULTS OF THE ECONOMIC ANALYSIS OF DIAGNOSTIC STRATEGIES FOR THE INVESTIGATION OF HEAVY MENSTRUAL BLEEDING

Deterministic results: Base case

The current recommended first line treatment for HMB in women not desiring immediate fertility, is the levonorgestrel intrauterine system treatment (LNG-IUS) otherwise known as the Mirena® coil (Bayer HealthCare Pharmaceuticals Inc. Wayne, USA) (142). The majority of women with HMB have no uterine pathology (known as dysfunctional uterine bleeding) or benign uterine pathologies such as small uterine fibroids or endometrial hyperplasia and all these conditions respond well in general to the LNG-IUS (161;162).

Thus, given the negligible chance of life-threatening disease, lack of recommendations stipulating the need for routine diagnostic testing and the known effectiveness and applicability of the LNG-IUS in HMB, the strategy using LNG-IUS without any preliminary diagnostic testing was chosen as the reference strategy. The costs and effects of the other diagnostic testing strategies were compared against this reference strategy. In addition, a recent cost-effectiveness analysis informed by IPD analysis of published trials for treatment of HMB suggested that surgical treatment with hysterectomy was more cost-effective than the

LNG-IUS(136) so a strategy of hysterectomy without diagnostic work up was also considered.

Table 9.1 reports the deterministic results, referencing all other diagnostic or treatment strategies to the LNG-IUS treatment alone base-case strategy.

Table 9.1 Determinist analysis results for the investigation of women with heavy menstrual bleeding

Strategy	Cost (£)	Effectiveness (satisfaction)
LNG-IUS alone	1067	0.9333
OPH alone	1078	0.9641
SIS alone	1083	0.9629
TVS alone	1085	0.9551
TVS + OPH	1139	0.9644
OPH and Ebx	1149	0.9674
SIS + OPH	1170	0.9645
EBx alone	1209	0.9460
SIS + Ebx	1223	0.9643
TVS+ OPH+Ebx	1227	0.9649
TVS + Ebx	1231	0.9539
SIS +OPH +Ebx	1256	0.9650
Hysterectomy alone	3182	0.9335

EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS = transvaginal ultrasound scan; LNG-IUS = levonorgestrel intrauterine system.

Outcomes

Direct treatment without preliminary diagnostic testing was less effective than treatment instigated after diagnostic testing. The least effective approach was the base case strategy of LNG-IUS treatment alone followed closely by surgical treatment with hysterectomy, both approaches resulting in satisfaction rates around 93.3-93.4%. The effectiveness of HMB management was similar across all testing strategies ranging from 94.6% to 96.7% rates of

satisfaction. The most effective strategy was combination testing with outpatient hysteroscopy and endometrial biopsy.

Costs

The LNG-IUS treatment alone base case strategy was the cheapest costing £1067 per woman treated for HMB in a secondary care setting and the strategy of hysterectomy for all women was the most expensive at £3182 per woman treated i.e. £2116 more than the approach of LNG-IUS treatment alone. The cheapest of the nine diagnostic testing strategies was the use of outpatient hysteroscopy alone, costing £1078 for every woman treated, i.e. £11 more than universal LNG-IUS treatment.

Cost-effectiveness and dominance

Only the testing strategies outpatient hysteroscopy (OPH) alone and outpatient hysteroscopy combined with endometrial biopsy (OPH + EBx) remain non-dominated by alternative empirical treatment or diagnostic testing strategies. It is clear from the analysis that the strategy OPH alone dominates the testing strategies SIS alone and TVS alone. The combination testing strategy TVS and OPH is excluded by extended dominance between OPH alone and OPH + EBx. The remaining seven alternate strategies are dominated by OPH + EBx. Table 9.2 presents the deterministic analysis restricted to the non-dominated competing strategies.

Table 9.2 Deterministic results for the non-dominated strategies for investigation of women with heavy menstrual bleeding

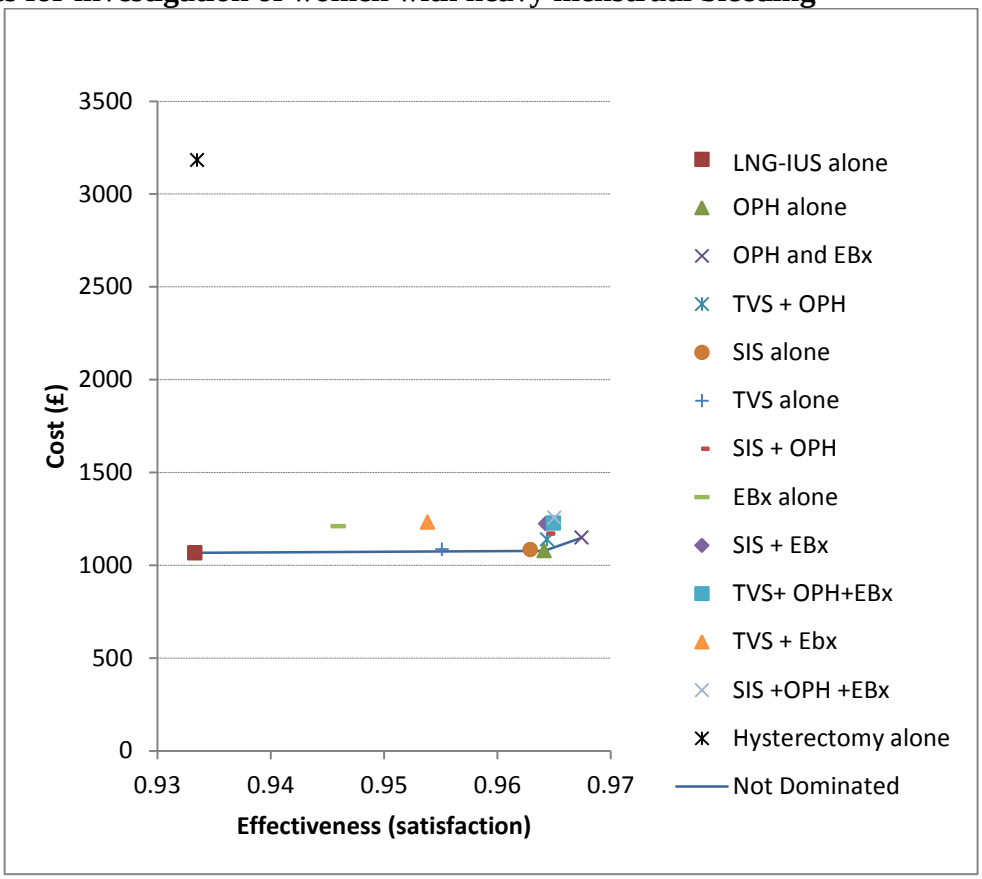
Strategy	Total Cost (£)	Incremental Cost (£)	Effectiveness (satisfaction)	Incremental effectiveness	ICER
LNG-IUS alone	1067		0.9333		
OPH alone	1078	11	0.9641	0.0308	359
OPH and EBx	1149	71	0.9674	0.0033	21500

Apparent anomalies with subtraction are due to rounding effects
EBx = endometrial biopsy; ICER = incremental cost-effectiveness ratio; LNG-IUS = levonorgestrel intrauterine system; OPH= outpatient hysteroscopy

The cheapest strategy is the base-case scenario of no testing and universal treatment with the LNG-IUS alone. The most effective strategy is the combination of initial testing with OPH + EBx, but this comes at a greater cost, generating an ICER of £21,500 i.e. the strategy requires an investment of £21,500 to gain an extra woman satisfied following treatment for HMB compared with investigation with OPH alone. The single test strategy of OPH is slightly less effective than the strategy of OPH with the addition of EBx, but is substantially less costly. The ICER for OPH is £359, i.e. an additional financial outlay of £360 is necessary to acquire an extra woman satisfied following treatment for HMB.

Figure 9.1 shows the total costs and effectiveness of alternative strategies for the diagnosis and treatment of HMB in secondary care. The line presented graphically joins the non-dominated strategies (OPH alone and OPH+EBx). Any strategy plotted above this line is not considered cost-effective in relation to the non-dominated strategies.

Figure 9.1 Cost-effectiveness plane showing the results of deterministic analysis of the strategies for investigation of women with heavy menstrual bleeding

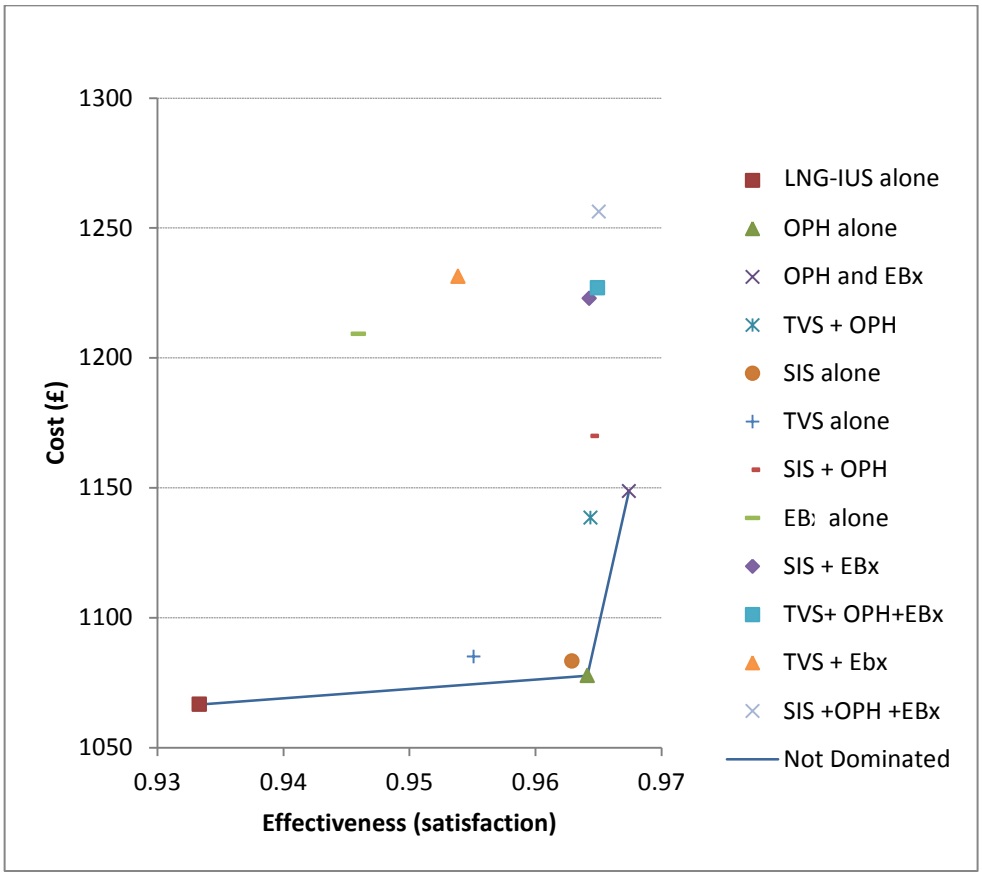


LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS= transvaginal ultrasound scan

It is clear that direct treatment with hysterectomy is the least cost-effective strategy. Replicating the figure and excluding the hysterectomy strategy reduces the scale of the y axis allowing closer examination of the remaining testing strategies.

Figure 9.2 reveals that the options "TVS alone" and "SIS alone" are sufficiently close to the boundary of dominance that it is worth checking for the uncertainty between these dominated alternatives in addition to the non-dominated options “OPH” and “OPH + EBx” through sensitivity analyses.

Figure 9.2 Cost-effectiveness plane showing the results of deterministic analysis of the strategies for investigation of women with heavy menstrual bleeding- hysterectomy excluded

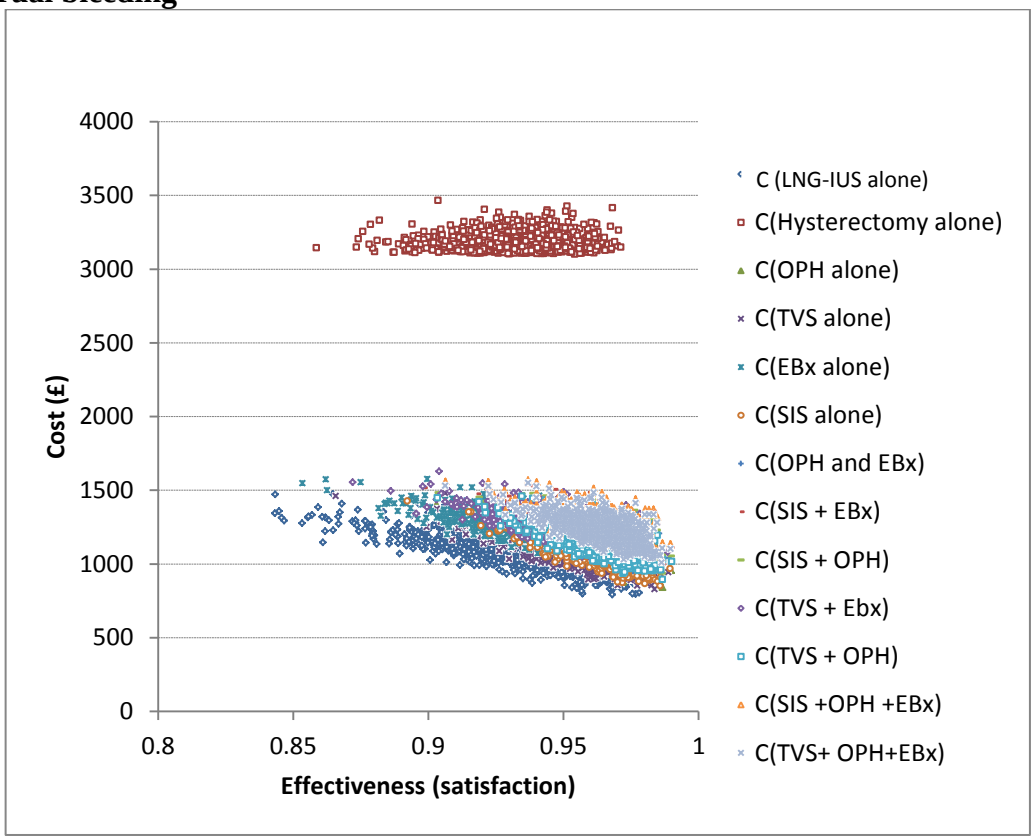


LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; TVS= transvaginal scan; SIS= saline infusion sonography

Probabilistic sensitivity analysis results: Base case

Figure 9.3 demonstrates the uncertainty surrounding the absolute expected cost and effectiveness of each of the strategies, with the true value lying somewhere within the 'cloud' of plotted points, probably where they are most densely clustered. It shows that hysterectomy is too expensive to be a competitive option but that there is overlap between the remaining strategies.

Figure 9.3 Scatterplot showing the uncertainty in costs and effectiveness within the model for each of the individual strategies for investigation of women with heavy menstrual bleeding

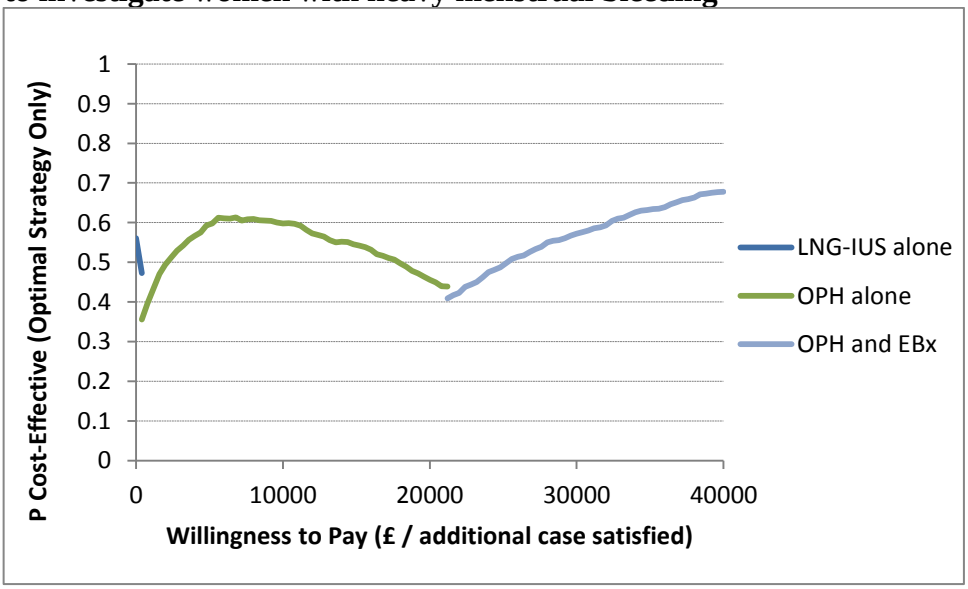


LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; TVS= transvaginal scan; SIS= saline infusion sonography

Figure 9.4 illustrates the overall uncertainty related to the optimal decision across a range of plausible willingness to pay (WTP) values, where the willingness to pay is measured in £ per additional case satisfied. When a model is linear in all parameters and they are sampled independently, the mean of the probabilistic results will be the same as the deterministic

result. This is true for the current model, as the only parameters which are not independently sampled are the prevalences, and these do not interact in the calculation of the model results. The cost-effectiveness acceptability frontier (CEAF) (Figure 9.4) is generated as follows. First, for any willingness to pay, the optimal option is determined based on the mean results. Then the proportion of model replications for which that was the optimal option is found and plotted. For example, considering a WTP of £10,000 per case satisfied, the preferred option based on the mean results is OPH alone, and this was optimal in around 60% of the model replications. Thus there is an estimated probability of 40% that there is a better option than OPH at that WTP. By definition, only the options which are not dominated in the mean results can appear on the CEAF. Sometimes the probability shown will be lower than 50%. It will often be the case that the option preferred on mean values is also the preferred option in the highest proportion of model replications, but this not always so. As the willingness to pay crosses the ICER between two non-dominated options, the choice of optimal option changes, and there will usually be a discontinuity in the curve.

Figure 9.4 Cost-effectiveness acceptability frontier showing the optimal investigative strategy across a range of willingness to pay thresholds for the sensitivity analysis of stratgies to investigate women with heavy menstrual bleeding



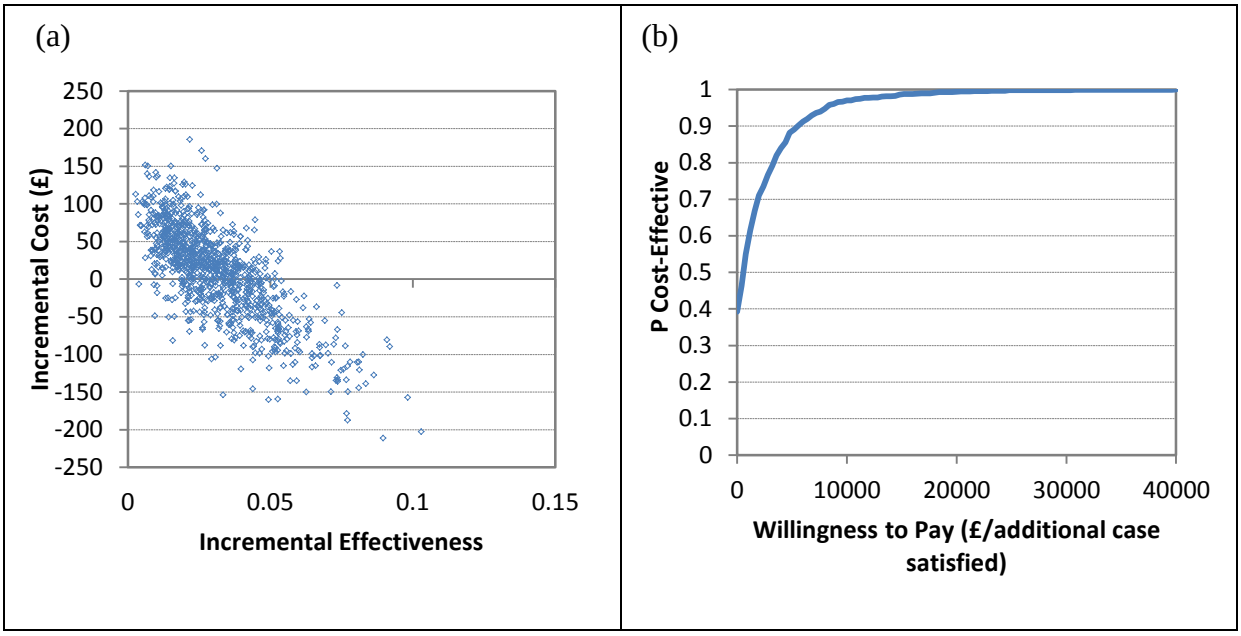
LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy

For the current model, the CEAF shows the same range of preferred options already shown in Table 9.2, but indicates that there is appreciable uncertainty about the preferred option across the whole range of WTP values plotted. To explore the uncertainty more fully, it is helpful to consider a range of appropriate pair wise comparisons between the different options. Comparisons are shown between adjacent non-dominated options. There are also options that are dominated on mean values, but whose mean values are close to the non-dominance lines shown on Figure 9.2. These options are compared to relevant non-dominated options.

Outpatient hysteroscopy versus levonorgestrel releasing intrauterine system

The cost-effectiveness plane (Figure 9.5a) shows the modelled uncertainty in the difference in costs between OPH alone and LNG-IUS alone. It shows that OPH alone is consistently more effective than LNG-IUS alone, and is likely (but not certain) to be more costly. The cost-effectiveness acceptability curve (CEAC) (Figure 9.5b) shows the proportion of model replications for which OPH alone is preferred to LNG-IUS alone at any given WTP. OPH is the preferred option at any willingness to pay over £360 per additional case satisfied, but there is considerable uncertainty when the WTP is just above this figure. However, by the time the WTP exceeds £8,000 per additional case satisfied, it is almost certain that OPH is preferred to LNG-IUS.

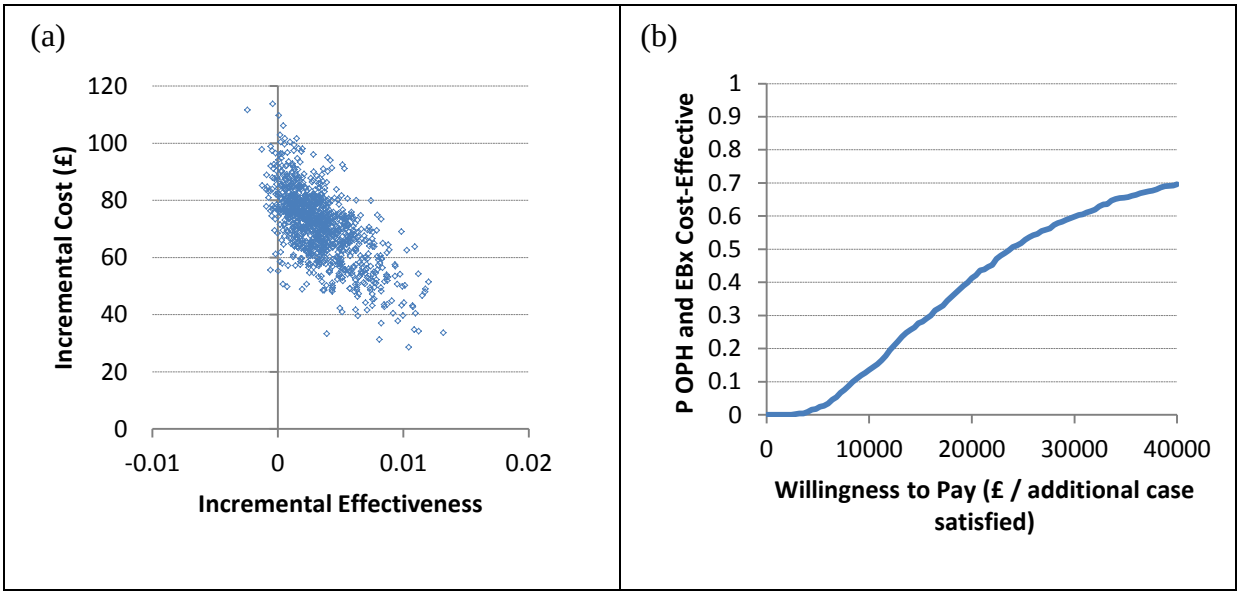
Figure 9.5 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Outpatient hysteroscopy alone strategy relative to the LNG-IUS alone strategy



Outpatient hysteroscopy and endometrial biopsy versus outpatient hysteroscopy

The graph (Figure 9.6a) shows the modelled uncertainty in the difference in costs between "OPH and EBx" and OPH alone. It shows that adding EBx to OPH increases the cost and is very likely to increase the effectiveness. The CEAC (Figure 9.6b) shows the proportion of model replications for which OPH and EB is preferred to OPH alone at any given willingness to pay per additional case satisfied. It is more likely than not that OPH + EBx is cost-effective compared to OPH above a WTP threshold of around £23,000. However, there is considerable uncertainty throughout the range of WTP values shown. About 30% of replications favour OPH alone even if the WTP is as high as £40,000 per additional case satisfied.

Figure 9.6 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Outpatient hysteroscopy and endometrial biopsy strategy relative to the outpatient hysteroscopy alone strategy



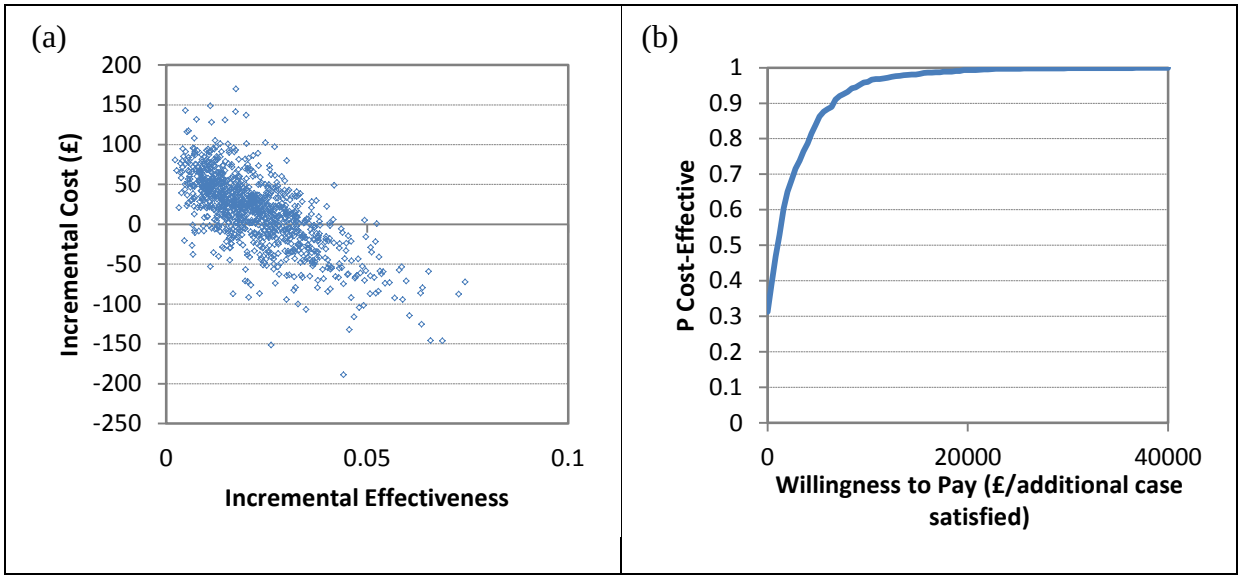
Assessment of potentially cost-effective competing strategies

In addition to the non-dominated testing strategies "OPH" and "OPH + EBx", the single testing strategies TVS and SIS were sufficiently close to the boundary of dominance to explore the level of uncertainty within the model pertaining to these two dominated strategies.

Transvaginal ultrasound scan versus levonorgestrel releasing intrauterine system

The graph (Figure 9.7a) shows the modelled uncertainty in the difference in costs between TVS alone and LNG-IUS alone. It shows that TVS alone is consistently more effective than LNG-IUS alone, and is likely (but not certain) to be more costly. The CEAC (Figure 9.7b) shows that it is more likely than not that TVS is cost-effective compared to LNG-IUS above a WTP threshold of around £1000 and this is almost certain at WTP thresholds beyond £9000.

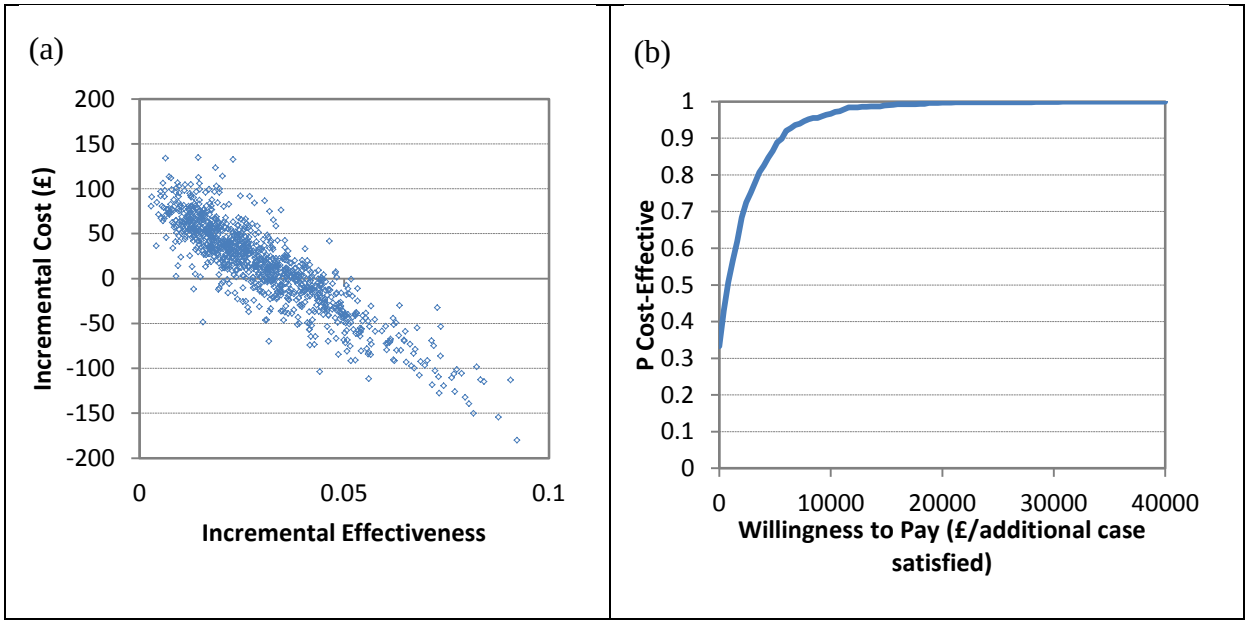
Figure 9.7 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Transvaginal ultrasound scan alone strategy relative to the LNG-IUS alone strategy



Saline infusion sonography versus levonorgestrel releasing intrauterine system

The graph (Figure 9.8a) shows the modelled uncertainty in the difference in costs between SIS alone and LNG-IUS alone. It shows that SIS alone is consistently more effective than LNG-IUS alone, and is likely (but not certain) to be more costly. The CEAC (Figure 9.8b) shows that the likelihood is that SIS is cost-effective compared to LNG-IUS above a WTP threshold of around £800. This is almost certainly the case at WTP thresholds beyond £8000.

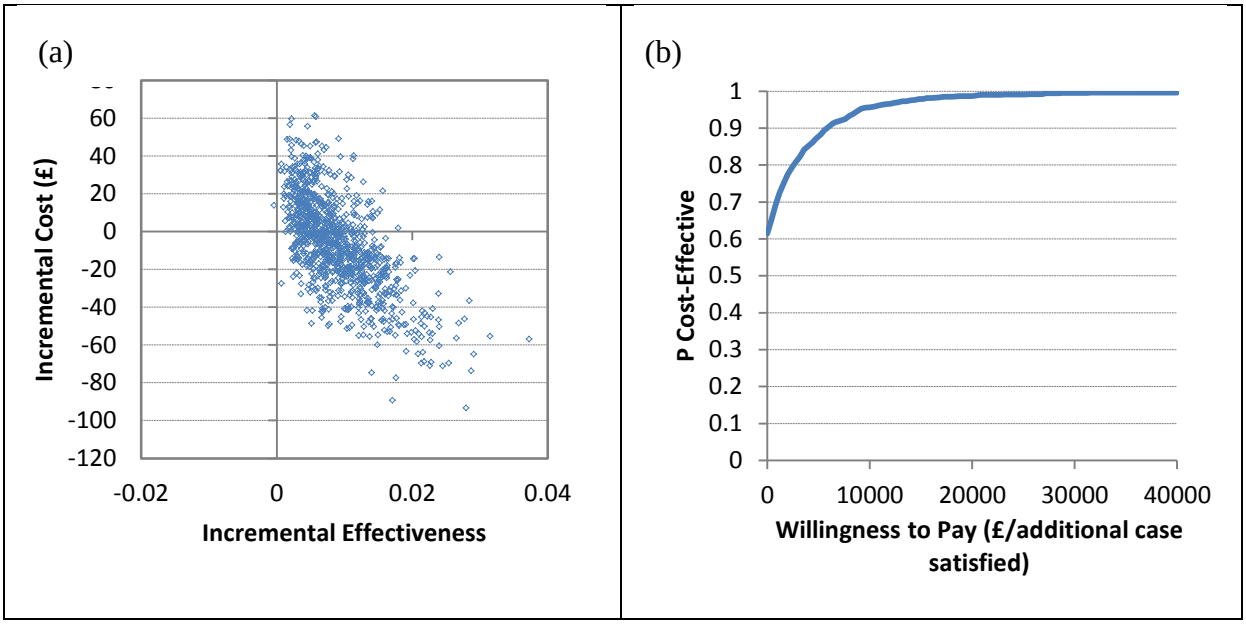
Figure 9.8 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Saline infusion sonography alone strategy relative to the LNG-IUS alone strategy



Outpatient hysteroscopy versus transvaginal ultrasound scan

The graph (Figure 9.9a) shows the modelled uncertainty in the difference in costs between OPH alone and TVS alone. It shows that OPH alone is almost certainly more effective than TVS alone but it is unclear whether it is more costly. The CEAC (Figure 9.9b) shows the proportion of model replications for which OPH alone is preferred to TVS alone at any given willingness to pay per additional case satisfied. The likelihood is that OPH is cost-effective compared to TVS above any WTP threshold and this is almost certain at WTP thresholds beyond £9000.

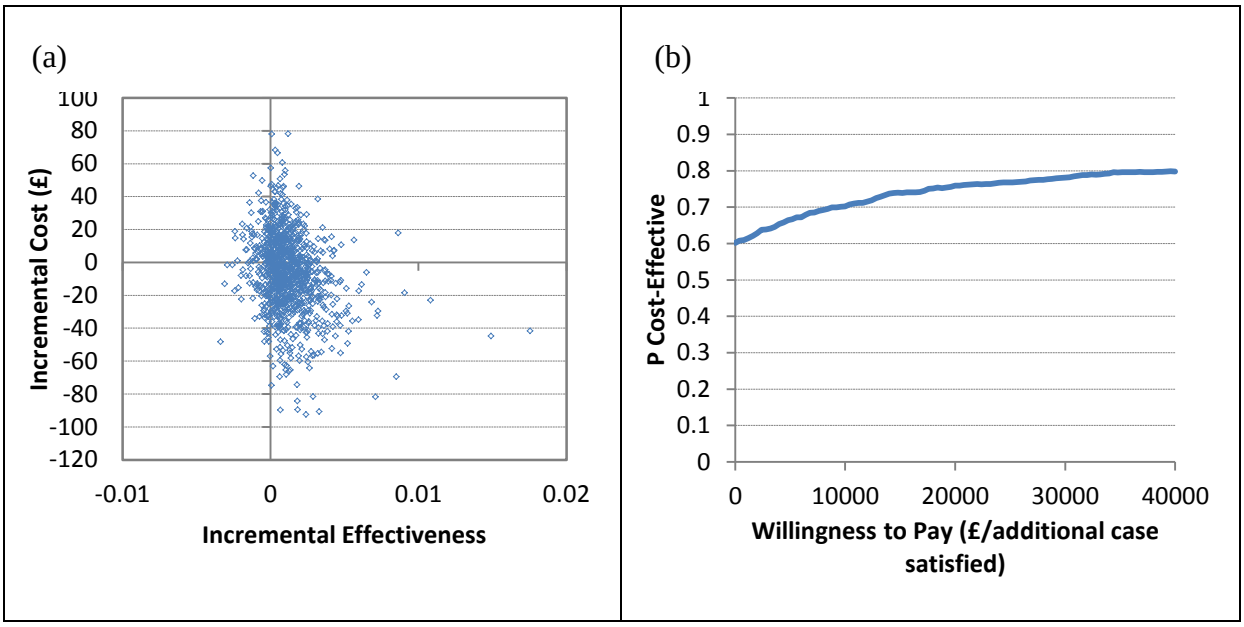
Figure 9.9 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Outpatient hysteroscopy alone strategy relative to the transvaginal ultrasound scan alone strategy



Outpatient hysteroscopy versus saline infusion sonography

The graph (Figure 9.10a) shows the modelled uncertainty in the difference in costs between OPH alone and SIS alone. It shows that OPH alone is likely to be more effective than SIS alone, and there is considerable uncertainty as to which is more costly. The CEAC (Figure 9.10b) shows the proportion of model replications for which OPH alone is preferred to SIS alone at any given willingness to pay per additional case satisfied. The likelihood is that OPH is cost-effective compared to SIS above any WTP threshold although there is considerable uncertainty throughout. Even at a WTP of £40,000 per additional case satisfied, SIS is preferred in 20% of model replications.

Figure 9.10 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Outpatient hysteroscopy alone strategy relative to the saline infusion sonography alone strategy



Deterministic sensitivity analysis results

Assessment of the impact of reducing the cost of saline infusion sonography

The probabilistic sensitivity analyses show uncertainty around whether OPH or SIS is the most cost-effective investigative strategy. To assess this uncertainty further, deterministic sensitivity analysis was performed to reduce the cost of SIS and determine at what cost it would become more cost-effective than OPH. Table 9.3 details the ICER values when the cost of SIS is reduced.

Table 9.3 Incremental cost-effectiveness ratio value for saline infusion sonography when the cost is varied

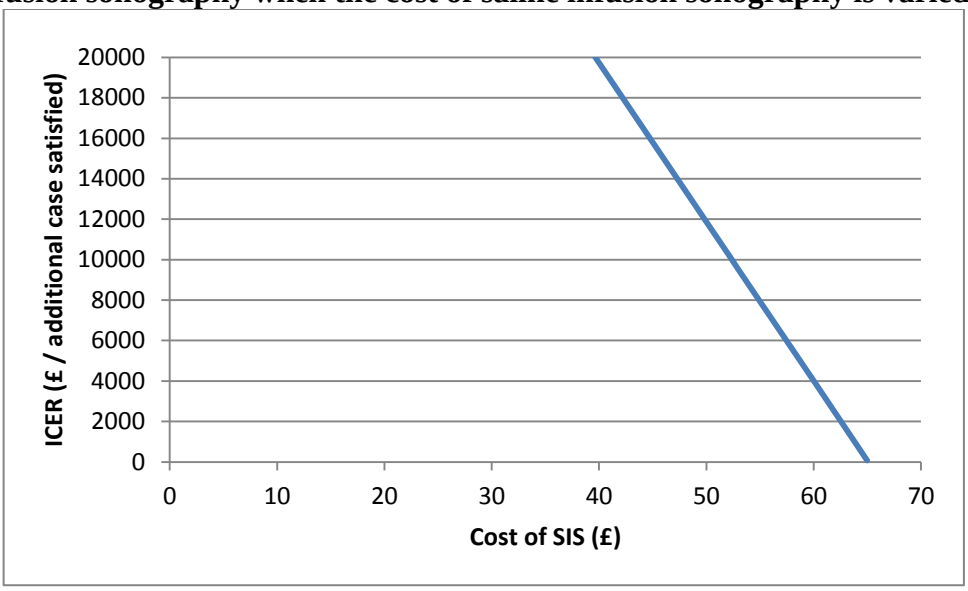
SIS cost £	ICER
65	76
60	4006
55	7937
53	9509
52	10295
50	11867
45	15797
35	23658

SIS= saline infusion scan; ICER= incremental cost-effectiveness ratio

In this analysis, the unit cost for SIS was reduced from £71 (base case cost), keeping all other variables fixed. When the cost was reduced to £65, the strategy "SIS alone" was no longer dominated by "OPH alone". However, the modelled ICER was £76 per additional case satisfied, suggesting that OPH alone is still highly cost-effective compared to SIS alone. As the cost of SIS reduces further, the ICER increases (see Figure 9.11). Considering an illustrative willingness to pay of £10,000 per case satisfied, the ICER goes above this figure when the cost of SIS drops to £52. In that case, OPH is no longer cost-effective compared to

SIS, and SIS becomes the preferred strategy (of the two) on cost-effectiveness grounds. It should also be noted that at a unit cost for SIS of £53 or lower, the strategy "SIS alone" becomes less costly, as well as remaining more effective, than LNG-IUS alone.

Figure 9.11 Incremental cost-effectiveness ratios between outpatient hysteroscopy and saline infusion sonography when the cost of saline infusion sonography is varied



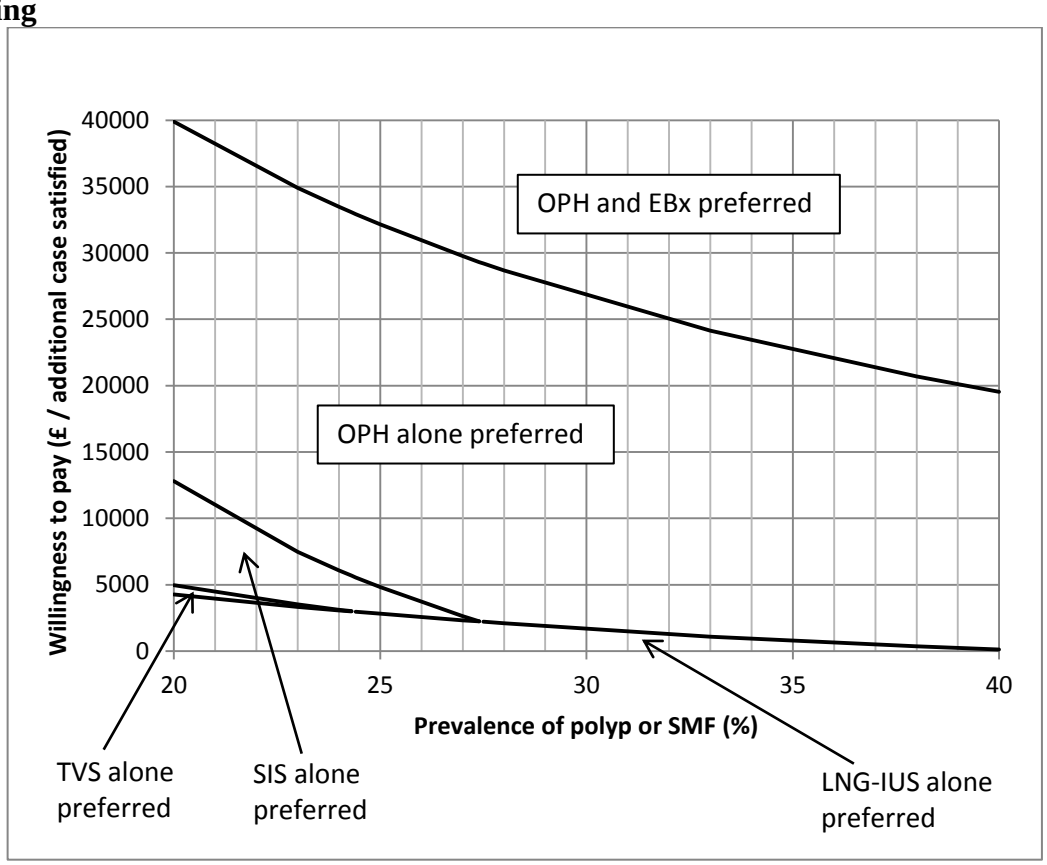
SIS= saline infusion scan; ICER= incremental cost-effectiveness ratio

Assessment of the impact of the prevalence of focal uterine pathology

A high prevalence of intracavity focal endometrial lesions will favour outpatient hysteroscopy over the imaging technologies TVS and SIS because it is more likely to diagnose the lesions and treatment can be initiated with only a small additional cost during the diagnostic procedure (the so called 'see & treat' approach). If the prevalence of endometrial polyps and submucous fibroids is over-estimated within the decision tree, OPH will falsely appear the most cost-effective. Similarly the prevalence of DUB may be an underestimate. To assess the effect of prevalence on the analysis the prevalence of polyps / SMF's was varied, keeping the prevalence of fibroids and endometrial disease fixed. The prevalence of dysfunctional uterine

bleeding was changed inversely to compensate for the change in prevalence of polyp or SMF. All other variables in the model were fixed at their point estimates. Figure 9.12 shows the preferred option at a range of values of willingness to pay per additional case satisfied, varying the prevalence of polyp or SMF. For example, at a prevalence of 30%, the combination of OPH and EBx is preferred if the willingness to pay per additional case satisfied is more than about £27,000, while OPH alone is preferred if this willingness to pay is between £2000 and £27,000. Only at a willingness to pay below £2000 per case satisfied is LNG-IUS alone preferred. For this prevalence, other options are dominated and so not preferred at any willingness to pay value. It is only at a prevalence of polyps/SMFs of 27% that SIS becomes a non-dominated option and at 24% when TVS becomes non-dominated.

Figure 9.12 Incremental cost-effectiveness ratios between non-dominated options at a variety of prevalence values for polyps / submucous fibroids and dysfunctional uterine bleeding



OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS = transvaginal ultrasound scan; LNG-IUS = levonorgestrel intrauterine system, SMF= submucous fibroid

Deterministic results: Women being managed during multiple clinic appointments

To reflect 'traditional' investigation and treatment of patients, over the course of multiple clinic appointments, the base case tree was adapted and the results of the deterministic analysis are displayed in Table 9.4 below.

Table 9.4 Deterministic results of cost-effectiveness analysis for women with heavy menstrual bleeding managed over multiple clinic appointments

Strategy	Cost(£)	Effectiveness (Satisfaction)
LNG-IUS alone	1067	0.9333
TVS alone	1204	0.9551
EBx alone	1214	0.9460
SIS alone	1217	0.9629
TVS + Ebx	1266	0.9540
SIS + EBx	1274	0.9643
OPH alone	1288	0.9641
TVS + OPH	1315	0.9644
OPH +EBx	1317	0.9674
SIS + OPH	1343	0.9644
TVS+ OPH+EBx	1391	0.9649
SIS +OPH +EBx	1418	0.9650
Hysterectomy alone	3182	0.9335

LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS – transvaginal ultrasound scan

Outcomes

As with the base case analysis, the 'no investigation' strategies were the least effective strategies for managing women. The most effective strategy for investigating women using a multiple clinic attendance as opposed to a 'one-stop' approach was the combination of OPH +EBx.

Costs

Costs for the 'no investigation' strategies (LNG-IUS alone and hysterectomy alone) remained unchanged. The costs of the investigative strategies however increased due to the additional appointments required with the costs for the investigation strategies ranging from £1204 to £1418 in this alternative analysis compared to £1078 to £1256 in the base case analysis.

Cost-effectiveness and dominance

The strategies "EBx alone", "TVS + EBx", "OPH alone", "SIS + OPH", "TVS + OPH + EBx", "SIS + OPH + EBx", and "Hysterectomy alone" are excluded by simple dominance and the strategies "TVS alone", "SIS + EBx" and "TVS + OPH" are excluded by extended dominance. The remaining three strategies are not dominated. In contrast to the base case analysis the strategy SIS alone is no longer dominated whereas "OPH alone" is. Table 9.5 displays the non-dominated strategies from deterministic analysis.

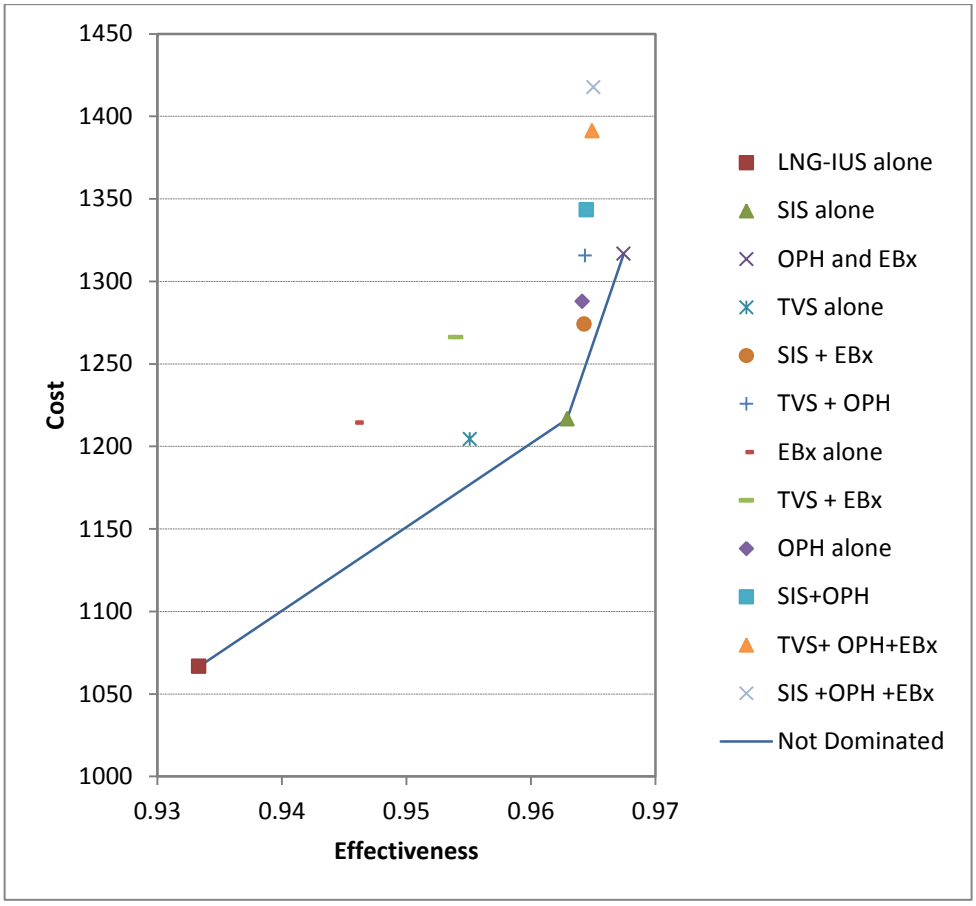
Table 9.5 Non-dominated strategies from the analysis of women presenting with heavy menstrual bleeding managed over multiple clinic appointments

Strategy	Cost (£)	Incremental Cost (£)	Effectiveness	Incremental Effectiveness	ICER
LNG-IUS alone	1067		0.9333		
SIS alone	1217	150	0.9629	0.0296	5070
OPH + EBx	1317	100	0.9674	0.0045	22100

EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; LNG-IUS = levonorgestrel intrauterine system

Using SIS to investigate women in this strategy costs an additional £5070 to make an extra women satisfied compared to not investigating and giving all women a LNG-IUS. OPH and EBx costs an additional £22,100 to the cost of SIS to gain a further satisfied patient. OPH alone does not appear as a non-dominated option in this analysis. The line on the cost-effectiveness plane in Figure 9.13 links the non-dominated strategies.

Figure 9.13 Cost-effectiveness plane showing the results of deterministic analysis for strategies to investigate women presenting with heavy menstrual bleeding managed over multiple clinic appointments. (Hysterectomy removed).

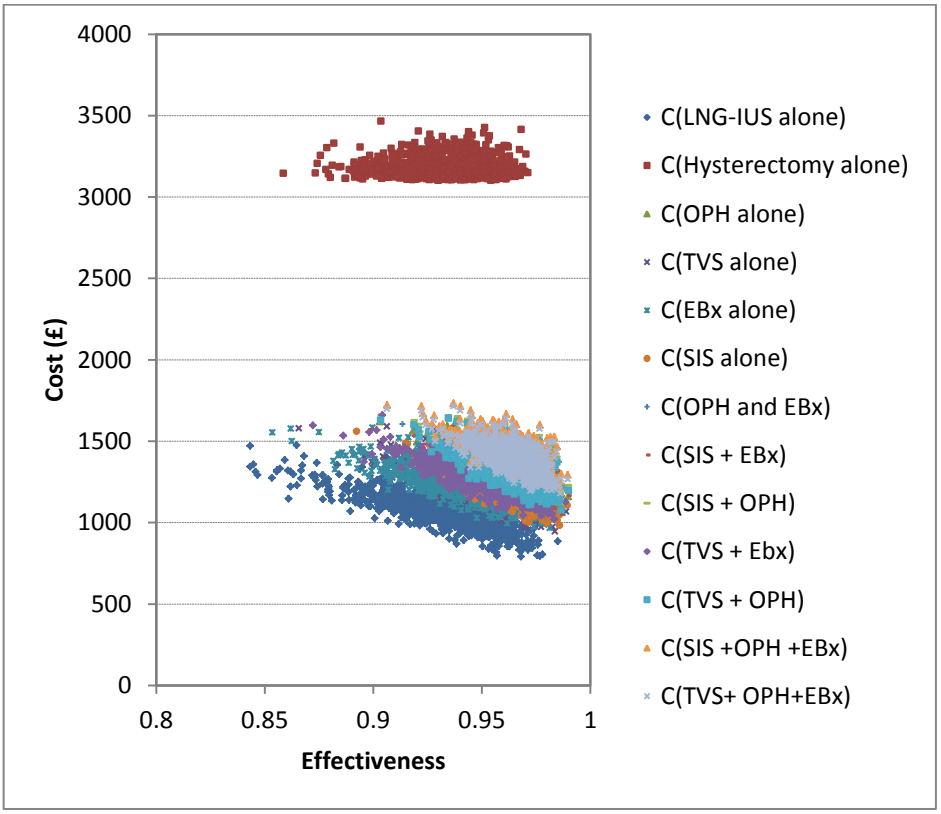


EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS = transvaginal ultrasound scan; LNG-IUS = levonorgestrel intrauterine system

Probabilistic sensitivity analysis results: Women being managed during multiple clinic appointments

In the cost-effectiveness scatterplot below (Figure 9.14) it is clear from the degree of overlap of the diagnostic strategies that there is uncertainty regarding which one might be considered most cost-effective when a range of values is sampled from the distributions of the data values.

Figure 9.14 Scatterplot showing the uncertainty in costs and effectiveness within the model for each of the individual strategies for investigating women with heavy menstrual bleeding managed over multiple clinic appointments



LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS = transvaginal ultrasound scan

The CEAF (Figure 9.15) illustrates the overall uncertainty related to the optimal decision across a range of plausible willingness to pay (WTP) values and shows that up to a WTP value of approximately £5000 LNG-IUS alone is cost-effective. However between £5000 and £20,000 SIS alone may be preferable although there is reasonable uncertainty as to whether this really is the optimal strategy with the probability lying between 40 and 60%. Above £20,000 OPH and EBx becomes the preferred strategy.

Figure 9.15 Cost-effectiveness acceptability frontier showing the optimal investigative strategies for women with heavy menstrual bleeding managed over multiple clinic appointments

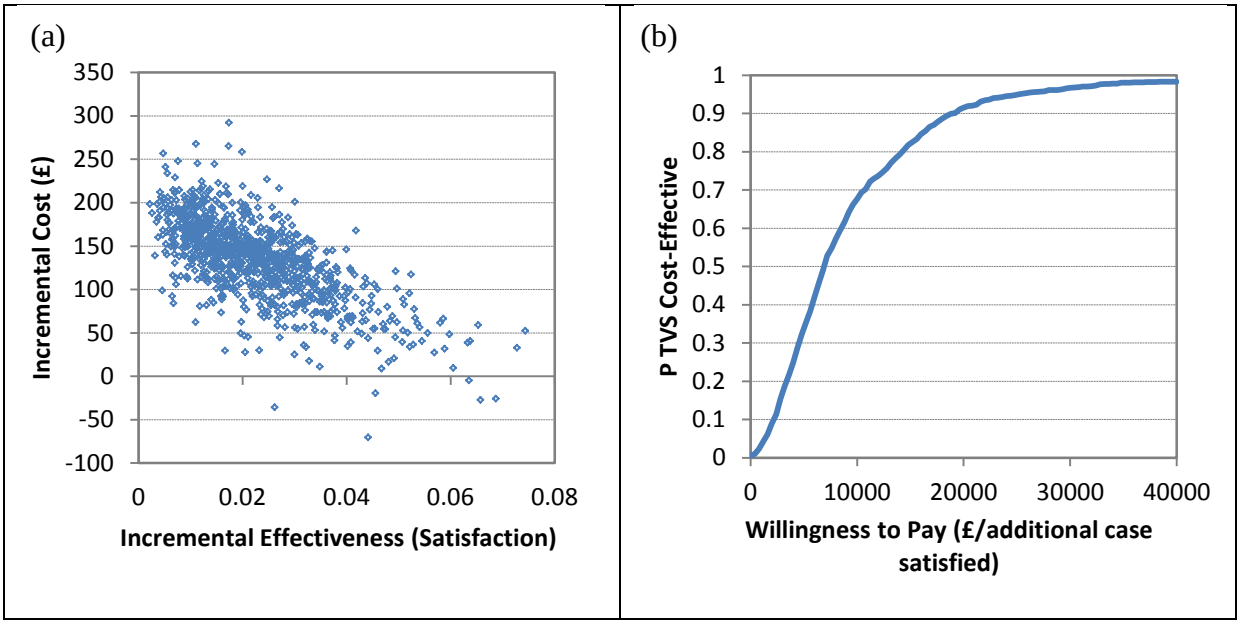
LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy

Probabilistic pair wise comparisons were made between the non-dominated strategies to explore the uncertainty between them. TVS was also compared to SIS alone because of its proximity to the line of non-dominance.

Transvaginal scan versus levonorgestrel intra-uterine system: Women with HMB managed over multiple clinic appointments

The scatterplot below (Figure 9.16a) shows that the strategy TVS alone is more effective than LNG-IUS alone and is very likely to be more costly per patient satisfied. The CEAC (Figure 9.16b) shows that above a WTP of £8000 TVS is probably a more cost effective option than LNG-IUS alone per woman satisfied but it is only at WTP above £20,000 that this is almost certain (p>0.9).

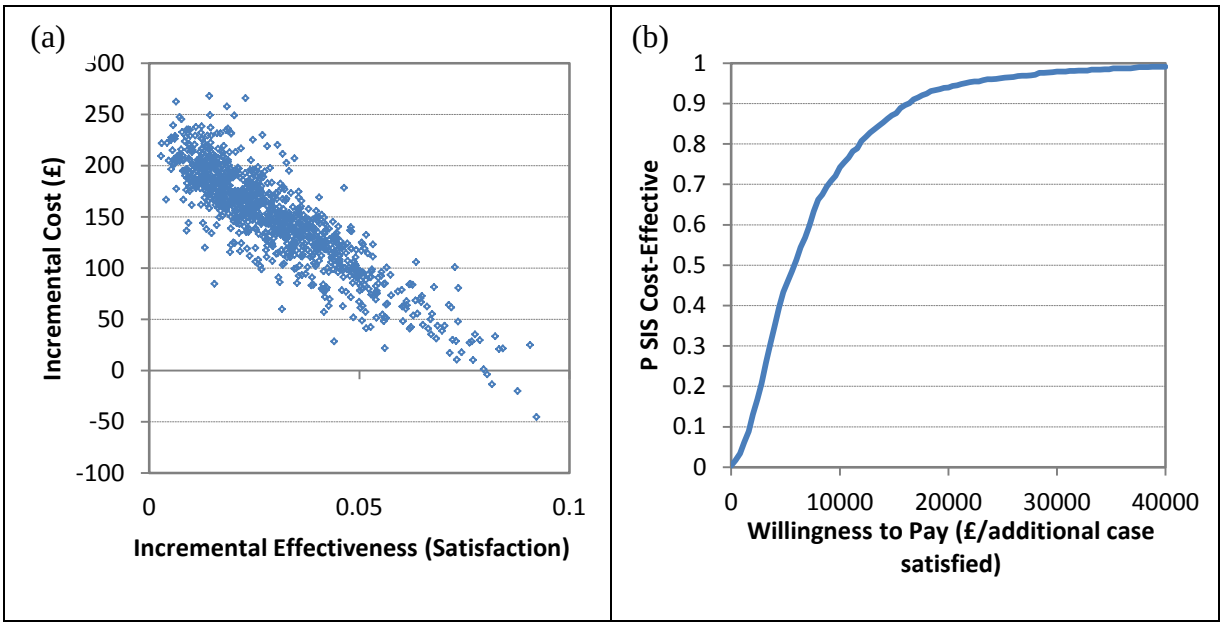
Figure 9.16 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): transvaginal ultrasound scan alone strategy relative to the LNG-IUS alone strategy for women with heavy menstrual bleeding managed over multiple clinic appointments



Saline infusion sonography versus levonorgestrel intra-uterine system: Women with HMB managed over multiple clinic appointments

The scatterplot depicted in Figure 9.17a shows that saline infusion scan is more effective than LNG-IUS alone but it is also probably more expensive. The CEAC (Figure 9.17b) shows that at a WTP of around £10,000 it is probable that SIS is the most cost-effective option and this becomes almost certain at a WTP of £20,000.

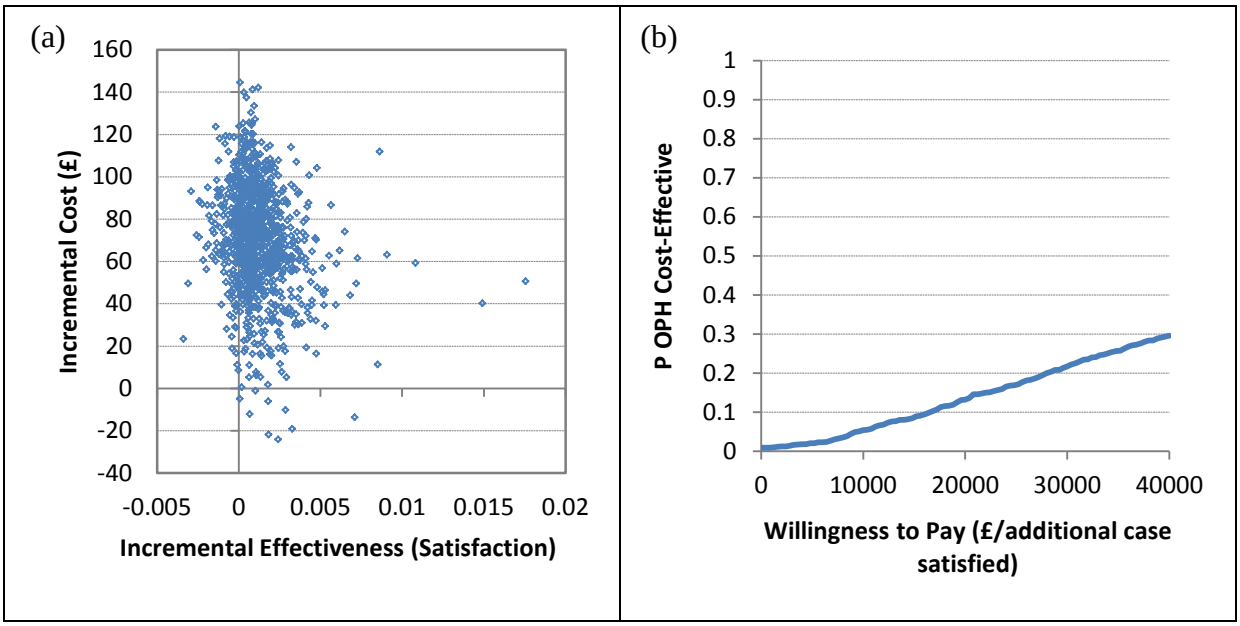
Figure 9.17 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): saline infusion sonography alone strategy relative to the LNG-IUS alone strategy for women with heavy menstrual bleeding managed over multiple clinic appointments



Outpatient hysteroscopy versus saline infusion sonography: Women with HMB managed over multiple clinic appointments

Figure 9.18a suggests that there is uncertainty between SIS and OPH but that OPH may be more effective than SIS. It also suggests that OPH is more expensive than SIS. The CEAC (Figure 9.18b) shows that even at a WTP of £40,000, OPH is unlikely to be the most cost-effective strategy ($p<0.3$).

Figure 9.18 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): outpatient hysteroscopy alone strategy relative to the saline infusion sonography alone strategy for women with heavy menstrual bleeding managed over multiple clinic appointments

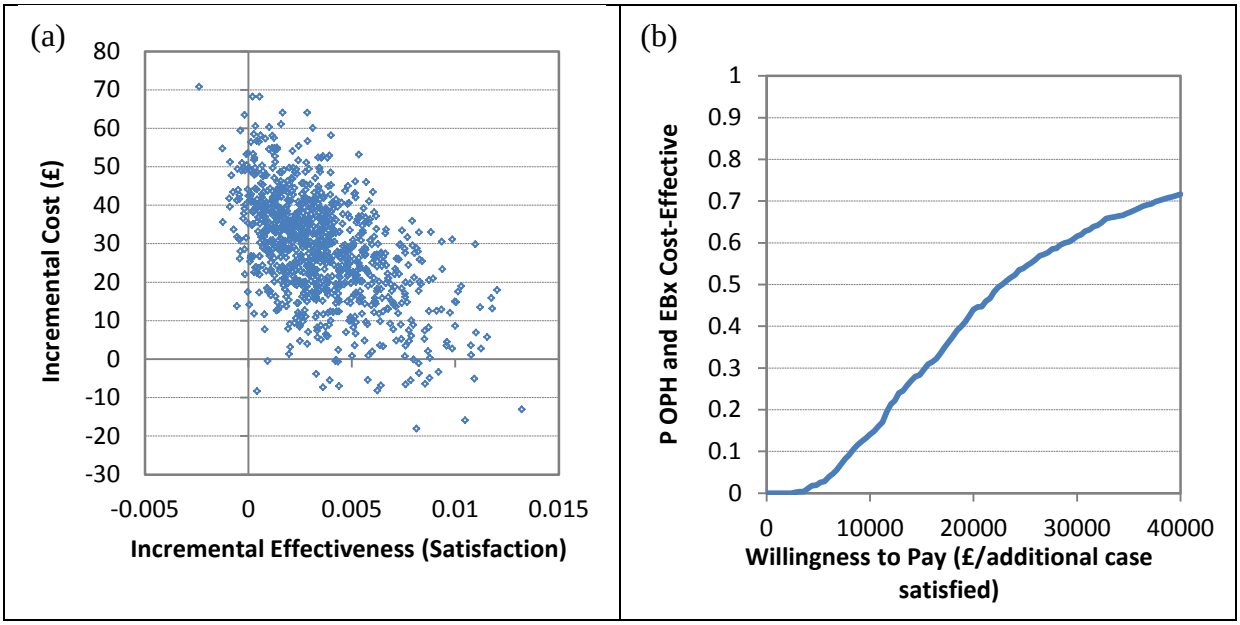


Outpatient hysteroscopy and endometrial biopsy versus outpatient hysteroscopy:

Women with HMB managed over multiple clinic appointments

Figure 9.19 shows that OPH and EBx is probably more effective and more expensive than OPH alone but that it is only becomes likely to be the most cost-effective of the two strategies at WTP values of above £20,000 and that even at WTP of £40,000 the probability of it being the most cost-effective strategy is only just above 0.7.

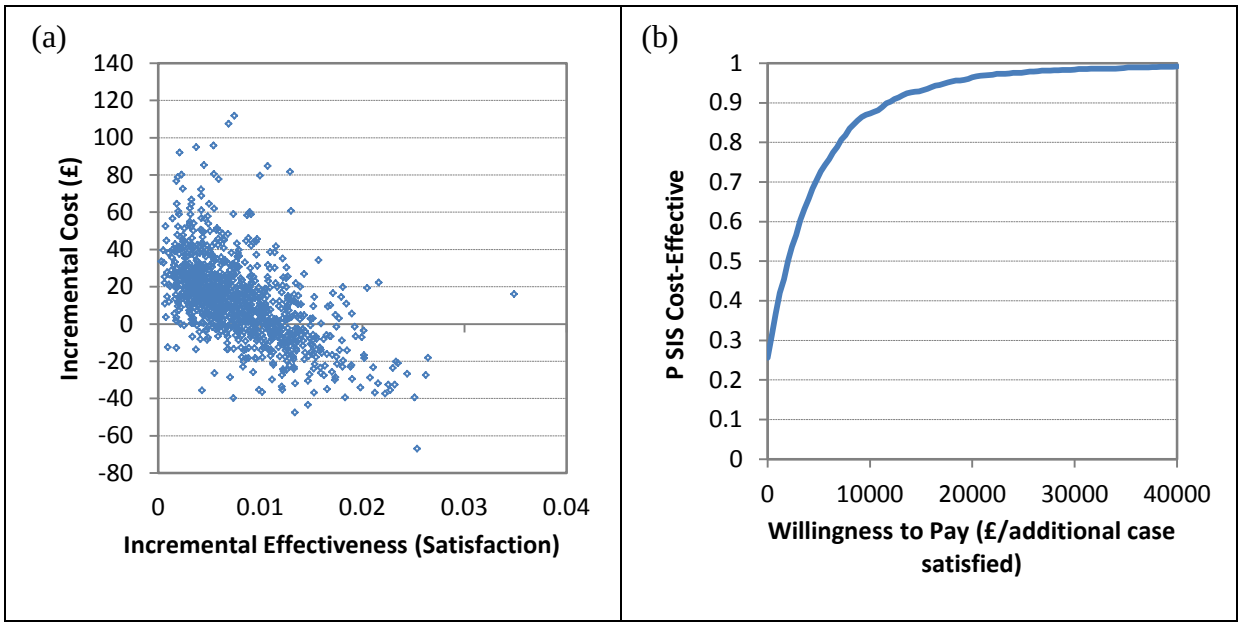
Figure 9.19 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): outpatient hysteroscopy with endometrial biopsy strategy relative to the outpatient hysteroscopy alone strategy for women with heavy menstrual bleeding managed over multiple clinic appointments.



Saline infusion sonography versus transvaginal scan: Women with HMB managed over multiple clinic appointments

The scatterplot below (Figure 9.20a) shows that SIS is more effective than TVS although it is probably a more expensive strategy. The CEAC (Figure 9.20b) shows that SIS is likely to be the most cost-effective strategy at a WTP of approximately £3000 but this becomes almost certain (p>0.9) at just over £10,000.

Figure 9.20 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): saline infusion sonography alone strategy relative to the transvaginal scan alone strategy for women with heavy menstrual bleeding managed over multiple clinic appointments.

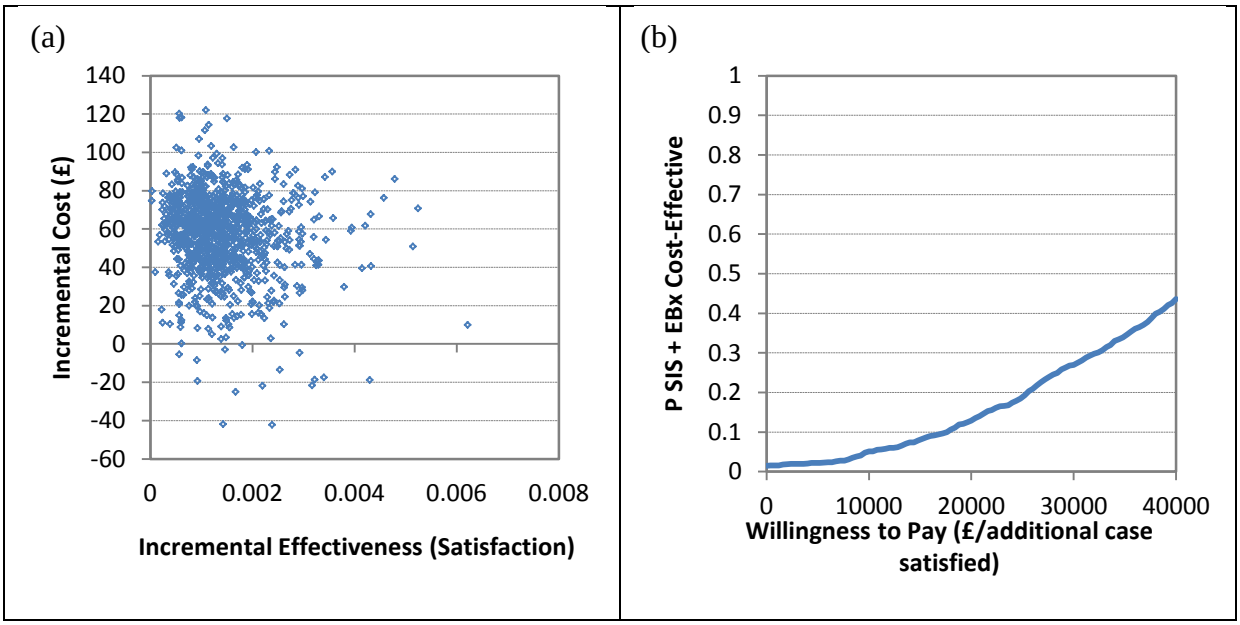


Saline infusion sonography and endometrial biopsy versus saline infusion sonography: Women with HMB managed over multiple clinic appointments

Figure 9.21a shows that SIS + EBx is more effective and more expensive than SIS alone.

Figure 9.21b shows that SIS + EBx is unlikely to be cost-effective at WTP values acceptable to health service providers.

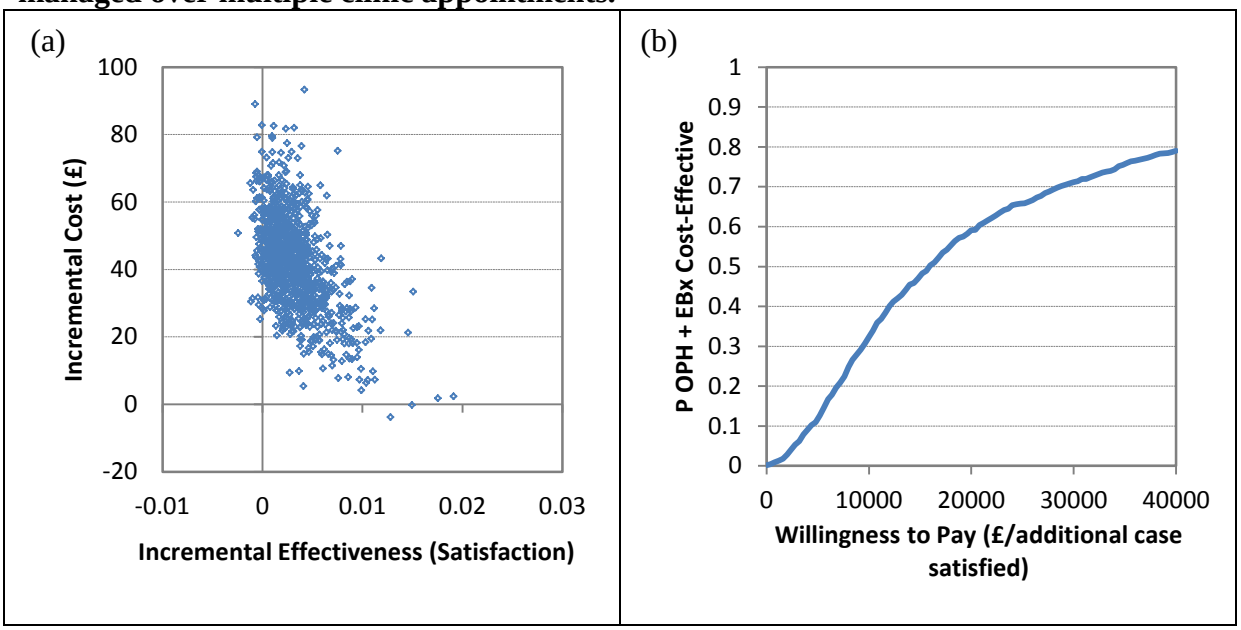
Figure 9.21 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): saline infusion sonography with endometrial biopsy strategy relative to the saline infusion sonography alone strategy for women with heavy menstrual bleeding managed over multiple clinic appointments.



Outpatient hysteroscopy and endometrial biopsy versus saline infusion sonography and endometrial biopsy: Women with HMB managed over multiple clinic appointments

The cost-effectiveness plane in Figure 9.22a shows that OPH+EBx is more effective and more expensive than SIS+EBx. The CEAC (Figure 9.22b) suggests that above £15,000 OPH and EBx is likely to be the most cost-effective test and that as the WTP increases so does the certainty.

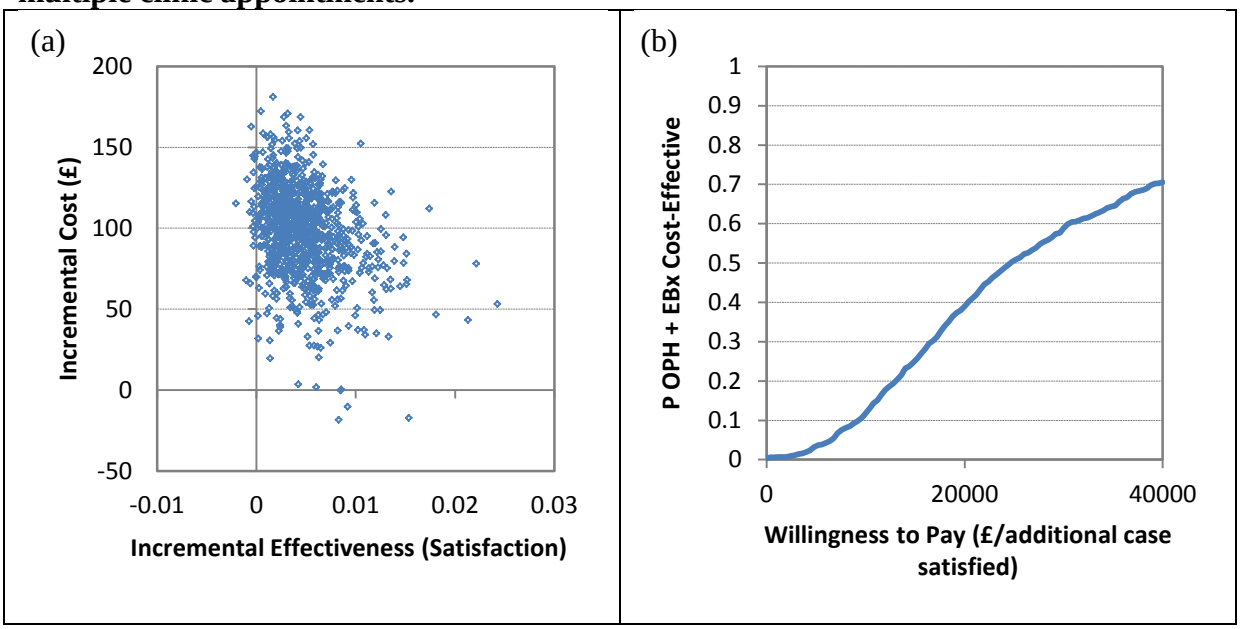
Figure 9.22 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): outpatient hysteroscopy with endometrial biopsy strategy relative to the saline infusion sonography with endometrial biopsy strategy for women with heavy menstrual bleeding managed over multiple clinic appointments.



Outpatient hysteroscopy and endometrial biopsy versus saline infusion sonography: Women with HMB managed over multiple clinic appointments

The scatterplot below (Figure 9.23a) shows that OPH and EBx is probably more effective and more expensive than SIS. The CEAC (Figure 9.23b) shows that above a WTP threshold of £25,000 OPH and EBx is likely to be the most cost-effective strategy, although the probability of this is till only 0.7 at a WTP of £40.000.

Figure 9.23 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): outpatient hysteroscopy with endometrial biopsy strategy relative to the saline infusion sonography alone strategy for women with heavy menstrual bleeding managed over multiple clinic appointments.



Deterministic results: Prior treatment with the LNG-IUS

The base case economic analysis assumed that the women presenting to the gynaecologist with HMB had not had any treatment in primary care. NICE recommend that women with HMB should be treated with a LNG-IUS in primary care and only be referred to a gynaecologist if symptoms persist, structural abnormality is expected or contraindications exist (142). In practice only around 25% of women referred from primary care have received prior treatment with the LNG-IUS (233). An alternative analysis was performed to examine the 'ideal' scenario, when women have already tried a LNG-IUS, and assess whether the preferred cost-effective investigative strategies are altered. Disease prevalence was adjusted to reflect the fact that women treated appropriately with a LNG-IUS in primary care (i.e. without intracavity pathology, endometrial cancer or large fibroids) were less likely to have persistent symptoms and need referral to a gynaecologist. It was assumed that fertility was not desired in this analysis, as in the base case analysis. The strategy LNG-IUS alone could no longer be used as the reference strategy (now being redundant) and was replaced by a strategy of 'no further intervention' i.e. attending clinic with a LNG-IUS in situ, seeing a gynaecologist but deciding not to have any further intervention.

Table 9.6 Deterministic results of cost-effectiveness analysis for women with heavy menstrual bleeding with a LNG-IUS in situ

Strategy	Cost (£)	Effectiveness (satisfaction)
No further intervention	1355	0.9039
OPH alone	1681	0.9633
SIS alone	1711	0.9633
TVS + OPH	1746	0.9633
SIS + OPH	1775	0.9633
TVS alone	1785	0.9633
OPH and EBx	1796	0.9628
TVS+ OPH+EBx	1840	0.9628
SIS + EBx	1846	0.9628
SIS +OPH +EBx	1864	0.9629
EBx alone	1942	0.9628
TVS + Ebx	1980	0.9639
Hysterectomy alone	3218	0.9378

LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS= transvaginal ultrasound scan

Outcomes

As before, the diagnostic strategies were more effective than the treatment only strategies. The most effective strategy was combination testing with transvaginal scan and endometrial biopsy however the difference between all of the diagnostic strategies was minimal, ranging from 96.28% to 96.39%.

Costs

The results presented in Table 9.6 show that all costs have increased compared with the base case analysis, reflecting the increased prevalence of organic uterine pathology requiring more expensive treatments. Adopting no further treatment and persevering with the LNG-IUS treatment alone (reference strategy) was the cheapest option, costing £1355 per woman treated for HMB in a secondary care setting. The strategy of hysterectomy for all women was the most expensive at £3218 per woman treated i.e. £1863 more than the approach of LNG-

IUS treatment alone. The cheapest diagnostic testing strategy was the use of outpatient hysteroscopy alone, costing £1681 for every woman treated, i.e. £326 more than continuation with LNG-IUS treatment.

Cost-effectiveness & dominance

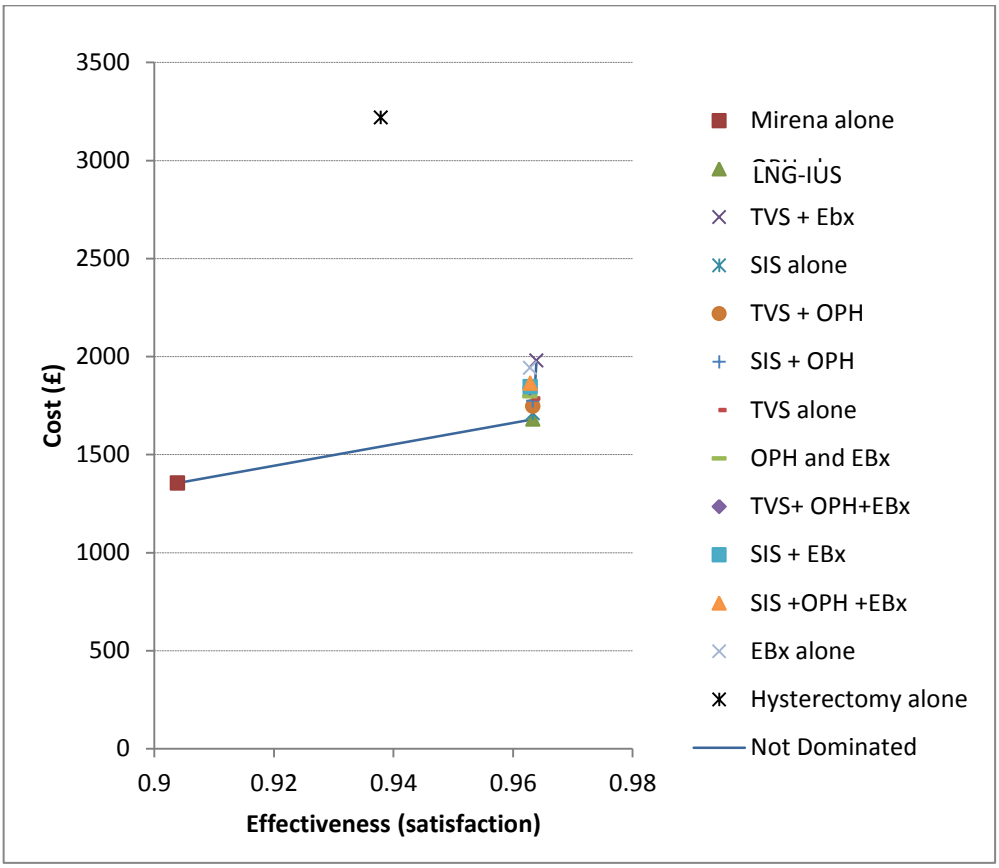
The testing strategies outpatient hysteroscopy (OPH) alone and transvaginal scan combined with endometrial biopsy (TVS + EBx) remain non-dominated by alternative empirical treatment or diagnostic testing strategies. The remaining strategies are all dominated by OPH alone except for hysterectomy which is dominated by TVS+EBx. Table 9.7 presents the deterministic analysis restricted to the non-dominated competing strategies.

Table 9.7 Non-dominated strategies from the analysis of women presenting with heavy menstrual bleeding with a LNG-IUS in situ

Strategy	Cost (£)	Incremental Cost (£)	Effectiveness	Incremental Effectiveness	ICER
No further intervention	1355		0.9039		
OPH alone	1681	326	0.9633	0.0594	5480
TVS + EBx	1980	299	0.9639	0.0006	516000

Apparent anomalies with subtraction are due to rounding effects.
EBx = endometrial biopsy; OPH = outpatient hysteroscopy; TVS=– transvaginal ultrasound scan ; ICER= incremental cost-effectiveness ratio

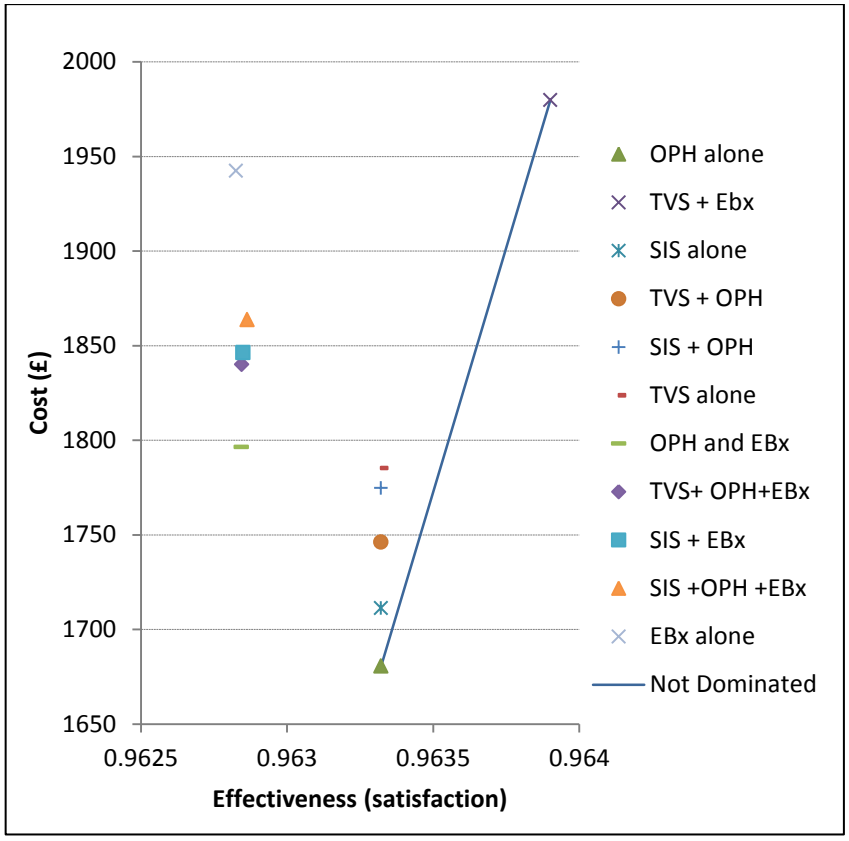
Figure 9.24 Cost-effectiveness plane showing the results of deterministic analysis for strategies to investigate women with heavy menstrual bleeding with a LNG-IUS in situ



LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS= transvaginal ultrasound scan

The line on the graph in Figure 9.24 joins the non-dominated strategies, LNG-IUS only, OPH alone and TVS and EBx. When LNG-IUS and hysterectomy are removed the relationship of the other strategies to the line of non-dominance is clearer (Figure 9.25).

Figure 9.25 Cost-effectiveness plane showing the results of deterministic analysis for strategies to investigate women with heavy menstrual bleeding with a LNG-IUS in situ. (Hysterectomy alone and LNG-IUS alone not shown)

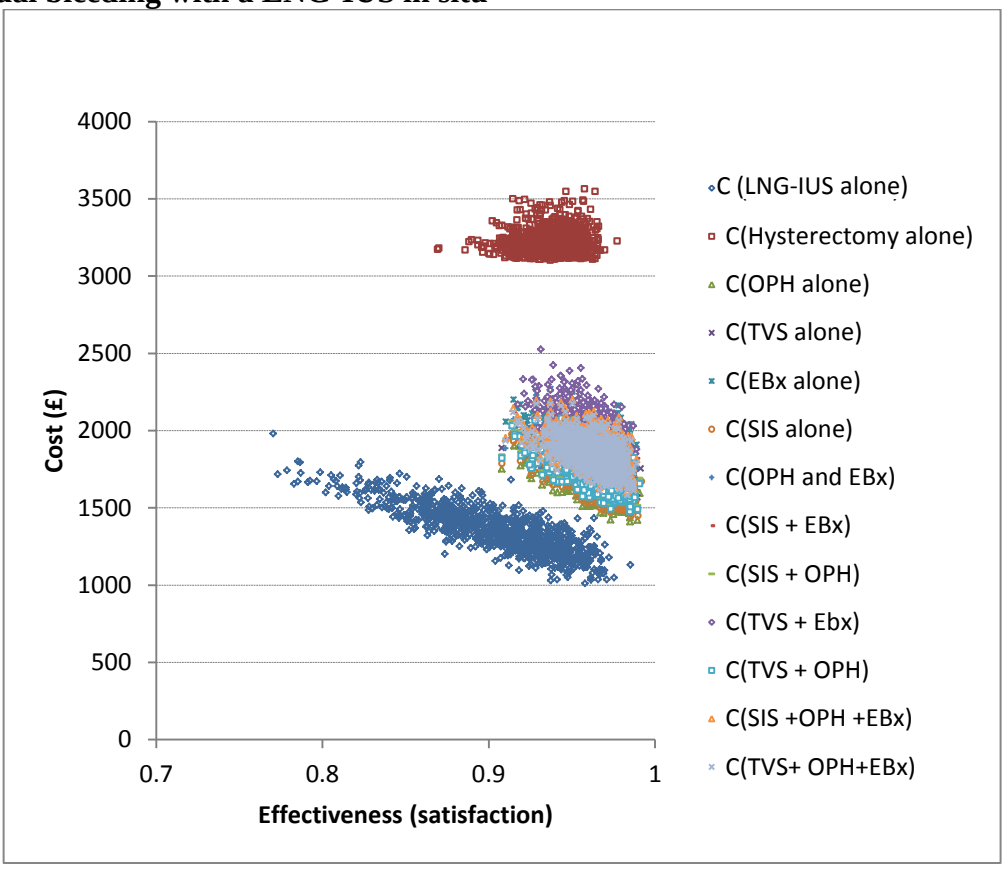


LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS – transvaginal ultrasound scan

Probabilistic sensitivity analysis results: Prior treatment with the LNG-IUS

In the cost-effectiveness scatterplot below (Figure 9.26) it is clear from the degree of overlap of the diagnostic strategies that there is uncertainty regarding which one might be considered most cost-effective when a range of values is sampled from the distributions of the data values.

Figure 9.26 Scatterplot showing the uncertainty in costs and effectiveness within the model for each of the individual strategies for investigating women with heavy menstrual bleeding with a LNG-IUS in situ

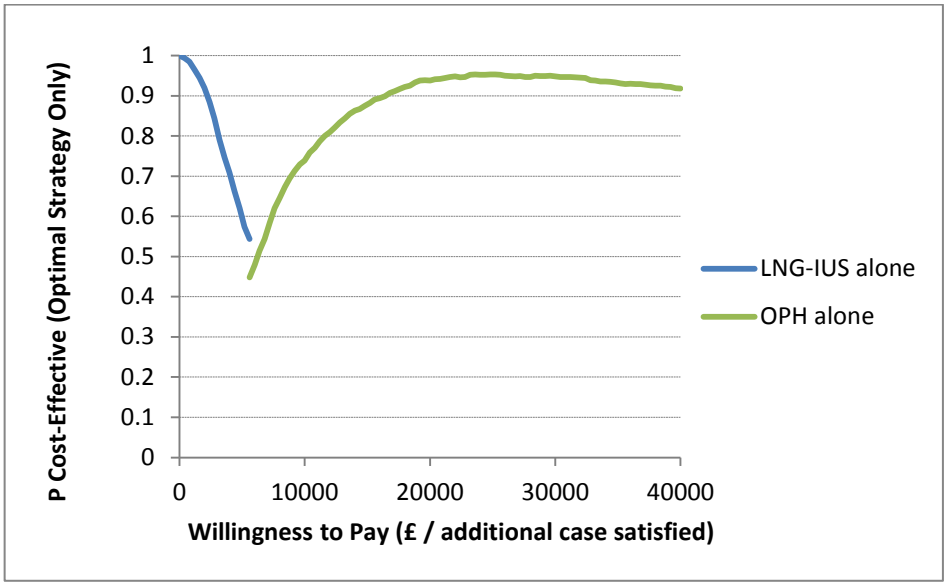


LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS= transvaginal ultrasound scan

The CEAF (Figure 9.27) illustrates the overall uncertainty related to the optimal decision across a range of plausible willingness to pay (WTP) values. The likelihood is that OPH is cost-effective compared with continuing with the LNG-IUS treatment at WTP thresholds or

around £20,000. It can be seen that OPH is the preferred option at lower WTP values but that there is considerable uncertainty as WTP falls below £10,000.

Figure 9.27 Cost-effectiveness acceptability frontier showing the optimal investigative strategies for women with heavy menstrual bleeding with a LNG-IUS in situ



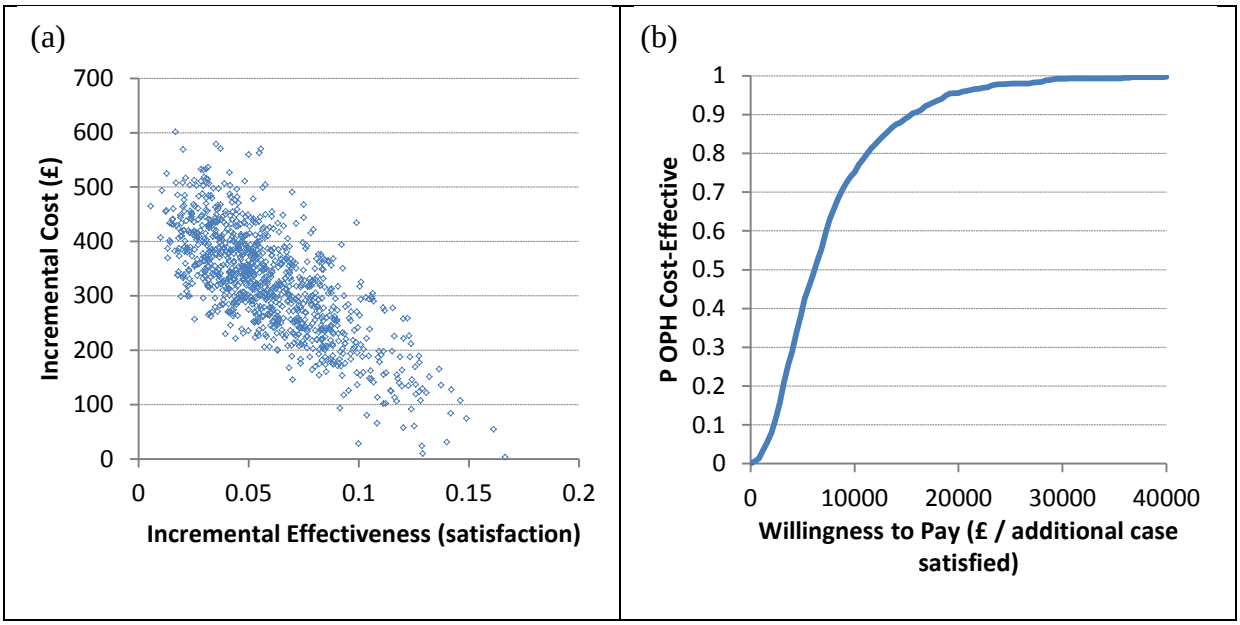
LNG-IUS = levonorgestrel intrauterine system; OPH = outpatient hysteroscopy

Probabilistic pair wise comparisons were made between the non-dominated strategies to explore the uncertainty between them. SIS was also compared to OPH alone because of its proximity to the line of non-dominance.

Outpatient hysteroscopy versus levonorgestrel intra-uterine system: Prior treatment with the LNG-IUS

The scatterplot below (Figure 9.28a) shows that OPH is almost certain to be more effective than LNG-IUS alone but it will be more costly per patient satisfied. The CEAC (Figure 9.28b) shows that above a WTP of £6000 OPH is probably a more cost effective option than LNG-IUS alone per woman satisfied. At a WTP above £15,000 this is almost certain (p>0.9).

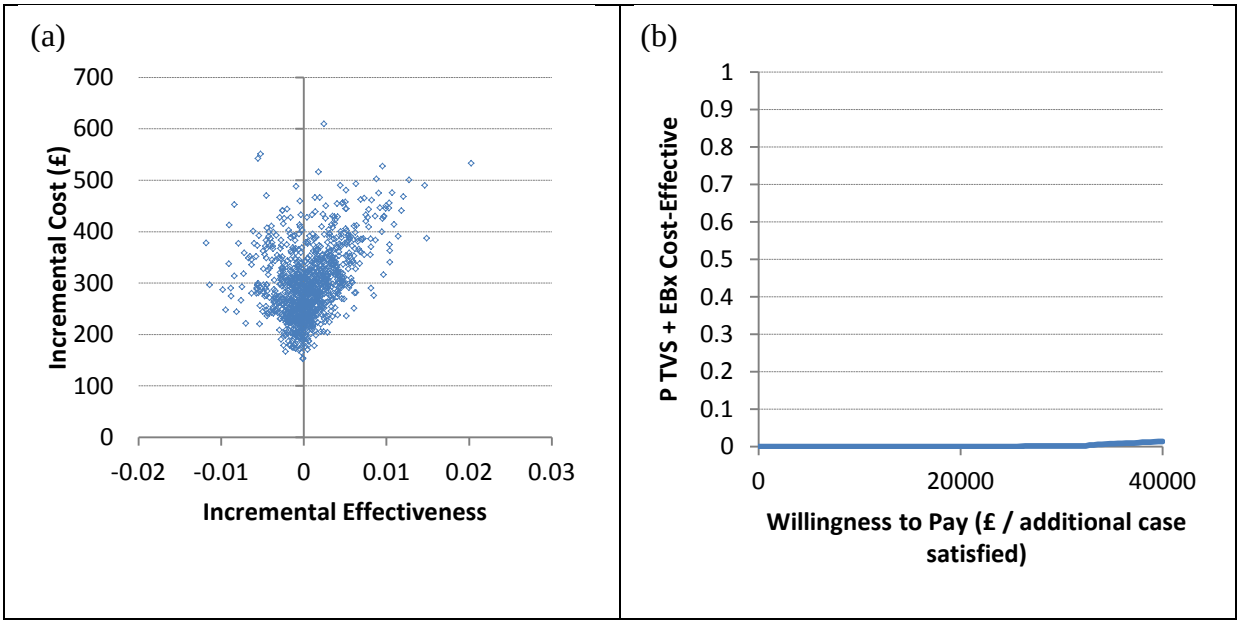
Figure 9.28 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Outpatient hysteroscopy alone strategy relative to the LNG-IUS alone strategy for women with heavy menstrual bleeding with a LNG-IUS in situ



Transvaginal ultrasound scan and endometrial biopsy versus outpatient hysteroscopy: Prior treatment with the LNG-IUS

The cost-effectiveness plane, Figure 9.29a shows that there is considerable overlap between 'TVS and EBx' and 'OPH alone'. It certainly is not clear which is the most effective strategy but TVS and EBx is the more costly of the two. For all WTP values between £0 and £40,000 per extra woman satisfied, OPH alone is almost definitely the most cost-effective option when compared to TVS and EBx (p>0.98) as displayed in the CEAC below (Figure 9.29b)

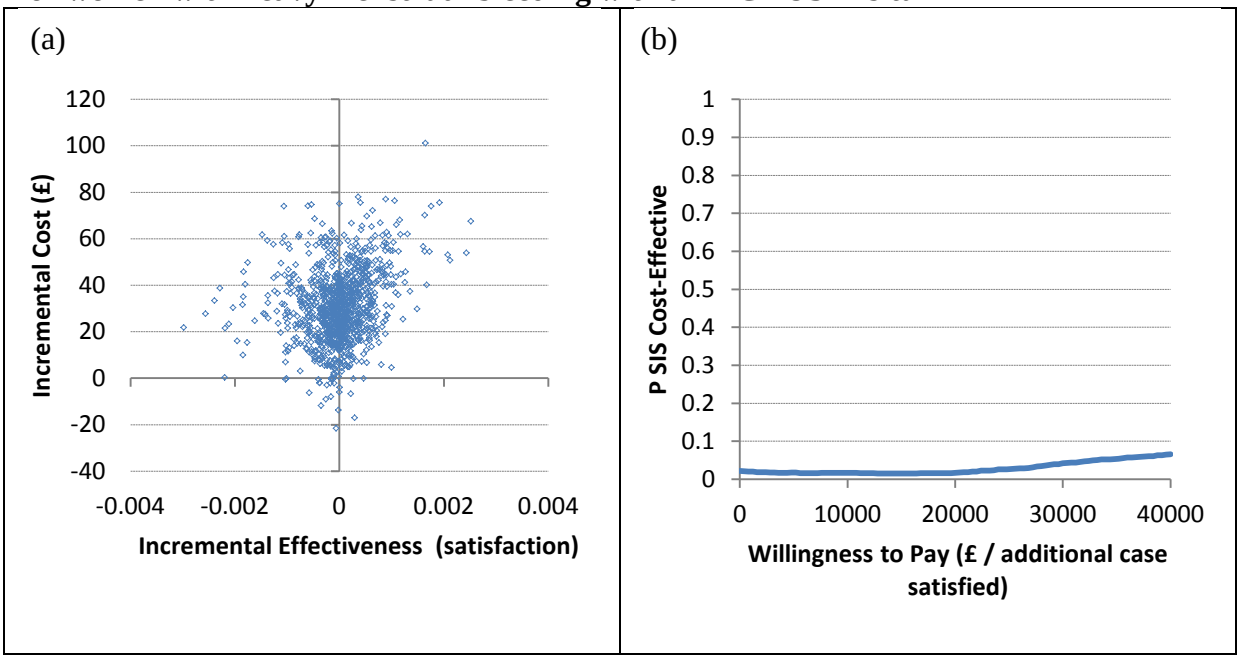
Figure 9.29 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Transvaginal scan and endometrial biopsy strategy relative to the outpatient hysteroscopy alone strategy for women with heavy menstrual bleeding with a LNG-IUS in situ



Saline infusion sonography versus outpatient hysteroscopy: Prior treatment with the LNG-IUS

SIS falls close to the line of non-dominance in the deterministic analysis therefore a comparison was made between SIS and the most cost-effective, non-dominated strategy, OPH alone. The graph, Figure 9.30a, shows that although there is likely to be little difference in effectiveness between the two strategies, SIS is almost certain to be the more costly strategy. The CEAC (Figure 9.30b) comparing SIS and OPH shows that SIS is extremely unlikely to be the most cost-effective option even at a WTP of £40,000 per additional woman satisfied.

Figure 9.30 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Saline infusion scan alone strategy relative to the outpatient hysteroscopy alone strategy for women with heavy menstrual bleeding with a LNG-IUS in situ



Deterministic analysis: Women wishing to preserve their fertility

Table 9.8 shows the deterministic analysis of the twelve strategies following re-configuration of the decision trees to reflect women who would not have a hysterectomy or an endometrial ablation to treat their HMB because they wished to maintain their long term fertility.

Table 9.8 Deterministic results of cost-effectiveness analysis for women with heavy menstrual bleeding who wish to preserve their fertility

Strategy	Cost (£)	Effectiveness (satisfaction)
LNG-IUS alone	421	0.6557
SIS alone	800	0.8467
OPH alone	844	0.8629
SIS + OPH	944	0.8649
TVS alone	740	0.8033
EBx alone	754	0.7419
TVS + Ebx	870	0.8020
TVS + OPH	913	0.8389
OPH and EBx	914	0.8618
SIS + EBx	971	0.8473
TVS+ OPH+EBx	971	0.8572
SIS +OPH +EBx	1003	0.8584

LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS= transvaginal ultrasound scan

Outcomes

Satisfaction rates are reduced when compared to the original analysis as optimal surgical interventions precluding future fertility are not available for women with large fibroids or those resistant to the LNG-IUS. This is reflected by the lower satisfaction rate of 65.6% for this analysis compared with 93.33% in the original when women receive LNG-IUS without any investigation. Satisfaction rates for the investigative strategies range from 74.19% for TVS to 86.49% for SIS and OPH. There is greater variation between the satisfaction rates in this analysis than in the base case when values varied marginally between 94.6% and 96.7%.

Costs

It should be noted that the costs decreased when compared to the original analysis. Cost is decreased because the more expensive treatments tend to be the surgical options (endometrial ablation and hysterectomy) which are contraindicated in women desiring preservation of their fertility. The cost of LNG-IUS alone has decreased to £421 from £1066 in the base case analysis because the women identified to have large fibroids do not undergo a hysterectomy and women who are dissatisfied with the LNG-IUS cannot be offered any further treatment. The cheapest investigative strategy in this analysis is TVS alone, costing £740 per patient. The most expensive strategy is the combination of SIS, OPH and EBx costing £1003 per patient.

Cost-effectiveness and dominance

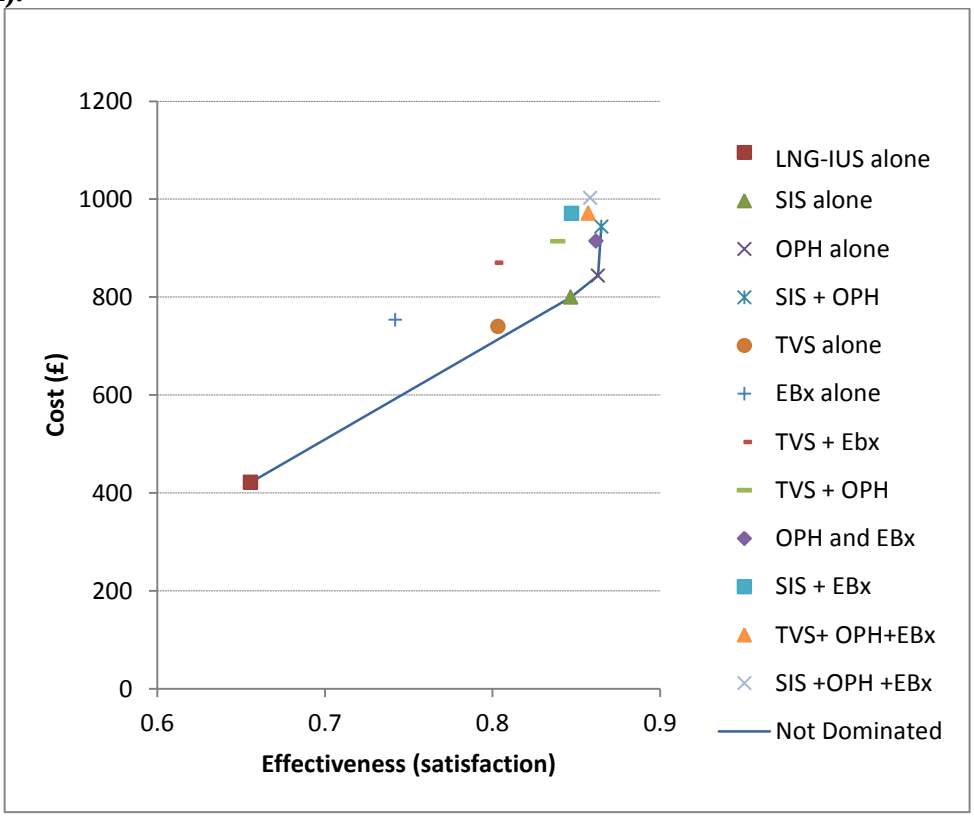
The strategy of EBx alone is dominated by TVS alone ,which in turn is dominated by extended dominance due to a blend of LNG-IUS alone and SIS alone. The remaining strategies are dominated by either OPH alone or SIS and OPH together. Once the dominated strategies were removed the testing strategies which remained were SIS alone, OPH alone and SIS and OPH together. This can be more clearly appreciated in Table 9.9. In contrast to the base case analysis, a combination strategy of OPH + EBx is not potentially cost-effective. Moreover, SIS alone or in combination with OPH is non-dominated whereas in women without the need to preserve their fertility (base case), SIS and related strategies were not cost-effective.

Table 9.9 Non-dominated strategies from the analysis of women presenting with heavy menstrual bleeding who wish to preserve their fertility

Strategy	Cost (£)	Incremental cost (£)	Effectiveness (satisfaction)	Incremental effectiveness	ICER
LNG-IUS alone	421		0.6557		
SIS alone	800	378	0.8467	0.1910	1980
OPH alone	844	44	0.8629	0.0162	2720
SIS + OPH	955	100	0.8649	0.0020	50300

Apparent anomalies with subtraction are due to rounding effects.
LNG-IUS = levonorgestrel intrauterine system; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; ICER= incremental cost-effectiveness ratio.

Figure 9.31 Total costs and effectiveness of the alternative strategies for the diagnostic work up of HMB for women wishing to preserve their fertility. (Hysterectomy has been excluded).



LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS= transvaginal ultrasound scan

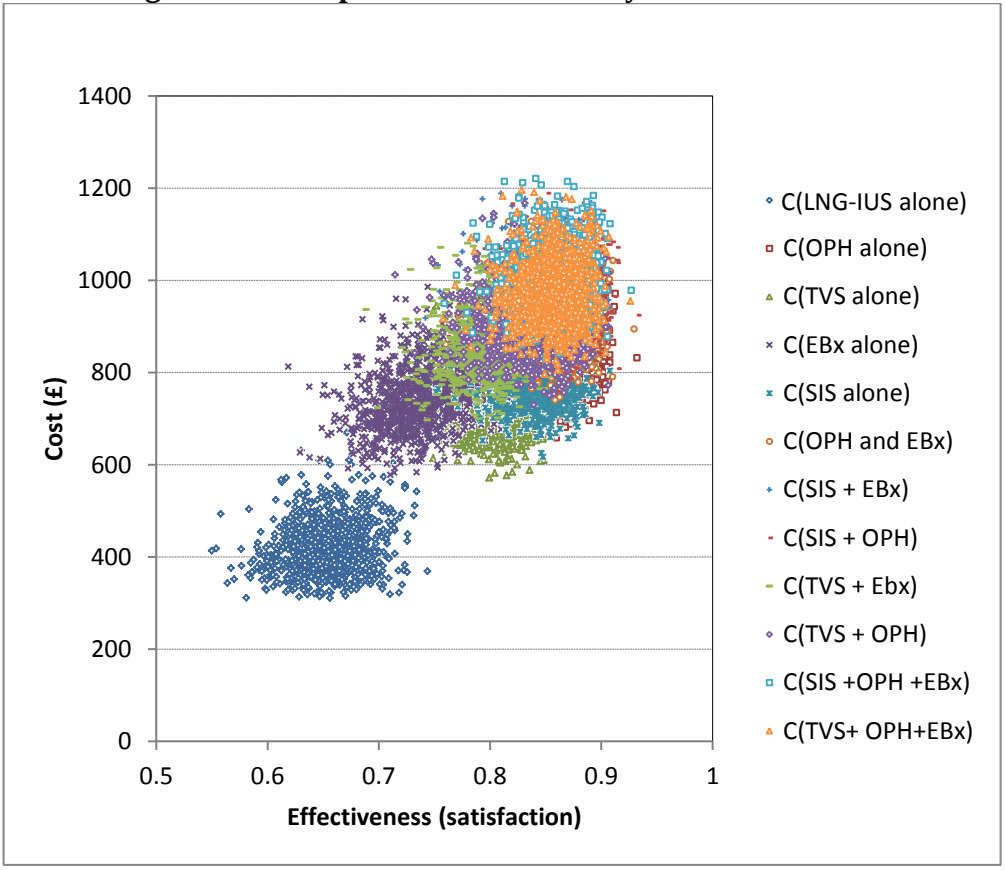
The line on the cost-effectiveness plane (Figure 9.31) joins the non-dominated strategies, starting with the base case of LNG-IUS which joins to SIS, followed by OPH and then SIS

and OPH. TVS lies close to this line and therefore when exploring the results TVS was included to see whether analysing the spread of results might suggest that TVS could become cost-effective when values are varied around their point estimates.

Probabilistic sensitivity analysis results: Women wishing to preserve their fertility

Figure 9.32 shows the uncertainty around the absolute cost and effectiveness values for each of the strategies. Hysterectomy alone has been removed as it is too expensive to be a competing strategy and removing it allows clearer presentation of the other strategies. There is overlap between strategies.

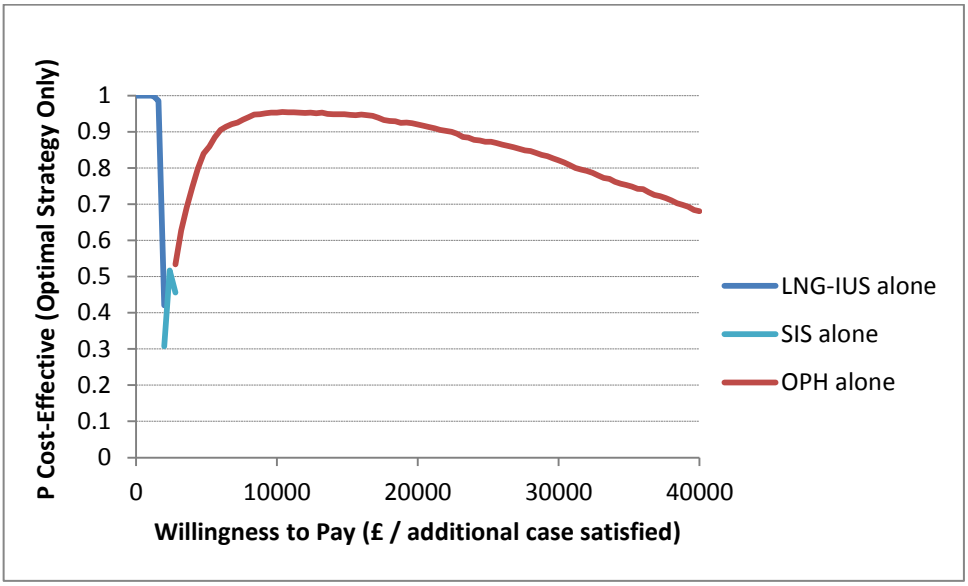
Figure 9.32 Scatterplot showing the uncertainty in costs and effectiveness within the model for each of the individual strategies for investigating women with heavy menstrual bleeding who wish to preserve their fertility



LNG-IUS = levonorgestrel intrauterine system; EBx = endometrial biopsy; OPH = outpatient hysteroscopy; SIS = saline infusion sonography; TVS – transvaginal ultrasound scan

The acceptability frontier in Figure 9.33 shows how likely the non-dominated strategies are to be the most cost-effective option at a range of WTP thresholds. The strategy SIS and OPH is not plotted on the CEAF because it only becomes cost-effective at a WTP too high to be acceptable to the NHS.

Figure 9.33 Cost-effectiveness acceptability frontier showing the preferred diagnostic strategy over a range of WTP thresholds for women who wish to preserve their fertility



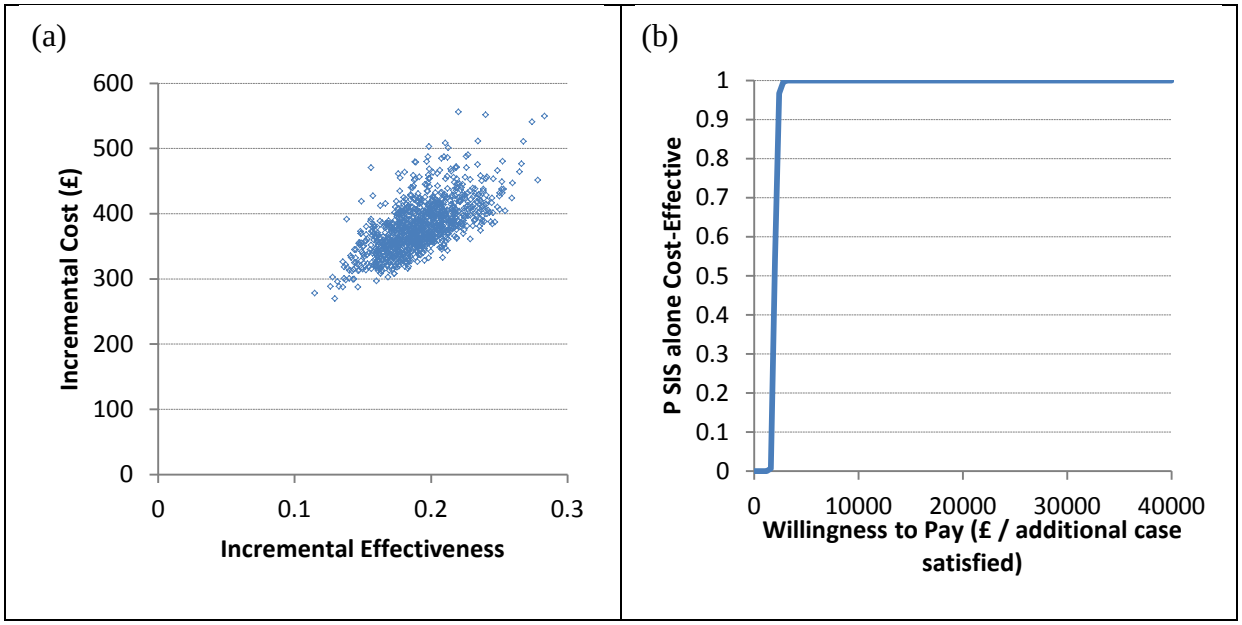
LNG-IUS = levonorgestrel intrauterine system; SIS = saline infusion sonography OPH = outpatient hysteroscopy.

The uncertainty represented in the CEAF is explored by considering pair wise comparisons between the adjacent non-dominated options. TVS is also explored because its mean is close to the non-dominance line.

SIS alone vs. LNG-IUS alone: Women wishing to preserve their fertility

Figure 9.34 shows that SIS is definitely more effective and more costly than LNG-IUS alone. The CEAC (Figure 9.34b) shows that at above a WTP of £2700 SIS is definitely (p=1) a more cost-effective option than using LNG-IUS alone.

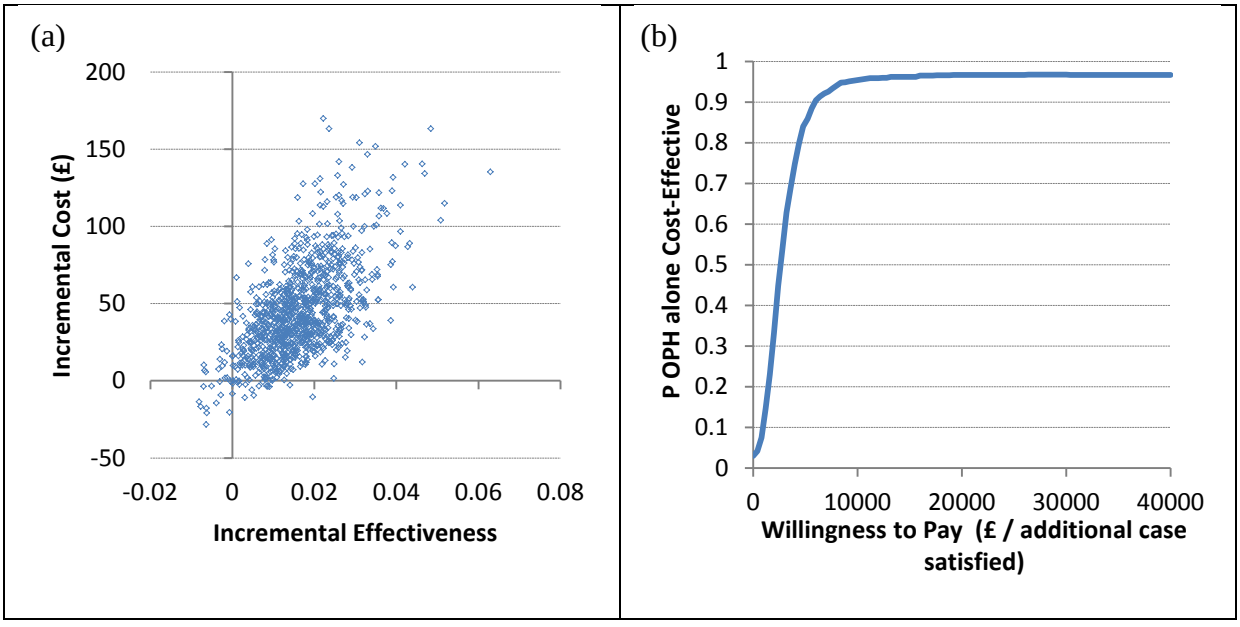
Figure 9.34 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Saline infusion sonography alone strategy relative to the LNG-IUS alone strategy for women wishing to preserve their fertility



Outpatient hysteroscopy versus saline infusion: Women wishing to preserve their fertility

Figure 9.35a shows that outpatient hysteroscopy is likely to be more effective and more expensive than saline infusion scan for investigating women with HMB who want to preserve their fertility. The CEAC (Figure 9.35b) shows that above a WTP of approximately £2500 to make one extra woman satisfied, OPH becomes likely to be the most cost effective strategy ($p>0.5$) and that at a WTP just above £5000 it has a greater than 90% chance of being the most cost-effective strategy when compared to SIS.

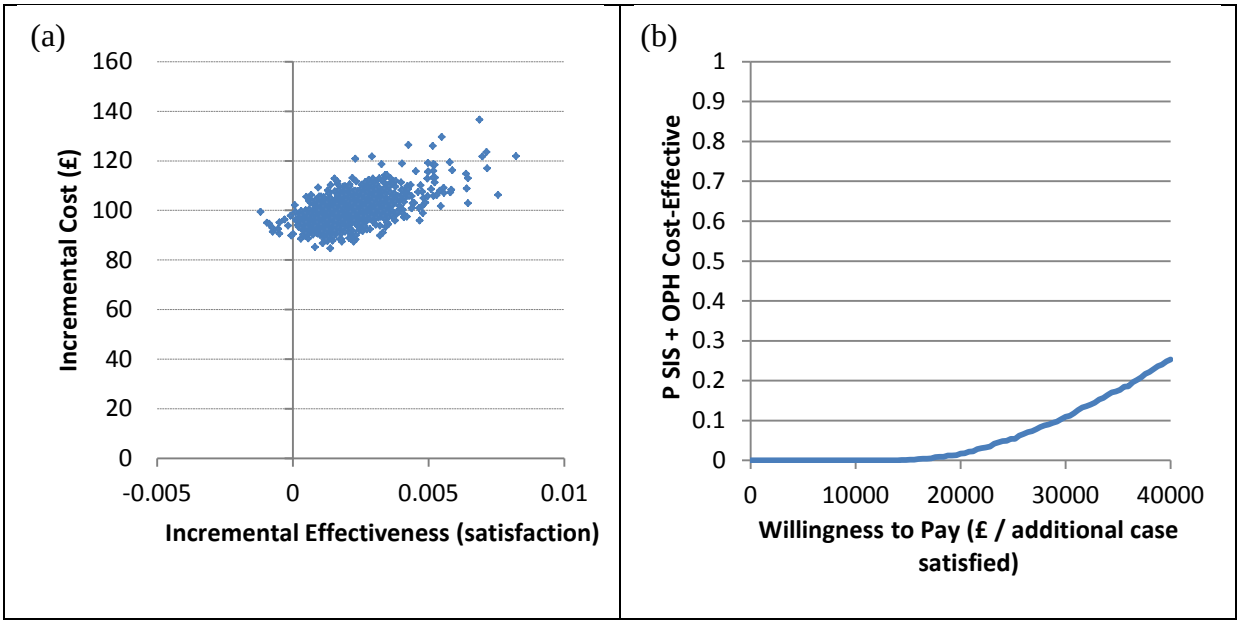
Figure 9.35 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Outpatient hysteroscopy alone strategy relative to the saline infusion sonography alone strategy for women wishing to preserve their fertility



Saline infusion sonography and outpatient hysteroscopy versus outpatient hysteroscopy: Women wishing to preserve their fertility

Figure 9.36a shows the cost-effectiveness plane comparing OPH with SIS to OPH alone. It shows that SIS with OPH is more costly than OPH alone and that this extra cost is almost certainly between £100 and £120. The two test combination is also probably but not definitely, the more effective strategy. The CEAC (Figure 9.36b) shows the proportion of model replications for which saline infusion scan and outpatient hysteroscopy is preferred to outpatient hysteroscopy alone at any given willingness to pay per additional case satisfied. It shows that even at a WTP of £40,000 there is considerable uncertainty that SIS and OPH is a more-cost-effective strategy than OPH alone (p=0.2).

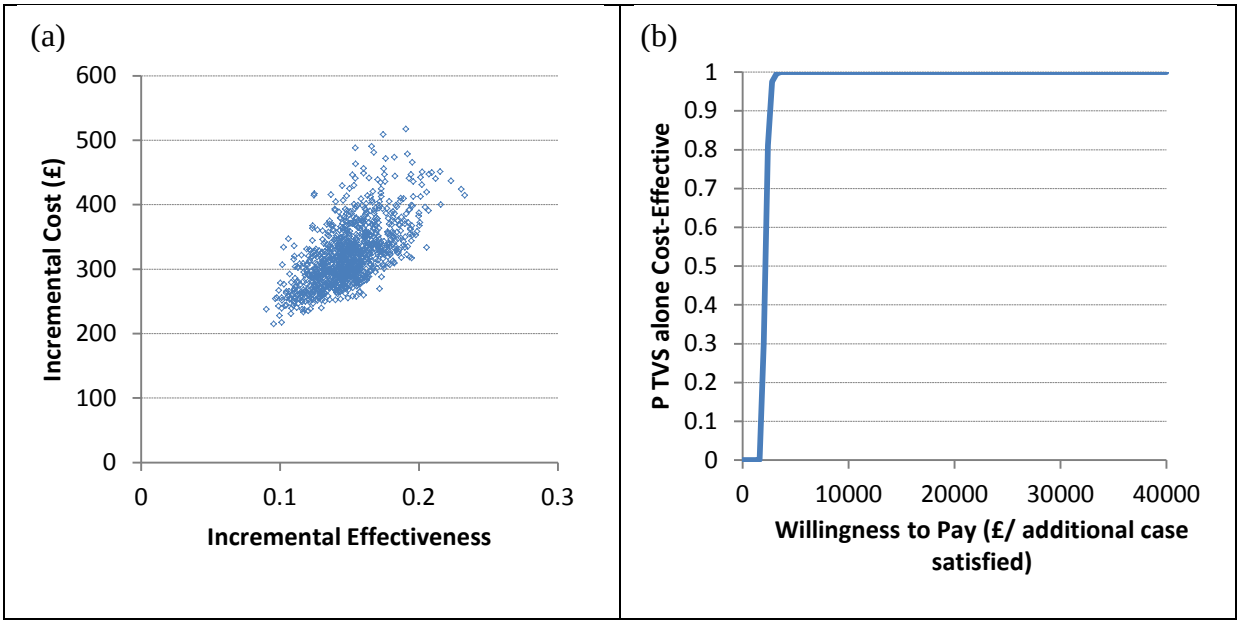
Figure 9.36 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Saline infusion sonography and outpatient hysteroscopy strategy relative to the outpatient hysteroscopy alone strategy for women wishing to preserve their fertility



Transvaginal ultrasound scan versus levonorgestrel intra-uterine system: Women wishing to preserve their fertility their fertility

The graph (Figure 9.37a) shows the modelled uncertainty in the difference in costs between TVS alone and LNG-IUS. It shows that TVS is more effective and more costly than giving all women an LNG-IUS without investigation. The CEAC (Figure 9.37b) shows the proportion of model replications for which transvaginal scan is preferred to LNG-IUS alone at any given willingness to pay per additional case satisfied. It shows that above a WTP of £3,000 TVS is definitely the most cost-effective option (p=1).

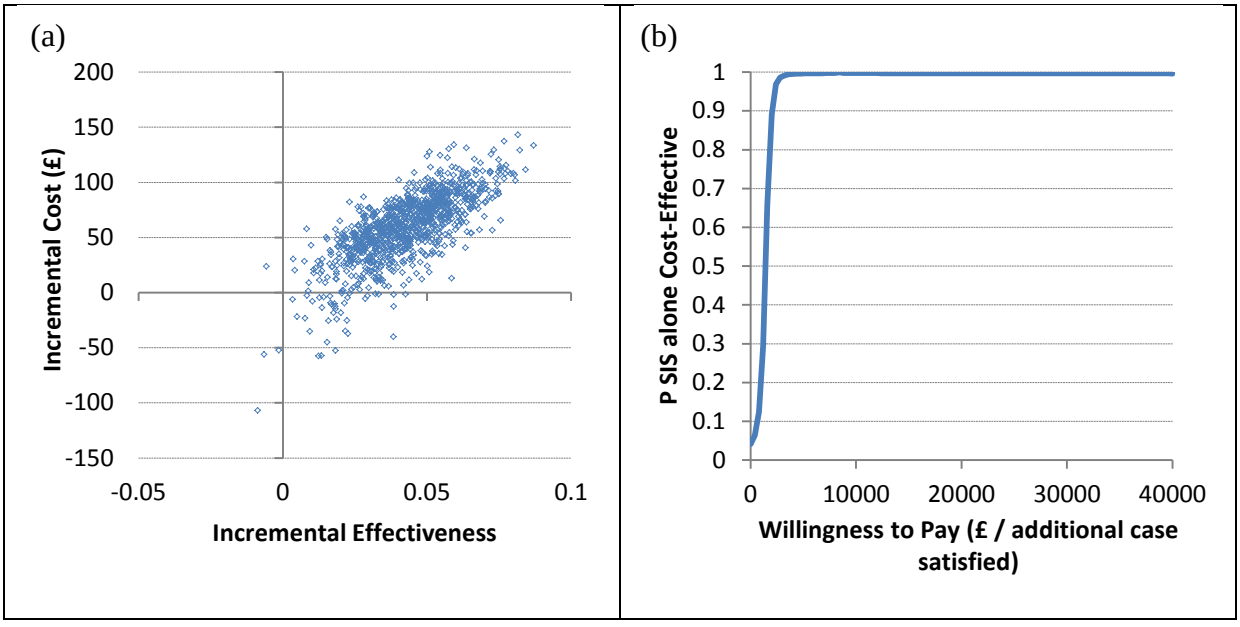
Figure 9.37 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Transvaginal ultrasound scan alone strategy relative to the LNG-IUS alone strategy for women wishing to preserve their fertility



Saline infusion sonography versus transvaginal ultrasound scan: Women wishing to preserve their fertility

The graph (Figure 9.38a) shows the modelled uncertainty in the difference in costs between SIS alone and TVS alone. It shows that SIS is probably more effective and more costly that TVS alone. The CEAC (Figure 9.38b) shows the proportion of model replications for which SIS is preferred to TVS alone at any given willingness to pay per additional case satisfied. It shows that above a WTP of approximately £4000 SIS alone is definitely the most cost-effective option when compared to TVS.

Figure 9.38 Cost-effectiveness plane (a) and cost-effectiveness acceptability curve (b): Saline infusion sonography alone strategy relative to the transvaginal ultrasound scan alone strategy for women wishing to preserve their fertility



CHAPTER 10

DISCUSSION OF THE ECONOMIC ANALYSIS OF DIAGNOSTIC STRATEGIES FOR THE INVESTIGATION OF HEAVY MENSTRUAL BLEEDING

Discussion of the main findings

The objective of this economic analysis was to evaluate the cost-effectiveness of diagnostic testing strategies for HMB. Universal treatment with the LNG-IUS without any preliminary investigation was chosen as the reference strategy to compare testing options against. This was because (i) not investigating or treating is an unacceptable alternative; (ii) the LNG-IUS is recommended by NICE as first line treatment of HMB. Treating all women with a LNG-IUS without preliminary testing resulted in high levels of satisfaction (93%) which were increased by approximately 4% if some form of currently available diagnostic testing was undertaken to guide treatment.

Base Case

The economic model which adopted a 'one-stop' setting for the base-case analysis reflects contemporary practice and will remain relevant as services evolve.

Two potentially cost-effective investigation strategies were identified; initial testing with outpatient hysteroscopy alone (OPH) or a combination strategy incorporating outpatient hysteroscopy with endometrial biopsy (OPH + EBx). Although the strategy OPH +EBx was

marginally more effective, the incremental cost-effectiveness ratio (ICER) was approximately £21,000 to gain one more satisfied patient compared to OPH, while OPH has an ICER of under £400 per additional case satisfied compared to LNG-IUS alone. Thus for relatively little additional investment by the NHS, the adoption of OPH in place of LNS-IUS alone will improve outcomes for women presenting with HMB. This improvement can be increased further if combination testing with OPH + EBx is introduced. This additional cost is contentious, but it can be tested by comparison to the £20,000-£30,000 per QALY NICE threshold at which interventions are considered cost-effective to implement within the NHS. Due to paucity of HRQL data, QALYs could not be used for the cost effectiveness analysis however an estimation can be made to give an approximate cost per QALY. It has been estimated that a woman's quality of life is reduced by 0.5 for the one week per month of heavy menses (234). This means that HMB is associated with a reduction of 0.125 QALY in any year, as the reduction of 0.5 applies for one quarter of the time overall. Considering a 45 year old woman with seven symptomatic years until menopause, future years need to be discounted at 3.5%, so that the annual QALY loss must be multiplied by $[1 + (1/1.035) + (1/1.035)^2 + (1/1.035)^3 + ... + (1/1.035)^6]$ or approximately 6.3 to give a total QALY loss of approximately 0.8 QALY. This means that an ICER of £21,000 per case satisfied is approximately equivalent to an ICER of £26,500/QALY, which falls within the £20,000-£30,000 per QALY threshold range used by NICE. Therefore, the strategy OPH+EBx is of borderline cost-effectiveness compared to initial investigation with OPH in isolation.

The certainty of the base-case results was assessed by probabilistic sensitivity analysis. Outpatient hysteroscopy remained the more cost-effective strategy even at relatively low willingness to pay thresholds. Outpatient hysteroscopy with EBx also remained stable however, to be at least 70% certain that it was a more cost-effective alternative than OPH

alone, the WTP threshold would need to be increased to around £40,000 per patient satisfied (~ £50,000 / QALY). Endometrial biopsy is most useful for diagnosing endometrial disease but the prevalence of endometrial hyperplasia and carcinoma is low in a premenopausal population estimated at around 5%. In populations of women where higher rates of endometrial disease are observed (e.g. epidemics of obesity), the benefit of EBx will have more influence on overall cost-effectiveness. However, substantially higher estimates of endometrial disease in an HMB population are unlikely.

Ultrasound is a convenient, minimally invasive, portable test that allows assessment of both the uterus and ovaries. It is universally available and can be incorporated easily into standard gynaecological examination. In view of the popularity of pelvic scanning and the fact that two scanning strategies came close to the boundary of dominance when the cost-effectiveness analysis was performed, further exploratory analyses were undertaken. Sensitivity analysis was performed to examine transvaginal ultrasound (TVS) and saline infusion sonography (SIS) to see whether there was uncertainty regarding them when compared to the most cost-effective strategy of OPH alone. However when compared to OPH, TVS was found to be almost certainly less effective and there was also a chance of it being more costly too therefore ruling it out as a primary diagnostic test. When SIS was compared to OPH there was significant doubt regarding which was the most effective approach. By increasing the willingness to pay threshold from £0 to £40,000, the likelihood that OPH was more cost effective than SIS increased further from 60% to 80%. Thus, at WTP levels acceptable to the NHS, OPH appears preferable to SIS as a first-line diagnostic test in HMB. However, clinicians who currently use SIS for first line investigation of HMB and are able to easily integrate SIS into their practice at low cost, may have less to gain by changing to OPH.

Furthermore, patients receive added reassurance from knowing that their ovaries have been examined as well as the uterine cavity, a benefit of scanning that is neglected by OPH.

In sensitivity analysis, the cost of SIS needed to be reduced from £71 to £52 to make it more cost-effective than OPH. This reduction in costs is unrealistic as SIS would have to cost less than the £55 which is the cost of a standard 2D transvaginal scan which is unfeasible given that it requires additional equipment (instillation catheter) and takes longer to perform; costs which have been estimated to be an extra 35% on top of transvaginal scan in a Dutch study (156).

Prevalence of focal uterine pathology

Sensitivity analyses were conducted to investigate whether the prevalence of polyps/SMFs could have biased the results towards OPH. The prevalence was reduced sequentially to determine at what prevalence an alternative option may be favoured. This analysis suggested that even if the estimate of polyps/SMFs was 10% less than had been stated in the base case (i.e. 28% instead of 38%), OPH would still remain the preferred option. The prevalence of polyps and submucous fibroids reported in the better quality prevalence studies used in the model reported values for both pathologies of around 20% (202;205), which approximates to the 40% prevalence quoted by NICE in their HMB guideline (30% submucous fibroids and 10% endometrial polyps) (142), so if 40% is a true reflection of disease then OPH is for certain the most cost-effective option. Even in different HMB populations it seems unlikely that the combined prevalence of endometrial polyps and submucous fibroids would be lower than 28%, thus there is reasonable certainty that OPH is the most cost-effective diagnostic strategy in HMB, even in populations with focal uterine pathology prevalence rates at the lower end of the plausible range.

Women managed over multiple clinic appointments

Whilst one-stop services are being increasingly developed, the traditional multi-stop model of care remains embedded in much of the NHS, therefore an adapted version of the model investigated the multi-stop approach to investigation and treatment of women with HMB. This analysis suggested that SIS alone, at an added cost of £5070 per additional patient satisfied or OPH and EBx at an added cost of £22,100 were the most cost effective strategies. OPH alone was not considered a cost-effective option in this analysis, however, costs were applied to OPH that made it less competitive than the other tests by dictating that concomitant treatment of polyps and fibroids could not be performed at the time of diagnostic hysteroscopy. This approach is practised at some centres across the UK to try and avoid delays in clinic running time, so this 'worst-case scenario' was used in the multi-stop analysis. OPH become relatively expensive because it required an additional consultant appointment whereas TVS and SIS were performed in the scan department by a sonographer and endometrial biopsy was performed at the initial consultant GOPD appointment. Interestingly, in the pairwise comparison between OPH and SIS, OPH was probably more effective than SIS but it was more expensive under the assumptions of the multi-stop model of care to a degree that OPH was no longer cost-effective compared with SIS. In both the one-stop base case model of care and the multi-stop reanalysis, the testing strategy of OPH combined with EBx was a non-dominated strategy. If the same QALY rules are applied to this strategy as to the base case results (see the discussion under ***'Base case'*** above) the cost per QALY for OPH+EBx was £27,625 which falls within the NICE threshold of £20,000 to £30,000. Thus, an initial testing approach for women presenting with HMB using OPH with EBx is potentially cost-effective regardless of the model of care. However, those able to provide a contemporary 'one-stop' service would need to weigh up the additional costs associated with

OPH+EBx over simply OPH alone to gain a further health benefit. Similarly, those Units utilising a traditional multi-stop set up would need to consider the much reduced costs of initial testing with SIS against the reduction in health benefit when compared to a combination of OPH + EBx.

It seems likely that the drive to provide outpatient testing and where possible simple concomitant treatments will continue in light of the convenience for patients and their doctors as well as the on-going improvement in health technologies. Therefore, because the base case analysis based upon the premise of a one-stop service, indicated that OPH was the optimal strategy (regardless of wish for fertility or prior treatment with LNG-IUS (see below)), it may be consistent to employ combination testing from the outset with OPH and EBx in hospitals that don't yet have 'one-stop' facilities in place. This would allow the services in these centres to evolve until they were able to offer 'one-stop' care based upon initial testing with OPH in women presenting with HMB. The alternative for these hospitals would be to adopt SIS as the first line test for investigating HMB, training doctors, nurses and sonographers in the technique. However, future re-investment in equipment and training to establish one-stop services based upon initial testing with OPH may become necessary if such service models become embedded.

Fertility preservation

Heavy menstrual bleeding is most common in parous women in their fifth decade of life (186). Thus, the majority of women presenting to secondary care have completed their families. However, some women with HMB do want to retain their fertility potential and to take account of this and to test the generalisability of the base case findings an additional

model was produced for women wishing to preserve their fertility which precluded certain surgical treatment options. The findings of this additional analysis were consistent with the base case scenario with OPH remaining the most cost-effective first line diagnostic test of choice. SIS was the closest, viable competing testing option. Adopting OPH rather than SIS, costs an additional £2720 to achieve an extra woman satisfied but this is likely to be considered affordable and worthwhile by health services. Moreover, at willingness to pay (WTP) thresholds of around £5000, there is a greater than 90% certainty of OPH being the most cost-effective option. Indeed, SIS only appeared to be cost-effective over a very narrow range of WTP values and even then there was considerable observed uncertainty.

Universal LNG-IUS treatment prior to referral

A further analysis using a modified decision model, was based upon the situation envisaged by NICE in their 2007 report into the management of HMB (142) where all women referred from primary care with HMB have received prior treatment with a LNG-IUS. Even in this scenario, OPH continued to be the favoured, cost-effective option with an ICER of £5480 for each additional woman satisfied and increasing certainty of cost-effectiveness with increasing, but viable, WTP levels. Although the combination of TVS and EBx was a more effective approach, it's ICER of over £500,000 prohibits its use as a sensible diagnostic strategy for adoption by the NHS.

'See and Treat'

Outpatient hysteroscopy is consistently the preferred first line testing strategy for women with HMB irrespective of their desire for future fertility and regardless of pre-referral treatment with the LNG-IUS. One consideration driving the economic benefits of OPH over other tests

is that the modality allows treatment for most pathology to be initiated at the same time as the diagnosis, thereby reducing the number of patient attendances and costs. This contemporary 'see & treat' ambulatory approach in gynaecological practice is increasingly being adopted. There are also additional benefits of embracing this philosophy not accounted for in the analysis e.g. improved safety, lowered infection risks, convenience, rapid discharge and recovery (6). Only 30% of women in the model required a further appointment in order to return for treatment at a later stage in the OPH testing strategy. This was because all women presenting with polyps or pathology suitable for treatment with a LNG-IUS could be treated at their first appointment if diagnosed correctly. For scanning modalities, concomitant treatment was still possible for the same proportion of women, however the cost is elevated slightly because of the additional cost of hysteroscopy and polypectomy for the 19% of women with endometrial polyps. Furthermore, the accuracy of TVS for the diagnosis of focal pathology is reduced compared with OPH. This consideration combined with the additional costs of the OPH needed to perform the polypectomy for both TVS and SIS scanning approaches, contributes to their reduced cost-effectiveness compared with OPH. This was even more apparent for strategic testing approaches utilising EBx from the outset where no simultaneous treatment was possible because of the necessity to await the EBx result before making a diagnosis and instituting therapy. 'Real time' bedside testing can be seen to confer an advantage in the efficiency of delivering care. Thus, it is the ability to concomitantly treat as well as diagnose intrauterine pathology with a high degree of accuracy that leads to OPH being the most cost-effective strategy testing strategy in HMB.

Strengths and limitations

The economic evaluation was based upon the construction of comprehensive, contemporary and clinically informed decision trees. All available testing strategies were modelled and a modern, 'one-stop' clinical environment for testing assumed. Test accuracy and performance data were mainly obtained from high quality systematic quantitative reviews of the literature. Other clinical parameter inputs, including treatment effectiveness and disease prevalence were obtained following systematic searches and selection based upon a rigorous evaluation of data quality. Data for the prevalence of fibroids were taken from a database of women from Birmingham and the surrounding area. It should be recognised that this may not be a true reflection of the UK prevalence of fibroids due to the large number of women from ethnic minorities. Producing a comprehensive series of reviews was not the aim of the economic modelling study so although data were identified using a systematic approach, 'systematic reviews' per se were not conducted for each clinical question. When data were not available in the published literature or there was uncertainty regarding the assumed diagnosis or need for further testing, a panel of senior gynaecologists was consulted.

The economic evaluation took the UK NHS as its perspective. This meant that only costs incurred by the NHS were included, and benefits were measured in patient satisfaction. The prime aim of testing in chronic benign conditions like HMB is to improve patient symptomatic outcomes. Thus the approach of evaluating effectiveness in terms of patient satisfaction within the HMB analysis was relevant. Patient satisfaction was chosen in order to (i) ensure consistency with previous research trials undertaken in the field (136) and (ii) because patient satisfaction is deemed to be the co-primary measure of importance (together

with menstrual bleeding) by the Cochrane Menstrual Disorders & Subfertility Group for reviews of interventions for heavy menstrual bleeding (193). Inevitably, this perspective will have excluded other potentially important costs and benefits. For example, the scarcity of HRQL data in AUB precluded a cost-utility analysis and comparison by health care decision makers with competing health care interventions. Whilst feasibility of testing was taken into account, the morbidity (anxiety, discomfort, complications) and psychological implications for women and their families was not. Similarly patient preference for testing was not incorporated into the models or the added value of individual tests outside of the focus of uterine assessment e.g. simultaneous assessment of the ovaries.

The findings of this analysis appear generalisable to modern practice in the UK because a contemporary, one-stop clinical setting was used and it was assumed that minor therapeutic interventions were implemented during the initial visit; when appropriate. Costs were derived from up-to-date HRG data (235); the cost of individual tests were derived and added to the cost of a standard new consultation. This method allowed different strategies to be compared fairly by breaking down the different aspects of each appointment. However, whilst this approach allowed costs in a contemporary 'one stop' clinical setting to be applied, the costs may not accurately reflect the true cost to the NHS. It is unlikely that the HRG codes precisely take account of costs from the clinician's perspective i.e. the additional time and disruption associated with combination testing either from the outset or conditional on preceding tests. For example, the 'one stop' diagnostic testing philosophy combined with the ability to provide concomitant treatment ('see & treat') is certainly convenient and efficient but the additional time required (which is somewhat unpredictable) necessitates the allocation of fewer appointment slots within such clinics. In sensitivity analysis the base case model was

adapted to reflect multi-stop diagnostic and treatment pathways to help inform health providers currently using traditional service models.

Whilst it is certainly the case that a one-stop approach is efficient, obviating the need for further appointments, the UK NHS perspective of this economic analysis may have underestimated the total cost savings of the one-stop service. If a wider social perspective was adopted, the economic benefits of minimising interference to women's lives by avoiding unnecessary follow up appointments and the consequent travel and waiting times, would probably have been substantial. If the costs of absence from paid work and household activities had been quantifiable in monetary units, they may not have been insignificant. Thus it is probable that a one-stop setting for investigation of HMB from a societal viewpoint would have been even more cost-effective compared with traditional multi-stop models of service delivery.

A variety of different benign pathologies underlie HMB and each pathology has its optimal first-line treatment. However, some pathologies e.g. DUB and endometrial hyperplasia, share the same 'optimal' first-line treatment i.e. the LNG-IUS. Moreover, erroneously diagnosed pathologies given 'incorrect' treatment, will generally, still respond to several treatments albeit to a suboptimal degree. Thus, the fact that HMB is usually of benign origin and often responds to treatment with the LNG-IUS to some degree, regardless of pathology, has raised uncertainty over the cost-effectiveness of *any* testing in HMB. It was for this reason that 'no investigation' but LNG-IUS treatment for all was used as the reference strategy against which all other testing options could be compared. However, the universal prescription of the LNG-IUS in secondary care to treat HMB is unlikely to be acceptable to either women who require

an explanation for their symptoms (and may not want a LNG-IUS although the model did not account for patient preferences) or clinicians who are aware that more effective, tailored treatments are available according to the underlying diagnosis. In primary care the situation is different with NICE recommending LNG-IUS as a first-line treatment without stipulating the need for diagnostic testing (142). In view of this, a scenario was modelled where all women with HMB referred to secondary care were refractory to treatment with the LNG-IUS. The inference from this alternate analysis, that investigation should be based upon first-line testing with OPH, was unchanged. Thus, given the data available, the model is comprehensive, pragmatic and relevant to current clinical practice.

Extensive probabilistic sensitivity analyses were conducted to allow for uncertainty, manipulating parameter inputs for clinical assumptions (disease prevalence, test performance, accuracy, and consequences of false diagnoses and effectiveness of treatments) and costs. Acceptability frontiers were drawn to aid assessment and interpretation. The most cost-effective testing strategies remained stable following sensitivity analyses increasing confidence in the conclusions To further evaluate the stability and also transferability of the findings in HMB, alternative models were produced to embrace scenarios where referral to secondary care is restricted to women who remain refractory to effective medical treatment (142) and where preservation of fertility is required.

Simplifications

The aim was to develop economic models that accurately and explicitly mirrored clinical practice. Some simplifications were necessary, driven by a desire to keep the extensive and comprehensive decision trees workable. One problem was how to account for failed testing

and discordance of tests within combination strategies. The accuracy of individual outpatient tests varies according to which pathology is under scrutiny. However, this does not mean that combination testing will be more cost-effective. The model comprehensively evaluated tests used in isolation (with additional testing conditional on the test outcome) and in combination from the outset (again with any further testing being conditional on the combination testing outcome). However, when combination testing was incomplete due to tests within the combination failing, clinicians would then face a dilemma as to what to do next .It was decided to simplify the model with the aim of maintaining consistency and minimising potential bias. Thus the approach used was that any test or tests that failed within a combination testing strategy were assumed to have not allowed a diagnosis to be arrived at (i.e. the testing strategy has failed) and recourse to hysteroscopy, D&C was the result. The limitation of this approach, is its clinical validity and relevance. Undoubtedly many clinicians would consider examination under anaesthesia with hysteroscopy D&C as the 'gold standard' test whereas others may pragmatically arrive at a diagnosis based upon the information provided by the successful tests within the combination strategy. However, there are a huge amount of potential test combinations and failure possibilities to consider. Moreover, it was hard to arrive at any consensus from the expert panel as to what subsequent testing or management decisions would then arise. Therefore the simplification of the model, such that a combination testing strategy was considered incomplete necessitating recourse to D&C, was reasonable in order to maintain consistency and minimise bias. Moreover, the failure rates of tests are generally low and so the impact of this model simplification should have been minimal.

Subtle differences between testing strategies may have been overlooked, for example it was assumed that women could only have one underlying pathology whereas in practice they may co-exist. The most common pathologies underlying HMB were accounted for in the model; DUB, polyps/SMFs, small and large fibroids and significant endometrial disease. Adenomyosis, a condition of the myometrium (uterine muscle) where ectopic endometrial tissue is found, can be associated with HMB but was excluded from the model as it tends to present with pain rather than HMB.

All relevant, widely employed testing modalities were modelled. Endometrial tissue sampling was assumed to be by outpatient EBx and inpatient D&C in failed cases. Endometrial biopsy can however be performed under direct vision by passing miniature forceps down the working channel of an outpatient hysteroscope. This method was not included as it is not widely used and is less likely to provide an adequate tissue sample for histological assessment compared with simpler, cheaper and universal outpatient EBx. Furthermore, OPH and SIS are accurate tests for the diagnosis of focal pathology without recourse to histological confirmation. In addition, focal endometrial disease (cancer and hyperplasia) necessitating a directed biopsy is rare with most endometrial conditions being global hormonally induced phenomena allowing 'blind' sampling technologies to obtain representative, diagnostic samples with a high level of accuracy (150;151).

Testing with magnetic resonance imaging was not examined because NICE recommend that it should not be used for diagnosis in women with HMB on the basis that there are no studies examining its use (142). One study compared MRI to TVS for identification of adenomyosis and found no significant difference between them (236). In addition, MRI is not suitable for

real time outpatient (‘office’) testing and is expensive and rarely used in the diagnosis of HMB unless there are concerns over the nature of uterine fibroids (an infrequent situation) or when suitability for uterine artery embolisation is being assessed.

Assumptions

As with all economic modelling exercises, assumptions had to be made when contentious clinical decision making or paucity of clinical data were encountered and these assumptions were ultimately endorsed by the expert clinical panel. One such area pertained to disease prevalence, estimates of which came from a variety of sources and this meant that to make them sum to one, the prevalence of one ‘disease’, DUB, needed to be a flexible value. The assigned value of 0.32 (32%) may not accurately reflect the true prevalence. However, published data and the expert panel considered this a reasonable estimate. As with the precision of all assumptions, they were subject to sensitivity analyses. In this particular case, the inferences of the base case analysis were not affected with varied, plausible estimates of DUB prevalence. A similar problem was encountered for some accuracy data such that the reciprocal false positive rate estimates, which had originated from diverse data sources, had to be manipulated to total one and these were tested in sensitivity analysis.

The selected outcome measure was satisfaction with treatment at one year because this is one of the most common outcomes measured in RCTs of interventions for HMB (184) and is clinically relevant. Moreover, the availability of other patient reported outcome measures e.g. health related quality of life data, (and especially their application to the specific scenarios that arose from the construction of the comprehensive decision trees) are scarce. Approximating data from published studies was decided to be an inaccurate method for

producing QALYs and so ‘cost per patient satisfied’ was used alone. In addition, the cyclical and intermittent nature of HMB makes it somewhat problematic to calculate QALY’s particularly as women are only affected by the condition for approximately 25% of the year and symptoms will naturally resolve in time once the menopause is reached. Systematic searching and quality appraisal were used to try and identify the optimal data, but with some of the interventions used for particular underlying diagnoses, satisfaction data were not explicitly available. In these cases it was assumed that the outcomes reported (e.g. “reduced bleeding”, “would recommend the treatment”, “cured of cancer”) were indirect measures of satisfaction.

Occasionally, satisfaction data were not reported at one year in which case the data collected closest to one year were used. Using ‘one year’, whilst reasonable in terms of evaluating medium term response, may favour conservative, ‘uterine-sparing’ procedures (the LNG-IUS, endometrial ablation and myomectomy) because their effectiveness reduces over time (136). In contrast, more invasive but definitive hysterectomy is not associated with recurrence of HMB symptoms. Thus, longer term outcome assessment may have made the option of ‘hysterectomy without diagnostic testing’ a more viable option. However, the objective and emphasis of the analysis was to estimate the cost-effectiveness of diagnostic testing. Thus, as long as the treatment options were appropriate and consistently applied according to the diagnosed pathology, the most cost-effective testing strategies should have been delineated. The base case analysis assumed included women to be 45 years old as this is the modal age for presentation to secondary care with HMB. Thus they could be expected to have an average of a further seven years of menstruation before the menopause.

The ability of OPH to facilitate the removal of uterine polyps in addition to simply providing a diagnosis has been highlighted. However, this presumed cost-efficient benefit may be blunted if uterine polyps are not causative of HMB, but simply an incidental finding. NICE were unable to find any data to link uterine polyps and HMB (142) although clinicians do assume some link (172;237). Two systematic reviews of generally low quality, observational studies do however, support the notion of polyp treatment being associated with a 75-100% improvement in HMB complaints (166;167). Even if polyps don't cause HMB they may negatively affect treatment (e.g. impairing the effectiveness of the LNG-IUS) and ultimately cause dissatisfaction (238;239). This may also be a psychological effect given that most women and their clinicians are unwilling to accept conservative management of detected uterine polyps (240). In addition to hysteroscopic surgical interventions such as polypectomy and myomectomy, other uterine sparing therapeutic interventions such as fitting of LNG-IUS or endometrial ablation, may not be successfully completed. For the purposes of the model it was assumed that all treatments were successfully performed given that the objective of the economic analysis was to examine the cost-effectiveness of *diagnostic testing* based upon test performance and accuracy, rather than an assessment of treatment efficacy.

Despite the need for assumptions arising in response to the 'holes' in the evidence base, the analytic modelling methodology allowed an extensive, comprehensive, contemporary and clinically relevant evaluation to be produced. An all-embracing randomised controlled trial, assessing the wide range of diagnostic strategies defined in the models would be a huge, impractical and ultimately futile undertaking.

Comparisons with existing guidance

Current NICE guidance published in 2007 for the management of HMB (142) recommends that TVS should be the diagnostic modality of choice when testing is considered and OPH employed if TVS is inconclusive. This advice was based upon a cost-effectiveness analysis, limited to the assessment of three single testing options; TVS, SIS and OPH. The outcome 'cost per correct diagnosis' did not take into account the range of pathologies under consideration for HMB, and the optimal treatments upon knowledge of the underlying diagnosis. A fuller evaluation is necessary in order to consider the consequences of erroneous diagnosis given that the *raison d'etre* of formulating a diagnosis is to inform and optimise clinical management. Women may serendipitously receive appropriate treatment following a false diagnosis, but more often than not, misdiagnosis results in misallocation of resources and consequent morbidity attributable to unnecessary procedures. In contrast, the comprehensive analysis performed in this thesis reflects the reality of diagnostic evaluation in day to day clinical practice in the UK.

CHAPTER 11

CONCLUSIONS

Summary of the findings of the systematic reviews of outpatient hysteroscopy

The systematic reviews of outpatient hysteroscopy showed that by making small adjustments to the way the procedure is carried out can affect the pain experienced by the patient. The reviews suggest that women attending for an outpatient hysteroscopy should take a non-steroidal anti-inflammatory prior to arriving in clinic to try and reduce pain post-operatively. When considering the effect on pain, the clinician performing the procedure may choose to use a flexible hysteroscope, as this was shown to be less painful. However, there were more failed procedures with flexible scopes and they are more expensive to maintain thus the clinician may decide that the benefits of using a rigid hysteroscope outweigh the increased level of pain, particularly when the pain scores were generally low overall (1.2-4.0). Although there was no difference between carbon dioxide and normal saline in terms of pain scores, normal saline has many other advantages (quicker procedure, reduced shoulder tip pain, acts as a lavage to wash away blood and bubbles and it can be used during bipolar operative procedures) that may prompt clinicians to favour it. Although injectable local anaesthetics were shown to reduce pain, it was unclear how clinically significant this finding was, especially when it was found that using the vaginoscopic technique reduces pain when compared to the traditional procedure. The vaginoscopic technique should be the default

method for conducting outpatient hysteroscopy. Finally, the use of cervical preparation was shown to not affect dilatation of the cervix or reduce pain during the procedure. Furthermore, although the systematic review in this thesis found no significant increase in side effects with the use of misoprostol, other meta-analyses of its use in inpatient procedures have found an association with genital tract bleeding and gastrointestinal symptoms (24;106;107).These findings led to the conclusion that routine cervical preparation with misoprostol prior to outpatient hysteroscopy should be avoided.

An important consideration when interpreting the results of the systematic reviews is that the primary studies tended to use hysteroscopes of 5.5mm in diameter which is much larger than the outpatient hysteroscopes being used today (approximately 3mm). Thus the findings of the reviews of local anaesthetic, cervical preparation and scope type may have even less clinical significance than was suggested by the results.

Ultimately, using a small hysteroscope, via a vaginoscopic approach with normal saline is likely to be acceptable to the majority of women who attend for outpatient hysteroscopy. Local anaesthetic and cervical preparation should not routinely be used, however, future research should investigate whether certain populations might benefit from these interventions (postmenopausal or nulliparous women).

Summary of the comparison of the SIGN and GRADE methods for assessing evidence quality

The comparison of the SIGN and GRADE methods for grading evidence quality in clinical guidelines found that SIGN gives higher gradings of evidence quality than GRADE. This may be because GRADE underestimates the quality but it seems more likely that this is due to SIGN overestimating the quality due to its less rigorous assessment of methodology. GRADE was found to be difficult to use because of the complex method of assessment and although the intention is that GRADE is standardised, there are numerous opportunities for subjectivity to be introduced. Neither GRADE nor SIGN appear to be the ideal method for classifying and displaying evidence quality. A hybrid version which performs an in-depth assessment but displays this data graphically rather than in tabulated form may result in more 'user-friendly' clinical guidance.

Summary of findings of the economic analysis of HMB

The economic analysis identified two potentially cost-effective testing strategies for the investigation of women with HMB. These were initial testing with OPH alone or in combination with EBx. To adopt a strategy of OPH, £360 needs to be invested to gain one more woman satisfied at one year compared to a strategy of empirical treatment with a LNG-IUS. Although a testing strategy of OPH +EBx is marginally more effective, the ICER is approximately £21,000 to gain one more satisfied patient compared to OPH. This approximates to around £26,500 per QALY which falls within the £20,000-£30,000 per QALY threshold. These findings were stable during sensitivity analyses, varying model

inputs including disease prevalence, test feasibility and accuracy, with OPH remaining more cost-effective than the LNG-IUS reference strategy even at relatively low willingness to pay thresholds. In women wishing to preserve their fertility, therapy with endometrial ablation and hysterectomy are contra-indicated. SIS was cost-effective in this situation, with an ICER of approximately £2000, but for an additional financial outlay of £2720, testing instead with OPH produces a further satisfied patient, which is likely to be considered affordable and worthwhile by the NHS. Sensitivity analysis also showed SIS to be a cost-effective testing option along with the combination testing strategy of OPH + EBx within the context of traditional multi-stop pathways, although such service models are likely to diminish over time with the on-going improvement and increasing availability of portable diagnostic health technologies. Outpatient hysteroscopy remains the most cost-effective testing option if a scenario is envisaged where only women with HMB refractory to the LNG-IUS, recommended first line treatment in general practice (142), are referred to secondary care for investigation. In this situation, it was estimated that £5480 extra funding is necessary for each additional woman satisfied. No other testing strategies fell within plausible willingness to pay ranges.

Therefore, the data are consistent in supporting OPH as the diagnostic testing strategy of choice for women referred to secondary care with HMB irrespective of their desire for future fertility and regardless of pre-referral treatment with the LNG-IUS. A combination strategy of OPH+EBx may be cost-effective at the upper NICE willingness to pay threshold, in women without a desire to retain their fertility who have not undergone pre-referral treatment with the LNG-IUS or in women investigated through a traditional multi-visit pathway.

Summary of the role of outpatient hysteroscopy as investigated by this thesis

Outpatient hysteroscopy is clearly an important intervention in gynaecological care not only as a diagnostic test but also as an operative procedure (111;241). However, there was no consensus on how to best perform the procedure until the systematic reviews and meta-analyses in this thesis were produced. The results led to development of a clinical guideline which is now available from the RCOG (website http://www.rcog.org.uk/womens-health/clinical-guidance/hysteroscopy-best-practice-outpatient-green-top-59) and is influencing patient care.

The economic analysis confirmed that outpatient hysteroscopy is not only cost-effective when compared to other outpatient diagnostic test but that it is likely to be the most cost-effective test for investigating women with HMB when used in a contemporary setting.

APPENDIX 1

A1.1 Search strategy for systematic review and meta-analysis of local anaesthesia for pain control during outpatient hysteroscopy

1.1a Medline (1950- September 2008)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. 1 OR 2
4. Vaginoscopy. Ti,ab
5. 3 OR 4
6. ANAESTHETICS, LOCAL/ OR LIDOCAINE/ OR BUPIVICAINE/ OR ANAESTHESIA, LOCAL/ OR PROCAINE
7. "local anaesthetic".ti,ab
8. (local AND anaesthe*).ti,ab
9. 6 OR 7 OR 8
10. 5 AND 9

1.1b EMBASE (1980 to September 2008)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. 1 OR 2
4. VAGINOSCOPY/
5. Vaginoscopy.ti,ab
6. 4 OR 5
7. 3 OR 6
8. LOCAL ANESTHTEIC AGENT/ OR LOCAL ANESTHESIA/ OR BUPIVICAINE/ OR LIDOCAINE/ OR MEPIVICAINE/ OR ROPIVICAINE/ OR PRILOCAINE/ OR LEVOBUPIVICAINE/ OR TETRACAINE/
9. "local anaesthetic".ti,ab
10. 8 OR 9
11. 7 AND 10

1.1c CINAHL (1981 to September 2008)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. Vaginoscopy.ti,ab
4. 1 OR 2 OR 3
5. ANESTHESIA, LOCAL/ OR ANESTHTICS, LOCAL/
6. "local anaesthetic".ti,ab
7. 5 OR 6
8. 4 AND 7

1.1d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND anaesthetic

A1.2 Search strategy for the systematic review of analgesia for pain control during outpatient hysteroscopy

1.2a Medline (1950- September 2008)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. 1 OR 2
4. Vaginoscopy. Ti,ab
5. 3 OR 4
6. ANALGEISA/
7. ANALGESICS/ OR ANALGESICS, NON-NARCOTIC/ OR ANALGESICS, OPIOID/
8. Analges*.ti,ab
9. 6 OR 7 OR 8
10. 5 AND 9

1.2b EMBASE (1980 to September 2008)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. 1 OR 2
4. VAGINOSCOPY/
5. Vaginoscopy.ti,ab
6. 4 OR 5
7. 3 OR 6
8. ANALGESIA/
9. ANALGESIC AGENT/
10. Analges*.ti,ab
11. 8 OR 9 OR 10
12. 7 AND 11

1.2c CINAHL (1981 to September 2008)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. Vaginoscopy.ti,ab
4. 1 OR 2 OR 3
5. ANALGESIA/
6. analgesia.ti,ab
7. analges*.ti,ab
8. ANALGESICS/ OR ANALGESICS, OPIOID/ OR ANALGESICS, NONNARCOTIC/ OR NARCOTICS/ OR TRAMADOL/ OR ANTIINFLAMMATORY AGENTS, NON-STEROIDAL/
9. 5 OR 6 OR 7 OR 8
10. 4 AND 9

1.2d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND analgesia

A1.3 Search strategy for the systematic review of conscious sedation for pain control during outpatient hysteroscopy

1.3a Medline (1950- September 2008)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. 1 OR 2
4. Vaginoscopy. Ti,ab
5. 3 OR 4
6. CONSCIOUS SEDATION/
7. "conscious sedation".ti,ab
8. 6 OR 7
9. HYPNOTICS AND SEDATIVES/
10. Sedative.ti,ab
11. 9 OR 10
12. 8 OR 11
13. 5 AND 12

1.3b EMBASE (1980 to September 2008)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. 1 OR 2
4. VAGINOSCOPY/
5. Vaginoscopy.ti,ab
6. 4 OR 5
7. 3 OR 6
8. CONSCIOUS SEDATION/
9. "conscious sedation".ti,ab
10. SEDATIVE AGENT/
11. Sedative.ti,ab
12. 8 OR 9 OR 10 OR 11
13. 7 AND 12

1.3c CINAHL (1981 to September 2008)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. Vaginoscopy.ti,ab
4. 1 OR 2 OR 3
5. CONSCIOUS SEDATION/
6. "conscious sedation".ti,ab
7. HYPNOTICS AND SEDATIVES/ OR SEDATIVES, BARBITURATE/ OR SEDATIVES, NONBARBITURATE/
8. Sedate*.ti,ab
9. 5 OR 6 OR 7 OR 8
10. 4 AND 9

1.3d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND sedation

A1.4 Search strategy for the systematic review of cervical preparation for pain control during outpatient hysteroscopy

1.4a Medline (1950- February 2010)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. 1 OR 2
4. Vaginoscopy. Ti,ab
5. 3 OR 4
6. MISOPROSTOL/ OR DINOPROSTONE
7. LAMINARIA/
8. PROSTAGLANDINS/ OR PROSTAGLANDINS, SYNTHETIC/
9. ESTROGENS/
10. (oestrogen OR estrogen).ti,ab
11. PROGESTERONE/
12. PROGESTINS/
13. CERVICAL RIPENING/
14. "cervical preparation".ti,ab
15. laminaria.ti,ab
16. prostaglan*.ti,ab
17. progest*.ti,ab
18. "cervical ripening".ti,ab
19. 6 AND 7 AND 8 AND 9 AND 10 AND 11 AND 12 AND 13 AND 14 AND 15 AND 16 AND 17 AND 18
20. 5 AND 20

1.4b EMBASE (1980 to February 2010)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. 1 OR 2
4. VAGINOSCOPY/
5. Vaginoscopy.ti,ab
6. 4 OR 5
7. 3 OR 6
8. MISOPROSTOL/ OR GEMEPROST/ OR PROSTAGLANDIN E2/ OR MIFEPRISTONE/ OR DILAPAN/ OR PROSTAGLANDIN/ OR UTERINE CERVIX DILATATION/
9. UTERINE CERVIX RIPENING/
10. 8 OR 9
11. "cervical ripening".ti,ab
12. 10 OR 11
13. LAMINARIA/
14. laminaria.ti,ab
15. 13 OR 14
16. 12 OR 15
17. 7 AND 16

1.4c CINAHL (1981 to February 2010)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. Vaginoscopy.ti,ab
4. 1 OR 2 OR 3
5. MISOPROSTOL.ti,ab
6. Laminaria.ti,ab
7. prostaglandins.ti,ab
8. (oestrogen OR estrogen).ti,ab
9. progest*.ti,ab
10. "cervical ripening".ti,ab
11. "cervical prep*".ti,ab
12. MISOPROSTOL/
13. PROSTAGLANDINS/
14. ESTROGENS/
15. PROGESTERONE/
16. CERVIX DILATATION AND EFFACEMENT/
17. 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
18. 4 AND 17

1.4d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND cervical

A1.5 Search strategy for the systematic review of the effect of the vaginoscopic approach to outpatient hysteroscopy on pain

1.5a Medline (1950- February 2009)

1. HYSTEROSCOPY/ae,mt [ae=Adverse Effects, mt=Methods]
2. hysteroscopy.ti,ab
3. Vaginoscopy.ti,ab
4. "no touch".ti,ab
5. HYSTEROSCOPY/
6. Vaginoscop*.ti,ab
7. 2 OR 5
8. 1 OR 3 OR 4 OR 6
9. 7 AND 8

1.5b EMBASE (1980 to February 2009)

1. exp HYSTEROSCOPY/
2. hysteroscopy.ti,ab
3. 1 OR 2
4. VAGINOSCOPY/
5. Vaginoscopy.ti,ab
6. "no touch".ti,ab
7. 1 OR 2
8. 3 OR 4 OR 5
9. Vaginoscop*.ti,ab
10. 7 OR 9
11. 6 AND 10

1.5c CINAHL (1981 to February 2009)

1. Hysteroscopy.ti,ab
2. HYSTEROSCOPY/AE,MT,AE,MT [AE=Adverse Effects, MT=Methods, AE=Adverse Effects, MT=Methods]
3. Vaginoscopy.ti,ab
4. “no touch”.ti,ab
5. 2 OR 3 OR 4
6. 1 AND 5
7. Vaginoscop*.ti,ab
8. 5 OR 7
9. HYSTEROSCOPY/
10. 1 OR 9
11. 8 AND 10

1.5d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND (vaginoscopy OR vaginoscopic OR "no-touch")

A1.6 Search strategy for the systematic review of the effect of distension media on pain during outpatient hysteroscopy

1.6a Medline (1950- February 2009)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. 1 OR 2
4. Vaginoscopy. Ti,ab
5. 3 OR 4
6. DEXTRANS/ OR SODIUM CHLORIDE/ OR MANNITOL/ OR SORBITOL/
7. "distension media".ti,ab
8. (uter* AND disten*).ti,ab
9. CARBON DIOXIDE
10. "carbon dioxide".ti,ab
11. 6 OR 7 OR 8 OR 9 OR 10
12. 5 AND 11

1.6b EMBASE (1980 to February 2009)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. 1 OR 2
4. VAGINOSCOPY/
5. Vaginoscopy.ti,ab
6. 4 OR 5
7. 3 OR 6
8. (uter* AND disten*).ti,ab
9. "distension media".ti,ab
10. SODIUM CHLORIDE/ OR CARBON DIOXIDE/
11. 8 OR 9 OR 10
12. 7 AND 11

1.6c CINAHL (1981 to February 2009)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. Vaginoscopy.ti,ab
4. 1 OR 2 OR 3
5. "distension media".ti,ab
6. NORMAL SALINE/ OR SALINE SOLUTION, HYPERTONIC/ OR SODIUM CHLORIDE/
7. DEXTRANS/
8. Dextrans.ti,ab
9. MANNITOL/
10. Mannitol.ti,ab
11. CARBON DIOXIDE/
12. "carbon dioxide".ti,ab
13. (uter* AND disten*).ti,ab
14. 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 Or 14 OR 15
15. 4 AND 14

1.6d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND distension

A1.7 Search strategy for systematic review of the effect on pain of the type of hysteroscope used for outpatient hysteroscopy

1.7a Medline (1950- February 2009)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. vaginoscopy. Ti,ab
4. flexible.ti,ab
5. flex*.ti,ab
6. rigid.ti,ab
7. rigid*.ti,ab
8. 1 OR 2 OR 3
9. 4 OR 5 OR 6 OR 7
10. 8 AND 9

1.7b EMBASE (1980 to February 2009)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. VAGINOSCOPY/
4. Vaginoscopy.ti,ab
5. Flex*.ti,ab
6. Rigid.to,ab
7. Rigid*.ti,ab
8. Flexible.ti,ab
9. 5 OR 6 OR 7 OR 8
10. 1 OR 2 OR 3 OR 4
11. 9 AND 10

1.7c CINAHL (1981 to February 2009)

1. HYSTEROSCOPY/
2. Hysteroscopy.ti,ab
3. Vaginoscopy.ti,ab
4. Flexible.ti,ab
5. Flex*.ti,ab
6. Rigid.ti,ab
7. Rigid*.ti,ab
8. 4 OR 5 OR 6 OR 7
9. 1 OR 2 OR 3
10. 8 AND 9

1.7d The Cochrane Library (Cochrane Central Register of Controlled Trials)

1. hysteroscopy AND (flexible OR rigid)

APPENDIX 2

Data retrieval form for systematic review and meta-analysis of local anaesthesia for pain control during outpatient hysteroscopy

The following form was used for data extraction from studies selected for use in the systematic review of local anaesthesia. The data extraction forms used for the other systematic reviews were adapted to evaluate the different interventions by changing the selection criteria and the secondary outcomes.

Reviewer ……. Paper No. …….. Name of 1st author & year……

Selection criteria (therapy study):

Ring the appropriate category(ies)

i)	population – women undergoing out-patient hysteroscopy	yes / no
ii)	intervention – use of local anaesthetic	yes / no
iii)	outcome – patient experience i.e. pain / feasibility	yes / no

Select this study (i-iii inclusive) yes / no

if no reject & specify reason

……..

Data Retrieval:

Study Design:

(1) Study Design RCT Yes [ ] No [ ]

(2) Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?

Yes [ ] No [ ]

Was the method to generate the sequence of randomization described?

Yes [ ] No [ ]

If yes was it:

appropriate (table of random numbers, computer generated etc)? [ ]

or

Inappropriate (patients were allocated alternately, or according to DOB etc.) [ ]

(3) Was the study described as blinded? Double [ ] Single [ ] Not blinded [ ] NR [ ]

If double blind was the method:

Appropriate (identical placebo, active placebo, dummy, etc.). [ ]

Or

Inappropriate (e.g. comparison of pill v. injection without double dummy). [ ]

(4) Was there a description of withdrawals and dropouts? Yes [ ] No [ ]

(Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.)

Population:

(1) Type of patient Premenopausal [ ] Postmenopausal [ ] Both [ ]

(2) No. patients recruited **A** original population n=……

B Pre-enrolment /randomisation n=……

exclusions (reasons e.g. pop characteristics)

…….

C actually recruited (**A-B**) n=……

D post-enrolment /randomisation n=……

exclusions (reasons e.g. missing data, drop-outs)

……..……..…

E analysable data **(C-D)** n=……

(3) Type of procedure Diagnostic [ ] Operative [ ]

Speculum used Yes [ ] No [ ] Sometimes [ ]

Scope type and size.....

Distension medium used .....…….....

Pipelle sample taken Yes [ ] No [ ] Sometimes [ ]

Intervention:

(1) Type & nature of anaesthesia

No in intervention group…….....…….....…….

What anaesthetic?

……..…Dose……..……....…….……....……

Method of administration (e.g. Direct cervical / paracervical)……

When administered?……..…….…….

No. in control group …….…….……..

Control method (e.g. placebo used etc.).....……..

(2) Description of technique (i.e. could we reproduce it) Adequate / Inadequate

Outcome:

(1) Method of assessing pain e.g. pain scores, VAS, use of post op analgesia, BP measurements, cortisol

……

……

(2) Was pain relief / assessment defined? yes / no

If so, how.....

(3) Pain results

	Intervention group	Control group
Number in group		
Values (e.g. mean, sd)		
Pain scores		

(4) Completeness of Follow up (%) >90 / 81-90 / <81 %

Secondary outcomes:

(1) Fail to perform procedure NR inter grp. n=……control grp n= .....

(2) Need for post-op analgesia NR inter grp. n=……. control grp. n=….....

(3) Complication rate NR inter grp. n=……. control grp. n=….....

(4) Vasovagal reactions NR inter grp. n=……. control grp. n=….....

Has 'vasovagal' been defined? yes / no

If so, how?.....

.....

(5) Patient admitted NR inter grp. n=……. control grp. n=….....

(6) Other (e.g. patient satisfaction) NR inter grp. n=……. control grp. n=….....

2x2 Contingency tables (RCT / controlled studies only):

Local Anaesthetic

Outcome→ Intervention↓	Pain	No / acceptable pain	Total
Anaesthetic			
Control / Comparison			
Total			

Vasovagal episodes

Outcome→ Intervention↓	Outcome present	Outcome absent	Total
Surgery			
Control / Comparison			
Total			

Other

Outcome→ Intervention↓	Outcome present	Outcome absent	Total
Surgery			
Control / Comparison			
Total			

APPENDIX 3

Jadad method for scoring the Quality of Randomised Controlled Trials (50)

1. Was the study described as randomized (this includes the use of words such as randomly, random, and randomisation)?
2. Was the study described as double blind?
3. Was there a description of withdrawals and dropouts?

Scoring the items:

Either give a score of 1 point for each ”yes” or 0 points for each “no.” There are no in-between marks.

Give 1 additional point if:

For question 1, the method to generate the sequence of randomisation was described **and** it was appropriate (table of random numbers, computer generated, etc.).

and/or:

If for question 2 the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.).

Deduct 1 point if:

For question 1, the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and/or:

For question 2, the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).

Guidelines for Assessment

1. Randomisation

A method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should be not regarded as appropriate.

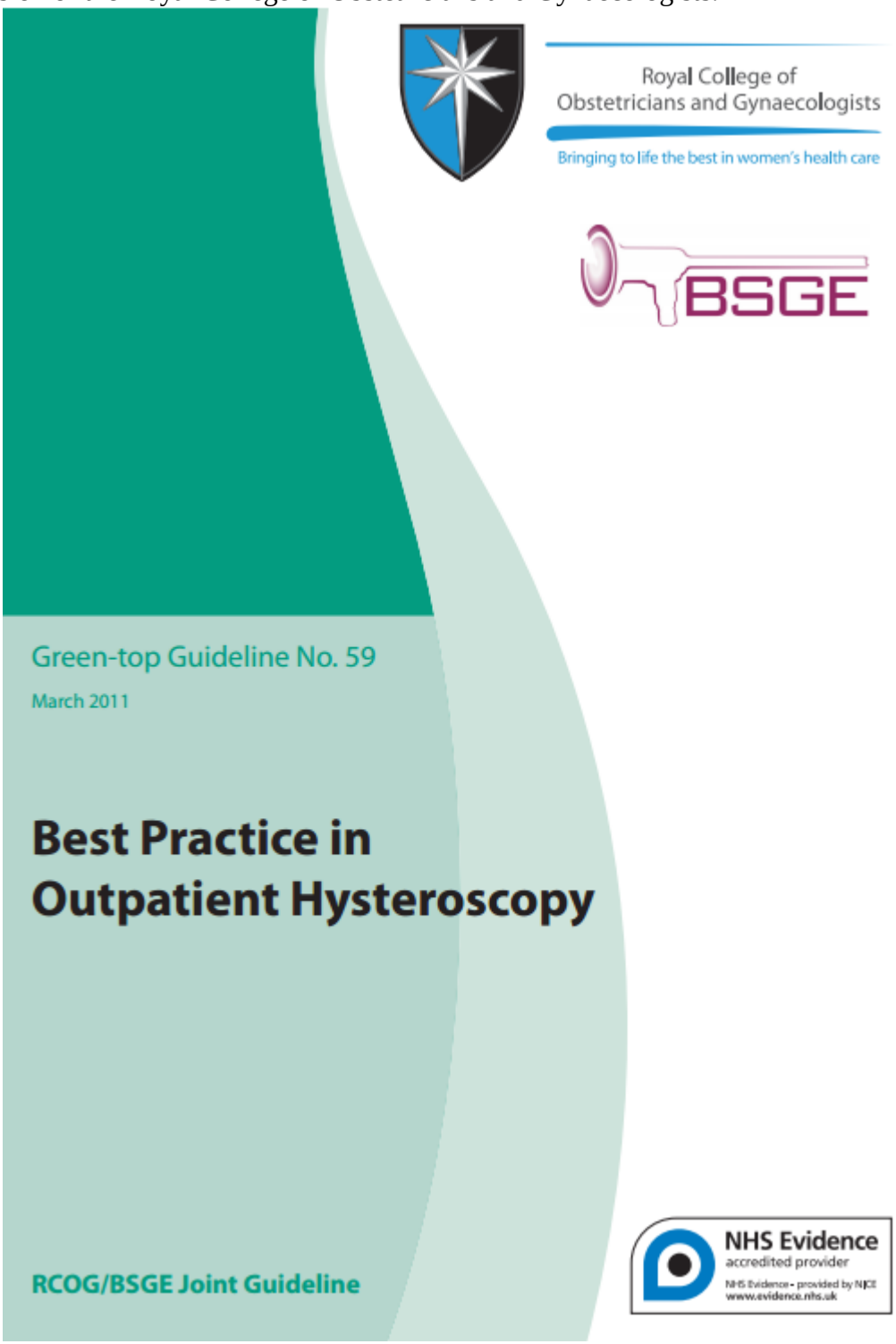
2. Double blinding
A study must be regarded as double blind if the word “double blind” is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

3. Withdrawals and dropouts
Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

APPENDIX 4

'Best Practice in Outpatient Hysteroscopy' Guideline

Reproduced from: Royal College of Obstetricians and Gynaecologists. *Best Practice in Outpatient Hysteroscopy*. Green-top Guideline No. 59. London: RCOG; 2011, with the permission of the Royal College of Obstetricians and Gynaecologists.



There is insufficient evidence to recommend 0° or fore-oblique optical lenses (i.e. 12°, 25° or 30° off-set lenses) for routine outpatient hysteroscopy. Choice of hysteroscope should be left to the discretion of the operator. ✓

Flexible hysteroscopes are associated with less pain during outpatient hysteroscopy compared with rigid hysteroscopes. However, rigid hysteroscopes may provide better images, fewer failed procedures, quicker examination time and reduced cost. Thus, there is insufficient evidence to recommend preferential use of rigid or flexible hysteroscopes for diagnostic outpatient procedures. Choice of hysteroscope should be left to the discretion of the operator. B

Distension medium

For routine outpatient hysteroscopy, the choice of distension medium between carbon dioxide and normal saline should be left to the discretion of the operator as neither is superior in reducing pain, although uterine distension with normal saline appears to reduce the incidence of vasovagal episodes. A

Uterine distension with normal saline allows improved image quality and allows outpatient diagnostic hysteroscopy to be completed more quickly compared with carbon dioxide. A

Operative outpatient hysteroscopy, using bipolar electrosurgery, requires the use of normal saline to act as both the distension and conducting medium. ✓

Local anaesthesia and cervical dilatation

Blind cervical dilatation to facilitate insertion of the miniature outpatient hysteroscope is unnecessary in the majority of procedures. Routine cervical dilatation is associated with pain, vasovagal reactions and uterine trauma and should be avoided. C

Cervical dilatation generally requires administration of local cervical anaesthesia. Standard protocols regarding the type, maximum dosage and route of administration of anaesthesia should be developed and implemented to help both recognise and prevent rare but potentially serious adverse effects resulting from systemic vascular absorption. ✓

Instillation of local anaesthetic into the cervical canal does not reduce pain during diagnostic outpatient hysteroscopy but may reduce the incidence of vasovagal reactions. A

Topical application of local anaesthetic to the ectocervix should be considered where application of a cervical tenaculum is necessary. A

Application of local anaesthetic into or around the cervix is associated with a reduction of the pain experienced during outpatient diagnostic hysteroscopy. However, it is unclear how clinically significant this reduction in pain is. Consideration should be given to the routine administration of intracervical or paracervical local anaesthetic, particularly in postmenopausal women. A

Miniaturisation of hysteroscopes and increasing use of the vaginoscopic technique may diminish any advantage of intracervical or paracervical anaesthesia. Routine administration of intracervical or paracervical local anaesthetic should be used where larger diameter hysteroscopes are being employed (outer diameter greater than 5 mm) and where the need for cervical dilatation is anticipated (e.g. cervical stenosis). ✓

Routine administration of intracervical or paracervical local anaesthetic is not indicated to reduce the incidence of vasovagal reactions. A

Conscious sedation

Conscious sedation should not be routinely used in outpatient hysteroscopic procedures as it confers no advantage in terms of pain control and the woman's satisfaction over local anaesthesia. A

Life-threatening complications can result from the use of conscious sedation. Appropriate monitoring and staff skills are mandatory if procedures are to be undertaken using conscious sedation. ✓

Vaginoscopy

Vaginoscopy reduces pain during diagnostic rigid outpatient hysteroscopy. A

Vaginoscopy should be the standard technique for outpatient hysteroscopy, especially where successful insertion of a vaginal speculum is anticipated to be difficult and where blind endometrial biopsy is not required. ✓

1. Purpose and Scope

The aim of this guideline is to provide clinicians with up-to-date, evidence-based information regarding outpatient hysteroscopy, with particular reference to minimising pain and optimising the woman's experience.

2. Background

Outpatient hysteroscopy is an established diagnostic test[1–3] that is in widespread use across the UK.[4–6] The procedure involves the use of miniaturised endoscopic equipment to directly visualise and examine the uterine cavity, without the need for formal theatre facilities or general or regional anaesthesia. Outpatient hysteroscopy is indicated primarily in the assessment of women with abnormal uterine bleeding,[1–3] but is also employed in the diagnostic work-up of reproductive problems. More recently, advances in endoscopic technology and ancillary instrumentation have facilitated the development of operative hysteroscopic procedures in an outpatient setting with or without the use of local anaesthesia. Common procedures include endometrial polypectomy,[6–8] removal of small submucous fibroids,[9] endometrial ablation,[10–13] removal of lost intrauterine devices and transcervical sterilisation.[14]

Outpatient hysteroscopy, whether diagnostic[1,15] or operative,[6–14] is successful, safe and well tolerated. However, as with any procedure requiring instrumentation of the uterus, outpatient hysteroscopy can be associated with significant pain,[16,17] anxiety and embarrassment.[18] This not only impacts upon women's satisfaction with their experience, but also limits the feasibility and possibly the safety, accuracy and effectiveness of the procedure. To minimise pain and discomfort, variations in hysteroscopic equipment, adaptations to the technique and use of pharmacological agents have been advocated. This guideline assesses these components along with issues relating to optimal service provision.

3. Identification and assessment of evidence

Four databases were systematically searched: MEDLINE (from 1950 to September 2008), EMBASE (from 1980 to September 2008), CINAHL (from 1981 to September 2008) and the Cochrane library. No restrictions were placed on the searches in an attempt to reduce selection bias. The databases were searched using the relevant MeSH terms and keywords. The main keywords used were 'hysteroscopy and vaginoscopy', which were used with combinations of the following words depending upon the area of hysteroscopy being examined: 'anaesthesia', 'analgesia', 'distension media', 'flexible', 'rigid', 'cervical preparation', 'conscious sedation', 'prostaglandins' and 'laminaria'. The results of the searches were systematically reviewed.

Systematic reviews of the literature were conducted, with meta-analyses where possible, to assess pain and feasibility of outpatient hysteroscopy. The definitions of the types of evidence used in this guideline originate from the US Agency for Healthcare Research and Quality. Where possible, recommendations are based on, and explicitly linked to, the evidence that supports them. Areas lacking evidence are highlighted and annotated as 'good practice points'.

4. Service provision

4.1 What is the ideal setting for performing hysteroscopy?

All gynaecology units should provide a dedicated outpatient hysteroscopy service to aid management of women with abnormal uterine bleeding. There are clinical and economic benefits associated with this type of service. A

Outpatient hysteroscopy should be conducted outside of the formal operating theatre setting in an appropriately sized, equipped and staffed treatment room with adjoining, private changing facilities and toilet. ✓

An outpatient hysteroscopy service offers a safe, convenient and cost-effective means of diagnosing and treating abnormal uterine bleeding as well as aiding the management of other benign gynaecological conditions (e.g. fertility control, subfertility and miscarriage and abnormal glandular cervical cytology).[19] A randomised controlled trial reported more rapid mobilisation postoperatively (0 minutes [range 0–5] versus 105 minutes [range 80–120], $P < 0.001$) and quicker recovery to preoperative levels (2 days [range 1–2.7] versus 3 days [range 2–4], $P < 0.05$) favouring diagnostic outpatient hysteroscopy compared with traditional day-case hysteroscopy under general anaesthesia.[20] The same study demonstrated high and equivalent levels of women's satisfaction with outpatient hysteroscopy in conscious women compared with day-case procedures under general anaesthesia. There were also economic benefits for women, the health service and society at large. Compared with day-case procedures under general anaesthesia, women undergoing outpatient hysteroscopy required significantly less time off work compared with the day-case group (0.8 days versus 3.3 days, $P < 0.001$) and experienced reduced loss of income and reduced travel costs. Costs per woman to the National Health Service were estimated to be substantially less for outpatient procedures.[21]

Evidence level 1+

4.2 What are the requirements for running an effective outpatient hysteroscopy service?

Outpatient hysteroscopy should be performed in an appropriately sized and fully equipped treatment room. This may be a dedicated hysteroscopy suite or a multi-purpose facility. ✓

The healthcare professional should have the necessary skills and expertise to carry out hysteroscopy. ✓

There should be a nurse chaperone regardless of the gender of the clinician. ✓

Written patient information should be provided before the appointment and consent for the procedure should be taken. ✓

Outpatient hysteroscopy should be performed in an appropriately sized and fully equipped treatment room. This may be a dedicated hysteroscopy suite or a multipurpose facility. Outpatient hysteroscopy can be associated with substantial anxiety,[18] so the treatment room should be private and patient friendly, with a separate, and ideally adjoining, changing area with a toilet. Adequate resuscitation facilities should be available, as should a comfortable recovery area with refreshment-making facilities. Access to onsite or offsite decontamination facilities of an appropriate standard is necessary. Outpatient hysteroscopy should not be performed in a formal operating theatre setting because this environment is likely to provoke anxiety in the woman and negate the economic advantages associated with avoiding use of expensive operating theatres. Appropriate staffing levels are required; these will vary according to local circumstances (patient populations, numbers seen per clinic) and the type of service offered (concomitant pelvic ultrasound, pure diagnostic service or diagnostic and therapeutic service). In general, there will be a complement of up to three support staff consisting of at least one registered general nurse and healthcare assistants. When possible, one of the staff members should act as the woman's advocate during the procedure to provide reassurance, explanation and support. Communication with the woman in this way may help alleviate anxiety and divert their attention, thereby minimising pain and embarrassment (the so-called 'vocal local').

Adequate, clear and simple written patient information should be provided with the appointment letter. The information will vary according to local circumstances and the type of service offered. Where simultaneous treatments are offered ('see and treat' services), it is important that this fact is reflected in the patient literature to facilitate informed choice. It is good clinical practice to obtain formal consent for outpatient hysteroscopy before the procedure. Practice should conform to recommendations on consent from the General Medical Council and the RCOG. The RCOG has produced Consent Advice No. 1: *Diagnostic hysteroscopy under general anaesthesia*,[22] which should be used in conjunction with RCOG Clinical Governance Advice No. 6: *Obtaining valid consent*.[25] Women should be able to access advice following any intervention (e.g. a direct line to the clinic and an out-of-hours contact number). Consideration should be given to allow direct access for GPs according to locally developed criteria and selected groups of women to aid streamlining of the service.

Evidence level 4

5. Analgesia

5.1 Do analgesics given before diagnostic hysteroscopy reduce the pain felt by women during the procedure?

Routine use of opiate analgesia before outpatient hysteroscopy should be avoided as it may cause adverse effects. B

Women without contraindications should be advised to consider taking standard doses of non-steroidal anti-inflammatory agents (NSAIDs) around 1 hour before their scheduled outpatient hysteroscopy appointment with the aim of reducing pain in the immediate postoperative period. B

A systematic review[24] identified six studies which examine the use of analgesics compared with controls before outpatient hysteroscopy.[25–30] All of these studies were randomised controlled trials. Three of the studies examined the use of opiate drugs[25–27] and three examined NSAIDs.[28–30]

Two of the opiate studies examined the use of 100 mg tramadol administered approximately 50 minutes before the outpatient hysteroscopy, one study giving the tramadol intramuscularly[25] and the second giving it as an intravenous infusion.[26] The first study found that the women who had received tramadol had significantly less pain at the end of the procedure than women in the intracervical block group and the women who received no medication ($P = 0.001$ and $P < 0.001$, respectively).[25] Although this was a low-quality study, the result was supported by those from the second, high-quality study which reported significantly lower pain scores in the tramadol group compared with placebo both during ($P < 0.012$) and 15 minutes after ($P < 0.008$) the procedure.[26] The third opiate study examined the use of sublingual buprenorphine 0.2 mg 40 minutes before the procedure compared with placebo. There was no significant pain reduction with the use of buprenorphine overall and when stratified for menopausal status and parity.[30] Two studies reported adverse effects.[26,30] The tramadol study found no significant difference between the groups in terms of incidence of nausea, vomiting or bradycardia.[26] Conversely, in the buprenorphine study there was a high incidence of adverse effects (nausea, vomiting and drowsiness) in the intervention group (38.8%) and none in the control group.[30]

Evidence level 1–

Three trials examined the use of NSAIDs before outpatient hysteroscopy.[28–30] One of these studies assessed the use of 50 mg oral diclofenac 1–2 hours before the procedure and found that it did not significantly reduce the pain experienced compared with placebo: mean (standard deviation) in the diclofenac group 3.0 (2.5) versus 3.0 (2.9) in the control group.[30] Vasovagal reactions were not reduced in the diclofenac group compared with the placebo group (four reactions and five reactions, respectively). The only adverse effects were in the diclofenac treatment group, but these were mild and self-limiting (one woman reported drug rash and one complained of epigastric pain). The second NSAID study compared the use of 500 mg oral

Evidence level 1–

mefenamic acid 1 hour before the procedure with placebo.[29] This study found that mefenamic acid did not significantly reduce the pain of the hysteroscopy; however, it did significantly reduce the pain experienced at 30 minutes ($P < 0.01$) and 60 minutes ($P < 0.05$). Adverse effects were not reported for either group. The final study examined the use of ketorolac 30 mg intramuscularly given with an intracervical block 45 minutes before the procedure, compared with cervical block alone.[28] The paper reports a significant reduction in pain with the addition of ketorolac; however, it does not report P values and there were only 12 women in each arm of the study, making it difficult to draw strong conclusions from the results.

Evidence level 1–

No studies were identified addressing the issue of timing of analgesia before outpatient hysteroscopy. The onset of action of these drugs means that to be effective they need to be given in advance of the woman's appointment. Optimal timing depends upon the agent used (half-life, rate of absorption, etc.) and the route of administration, but in general simple, non-opioid analgesics given orally, such as 1000 mg paracetamol or 400 mg ibuprofen, should be taken around 1 hour before the scheduled appointment time. Thus, it is likely to be more practical to advise women to take simple analgesics in advance of their appointment rather than administer them in hospital. Routine patient information leaflets posted to the woman with details of their appointment can advise them to consider taking simple analgesics before they attend their appointment, with the proviso that they have taken them before without ill effects. This approach is likely to be of more benefit in those units offering simultaneous hysteroscopic diagnosis and treatment (i.e. the 'see and treat' clinic), where the levels of discomfort experienced are likely to be increased.

Evidence level 4

6. Cervical preparation

6.1 *Does cervical preparation reduce uterine trauma, failure to access the uterine cavity or pain associated with outpatient hysteroscopy?*

Routine cervical preparation before outpatient hysteroscopy should not be used in the absence of any evidence of benefit in terms of reduction of pain, rates of failure or uterine trauma.

A

Uterine trauma (lacerations to the cervix or uterine perforation) is recognised with blind and endoscopic instrumentation of the uterus,[1,31–34] with an estimated perforation incidence of 0.002–1.7%. The incidence of uterine trauma is low for diagnostic outpatient hysteroscopy performed with small-diameter endoscopes (outer sheath diameter under 5.5 mm) under direct vision.[1] Factors associated with uterine trauma include the need for blind dilatation, cervical stenosis (e.g. atrophy, cervical surgery, previous caesarean section, nulliparity), a tortuous cervical canal (e.g. in association with fibroids) and a deviated uterine cavity (e.g. acute flexion, pelvic adhesions, fibroids).[15,19]

Prostaglandin or misoprostol administration before diagnostic hysteroscopy performed under general anaesthesia is associated with a reduction in cervical resistance and need for cervical dilatation in premenopausal women[35–37] compared with placebo, although no such benefit was noted in postmenopausal women.[41,41]

A systematic review of the use of cervical preparation before outpatient hysteroscopy identified five randomised controlled trials,[42–46] with administration of prostaglandin regimens varying from 4 hours to 30 hours before hysteroscopy.[47] No reduction in the incidence of lacerations to the cervix with the use of vaginal prostaglandins was demonstrated in the three trials[42,43,46] assessing this outcome (OR 0.59, 95% CI 0.22–1.55).[47]

Evidence level 1+

Prostaglandins are associated with gastrointestinal adverse effects and are contraindicated in severe uncontrolled asthma, chronic adrenal failure, acute porphyria, renal or hepatic impairment and breastfeeding.[48] Four heterogeneous trials assessed the incidence of genital tract bleeding associated with vaginal prostaglandins before outpatient hysteroscopy[42,44–46] and found no increased risk with the use of prostaglandins (OR 1.32, 95% CI 0.52–3.40).[47]

Evidence level 1+

The main reason for failure to successfully perform an outpatient hysteroscopy is inability to access the uterine cavity as a result of cervical stenosis; this is most commonly encountered in the postmenopausal population.[19] Two randomised controlled trials[43,44] have assessed the feasibility of outpatient hysteroscopy after vaginal prostaglandins and a meta-analysis showed no reduction in failure rates (OR 2.12, 95% CI 0.64–7.04).[47]

Evidence level 1+

One randomised controlled trial included in the systematic review examined the use of oral mifepristone. There were no failed hysteroscopies in the study.[47]

Evidence level 1+

Two studies examined the use of misoprostol 400 micrograms given vaginally before hysteroscopy to premenopausal women. The drugs were administered 4 hours before hysteroscopy in one of the studies[42] and 6 hours before hysteroscopy in the other.[45] The low-quality study[42] found that pain during cervical dilatation was significantly reduced after the use of prostaglandin compared with placebo ($P < 0.05$); however, the other, high-quality study[45] found no significant reduction in pain during the hysteroscopy with the use of misoprostol ($P = 0.72$).

Evidence level 1+

One study[43] examined the use of misoprostol 200 micrograms given vaginally 8 hours before hysteroscopy to postmenopausal women. The median pain scores as the hysteroscope passed through the cervical os were five in the intervention group and seven in the placebo group ($P = 0.02$). When the pain severity was assessed by comparing the number of women scoring more than six on the visual analogue scale (i.e. considerable pain), there were significantly fewer in the intervention group ($P = 0.0132$). However, no significant difference between the groups was identified when assessing the presence of pain during clamping of the cervix ($P = 0.74$), during the examination ($P = 0.32$) or during the endometrial biopsy ($P = 0.19$).

Evidence level 1+

Two studies included both pre- and postmenopausal women in their study populations.[44,46] One of the studies[42] gave misoprostol 400 micrograms vaginally 4–6 hours before the hysteroscopy and found that pain at the end of the procedure was significantly less in the intervention group compared with the group receiving no medication ($P = 0.03$). This was judged to be a low-quality study owing to the lack of blinding. The second study[46] gave the same dose of misoprostol 12–24 hours before the procedure and assessed pain after the cervix was dilated to 6 mm. Pain was found to be significantly less in the misoprostol group ($P = 0.004$; when adjusted for baseline pain score $P = 0.01$). This study subgrouped the women according to menopausal status and found that there was a significant reduction in pain for postmenopausal women given misoprostol ($P = 0.004$; when adjusted for baseline scores $P = 0.006$) but not for premenopausal women ($P = 0.56$; when adjusted for baseline scores $P = 0.77$). This was a high-quality study.

Evidence level 1+

One trial assessed oral mifepristone in premenopausal women[49] and found no benefit in terms of reduction in pain experienced during outpatient hysteroscopy (mean pain score 33.4 ± 23.5 versus 37.0 ± 30.0, $P = 0.60$).

Evidence level 1+

No comparative studies were identified for other methods of cervical dilatation before outpatient hysteroscopy (e.g. local/systemic administration of estrogens or osmotic agents).

7. Type of hysteroscope

7.1 What size and angle of hysteroscope should be used in the outpatient setting?

Miniature hysteroscopes (2.7 mm with a 3–3.5 mm sheath) should be used for diagnostic outpatient hysteroscopy as they significantly reduce the discomfort experienced by the woman. A

There is insufficient evidence to recommend 0° or fore-oblique optical lenses (i.e. 12°, 25° or 30° off-set lenses) for routine outpatient hysteroscopy. Choice of hysteroscope should be left to the discretion of the operator. ✓

Four randomised controlled trials have examined how the diameter of hysteroscopes with an outer sheath affects pain during outpatient hysteroscopy.[50–53] One of the studies looked exclusively at postmenopausal women and found that there was significantly less pain associated with outpatient hysteroscopy when a 3.5 mm diameter hysteroscopy system as opposed to a 5 mm diameter system was used ($P < 0.01$), although the procedural success rate was not significantly increased.[52] The remaining three papers compared 5 mm hysteroscopy assemblies with 3 mm,[53] 3.3 mm[51] or 3.5 mm[50] mini-hysteroscopy set-ups. Procedural pain was significantly reduced with the smaller-diameter hysteroscopes in two of the trials ($P < 0.0001$ in both studies);[50,51] however, the third trial found no significant difference.[53] One of the studies reported the procedural success rate and visualisation of the cavity to be significantly better with mini-hysteroscopy ($P < 0.0001$);[50] by contrast, the procedural success rate was not significantly better in the other trial reporting this outcome.[53] Evidence level 1+

No studies were identified that compared 0° hysteroscopes with off-set distal lenses (e.g. 12°, 30°). Off-set lenses offer a wider field of view, a property that can be advantageous in visualising the corneal recesses and tubal ostia within the uterine cavity with minimal external movement of the hysteroscope. Fore-oblique lenses facilitate visualisation of ancillary instrumentation and so are advantageous for operative hysteroscopy. However, 0° hysteroscopes are more intuitive, facilitating entry into the uterine cavity through the cervical canal, which may reduce the need for cervical dilatation as well as minimising discomfort and uterine trauma. Evidence level 4

7.2 Should rigid or flexible hysteroscopes be used routinely in the outpatient setting?

Flexible hysteroscopes are associated with less pain during outpatient hysteroscopy compared with rigid hysteroscopes. However, rigid hysteroscopes may provide better images, fewer failed procedures, quicker examination time and reduced cost. Thus, there is insufficient evidence to recommend preferential use of rigid or flexible hysteroscopes for diagnostic outpatient procedures. Choice of hysteroscope should be left to the discretion of the operator. B

Two small randomised controlled trials compared the pain experienced during outpatient hysteroscopy with the use of a flexible hysteroscope versus a rigid hysteroscope.[54,55] Neither study presented data according to menopausal state or parity. Both studies found that use of the flexible hysteroscope significantly reduced the woman's pain experience during the procedure ($P = 0.0001$ and $P < 0.001$, respectively). One of the studies reported no difference between the flexible and rigid groups in terms of procedure time and image view. There were no failed hysteroscopies in either group.[54] The other study found that rigid scopes gave significantly better image quality ($P < 0.001$) and significantly shortened the time taken to perform the procedure ($P = 0.003$). There were two failed hysteroscopies in the flexible group owing to cervical stenosis and these women were excluded from the analysis. Five more women in the flexible group had to be changed to a rigid hysteroscope because of inability to negotiate the cervical Evidence level 1+

canal or inadequate visualisation. There were no failed hysteroscopies or change to flexible scopes in the rigid group. This study also reported that rigid hysteroscopes were cheaper to purchase and easier to sterilise and maintain than flexible hysteroscopies.[55]

Evidence level 1+

Operative outpatient hysteroscopy using miniature mechanical and electrosurgical equipment is becoming more established. These technologies generally require the use of rigid hysteroscopies.[39] Units offering both hysteroscopic diagnosis and treatment in the outpatient setting should consider the versatility of respective hysteroscopes and relative resource implications when planning the composition of endoscopic equipment.

8. Distension medium

8.1 Which uterine distension medium should be used during outpatient hysteroscopy?

For routine outpatient hysteroscopy, the choice of distension medium between carbon dioxide and normal saline should be left to the discretion of the operator as neither is superior in reducing pain, although uterine distension with normal saline appears to reduce the incidence of vasovagal episodes.

A

Uterine distension with normal saline allows improved image quality and allows outpatient diagnostic hysteroscopy to be completed more quickly compared with carbon dioxide.

A

Operative outpatient hysteroscopy, using bipolar electrosurgery, requires the use of normal saline to act as both the distension and conducting medium.

✓

8.2 Does the type of distension medium affect pain experience during outpatient hysteroscopy?

A systematic review identified seven studies[56–62] that looked at whether normal saline or carbon dioxide uterine distension media were associated with less pain during outpatient hysteroscopy.[62] One study was considered a duplication of data[61] from an earlier study by the same group.[56] Therefore, six studies were included in the meta-analysis.[56–60,62] The meta-analysis showed there to be no significant difference between the pain experienced with the use of carbon dioxide versus normal saline for outpatient hysteroscopy (standard mean difference [SMD] 0.34, 95% CI −0.12 to 0.80).[63]

Evidence level 1++

Uterine distension pressures need to be sufficient to allow systematic inspection of the entire uterine cavity. However, care is needed to ensure that pressures are minimised to avoid overdistension of the uterus and consequent pain.

Evidence level 4

8.3 Which distension medium causes the fewest vasovagal episodes during outpatient hysteroscopy?

The incidence of vasovagal episodes was reported in three of the randomised controlled trials.[57,59,60] A meta-analysis of these results showed there to be significantly fewer vasovagal episodes with the use of normal saline compared with carbon dioxide (OR 3.24, 95% CI 1.23–8.54).[65]

Evidence level 1++

8.4 *Which distension medium produces the best image quality during outpatient hysteroscopy?*

Four randomised controlled trials evaluated image quality for each of the distension media.[56,57,59,62] Three studies reported no significant difference in image quality between carbon dioxide and normal saline;[56,57,59] however, one of these studies reported changing the distension medium from carbon dioxide to normal saline in eight (10.1%) women. One study found a statistically significant increased risk of unsatisfactory view on hysteroscopy (RR 4.75, 95% CI 1.61–16.4) with the use of carbon dioxide. This was mainly attributed to bubbles and bleeding. Of the 19 women who had an unsatisfactory view at hysteroscopy using carbon dioxide, 17 were changed to normal saline and an improved view was reported in 11 (64.7%).[62] Normal saline produces lavage of the cavity and so washes away any blood or mucus which otherwise might obscure the view.

Evidence level 1+

8.5 *Which distension medium allows the quickest procedure?*

Four randomised controlled trials compared procedure times between normal saline and carbon dioxide.[56–59] All four found that hysteroscopies using normal saline were significantly quicker. This remained significant when the results were meta-analysed (SMD 1.32, 95% CI 1.17–1.48).[65]

Evidence level 1++

8.6 *Which distension medium should be used for operative procedures?*

Normal saline should be used as the distension medium when bipolar intrauterine equipment is used for hysteroscopic surgery. Thus, it is more practical to perform diagnostic procedures with normal saline in units offering simultaneous diagnosis and treatment as this avoids having to swap distension media should operative procedures need to be carried out. Hysteroscopic sterilisation requires fluid distension medium; the choice of normal saline or glycine depends upon the specific technology adopted.

Evidence level 4

9. Local anaesthesia and cervical dilatation

9.1 *Should routine dilatation of the cervical canal be used before insertion of the hysteroscope in an outpatient setting?*

Blind cervical dilatation to facilitate insertion of the miniature outpatient hysteroscope is unnecessary in the majority of procedures. Routine cervical dilatation is associated with pain, vasovagal reactions and uterine trauma and should be avoided.

C

Cervical dilatation generally requires administration of local cervical anaesthesia. Standard protocols regarding the type, maximum dosage and route of administration of anaesthesia should be developed and implemented to help both recognise and prevent rare but potentially serious adverse effects resulting from systemic vascular absorption.

✓

Blind dilatation of the cervix to instrument the uterine cavity is commonly performed under general anaesthesia and is associated with cervical and uterine trauma.[1,31–34] In addition, in the conscious woman, dilatation of the cervix causes pain and discomfort and generally requires the use of local anaesthesia.[19] No randomised controlled trials or large comparative observational studies examining the routine or selective use of blind cervical dilatation before outpatient hysteroscopy were identified.

Evidence level 4

9.2 Should topical local anaesthetic be administered before outpatient hysteroscopy?

Instillation of local anaesthetic into the cervical canal does not reduce pain during diagnostic outpatient hysteroscopy but may reduce the incidence of vasovagal reactions. A

Topical application of local anaesthetic to the ectocervix should be considered where application of a cervical tenaculum is necessary. A

A systematic review identified three randomised controlled trials comparing the application of topical local anaesthetic to the ectocervix.[64–66] Two of these studies were meta-analysed.[65,66] One used lidocaine 5% spray on the ectocervix and canal,[65] while the other used 2% lignocaine gel rubbed over the surface of the cervix;[66] both used a placebo as a control. Meta-analysis of these two studies found that there was no significant pain reduction with the use of topical application of local anaesthetic to the cervix (SMD −0.32, 95% CI −0.97 to 0.33).[67] Another randomised controlled trial using lignocaine 2% aerosol spray, which could not be included in the meta-analysis as it reported its results as medians rather than means, demonstrated a reduction in pain as measured on a 100 mm visual analogue scale when applying a cervical tenaculum as part of the hysteroscopy procedure using a rigid 5.5 mm diagnostic hysteroscope (visual analogue scale score 9 versus 18, $P = 0.005$), but no significant reduction in the pain associated with the hysteroscopic procedure itself.[64] Evidence level 1++

A systematic review identified five randomised controlled trials comparing the transcervical application of local anaesthetic.[62,68–71] Three trials injected the anaesthetic through the cervical canal into the uterine cavity.[68,69,71] Two of these studies used 5 ml of 2% lignocaine[69,71] and one used 2 ml of 2% mepivacaine.[68] All three used normal saline as their control substance. Two of the studies mixed lignocaine with the distension medium. One used 18 ml of lignocaine (strength not stated) per 250 ml of normal saline combined with an intracervical block and compared it with normal saline as the distension medium with an intracervical block.[70] The second study used 40 ml of 2% lignocaine per 500 ml of normal saline and compared it with normal saline as the distension medium.[62] No significant reduction in pain during hysteroscopy was demonstrated (SMD −0.11, 95% CI −0.31 to 0.10).[67] Evidence level 1++

Vasovagal episodes were significantly reduced with the use of topical anaesthesia (Peto OR 0.35, 95% CI 0.15–0.79), but this apparent reduction was limited to the use of transcervical topical application only (Peto OR 0.29, 95% CI 0.12–0.74).[67] Evidence level 1++

9.3 Should injectable local anaesthetic be administered to the cervix and/or paracervix before outpatient hysteroscopy?

Application of local anaesthetic into or around the cervix is associated with a reduction of the pain experienced during outpatient diagnostic hysteroscopy. However, it is unclear how clinically significant this reduction in pain is. Consideration should be given to the routine administration of intracervical or paracervical local anaesthetic, particularly in postmenopausal women. A

Miniaturisation of hysteroscopes and increasing use of the vaginoscopic technique may diminish any advantage of intracervical or paracervical anaesthesia. Routine administration of intracervical or paracervical local anaesthetic should be used where larger diameter hysteroscopes are being employed (outer diameter greater than 5 mm) and where the need for cervical dilatation is anticipated (e.g. cervical stenosis). ✓

Routine administration of intracervical or paracervical local anaesthetic is not indicated to reduce the incidence of vasovagal reactions. A

A systematic review identified five randomised controlled trials comparing the use of direct intracervical injection of local anaesthetic before outpatient hysteroscopy with control (placebo, vaginoscopy or nil).[25,72-75] No significant reduction in pain was noted in the four trials[25,72,73,75] included in the meta-analysis (SMD −0.05, 95% CI −0.71 to 0.60).[67] However, intracervical injection of local anaesthetic was found to reduce pain with hysteroscopy (SMD −0.36, 95% CI −0.61 to −0.10) when the trial comparing local anaesthesia with vaginoscopy was excluded.[75]

Evidence level 1++

A systematic review identified six randomised controlled trials comparing the use of paracervical injection of local anaesthetic before outpatient hysteroscopy with control (placebo or nil).[52,76-80] Meta-analysis showed a significant reduction in pain (SMD −1.28, 95% CI −2.22 to −0.35),[67] although the studies were heterogenous. If the analysis was stratified by menopausal status, the heterogeneity between studies remained, but a significant reduction in pain was observed in the two studies with a purely postmenopausal population[52,78] (SMD −1.12, 95% CI −2.23 to −0.01).[67]

Evidence level 1++

The same systematic quantitative review did not find a reduction in vasovagal reactions associated with diagnostic outpatient hysteroscopy with the use of injectable cervical anaesthetics[52,74,77-79] (OR 0.89, 95% CI 0.54–1.46).[67] However, the heterogeneity of study populations and variations in the definition of vasovagal episodes are likely to have affected this finding. Larger-scale studies of homogeneous populations with standardised interventions (equipment, technique, etc.) and definitions of vasovagal episodes are required to confirm or refute these findings.

Evidence level 1+

10. Conscious sedation

10.1 Should conscious sedation be used to reduce pain associated with outpatient hysteroscopic procedures?

Conscious sedation should not be routinely used in outpatient hysteroscopic procedures as it confers no advantage in terms of pain control and the woman's satisfaction over local anaesthesia.

A

Life-threatening complications can result from the use of conscious sedation. Appropriate monitoring and staff skills are mandatory if procedures are to be undertaken using conscious sedation.

✓

Conscious sedation is used widely in outpatient endoscopic procedures of the gastrointestinal system. It is less commonly employed in outpatient hysteroscopy. One randomised controlled trial reported the use of conscious sedation using 0.25 mg fentanyl intravenous with 0.5 mg atropine and 2 mg midazolam immediately before operative outpatient hysteroscopy – polypectomy, myomectomy, septoplasty and adhesiolysis using the Versapoint™ (Ethicon Inc.) bipolar electrode intrauterine system – compared with paracervical anaesthesia with 10 ml 1% mepivacaine hydrochloride without sedation. There were no significant differences between local anaesthesia and conscious sedation in terms of pain control during the procedure, postoperative pain or the woman's satisfaction.[78]

Evidence level 1+

Sedative drugs (anaesthetics, anxiolytics and opioids) are administered by oral, intravenous, transmucosal or inhalational routes. Any drug that depresses the central nervous system has the potential to impair respiration, circulation or both. Close monitoring of the woman must be undertaken by a designated staff member to ensure maintenance of continuous verbal contact and adequate oxygen saturation. Monitoring of blood pressure and electrocardiogram should be considered in high-risk cases and staff trained in acute airway management and anaesthetic support should be immediately available.

Evidence level 4

11. Vaginoscopy

11.1 Does a vaginoscopic approach to outpatient hysteroscopy reduce pain and increase the feasibility of the procedure?

Vaginoscopy reduces pain during diagnostic rigid outpatient hysteroscopy. A

Vaginoscopy should be the standard technique for outpatient hysteroscopy, especially where successful insertion of a vaginal speculum is anticipated to be difficult and where blind endometrial biopsy is not required. ✓

Vaginoscopy or the 'no touch' approach to hysteroscopy refers to a technique where the hysteroscope is introduced into the vagina, through the cervical canal and into the uterine cavity without the need for a vaginal speculum or cervical instrumentation. A systematic review identified six small randomised controlled trials comparing the vaginoscopic versus traditional outpatient hysteroscopy.[75,81–85] There were no significant differences in feasibility (failed procedures) between the techniques (OR 1.28, 95% CI 0.74–2.24), but vaginoscopy was associated with significantly less procedural pain (SMD −0.44, 95% CI −0.65 to −0.22)[86] in the four studies evaluating this outcome.[75,81,82,84] Evidence level 1++

Larger studies are indicated to better assess the feasibility of vaginoscopy in relation to the characteristics of the woman (e.g. body mass index, menopausal status, parity, caesarean section) and type of hysteroscope (size, angle, rigid/flexible endoscopes) and the risk of ascending pelvic infection. Vaginoscopy allows increased external movement of the hysteroscope. Future studies should assess whether this manoeuvrability improves the feasibility and effectiveness of operative hysteroscopy.

12. Suggested audit topics

- Patient satisfaction with elements of the outpatient hysteroscopy service.
- Complications (e.g. infection, vasovagal reactions, uterine trauma) of diagnostic and operative outpatient hysteroscopy.
- Failure rate of diagnostic and operative outpatient hysteroscopy and reasons for failures.
- Rates of cervical dilatation in outpatient hysteroscopy stratified by parity and menopausal status.
- Standards of documentation.
- Use of analgesia post-procedure.
- Percentage of women provided with written information and asked for written consent.

13. Recommendations for research

- Optimal type and timing of analgesia in diagnostic and operative outpatient hysteroscopy.
- Effect of cervical preparation with prostaglandins and/or local estrogens on pain relief and feasibility of outpatient hysteroscopy in postmenopausal women.
- Safety and acceptability of hysteroscopy according to angle of distal optical lens.
- Effect of local anaesthetic on pain reduction according to menopausal status and parity.
- Effectiveness of vaginoscopic approach to outpatient hysteroscopy in relieving pain compared with traditional approaches with and without local anaesthesia.
- Feasibility and safety of vaginoscopy in relation to the woman's characteristics and type of hysteroscope.
- Effect of vaginoscopy and local anaesthesia on the incidence of vasovagal episodes associated with diagnostic and operative outpatient hysteroscopy.
- Effectiveness of warming fluid distension media on relieving pain in outpatient hysteroscopy.

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APPENDIX 1
Terminology

Conscious sedation

Conscious sedation refers to an arousable but drowsy state in which a woman can communicate and maintain an airway. Sedation techniques aim to make potentially unpleasant interventions more acceptable. However, there is potential for the drugs to impair respiration, circulation or both. This dictates that the operator should have advanced training in airway management and anaesthesia.

Direct 'intracervical' cervical anaesthesia

Local anaesthetic is injected directly into the cervix ('intracervical' or 'direct' cervical block). The anaesthetic solution should be distributed equally to all cervical quadrants. The majority of the anaesthetic should be injected at the deepest possible point in each quadrant, with some distributed evenly along the length of the cervix as the needle is withdrawn.

Outpatient hysteroscopy (office/ambulatory)

The term outpatient hysteroscopy encompasses 'office' and 'ambulatory' hysteroscopy.

Paracervical anaesthesia

Local anaesthetic is injected into the vaginal mucosa at the cervicovaginal junction. One to two millilitres of anaesthetic is injected to produce swelling and blanching of the tissue around the cervix. The needle is then advanced into the vaginal vault and the anaesthetic is delivered to a depth of 1–2.5 cm. Care should be taken to aspirate before injection to avoid inadvertent intravascular injection. The injection site may be 'tracked' by injecting as the needle progresses. The standard bilateral injections are at the 4 o'clock and 8 o'clock positions, although 3 o'clock and 9 o'clock positions are often used.

Procedural pain

For the purpose of this guideline, 'procedural pain' is defined as an overall, global assessment of pain associated with outpatient hysteroscopy. If a global score was not given, the pain experienced during inspection of the cavity was used.

Topical anaesthesia/transcervical

Anaesthetic gels such as Instillagel® (Clinined Ltd, High Wycombe, UK: lidocaine hydrochloride 2% and chlorhexidine gluconate solution 0.25%), creams such as emla® (AstraZeneca Pty Ltd, North Ryde, Australia: lidocaine 2.5% and prilocaine 2.5%) or sprays such as xylocaine (lidocaine 10%) are applied to the ectocervix, cervical canal or into the uterine cavity. Absorption through mucous membranes may be slow and unreliable, so sufficient time should be allowed for the anaesthetic to work.

Vaginoscopy

The vaginoscopic or 'no-touch' technique involves introducing the hysteroscope into the vagina without a speculum or cervical instrumentation. The labia minora are then held closed and the table tilted backwards to keep the distension medium inside the vagina. The hysteroscope is slowly advanced to visualise the cervix and identify the cervical os. The scope then traverses the cervical canal and passes into the uterine cavity.

Vasovagal reaction

Vasovagal reactions are caused by stimulation of the parasympathetic nervous system. The cervix receives parasympathetic innervation from the sacral nerves. Manipulation and dilatation of the cervix can lead to stimulation of the parasympathetic nervous system, which causes hypotension and bradycardia and causes women to feel sick and faint. They may display clinical signs such as pallor, sweating and reduced conscious state. Most women will recover rapidly if the procedure is stopped and instruments removed and they are put in the supine or recovery position. Cool fanning, fluids and reassurance will hasten recovery. In rare cases, atropine may need to be given.

Appendix 2

Clinical guidelines are:'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No. 1: *Development of RCOG Green-Top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/womens-health/clinical-guidance/development-rcog-green-top-guidelines-policies-and-processes). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1-	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

This guideline was produced on behalf of the British Society of Gynaecological Endoscopists and the Royal College of Obstetricians and Gynaecologists by:

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The final version is the responsibility of both the Guidelines Committee of the RCOG and the Guidelines and Audit Committee of the British Society of Gynaecological Endoscopists.

The guideline review process will commence in 2014 unless evidence requires earlier review.

APPENDIX 5

GRADE tables for 'Best Practice in Hysteroscopy' Guideline recommendations with corresponding SIGN gradings

A5.1 Analgesia

Do analgesics given prior to diagnostic hysteroscopy reduce the pain felt during the procedure?

Routine use of opiate analgesia prior to outpatient hysteroscopy should be avoided as it may cause adverse side effects

Question: Should tramadol be used for pain relief prior to outpatient hysteroscopy?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tramadol	Control	Relative (95% CI)	Absolute		
Pain with im tramadol (measured with: Visual analogue scale; range of scores: 0-20; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	40	40	-	MD 3.3 lower (4.96 to 1.64 lower)	⊕OOO VERY LOW	CRITICAL
Pain with iv tramadol (measured with: Visual analogue scale; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	25	25	-		⊕OOO VERY LOW	CRITICAL
Side effects with iv tramadol												
1	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	4/25 (16%)	2/25 (8%)	-	80 fewer per 1000 (from 80 fewer to 80 fewer)	⊕OOO VERY LOW	CRITICAL

[1] Randomisation not described and no blinding. Unclear who assessed the pain scores but likely to be the surgeons.
[2] Only one small study.
[3] This is the only study identified.
[4] The study does not accurately report the point estimate and confidence intervals it displays them on a graph that cannot be reliably read. Reports that the result is significant p<0.012 and p<0.008.
[5] Not clear whether the study was blinded.

Question: Should sublingual buprenorphine be used for pain relief prior to outpatient hysteroscopy?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sublingual buprenorphine	Control	Relative (95% CI)	Absolute		
Pain (measured with: Visual analogue scale; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	reporting bias[4]	80	84	-	MD 0.1 higher (0.27 lower to 0.47 higher)	⊕OOO VERY LOW	CRITICAL
Presence of side effects associated with buprenorphine												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3,5]	reporting bias[4]	31/80 (38.8%)	0%	OR 107.55 (6.44 to 1796.46)	-	⊕OOO VERY LOW	IMPORTANT

[1] Not clear whether the study was blinded.
[2] Pain was assessed by a nurse who was observing the facial expressions of the patients and not the patients themselves.
[3] This is single study with a small population.
[4] This was the only study identified.
[5] The confidence interval is very wide.

SIGN grading: B

Patients, without contra-indications, should be advised to consider taking standard doses of non-steroidal anti-inflammatory agents around one hour before their scheduled outpatient hysteroscopy appointment with the aim of reducing pain in the immediate post-operative period.

Question: Should non-steroidal anti-inflammatory drugs (NSAIDs) be used for pain relief prior to outpatient hysteroscopy?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Control	Relative (95% CI)	Absolute		
Visual analogue scale pain score with oral diclofenac (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious	reporting bias	92	89	-	MD 0 higher (0.79 lower to 0.79 higher)	⊕⊕OO LOW	CRITICAL
Visual analogue scale pain score with im ketorolac (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	12	12	-	MD 1.1 lower (3.35 lower to 1.16 higher)	⊕OOO VERY LOW	CRITICAL
Visual analogue scale pain score with oral mefenamic acid (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	49	46	-	MD 0 higher (0 to 0 higher)	⊕⊕OO LOW	CRITICAL

[1] There is no description of randomisation and the study is not blinded.
[2] This is a single study with a very small population.
[3] This was the only study identified.
[4] This is only one small study.
[5] This is the only identified study.

SIGN grading: B

A5.2 Cervical Preparation

Does cervical preparation reduce uterine trauma, failure to access the uterine cavity or pain associated with outpatient hysteroscopy?

Cervical preparation prior to outpatient hysteroscopy should not be used in the absence of any evidence of benefit in terms of reduction in pain, rates of failure or uterine trauma.

Question: Should Vaginal Prostaglandins be used in women undergoing outpatient hysteroscopy?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginal Prostaglandins	Control	Relative (95% CI)	Absolute		
Premenopausal women: pain score during dilatation (range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	reporting bias[3]	22	21	-	0 higher (0 to 0 higher)	⊕OOO VERY LOW	CRITICAL
Premenopausal: pain reduction during hysteroscopy												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	reporting bias[3]	6/13 (46.2%)	12/23 (52.2%)	RR 0.88 (0.44 to 1.79)	63 fewer per 1000 (from 292 more to 412 more)	⊕OOO VERY LOW	CRITICAL
Postmenopausal: pain reduction during the procedure (measured with: visual analogue scale; Better indicated by lower values)												
1	randomised trials	serious[6]	serious[7]	no serious indirectness	no serious imprecision	reporting bias[3]	60	60	-	0 higher (0 to 0 higher)	⊕OOO VERY LOW	CRITICAL
Mixed population: pain (measured with: Visual analogue scale; range of scores: 0-10; Better indicated by lower values)												
1	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	serious[9]	reporting bias[3]	50	50	-	0 higher (0 to 0 higher)	⊕OOO VERY LOW	CRITICAL
Mixed population: pain after dilatation (measured with: Visual analogue scale; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9,10]	reporting bias[3]	50	51	-	MD 12.3 lower (13.69 to 10.91 lower)	⊕⊕OO LOW	CRITICAL
Premenopausal: adequate dilatation												
1	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	20/22 (90.9%)	6/21 (28.6%)	OR 25 (4.41 to 141.68)	623 more per 1000 (from 352 more to 697 more)	⊕OOO VERY LOW	IMPORTANT

Postmenopausal- need for dilatation												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[13]	reporting bias[3]	10/58 (17.2%)	12/59 (20.3%)	OR 0.82 (0.32 to 2.06)	30 fewer per 1000 (from 128 fewer to 141 more)	⊕OOO VERY LOW	IMPORTANT
Needs dilatation- mixed population												
1	randomised trials	very serious[8]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	15/50 (30%)	11/50 (22%)	OR 1.52 (0.62 to 3.74)	80 more per 1000 (from 71 fewer to 293 more)	⊕OOO VERY LOW	IMPORTANT
Force needed to dilate at 6mm- mixed population (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	50	51	-	SMD 0.48 lower (0.88 to 0.09 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Misoprostol in postmenopausal women- failed hysteroscopies												
1	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	serious[14]	reporting bias[3]	4/60 (6.7%)	4/60 (6.7%)	OR 1 (0.24 to 4.2)	0 fewer per 1000 (from 50 fewer to 164 more)	⊕OOO VERY LOW	IMPORTANT
Misoprostol in premenopausal women- failed hysteroscopies												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[15]	reporting bias[3]	7/20 (35%)	1/24 (4.2%)	OR 12.38 (1.37 to 112.1)	308 more per 1000 (from 15 more to 788 more)	⊕OOO VERY LOW	IMPORTANT
Cervical lacerations												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[14]	reporting bias[16]	8/125 (6.4%)	13/131 (9.9%)	OR 0.59 (0.22 to 1.55)	38 fewer per 1000 (from 76 fewer to 47 more)	⊕⊕OO LOW	CRITICAL
Cervical Bleeding												
4	randomised trials	no serious risk of bias	serious[17]	no serious indirectness	serious[13]	reporting bias[18]	21/135 (15.6%)	12/141 (8.5%)	OR 1.32 (0.52 to 3.4)	24 more per 1000 (from 39 fewer to 155 more)	⊕OOO VERY LOW	CRITICAL

[1] Randomisation not described and not blinded.
[2] Only one study with a very small population and a large effect so results are less likely to be accurate.
[3] Only a single study was identified.
[4] 33% of the women randomised to misoprostol did not undergo hysteroscopy and therefore could not be assessed.
[5] The population size is very small. The confidence interval includes 'no effect'.
[6] Probable reporting bias as multiple evaluations of pain are reported. Blinding suggested but unclear.
[7] Results are confusing with no clear evidence of effect.
[8] No blinding as compared to nothing rather than placebo.
[9] Only one study with a small population so results less likely to be accurate.
[10] Single study with population size that was calculated based on the outcome 'dilatation' and not pain.
[11] Randomisation not described and study not blinded.
[12] Blinding suggested but unclear.

[13] The confidence interval contains no effect.
[14] Confidence interval includes 'no effect'. Also a small number of events.
[15] A single study with a small population and wide confidence intervals.
[16] Only three small trials.
[17] Significant heterogeneity which can only be partially explained by different administration times and doses.
[18] Only four small trials.

Question: Should Mifepristone be used in women undergoing outpatient hysteroscopy?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mifepristone	Control	Relative (95% CI)	Absolute		
Pain after cervical dilatation (measured with: Visual analogue scale; range of scores: 0-100; Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	reporting bias[2]	28	30	-	MD 3.6 lower (17.42 lower to 10.22 higher)	⊕⊕OO LOW	CRITICAL

[1] Results are from one small study with a wide confidence interval.
[2] Only one study identified.

SIGN grading: A

A5.3 Type of Hysteroscope

Should rigid or flexible hysteroscopes be used routinely in the outpatient setting?

Flexible hysteroscopes are associated with less pain during outpatient hysteroscopy compared with rigid hysteroscopes. However, rigid hysteroscopes may provide better images, fewer failed procedures, quicker examination time and reduced cost Thus there is insufficient evidence to recommend preferential use of rigid or flexible hysteroscopes for diagnostic, outpatient procedures and choice of hysteroscope should be left to the discretion of the operator

Question: What type of hysteroscope should be used for outpatient hysteroscopy?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Flexible hysteroscopes	Rigid hysteroscopes	Relative (95% CI)	Absolute		
Pain score (measured with: Visual analogue scale; range of scores: 0-10; Better indicated by lower values)												
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	110	115	-	not pooled	⊕⊕OO LOW	IMPORTANT
Failures (assessed with: Occurrence vs. non-occurrence)												
2	randomised trials	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[2,4]	reporting bias[3]	5/112 (4.5%)	0/115 (0%)	OR 11.81 (0.64 to 217.75)	-	⊕⊕OO LOW	IMPORTANT

[1] The only limitation is that the studies were not double blinded however this would be impossible to do.
[2] Small sample sizes encourage imprecision.
[3] Only two small studies. Likely that studies finding no advantage of one hysteroscope over the other are not published.
[4] Small number of events.

SIGN grading: B

A5.4 Distension Media

Which uterine distension medium should be used during outpatient hysteroscopy?

The choice of distension media, for routine outpatient hysteroscopy, between carbon dioxide and normal saline should be left to the discretion of the operator as neither is superior in reducing pain, although uterine distension with normal saline appears to reduce the incidence of vasovagal episodes.
Uterine distension with Normal saline allows outpatient diagnostic hysteroscopy to be completed more quickly compared with carbon dioxide.

Question: Which is the best distension medium for outpatient hysteroscopy?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Normal saline	Carbon dioxide	Relative (95% CI)	Absolute		
Pain score (Better indicated by lower values)												
6	randomised trials	very serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	540	569	-	SMD 0.34 higher (0.12 lower to 0.8 higher)	⊕OOO VERY LOW	CRITICAL
Shoulder tip pain												
5	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/472 (1.9%)	55/448 (12.3%)	OR 0.19 (0.09 to 0.4)	97 fewer per 1000 (from 70 fewer to 110 fewer)	⊕⊕OO LOW	CRITICAL
Vasovagal episodes												
3	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	5/210 (2.4%)	18/210 (8.6%)	OR 0.31 (0.12 to 0.82)	57 fewer per 1000 (from 14 fewer to 75 fewer)	⊕OOO VERY LOW	IMPORTANT
Procedure time (Better indicated by lower values)												
4	randomised trials	very serious[1]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	434	401	-	SMD 1.32 lower (1.48 to 1.17 lower)	⊕⊕OO LOW	IMPORTANT
Unsatisfactory hysteroscopic view												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	reporting bias[6]	4/100 (4%)	19/100 (19%)	RR 4.75 (1.61 to 16.4)	712 more per 1000 (from 116 more to 1000 more)	⊕OOO VERY LOW	CRITICAL

[1] Poor randomisation methods (quasi-randomised in some cases) and lack of allocation concealment in most studies. Neither patient nor operator was blinded but this would not be possible.
[2] High heterogeneity that cannot be explained by differences in technique.
[3] Outcome reported in just three of the six identified trials.
[4] High heterogeneity but all studies in favour of normal saline and heterogeneity can be explained by the two studies that don't using a speculum showing the largest effect size.
[5] Single study therefore imprecise.
[6] This is the only study that reports a difference.

SIGN grading: A

A5.5 Local anaesthesia and cervical dilatation

Should topical local anaesthetic be administered prior to outpatient hysteroscopy?

Injection of local anaesthetic into the cervical canal does not reduce pain during diagnostic outpatient hysteroscopy

Should injectable local anaesthetic be administered to the cervix and / or para-cervix prior to outpatient hysteroscopy?

Injection of local anaesthetic into or around the cervix is associated with reduction in pain experienced during outpatient diagnostic hysteroscopy. However, it is unclear how clinically significant this reduction in pain is. Consideration should be given to the routine administration of intracervical or paracervical local anaesthetic, particularly in postmenopausal women.

Routine administration of intracervical or paracervical local anaesthetic is not indicated to reduce the incidence of vasovagal reaction.

Question: Should local anaesthetic be used in women undergoing outpatient hysteroscopy?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Local anaesthetic	Control	Relative (95% CI)	Absolute		
pain score with topical local anaesthetic (Better indicated by lower values)												
2	randomised trials	no serious risk of bias	no serious inconsistency[1]	no serious indirectness	serious[2]	reporting bias[3]	312	306	-	SMD 0.32 lower (0.97 lower to 0.33 higher)	⊕⊕OO LOW	CRITICAL
pain score with transcervical anaesthetic (measured with: Visual analogue scale; range of scores: 0-10; Better indicated by lower values)												
5	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	276	270	-	SMD 0.11 lower (0.31 lower to 0.1 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain score with intracervical anaesthetic block (Better indicated by lower values)												
3	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	reporting bias[7]	123	116	-	SMD 0.36 lower (0.61 to 0.1 lower)	⊕OOO VERY LOW	CRITICAL

pain with paracervical anaesthetic block (Better indicated by lower values)											
5	randomised trials	very serious[8]	serious[9]	no serious indirectness	serious[10]	none	335	337	-	SMD 1.28 lower (2.22 to 0.35 lower)	⊕OOO VERY LOW	CRITICAL
Vasovagal attacks											
9	randomised trials	serious[8]	serious[11]	no serious indirectness	no serious imprecision	none	40/635 (6.3%)	56/629 (8.9%)	OR 0.69 (0.45 to 1.05)	26 fewer per 1000 (from 47 fewer to 4 more)	⊕⊕OO LOW	IMPORTANT

[1] Studies use different strengths of lignocaine which may explain the heterogeneity. However, stratifying for strength of anaesthetic agent would result in multiple, small sub-groups.
[2] Wide confidence intervals with a small effect size.
[3] Only two studies included.
[4] Poor allocation concealment.
[5] Details of randomisation and allocation concealment are unclear.
[6] Small population size.
[7] Only 3 small studies identified.
[8] Poor allocation concealment. Details of randomisation unclear and some studies not blinded.
[9] Heterogeneity is high. When the study with greatest effect size is removed I2 is still 90%. Two studies do not overlap with any of the other studies.
[10] Wide confidence intervals.
[11] Heterogeneous. The studies use different methods and use different administration of local anaesthetic.

SIGN grading: A

A5.6 Conscious sedation

Should conscious sedation be used to reduce pain associated with outpatient hysteroscopic procedures?

Conscious sedation should not be routinely used in outpatient hysteroscopic procedures, as it confers no advantage in terms of pain control and patient satisfaction over local anaesthesia.

Question: Does conscious sedation reduce pain during outpatient hysteroscopy?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Conscious sedation versus intracervical block	Control	Relative (95% CI)	Absolute		
Pain score (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	reporting bias[3]	84	82	-	MD 0.2 lower (0.43 lower to 0.03 higher)	⊕OOO VERY LOW	CRITICAL

[1] Allocation concealment not clear. Not blinded.
[2] Single study and small population therefore imprecise.
[3] Only a single study identified.

SIGN grading: A

A5.7 Vaginoscopy

Does a vaginoscopic approach to outpatient hysteroscopy reduce pain and increase the feasibility of the procedure?

Vaginoscopy reduces pain during diagnostic rigid outpatient hysteroscopy.

Question: Should the vaginoscopic technique be used for outpatient hysteroscopy?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vaginoscopy	Control	Relative (95% CI)	Absolute		
Pain score (Better indicated by lower values)												
4	randomised trials	serious[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	reporting bias[3]	472	439	-	SMD 0.44 lower (0.65 to 0.22 lower)	⊕⊕OO LOW	CRITICAL
Failed procedures												
5	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[3]	39/584 (6.7%)	25/550 (4.5%)	OR 1.28 (0.74 to 2.24)	12 more per 1000 (from 11 fewer to 51 more)	⊕OOO VERY LOW	IMPORTANT

[1] Poor allocation concealment.
[2] Heterogeneity can be explained by the fact that the traditional technique varied between studies.
[3] Only a small number of trials and they mainly have positive results.
[4] Wide confidence interval.

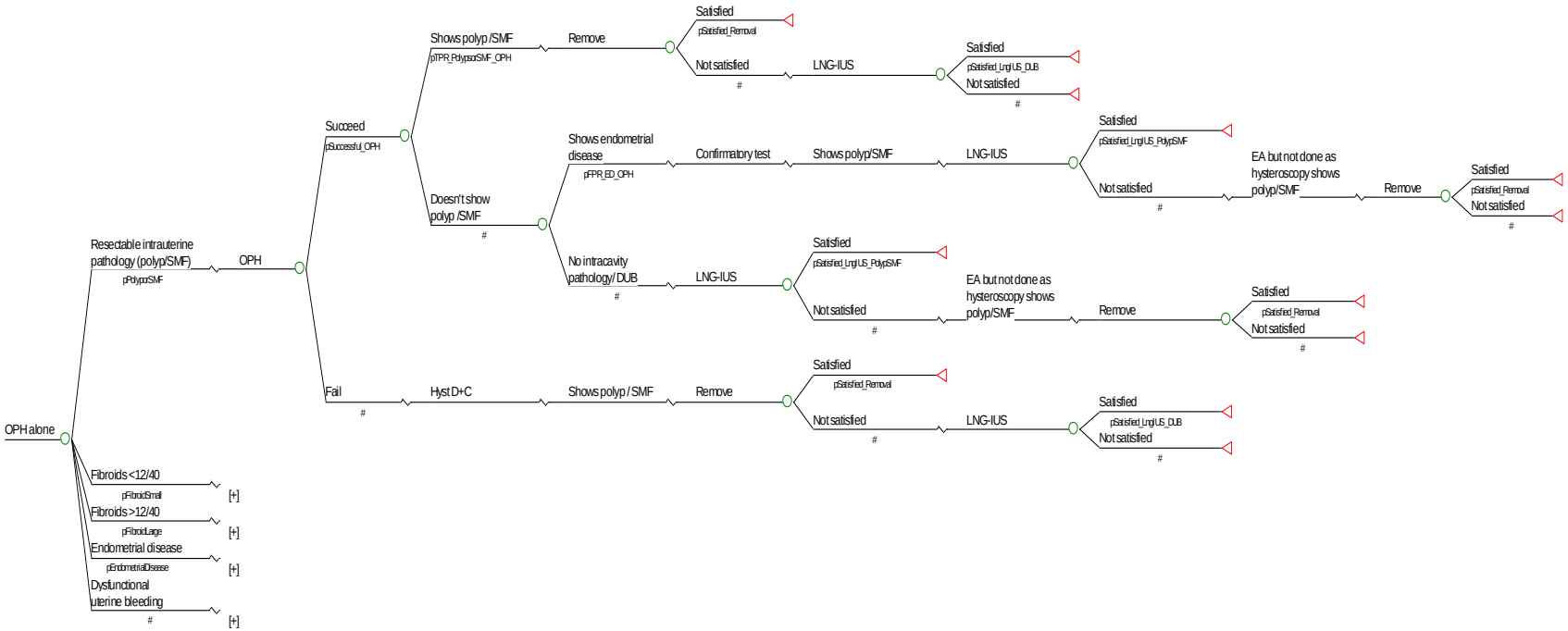
SIGN grading: A

APPENDIX 6

Decision trees for the economic analysis of heavy menstrual bleeding

The heavy menstrual bleeding decision trees are too large to be displayed in their entirety therefore an expanded branch from the outpatient hysteroscopy tree is shown below. Table 3.2 shows the diagnosis made and the treatments given for all branches within the decision tree.

A6.1 Expanded branch from the outpatient hysteroscopy strategy for investigation of HMB



A6.2 Diagnosis and treatments from the decision tree for investigation of women with HMB

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
LNG-IUS only	Polyp / SMF				LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
	Fibroids <12				LNG-IUS	EA
	Fibroids >12				LNG-IUS	EA
					Hysterectomy if bimanual exam suggests >12 weeks size	GP appt
	ED				LNG-IUS	Hysterectomy
	DUB				LNG-IUS	EA
Hysterectomy only	Polyp / SMF				Hysterectomy	GP appt
	Fibroids <12				Hysterectomy	GP appt
	Fibroids >12				Hysterectomy	GP appt
	ED				Hysterectomy	GP appt
	DUB				Hysterectomy	GP appt
OPH alone	Polyp / SMF	Polyp / SMF			Resection	LNG-IUS
		Endometrial disease	Polyp / SMF		LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
		DUB			LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
	Fibroids < 12	Normal cavity			LNG-IUS	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
		Polyp / SMF			Resection but as normal endometrium LNG-IUS inserted	EA
		ED	Normal endometrium		LNG-IUS	EA
	Fibroids >12	Normal cavity	>12 by bimanual exam		Hysterectomy	GP appt
			<12 by bimanual exam		LNG-IUS	
		Polyp / SMF	>12 by bimanual exam		Hysterectomy	GP appt
			<12 by bimanual exam		Resection but as normal endometrium LNG-IUS inserted	EA
		ED	>12 by bimanual exam	Normal endometrium	Hysterectomy	GP appt
			<12 by bimanual exam	Normal endometrium	LNG-IUS	EA
	ED	ED	Hyperplasia		LNG-IUS	Hysterectomy
			Cancer		Hysterectomy	GP appt
		Polyp / SMF			Resection- histology shows hyperplasia / cancer so get LNG-IUS/ hysterectomy	Hysterectomy / GP visit
		DUB			LNG-IUS	Hysterectomy as EBx prior to EA shows ED
	DUB	DUB			LNG-IUS	EA
		Polyp / SMF			Resection but as normal endometrium LNG-IUS inserted	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
TVS alone and SIS alone	Polyp / SMF	Polyp / SMF			Resection	LNG-IUS
		Fibroids <12			LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
		ED	Polyp / SMF		Resection	LNG-IUS
		DUB			LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
	Fibroids <12	Fibroids < 12			LNG-IUS	EA
		Polyp / SMF			Resection but as normal endometrium LNG-IUS inserted	EA
		ED	Normal endometrium		LNG-IUS	EA
		DUB			LNG-IUS	EA
	Fibroids >12	Fibroids >12	>12 by bimanual exam		Hysterectomy	GP appt
			<12 by bimanual exam		LNG-IUS	EA
		Polyp / SMF	>12 by bimanual exam		Hysterectomy	GP appt
			<12 by bimanual exam		Resection but as normal endometrium LNG-IUS inserted	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
		Fibroids <12	>12 by bimanual exam		Hysterectomy	GP appt
			<12 by bimanual exam		LNG-IUS	EA
	ED	ED	Hyperplasia		LNG-IUS	Hysterectomy
			Cancer		Hysterectomy	GP appt
		Polyp / SMF			Resection- histology shows hyperplasia / cancer so get LNG-IUS/ hysterectomy	Hysterectomy / GP visit
		Fibroids <12			LNG-IUS	Hysterectomy as EBx prior to EA shows ED
		DUB			LNG-IUS	Hysterectomy as EBx prior to EA shows ED
	DUB	DUB			LNG-IUS	EA
		Polyp / SMF			Resection but as normal endometrium LNG-IUS inserted	EA
		Fibroids <12			LNG-IUS	EA
		ED	Normal endometrium		LNG-IUS	EA
EBx alone	Polyp / SMF	Polyp / SMF			Resection	LNG-IUS
		DUB			LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
		Complex hyperplasia			LNG-IUS	Hysterectomy

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
	Fibroids <12	Normal cavity			LNG-IUS	EA
		Polyp / SMF			Resection but no lesion seen so LNG-IUS inserted	EA
		Complex hyperplasia			LNG-IUS	Hysterectomy
	Fibroids > 12	Normal cavity	>12 by bimanual exam		Hysterectomy	GP appt
			<12 by bimanual exam		LNG-IUS	EA
		Polyp / SMF	>12 by bimanual exam		Hysterectomy	GP appt
			<12 by bimanual exam		Resection but no lesion seen so LNG-IUS inserted	EA
		Complex hyperplasia	>12 by bimanual exam		Hysterectomy	GP appt
			<12 by bimanual exam		LNG-IUS	Hysterectomy
	ED	Complex hyperplasia			LNG-IUS	Hysterectomy
		Atypia / cancer			Hysterectomy	GP appt
		Polyp / SMF			Resection- histology shows hyperplasia / cancer so get LNG-IUS/ hysterectomy	Hysterectomy / GP visit
		DUB			LNG-IUS	Hysterectomy as BX prior to EA shows ED

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
	DUB	Normal cavity			LNG-IUS	EA
		Polyp / SMF			Resection but as normal endometrium LNG-IUS inserted	EA
OPH and EBx	Polyp / SMF	Polyp / SMF	Polyp / SMF		Resection	LNG-IUS
			DUB		Resection	LNG-IUS
			Complex hyperplasia		Resection followed by LNG-IUS	Hysterectomy
		ED	Polyp / SMF		LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
			DUB		LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
			Complex hyperplasia		LNG-IUS	Hysterectomy
		Normal cavity	Polyp / SMF		LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
			DUB		LNG-IUS	EA
			Complex hyperplasia		LNG-IUS	Hysterectomy
	Fibroids <12	DUB	DUB		LNG-IUS	EA
			Polyp / SMF		LNG-IUS	EA
			Complex hyperplasia		LNG-IUS	Hysterectomy

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
		Polyp / SMF	DUB		Resection but as normal endometrium LNG-IUS inserted	EA
			Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
			Complex hyperplasia		Resection followed by LNG-IUS	Hysterectomy
		ED	DUB		LNG-IUS	EA
			Polyp / SMF		LNG-IUS	EA
			Complex hyperplasia		LNG-IUS	Hysterectomy
	Fibroids >12	DUB	DUB	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	LNG-IUS	EA
			Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	LNG-IUS	EA
			Complex Hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	LNG-IUS	Hysterectomy
		Polyp / SMF	DUB	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA
			Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA
			Complex Hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	Resection followed by LNG-IUS	Hysterectomy

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
		ED	DUB	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	LNG-IUS	EA
			Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	LNG-IUS	EA
			Complex Hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	LNG-IUS	Hysterectomy
	ED	ED	Complex hyperplasia		LNG-IUS	Hysterectomy
			Cancer / atypia		Hysterectomy	GP appt
			Polyp /SMF		LNG-IUS	Hysterectomy as pre ablation EBx shows ED
			DUB		LNG-IUS	Hysterectomy as pre ablation EBx shows ED
		Polyp / SMF	Complex hyperplasia		Resection followed by LNG-IUS	Hysterectomy
			Cancer / atypia		Hysterectomy	GP appt
			Polyp /SMF		Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
			DUB		Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
		DUB	Complex hyperplasia		LNG-IUS	Hysterectomy
			Cancer / atypia		Hysterectomy	GP appt

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
			Polyp /SMF		LNG-IUS	Hysterectomy as pre ablation EBx shows ED
			DUB		LNG-IUS	Hysterectomy as pre ablation EBx shows ED
	DUB	DUB	DUB		LNG-IUS	EA
			Polyp /SMF		LNG-IUS	EA
		Polyp/SMF	DUB		Resection followed by LNG-IUS	EA
			Polyp /SMF		Resection but as normal endometrium LNG-IUS inserted	EA
		ED	DUB		LNG-IUS	EA
			Polyp /SMF		LNG-IUS	EA
SIS and EBx and TVS and EBx	Polyp/SMF	Polyp/SMF	Polyp/SMF		Resection	LNG-IUS
			DUB		Resection	LNG-IUS
			Complex hyperplasia		Resection followed by LNG-IUS	Hysterectomy
		Fibroids <12	Polyp/SMF		Resection	LNG-IUS
			DUB		LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
			Complex hyperplasia		LNG-IUS	Hysterectomy

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
		ED	Polyp/SMF		Resection	LNG-IUS
			DUB		LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
			Complex hyperplasia		LNG-IUS	Hysterectomy
		DUB	Polyp/SMF		LNG IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
			DUB		LNG-IUS	LNG-IUS Resection- lesion diagnosed at pre-ablation
			Complex hyperplasia		LNG-IUS	Hysterectomy
	Fibroids <12	Fibroids <12	DUB		LNG-IUS	EA
			Polyp/SMF		Resection but as normal endometrium LNG-IUS inserted	EA
			Complex hyperplasia		LNG-IUS	Hysterectomy
		Polyp / SMF	DUB		Resection but as normal endometrium LNG-IUS inserted	EA
			Polyp/SMF		Resection but as normal endometrium LNG-IUS inserted	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
			Complex hyperplasia		Resection but as normal endometrium LNG-IUS inserted	Hysterectomy
		ED	DUB		LNG-IUS	EA
			Polyp/SMF		Resection but as normal endometrium LNG-IUS inserted	EA
			Complex hyperplasia		LNG-IUS	Hysterectomy
		DUB	DUB		LNG-IUS	EA
			Polyp/SMF		LNG-IUS	EA
			Complex hyperplasia		LNG-IUS	Hysterectomy
	Fibroids >12	Fibroid >12	DUB	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	LNG-IUS	EA
			Polyp/SMF	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA
			Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	LNG-IUS	Hysterectomy
		Polyp / SMF	DUB	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA
			Polyp/SMF	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
			Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	Resection followed by LNG-IUS	Hysterectomy
		Fibroid <12	DUB	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	LNG-IUS	EA
			Polyp/SMF	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA
			Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
				<12 by bimanual exam	LNG-IUS	Hysterectomy
	ED	ED	Complex hyperplasia		LNG-IUS	Hysterectomy
			Cancer / atypia		Hysterectomy	GP appt
			Polyp / SMF		Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
			DUB		LNG-IUS	Hysterectomy as pre-ablation testing shows ED
		Polyp / SMF	Complex hyperplasia		Resection followed by LNG-IUS	Hysterectomy
			Cancer / atypia		Resection followed by hysterectomy	GP appt
			Polyp / SMF		Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
			DUB		Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
		Fibroids < 12	Complex hyperplasia		LNG-IUS	Hysterectomy
			Cancer / atypia		Hysterectomy	GP appt
			Polyp / SMF		Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
			DUB		LNG-IUS	Hysterectomy as pre-ablation testing shows ED
		DUB	Complex hyperplasia		LNG-IUS	Hysterectomy
			Cancer / atypia		Hysterectomy	GP appt
			Polyp / SMF		LNG-IUS	Hysterectomy as pre-ablation testing shows ED
			DUB		LNG-IUS	Hysterectomy as pre-ablation testing shows ED
	DUB	DUB	DUB		LNG-IUS	EA
			Polyp / SMF		LNG-IUS	EA
		Polyps / SMF	DUB		Resection but as normal endometrium LNG-IUS inserted	EA
			Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
		Fibroids < 12	DUB		LNG-IUS	EA
			Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
		ED	DUB		LNG-IUS	EA
			Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
SIS and OPH and TVS and OPH	Polyp / SMF	Polyp / SMF	Polyp / SMF		Resection	LNG-IUS
			ED	Polyp/SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
			DUB		LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
		Fibroid <12	Polyp / SMF		Resection	LNG-IUS
			ED	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
			DUB		LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
		ED	Polyp / SMF		Resection	LNG-IUS
			ED	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
			DUB		LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
		DUB	Polyp / SMF		Resection	LNH-IUS
			ED	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
			DUB		LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
	Fibroids <12	Fibroids <12	DUB		LNG-IUS	EA
			Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
			ED	Normal endometrium	LNG-IUS	EA
		Polyp / SMF	DUB		LNG-IUS	EA
			Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
			ED	Normal endometrium	LNG-IUS	EA
		ED	DUB	Normal endometrium	LNG-IUS	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3		First Treatment	Second treatment
			Polyp / SMF			Resection but as normal endometrium LNG-IUS inserted	EA
			ED	Normal endometrium		LNG-IUS	EA
		DUB	DUB			LNG-IUS	EA
			Polyp / SMF			Resection but as normal endometrium LNG-IUS inserted	EA
			ED	Normal endometrium		LNG-IUS	EA
	Fibroids >12	Fibroids > 12	DUB	>12 by bimanual exam		Hysterectomy	GP appt
				<12 by bimanual exam		LNG-IUS	EA
			Polyp / SMF	>12 by bimanual exam		Hysterectomy	GP appt
				<12 by bimanual exam		Resection but as normal endometrium LNG-IUS inserted	EA
			ED	>12 by bimanual exam		Hysterectomy	GP appt
				<12 by bimanual exam	Normal endometrium	LNG-IUS	EA
		Polyp / SMF	DUB	>12 by bimanual exam		Hysterectomy	GP appt
				<12 by bimanual exam		LNG-IUS	EA
			Polyp / SMF	>12 by bimanual exam		Hysterectomy	GP appt
				<12 by bimanual exam		Resection but as normal endometrium LNG-IUS inserted	EA
			ED	>12 by bimanual exam		Hysterectomy	GP appt
				<12 by bimanual exam	Normal endometrium	LNG-IUS	EA
		Fibroid <12	DUB	>12 by bimanual exam		Hysterectomy	GP appt
				<12 by bimanual exam		LNG-IUS	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3		First Treatment	Second treatment
			Polyp / SMF	>12 by bimanual exam		Hysterectomy	GP appt
				<12 by bimanual exam		Resection but as normal endometrium LNG-IUS inserted	EA
			ED	>12 by bimanual exam		Hysterectomy	GP appt
				<12 by bimanual exam	Normal endometrium	LNG-IUS	EA
	ED	ED	ED	Complex hyperplasia		LNG-IUS	Hysterectomy
				Cancer / atypia		Hysterectomy	GP appt
			Polyp / SMF			Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
			DUB	Complex hyperplasia		LNG-IUS	Hysterectomy
				Cancer / atypia		Hysterectomy	GP appt
		Polyp / SMF	ED	Complex hyperplasia		LNG-IUS	Hysterectomy
				Cancer / atypia		Hysterectomy	GP appt
			Polyp / SMF			Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
			DUB			LNG-IUS	Hysterectomy as pre-ablation testing shows ED
		Fibroid <12	ED	Complex hyperplasia		LNG-IUS	Hysterectomy
				Cancer / atypia		Hysterectomy	GP appt
			Polyp / SMF			Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
			DUB		LNG-IUS	Hysterectomy as pre-ablation testing shows ED
		DUB	ED	Complex hyperplasia	LNG-IUS	Hysterectomy
				Cancer / atypia	Hysterectomy	GP appt
			Polyp / SMF		Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
			DUB		LNG-IUS	Hysterectomy as pre-ablation testing shows ED
	DUB	DUB	DUB		LNG-IUS	EA
			Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
			ED	Normal endometrium	LNG-IUS	EA
		Polyp / SMF	DUB		LNG-IUS	EA
			Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
			ED	Normal endometrium	LNG-IUS	EA
		Fibroids <12	DUB		LNG-IUS	
			Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
			ED	Normal endometrium	LNG-IUS	EA
		ED	DUB	Normal endometrium	LNG-IUS	EA
			Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
			ED	Normal endometrium	LNG-IUS	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
SIS and OPH and EBx and TVS and OPH and EBx	Polyp / SMF	Polyp / SMF	Polyp / SMF	Polyp / SMF	Resection	LNG-IUS
				DUB	Resection	LNG-IUS
				Complex hyperplasia	Resection followed by LNG-IUS	Hysterectomy
			ED	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				DUB	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				Complex hyperplasia	LNG-IUS	Hysterectomy
			DUB	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				DUB	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				Complex hyperplasia	LNG-IUS	Hysterectomy
		Fibroids <12	Polyp / SMF	Polyp / SMF	Resection	LNG-IUS
				DUB	Resection	LNG-IUS
				Complex hyperplasia	Resection followed by LNG-IUS	Hysterectomy

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
			ED	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				DUB	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				Complex hyperplasia	LNG-IUS	Hysterectomy
			DUB	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				DUB	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				Complex hyperplasia	LNG-IUS	Hysterectomy
		ED	Polyp / SMF	Polyp / SMF	Resection	LNG-IUS
				DUB	Resection	LNG-IUS
				Complex hyperplasia	Resection followed by LNG-IUS	Hysterectomy
			ED	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				DUB	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				Complex hyperplasia	LNG-IUS	Hysterectomy

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
			DUB	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				DUB	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				Complex hyperplasia	LNG-IUS	Hysterectomy
		DUB	Polyp / SMF	Polyp / SMF	Resection	LNG-IUS
				DUB	Resection	LNG-IUS
				Complex hyperplasia	Resection followed by LNG-IUS	Hysterectomy
			ED	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				DUB	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				Complex hyperplasia	LNG-IUS	Hysterectomy
			DUB	Polyp / SMF	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				DUB	LNG-IUS	Resection- lesion diagnosed at pre-ablation hysteroscopy
				Complex hyperplasia	LNG-IUS	Hysterectomy

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
				Polyp / SMF	LNG-IUS	EA
				Complex hyperplasia	LNG-IUS	Hysterectomy
			Polyp / SMF	DUB	Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF	Resection but as normal endometrium LNG-IUS inserted	EA
				Complex hyperplasia	Resection followed by LNG-IUS	Hysterectomy
			ED	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA
				Complex hyperplasia	LNG-IUS	Hysterectomy
		Polyp / SMF	DUB	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA
				Complex hyperplasia	LNG-IUS	Hysterectomy
			Polyp / SMF	DUB	Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF	Resection but as normal endometrium LNG-IUS inserted	EA
				Complex hyperplasia	Resection followed by LNG-IUS	Hysterectomy
			ED	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA
				Complex hyperplasia	LNG-IUS	Hysterectomy
		ED	DUB	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA
				Complex hyperplasia	LNG-IUS	Hysterectomy

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3		First Treatment	Second treatment
			Polyp / SMF	DUB		Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
				Complex hyperplasia		Resection followed by LNG-IUS	Hysterectomy
			ED	DUB		LNG-IUS	EA
				Polyp / SMF		LNG-IUS	EA
				Complex hyperplasia		LNG-IUS	Hysterectomy
		DUB	DUB	DUB		LNG-IUS	EA
				Polyp / SMF		LNG-IUS	EA
				Complex hyperplasia		LNG-IUS	Hysterectomy
			Polyp / SMF	DUB		Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF		Resection but as normal endometrium LNG-IUS inserted	EA
				Complex hyperplasia		Resection followed by LNG-IUS	Hysterectomy
			ED	DUB		LNG-IUS	EA
				Polyp / SMF		LNG-IUS	EA
				Complex hyperplasia		LNG-IUS	Hysterectomy
	Fibroids > 12	Fibroids > 12	DUB	DUB	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA
				Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3		First Treatment	Second treatment
					<12 by bimanual exam	LNG-IUS	EA
				Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	Hysterectomy
			Polyp / SMF	DUB	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA
				Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	Resection followed by LNG-IUS	Hysterectomy
			ED	DUB	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA
				Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA
				Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	Hysterectomy

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3		First Treatment	Second treatment
		Polyp / SMF	DUB	DUB	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA
				Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA
				Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	Hysterectomy
			Polyp / SMF	DUB	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA
				Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	Resection followed by LNG-IUS	Hysterectomy
			ED	DUB	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3		First Treatment	Second treatment
				Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA
				Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	Hysterectomy
		Fibroids < 12	DUB	DUB	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA
				Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA
				Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	Hysterectomy
			Polyp / SMF	DUB	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	Resection but as normal endometrium LNG-IUS inserted	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3		First Treatment	Second treatment
				Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	Resection followed by LNG-IUS	Hysterectomy
			ED	DUB	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA
				Polyp / SMF	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	EA
				Complex hyperplasia	>12 by bimanual exam	Hysterectomy	GP appt
					<12 by bimanual exam	LNG-IUS	Hysterectomy
	ED	ED	ED	Complex hyperplasia		LNG-IUS	Hysterectomy
				Cancer / atypia		Hysterectomy	GP appt
				Polyp / SMF		LNG-IUS	Hysterectomy as pre-ablation testing shows ED
				DUB		LNG-IUS	Hysterectomy as pre-ablation testing shows ED
			Polyp / SMF	Complex hyperplasia		Removal followed by LNG-IUS	Hysterectomy
				Cancer / atypia		Removal followed by hysterectomy	GP appt

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
				Polyp / SMF	Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
				DUB	Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
			DUB	Complex hyperplasia	LNG-IUS	Hysterectomy
				Cancer / atypia	Hysterectomy	GP appt
				Polyp / SMF	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
				DUB	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
		Polyp / SMF	ED	Complex hyperplasia	LNG-IUS	Hysterectomy
				Cancer / atypia	Hysterectomy	GP appt
				Polyp / SMF	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
				DUB	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
			Polyp / SMF	Complex hyperplasia	LNG-IUS	Hysterectomy
				Cancer / atypia	Hysterectomy	GP appt
				Polyp / SMF	Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
				DUB	Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
			DUB	Complex hyperplasia	LNG-IUS	Hysterectomy
				Cancer / atypia	Hysterectomy	GP appt
				Polyp / SMF	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
				DUB	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
		Fibroids <12	ED	Complex hyperplasia	LNG-IUS	Hysterectomy
				Cancer / atypia	Hysterectomy	GP appt
				Polyp / SMF	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
				DUB	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
			Polyp / SMF	Complex hyperplasia	Removal followed by LNG-IUS	Hysterectomy
				Cancer / atypia	Removal followed by hysterectomy	GP appt
				Polyp / SMF	Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
				DUB	Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
			DUB	Complex hyperplasia	LNG-IUS	Hysterectomy
				Cancer / atypia	Hysterectomy	GP appt
				Polyp / SMF	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
				DUB	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
		DUB	ED	Complex hyperplasia	LNG-IUS	Hysterectomy
				Cancer / atypia	Hysterectomy	GP appt
				Polyp / SMF	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
				DUB	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
			Polyp / SMF	Complex hyperplasia	LNG-IUS	Hysterectomy
				Cancer / atypia	Hysterectomy	GP appt
				Polyp / SMF	Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt
				DUB	Resection but histology shows complex hyperplasia / cancer so LNG-IUS/hysterectomy	Hysterectomy / GP appt

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
			DUB	Complex hyperplasia	LNG-IUS	Hysterectomy
				Cancer / atypia	Hysterectomy	GP appt
				Polyp / SMF	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
				DUB	LNG-IUS	Hysterectomy as pre-ablation testing shows ED
	DUB	DUB	DUB	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA
			Polyp / SMF	DUB	Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF	Resection but as normal endometrium LNG-IUS inserted	EA
			ED	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA
		Polyp / SMF	DUB	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA
			Polyp / SMF	DUB	Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF	Resection but as normal endometrium LNG-IUS inserted	EA
			ED	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA
		Fibroid <12	DUB	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA

A6.2 continued

Strategy	True pathology	Diagnosis from test 1	Diagnosis from test 2	Diagnosis from test 3	First Treatment	Second treatment
			Polyp / SMF	DUB	Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF	Resection but as normal endometrium LNG-IUS inserted	EA
			ED	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA
		ED	DUB	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA
			Polyp / SMF	DUB	Resection but as normal endometrium LNG-IUS inserted	EA
				Polyp / SMF	Resection but as normal endometrium LNG-IUS inserted	EA
			ED	DUB	LNG-IUS	EA
				Polyp / SMF	LNG-IUS	EA

APPENDIX 7

Search strategies for collection of data to populate the decision trees for the economic analysis of heavy menstrual bleeding

A7.1a Medline search strategy for prevalence of endometrial polyps

1 endometrial.ti,ab
2 endometr*.ti,ab
3 uterine.ti,ab
4 uter*.ti,ab
5 exp UTERINE DISEASES/
6 uterus.ti,ab
7 exp UTERUS/
8 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9 polyp.ti,ab
10 polyp*.ti,ab
11 exp POLYPS/
12 9 OR 10 OR 11
13 8 AND 12
14 hysteroscopy.ti,ab
15 exp HYSTEROSCOPY/
16 hysteroscop*.ti,ab
17 14 OR 15 OR 16
18 sensitiv*.ti,ab
19 exp "SENSITIVITY AND SPECIFICITY"/
20 diagnos*.ti,ab
21 DIAGNOSIS/
22 diagnostic*.ti,ab
23 DIAGNOSIS, DIFFERENTIAL/
24 *DIAGNOSIS/
25 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24
26 13 AND 17 AND 25

A7.1b Embase search strategy for prevalence of endometrial polyps

1	endometrial.ti,ab
2	endometr*.ti,ab
3	exp ENDOMETRIAL DISEASE/
4	uter*.ti,ab
5	uterine.ti,ab
6	exp UTERUS/
7	uterus.ti,ab
8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
9	polyp.ti,ab
10	polyp*.ti,ab
11	exp POLYP/ OR exp ENDOMETRIUM POLYP/
12	9 OR 10 OR 11
18	8 AND 12
19	hysteroscopy.ti,ab
20	exp HYSTEROSCOPY/
21	hysteroscop*.ti,ab
22	19 OR 20 OR 21
23	18 AND 22
24	sensitiv*.ti,ab
25	exp "SENSITIVITY AND SPECIFICITY"/
26	diagnos*.ti,ab
27	DIAGNOSIS/
28	DIFFERENTIAL DIAGNOSIS/
29	DIAGNOSTIC TEST/
30	24 OR 25 OR 26 OR 27 OR 28 OR 29
31	18 AND 30
32	22 AND 31

A7.2a Medline search strategy for prevalence of fibroids

1 prevalence.ti,ab
2 exp PREVALENCE/
3 1 OR 2
4 exp LEIOMYOMA/
5 fibroid.ti,ab
6 leiomyoma.ti,ab
7 exp MYOMA/
8 fibromyoma.ti,ab
9 leiofibromyoma.ti,ab
10 fibroleiomyoma.ti,ab
11 fibroma.ti,ab
12 exp FIBROMA/
13 myoma*.ti,ab
14 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15 sonogr*.ti,ab
16 hysterosonogr*.ti,ab
17 ultrasound.ti,ab
18 exp ULTRASONOGRAPHY/
19 ((transvaginal scan)).ti,ab
20 hysterosco*.ti,ab
21 exp HYSTEROSCOPY/
22 sonohyster*.ti,ab
23 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
24 3 AND 14 AND 23

A7.2b Embase search strategy for prevalence of fibroids

1 prevalence.ti,ab
2 exp PREVALENCE/
3 fibroid*.ti,ab
4 exp LEIOMYOMA/ OR exp UTERUS MYOMA/
5 leiomyoma.ti,ab
6 myoma*.ti,ab
7 exp MYOMA/
8 fibromyoma.ti,ab
9 leiofibromyoma.ti,ab
10 fibroleiomyoma.ti,ab
11 fibroma.ti,ab
12 exp FIBROMA/
13 1 OR 2
14 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12
15 sonogra*.ti,ab
16 hysterosonogra*.ti,ab
17 sonohyster*.ti,ab
18 ultrasound.ti,ab
19 exp ULTRASOUND/
20 ((transvaginal scan)).ti,ab
21 hysterosco*.ti,ab
22 exp HYSTEROSCOPY/
23 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22
24 13 AND 14 AND 23

A7.3a Medline search strategy for the prevalence of endometrial hyperplasia

1	exp HEMORRHAGE/
2	bleeding.ti,ab
3	exp BLOOD/
4	blood.ti,ab
5	exp MENORRHAGIA/
6	menorrhagia.ti,ab
7	menstr*.ti,ab
8	exp MENSTRUAL CYCLE/
9	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
10	prevalence.ti,ab
11	exp PREVALENCE/
12	10 OR 11
24	uterine.ti,ab
25	uterus.ti,ab
26	exp UTERUS/
27	uter*.ti,ab
28	endometrial.ti,ab
29	exp ENDOMETRIAL HYPERPLASIA/
30	endometr*.ti,ab
31	hyperplas*.ti,ab
32	hyperplasia.ti,ab
33	exp HYPERPLASIA/
34	24 OR 25 OR 26 OR 27 OR 28 OR 30
35	29 OR 31 OR 32 OR 33
37	9 AND 12 AND 34 AND 35

A7.3b Embase search strategy for the prevalence of endometrial hyperplasia

1 hemorrhage.ti,ab
2 exp BLEEDING/
3 bleed*.ti,ab
4 blood*.ti,ab
5 exp BLOOD/
6 bleeding.ti,ab
7 exp MENORRHAGIA/
8 menorrhagia.ti,ab
9 menstr*.ti,ab
10 exp MENSTRUAL CYCLE/
11 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
12 prevalence.ti,ab
13 exp PREVALENCE/
14 12 OR 13
15 uterus.ti,ab
16 exp UTERUS/
17 uter*.ti,ab
18 uterine.ti,ab
19 endometrial.ti,ab
20 exp ENDOMETRIAL DISEASE/
21 endometr*.ti,ab
22 hyperplas*.ti,ab
23 exp HYPERPLASIA/ OR exp ENDOMETRIUM HYPERPLASIA/
24 15 OR 16 OR 17 OR 18 OR 19 OR 21
25 20 OR 22 OR 23
26 24 AND 25
27 11 AND 15 AND 27

A7.4a Medline search strategy for the prevalence of endometrial cancer

1 exp HEMORRHAGE/
2 bleeding.ti,ab
3 exp BLOOD/
4 blood.ti,ab
5 exp MENORRHAGIA/
6 menorrhagia.ti,ab
7 menstr*.ti,ab
8 exp MENSTRUAL CYCLE/
9 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
10 prevalence.ti,ab
11 exp PREVALENCE/
12 15 OR 16
13 uterine.ti,ab
14 uterus.ti,ab
15 exp UTERUS/
16 uter*.ti,ab
17 endometrial.ti,ab
19 endometr*.ti,ab
20 cancer.ti,ab
21 exp NEOPLASMS/
22 malignan*.ti,ab
23 ((Endometrial cancer)).ti,ab
24 exp ENDOMETRIAL NEOPLASMS/
25 13 OR 14 OR 15 OR 16 OR 17 OR 19
26 20 OR 21 OR 22 OR 23 OR 24
27 9 AND 12 AND 25 AND 26

A7.4b Embase search strategy for the prevalence of endometrial cancer

1 hemorrhage.ti,ab
2 exp BLEEDING/
3 bleed*.ti,ab
4 blood*.ti,ab
5 exp BLOOD/
6 bleeding.ti,ab
7 exp MENORRHAGIA/
8 menorrhagia.ti,ab
9 menstr*.ti,ab
10 exp MENSTRUAL CYCLE/
11 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10
12 prevalence.ti,ab
13 exp PREVALENCE/
14 12 OR 13
15 uterus.ti,ab
16 exp UTERUS/
17 uter*.ti,ab
18 uterine.ti,ab
19 cancer.ti,ab
20 exp NEOPLASM/
21 malignan*.ti,ab
22 (endometrial AND cancer).ti,ab
23 endometrial.ti,ab
24 exp ENDOMETRIAL DISEASE/
25 endometr*.ti,ab
26 15 OR 16 OR 17 OR 18 OR 23 OR 24 OR 25
27 19 OR 20 OR 21
28 26 AND 27
29 22 OR 28
30 11 AND 14 AND 29

A7.5a Medline search strategy for reviews of outpatient hysteroscopy

1 exp HYSTEROSCOPY/
2 hysteroscopy.ti,ab
3 hysteroscop*.ti,ab
4 1 OR 2 OR 3
5 4 [Limit to: Review Articles]

A7.5b Embase search strategy for reviews of outpatient hysteroscopy

1 exp HYSTEROSCOPY/
2 hysteroscopy.ti,ab
3 hysteroscop*.ti,ab
4 1 OR 2 OR 3
5 4 [Limit to: (Publication Types Review)]

A7.6a Medline search strategy for studies of transvaginal ultrasound and heavy menstrual bleeding

1 (transvaginal AND ultrasound).ti,ab
2 exp ULTRASONOGRAPHY/
3 sonogra*.ti,ab
4 transvaginal.ti,ab
5 vaginal.ti,ab
6 2 OR 3
7 4 OR 5
8 6 AND 7
9 1 OR 8
10 "abnormal uterine bleeding".ti,ab
11 exp METRORRHAGIA/ OR exp MENORRHAGIA/
12 menorrhagia.ti,ab
13 10 OR 11 OR 12
14 9 AND 13

A7.6b Embase search strategy for studies of transvaginal ultrasound and heavy menstrual bleeding

1 (transvaginal AND ultrasound).ti,ab
2 exp ULTRASOUND/
3 sonogra*.ti,ab
4 transvaginal.ti,ab
5 vaginal.ti,ab
6 4 OR 5
7 2 OR 3
8 6 AND 7
9 1 OR 8
10 exp MENORRHAGIA/ OR exp UTERUS BLEEDING/
11 "abnormal uterine bleeding".ti,ab
12 menorrhagia.ti,ab
13 10 OR 11 OR 12
14 9 AND 13

A7.7a Medline search strategy for studies of saline infusion sonography and heavy menstrual bleeding

1 exp MENORRHAGIA/
2 menorrhagia.ti,ab
3 hypermenorrhea.ti,ab
4 (heavy ADJ menstrual ADJ bleeding).ti,ab
5 (heavy ADJ menstrua*).ti,ab
6 "abnormal uterine bleeding".ti,ab
7 1 OR 2 OR 3 OR 4 OR 5 OR 6
8 exp SODIUM CHLORIDE/ AND exp ULTRASONOGRAPHY/
9 (saline AND infusion AND sonography).ti,ab
10 (sono AND hysterosonography).ti,ab
11 (saline AND hysterosonography).ti,ab
12 (saline AND hysterography).ti,ab
13 sonohysterography.ti,ab
14 8 OR 9 OR 10 OR 11 OR 12 OR 13
15 7 AND 14

A7.7b Embase search strategy for studies of saline infusion sonography and heavy menstrual bleeding

1 exp MENORRHAGIA/
2 menorrhagia.ti,ab
3 hypermenorrhea.ti,ab
4 (heavy ADJ menstrual ADJ bleeding).ti,ab
5 (heavy ADJ menstrua*).ti,ab
6 "abnormal uterine bleeding".ti,ab
7 1 OR 2 OR 3 OR 4 OR 5 OR 6
8 exp SODIUM CHLORIDE/ AND exp ULTRASONOGRAPHY/
9 (saline AND infusion AND sonography).ti,ab
10 (sono AND hysterosonography).ti,ab
11 (saline AND hysterosonography).ti,ab
12 (saline AND hysterography).ti,ab
13 sonohysterography.ti,ab
14 8 OR 9 OR 10 OR 11 OR 12 OR 13
15 7 AND 14

A7.8a Medline search strategy for reviews of endometrial biopsy

1	(endometrial AND biopsy).ti,ab
2	exp ENDOMETRIUM/
3	endometr*.ti,ab
4	exp BIOPSY/
5	biopsy.ti,ab
6	sampling.ti,ab
7	2 OR 3
8	4 OR 5 OR 6
9	7 AND 8
10	1 OR 9
11	10 [Limit to: Review Articles]

A7.8b Embase search strategy for reviews of endometrial biopsy

1	(endometrial AND biopsy).ti,ab
2	exp ENDOMETRIUM BIOPSY/
3	exp ENDOMETRIUM/
4	endometr*.ti,ab
5	biopsy.ti,ab
6	exp BIOPSY/
7	sampling.ti,ab
8	exp SAMPLING/
9	5 OR 6 OR 7 OR 8
10	3 OR 4
11	9 AND 10
12	1 OR 2 OR 11
13	12 [Limit to: (Publication Types Review)]

A7.9a Medline search strategy for studies of LNG-IUS for heavy menstrual bleeding

1 menorrhag*.ti,ab
2 exp MENORRHAGIA/
3 "heavy menstrual blee*".ti,ab
4 menometrorrhagia.ti,ab
5 METRORRHAGIA/
6 hypermenorrh*.ti,ab
7 1 OR 2 OR 3 OR 4 OR 5 OR 6
8 mirena.ti,ab
9 exp LEVONORGESTREL/
10 "intrauterine device".ti,ab
11 "intrauterine system".ti,ab
12 INTRAUTERINE DEVICES, MEDICATED/ OR INTRAUTERINE
13 IUS.ti,ab
14 IUD.ti,ab
15 LNG-IUS.ti,ab
16 levonorgestrel-releasing.ti,ab
17 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
18 7 AND 17

A7.9b Embase search strategy for studies of LNG-IUS for heavy menstrual bleeding

1 menorrhag*.ti,ab
2 exp MENORRHAGIA/
3 "heavy menstrual bleed*".ti,ab
4 exp MENSTRUATION DISORDER/
5 menometorrhagia.ti,ab
6 hypermenorrh*.ti,ab
7 1 OR 2 OR 3 OR 4 OR 5 OR 6
8 mirena.ti,ab
9 exp LEVONORGESTREL/
10 "intrauterine system".ti,ab
11 IUS.ti,ab
12 LNG-IUS.ti,ab
13 IUD.ti,ab
14 "intrauterine device".ti,ab
15 levonorgestrel-releasing.ti,ab
16 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
17 7 AND 16

A7.10a Medline search strategy for patient satisfaction after endometrial ablation

1 "endometrial ablation".ti,ab
2 exp ENDOMETRIAL ABLATION TECHNIQUES/
3 satisfaction.ti,ab
4 exp PATIENT SATISFACTION/
5 1 OR 2
6 3 OR 4
7 5 AND 6

A7.10b Embase search strategy for patient satisfaction after endometrial ablation

1 "endometrial ablation".ti,ab
2 exp ENDOMETRIUM ABLATION/
3 satisfaction.ti,ab
4 exp PATIENT SATISFACTION/ OR exp SATISFACTION/
5 3 OR 4
6 1 OR 2
7 5 AND 6

A7.10c Medline search for endometrial ablation and fibroids

1 fibroid*.ti,ab
2 UTERUS MYOMA/ OR LEIOMYOMA/
3 myoma.ti,ab
4 leiomyoma.ti,ab
5 1 OR 2 OR 3 OR 4
6 (endometrial AND ablation).ti,ab
7 exp ENDOMETRIAL ABLATION TECHNIQUES/
7 6 OR 7
9 5 AND 8

A7.10d Embase search for endometrial ablation and fibroids

1 ((endometrial ablation)).ti,ab
2 exp ENDOMETRIUM ABLATION/
3 1 OR 2
4 fibroid*.ti,ab
5 UTERUS MYOMA/ OR LEIOMYOMA/
6 myoma.ti,ab
7 leiomyoma.ti,ab
8 4 OR 5 OR 6 OR 7
9 3 AND 8

A7.11a Medline search strategy for satisfaction with hysterectomy as a treatment for fibroids

1 exp HYSTERECTOMY/
2 exp LEIOMYOMA/
3 exp PERSONAL SATISFACTION/
4 satisfaction.ti,ab
5 3 OR 4
6 1 AND 2 AND 5

A7.11b Embase search strategy for satisfaction with hysterectomy as a treatment for fibroids

1 exp HYSTERECTOMY/
2 exp LEIOMYOMA/
3 satisfaction.ti,ab
4 exp SATISFACTION/
5 3 OR 4
6 1 AND 2 AND 5

A7.12a Medline search strategy for satisfaction after endometrial polypectomy

1 polypectomy.ti,ab
2 (endometrial AND polyp).ti,ab
3 exp POLYPS/ AND exp ENDOMETRIUM/
4 removal.ti,ab
5 1 OR 4
6 2 OR 3
7 5 AND 6

A7.12b Embase search strategy for satisfaction after endometrial polypectomy

1 polypectomy.ti,ab
2 exp POLYPECTOMY/
3 (endometrial AND polyp).ti,ab
4 exp ENDOMETRIUM POLYP/
5 removal.ti,ab
6 1 OR 2 OR 5
7 3 OR 4
8 6 AND 7

A7.12c Medline search strategy for satisfaction after transcervical resection of a fibroid

1 (transcervical AND resection AND fibroid).ti,ab
2 exp LEIOMYOMA/
3 (hysteroscopic AND removal).ti,ab
4 myomectomy.ti,ab
5 exp GYNECOLOGIC SURGICAL PROCEDURES/
6 fibroid.ti,ab
7 (submucosal AND fibroid).ti,ab
8 submuc*.ti,ab
9 6 AND 8
10 2 AND 8
11 1 OR 3 OR 4 OR 5
12 7 OR 9 OR 10
13 11 AND 12
14 satisf*.ti,ab
15 satisfaction.ti,ab
16 14 OR 15
17 13 AND 16

A7.12d Embase search strategy for satisfaction after transcervical resection of a fibroid

1 (transcervical AND resection AND fibroid).ti,ab
2 fibroid.ti,ab
3 exp UTERUS MYOMA/ OR exp LEIOMYOMA/
4 (hysteroscopic AND removal).ti,ab
5 myomectomy.ti,ab
6 exp MYOMECTOMY/
7 submuc*.ti,ab
8 (submucosal AND fibroid).ti,ab
9 2 OR 3
10 7 AND 9
11 8 OR 10
12 1 OR 4 OR 5 OR 6
13 11 AND 12
14 satisf*.ti,ab
15 satisfaction.ti,ab
16 exp SATISFACTION/ OR exp PATIENT SATISFACTION/
17 14 OR 15 OR 16
18 13 AND 17

A7.13a Medline search strategy for satisfaction after dilatation and curettage

1 D+C.ti,ab
2 exp "DILATATION AND CURETTAGE"/
3 curettage.ti,ab
4 CURETTAGE/
5 ((heavy menstrual bleeding)).ti,ab
6 exp MENORRHAGIA/
7 5 OR 6
8 1 OR 2 OR 3 OR 4
9 7 AND 8

A7.13b Embase search strategy for satisfaction after dilatation and curettage

1 D+C.ti,ab
2 exp "DILATATION AND CURETTAGE"/
3 curettage.ti,ab
4 CURETTAGE/
5 ((heavy menstrual bleeding)).ti,ab
6 exp MENORRHAGIA/
7 5 OR 6
8 1 OR 2 OR 3 OR 4
9 7 AND 8

A7.14a Medline search strategy for satisfaction after uterine artery embolisation

1 "uterine artery embolis*".ti,ab
2 "uterine artery emboliz*".ti,ab
3 UAE.ti,ab
4 exp UTERINE ARTERY EMBOLIZATION/
5 1 OR 2 OR 3 OR 4
6 satisfaction.ti,ab
7 satisf*.ti,ab
8 6 OR 7
9 5 AND 8

A7.14b Embase search strategy for satisfaction after uterine artery embolisation

1 "uterine artery embolis*".ti,ab
2 "uterine artery emboliz*".ti,ab
3 UAE.ti,ab
4 exp UTERINE ARTERY EMBOLIZATION/
5 1 OR 2 OR 3 OR 4
6 satisfaction.ti,ab
7 exp SATISFACTION/ OR exp PATIENT SATISFACTION/
8 satisf*.ti,ab
9 6 OR 7 OR 8
10 5 AND 9

A7.15a Medline search strategy for satisfaction after myomectomy

1 myomectomy.ti,ab
2 satisf*.ti,ab
3 2 AND 3

A7.15b Embase search strategy for satisfaction after myomectomy

1 myomectomy.ti,ab
2 satisf*.ti,ab
3 2 AND 3

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