AMBULATORY DIAGNOSIS OF ENDOMETRIAL PATHOLOGY

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ABSTRACT

The aim of this thesis was to determine the diagnostic accuracy of outpatient endometrial evaluation using endometrial biopsy (EB), ultrasound scan (USS) and hysteroscopy (OPH) by conducting systematic quantitative reviews of the published literature. The optimum diagnostic strategy in terms of cost-effectiveness (cost per life year gained), was then established for the investigation of women with post-menopausal bleeding (PMB) for endometrial cancer, using the review data in a decision analysis designed to reflect current service provision. Meta-analyses showed that a positive test result following EB or OPH was more useful for predicting endometrial disease than USS, whereas a negative test result following USS was more useful for excluding endometrial disease than EB or OPH. The economic model included 12 diagnostic strategies and indicated that a strategy based on initial diagnosis with USS, using a 5mm double layer endometrial thickness cut-off, was the most cost-effective. Sensitivity analyses showed that initial investigation with EB or USS using a 4mm cut-off were also potentially cost-effective (incremental cost-effectiveness ratios under £30,000 per life year gained) at their most favorable estimates of diagnostic performance, in women under 65 years and at disease prevalence of 10% or more. The choice between initial testing with EB or USS will therefore depend upon patient age and preference, disease prevalence and the availability of high quality USS. In most circumstances women presenting for the first time with PMB should undergo initial evaluation with pelvic ultrasound using a threshold of 4mm or 5mm to define abnormal results.

DEDICATION

To Chris, Laura, Alice and Joe

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ABBREVIATIONS

ABS	Abdominal Ultrasound Scan
BWH	Birmingham Women's Hospital
CEA	Cost-Effectiveness Analysis
CI	Confidence Interval
D&C	Dilatation of the cervix and Curettage of the endometrium
D	Dominated
DB	Directed Biopsy
dOR	diagnostic Odds Ratio
EB	Endometrial Biopsy
Eca	Endometrial cancer
Ehyp	Endometrial hyperplasia
ET	Endometrial Thickness
FIGO	International Federation of Gynaecology and Obstetrics
FNR	False Negative Rate
FPR	False Positive Rate
HRT	Hormone Replacement Therapy
Hyst	Hysterectomy
ICER	Incremental Cost-Effectiveness Ratio
LR	Likelihood Ratio
LYG	Life Year Gained
MeSH	Medical Subject Heading

NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NS	Not Specified
OB	Outpatient Biopsy
OPH	Outpatient Hysteroscopy
QALY	Quality Adjusted Life Year
TAH	Total Abdominal Hysterectomy
TNR	True Negative Rate
TPR	True Positive Rate
TVS	Transvaginal Ultrasound Scan
tw	textword
USS	Ultrasound Scan
WMCIU	West-Midlands Cancer Intelligence Unit

CHAPTER I

BACKGROUND

1.1 The underlying problem

Postmenopausal bleeding (PMB), unscheduled bleeding on hormone replacement therapy (HRT) and menorrhagia are common gynecological problems.[71 310] The main aim of investigations for abnormal uterine bleeding is to exclude serious intrauterine pathology, namely endometrial cancer and hyperplasia,[232] conditions most prevalent in postmenopausal women.

Traditional investigation of women with postmenopausal bleeding using inpatient blind dilatation of the cervix and curettage of the endometrium (D&C) is now considered out-dated practice and has been replaced by initial outpatient endometrial evaluation using miniature endometrial biopsy (EB) devices, transvaginal ultrasound scan (USS) and outpatient hysteroscopy (OPH).[310] However, despite the widely accepted advantages of outpatient investigation, there is uncertainty regarding the individual value of these tests and the best sequence or combination in which to use them. Consequently practice varies throughout Europe and North America,[3,59,70,251,296,326] largely dependent upon prejudice (of individual clinicians) and pragmatism (resources available to them).

The main aim of investigating women with PMB is to exclude endometrial cancer and its precursor, endometrial hyperplasia. The incidence of endometrial cancer has increased during the last decade.[251,272] Unlike other malignancies affecting women, endometrial cancer often presents at an early stage with the possibility of curative treatment by hysterectomy.[251] Prognosis is increasingly bleak the more advanced the disease. As there have been no recent advances in the treatment of endometrial cancer that can be expected to increase survival, the importance of accurate and timely diagnosis of endometrial cancer is paramount in order to reduce mortality further.

This thesis assesses the diagnostic accuracy of currently available outpatient tests for the clinical investigation of women with PMB for endometrial cancer and hyperplasia. Moreover, the thesis examines the cost-effectiveness of strategies utilising EB, USS and OPH for the diagnosis of endometrial cancer.

1.1.1 Aetiology and epidemiology of postmenopausal bleeding

PMB is a common clinical problem in both general practice and hospital settings.[1,89,310] Women are most likely to present with this symptom in the sixth decade of life[272] where consultation rates in primary care for PMB are 14.3/1000 population.[1,272] Similarly, in the hospital setting, abnormal patterns of uterine bleeding account for more than 70% of all gynaecological consultations in the peri- and post-menopausal years.[310] At the Birmingham Women's Hospital (BWH), which serves a female population of 220,000 (of which one can assume 80,000 are postmenopausal), approximately 1000 women are seen each year with PMB (incidence 12.5/1000 population).

In most instances (90-95%), PMB results from benign causes such as intrauterine structural pathologies (polyps, fibroids) or prescription of exogenous hormones. Often, bleeding arises from apparently normal atrophic endometrium and is thought to be due to superficial petechial haemorrhages and mucosal ulceration.[278,342] However, the main aim of investigations for PMB is to exclude endometrial cancer,[232] which presents with this symptom in over 95% of cases.[250] The probability of endometrial cancer in women presenting with PMB is approximately 5-10%[16,146,149,251] and therefore referral of such women for further investigation in secondary care is mandatory. Published recommendations state that women should be seen within 2-6 weeks of referral.[251] On referral, some additional means of endometrial assessment are performed, as it is not possible to exclude cancer on clinical assessment alone. Traditionally, abnormal uterine bleeding has been investigated with blind D&C under general anaesthetic but now there is a trend towards minimally invasive, outpatient investigations utilising EB, USS and OPH first (see current service provision below).[251]

Although cervical cancer can present with PMB, most women with this condition present below the age of 55 years with intermenstrual bleeding, postcoital bleeding, vaginal discharge or pain.[251,259] The diagnosis is made from clinical examination and cervical biopsy. The diagnosis of cervical cancer is not considered further in this thesis.

1.1.2 The epidemiology and management of endometrial cancer

Endometrial cancer represents the most common female pelvic genital malignancy in the western world[136] and is increasingly common among more affluent populations[272] and increases with the adoption of more westernised lifestyles.[272] The aetiology of endometrial cancer is unknown, but several factors are known to increase or decrease the likelihood of

developing endometrial cancer. The most important of these appear to be age, obesity and unopposed endogenous or exogenous oestrogen production.[272]

In England and Wales, there are around 4000 new cases of endometrial cancer per annum (440 in the West Midlands), representing almost 4% of all cancer cases in women, in whom it is ranked 5th.[251,272] Incidence rates are approximately 50 per 100,000 population in women over 60 years. The overall age-standardised rate has remained close to 12/100,000 since the 1970s, but in women aged 55-74 rates have increased slightly in the 1990s.[251] The lifetime risk of developing endometrial cancer has been estimated to be 1.4%. An average general practitioner with a list size of 2000 would expect to see 1 new case of endometrial cancer every 6 years. In contrast to the trends in incidence, there have been long-term declines in mortality from cancer of the uterus. The age-standardised rate has halved – from 6/100,000 in 1950 to 3/100,000 in 1999. In England and Wales survival was only slightly below the European average, but was well below that in the Netherlands, Germany, France and more than 10% below rates in the USA.[272] Overall 5-year survival is around 77%, and improves with early stage localised disease. Around 70% of women diagnosed with endometrial cancer have early stage disease and 5-year survival is around 87%. Survival is worse for later stage disease at around 60% and is as low as 19% with the most advanced stage of disease.[72] If detected at an early stage, endometrial cancer is curable in most cases, usually by surgery (hysterectomy) and/or radiotherapy. As there have been no recent advances in the treatment of endometrial cancer that can be expected to increase survival, the importance of accurate and timely diagnosis of endometrial cancer is paramount in order to reduce mortality further.

1.1.3 The epidemiology and management of endometrial hyperplasia

Endometrial hyperplasia is more prevalent than endometrial cancer and affects both pre and postmenopausal women.[10,199,206] The probability of endometrial hyperplasia in women presenting with postmenopausal bleeding (with or without HRT) is approximately 15%.[63,206] The risk factors for developing hyperplastic endometrium are the same as for endometrial cancer and thus relate mainly to unopposed oestrogen exposure. Endometrial hyperplasia is categorised histologically by the degree of architectural disruption (simple or complex hyperplasia) and by the presence of abnormal cytology (atypia). The importance of endometrial hyperplasia relates not only to the symptoms of genital tract bleeding it can cause, but to its oncogenic potential. The natural history of endometrial hyperplasia is not fully understood.[125] What is known is that a proportion of simple and complex hyperplastic processes will regress without treatment[199] although the time scale over which such regression may occur is unclear. However, a small proportion (estimated to be between 1 and 3%[199]) will progress to frank endometrial cancer. The main prognostic factor is the presence of atypical cells. Malignant progression has been reported to occur in 30% of atypical endometrial hyperplasias if left untreated.[120,175,199]

Management depends upon accurate and timely diagnosis. Endometrial hyperplasia without atypia can be managed without the need for treatment as the condition may regress spontaneously, but regular endometrial assessment is required to exclude disease progression.[120,125,199] Medical treatments include systemic (oral/parenteral)[120,125,339] or local (intrauterine) progestogens to reverse the oestrogen dominant milieu.[267,288] Traditional treatment is with hysterectomy.[120,339] In the presence of atypical cells, hysterectomy is usually recommended in view of the potential for malignant transformation.[120] Erroneous diagnosis

can thus be detrimental to patients. For example, unnecessary surgery may be performed for false positive diagnoses of hyperplastic endometrium whereas false negative diagnoses can result in progression to endometrial cancer.

1.2 Investigation of women with postmenopausal bleeding

The traditional investigation for PMB was inpatient dilatation of the cervix and curettage of the endometrium (D&C).[152] This is now considered out dated practice[71] and has been largely replaced by the development of minimally invasive diagnostic tools for use in the outpatient setting. These new diagnostic modalities include outpatient endometrial biopsy (EB), transvaginal ultrasonography (USS) and outpatient hysteroscopy (OPH). (Table 1-1).

Table 1.1 Diagnostic modalities available to detect endometrial cancer and hyperplasia in women with postmenopausal bleeding

Features	Endometrial Biopsy	Ultrasound	Hysteroscopy	Prevailing clinical opinion
Safety	‿	‿‿	‿‿	All safe,[12,62,63,160,303] endometrial biopsy has more potential for trauma as it is a blind procedure
Acceptability	‾	‿‿	‿	All acceptable [210109,195], ultrasound least painful and invasive, endometrial biopsy most painful[320]
Feasibility	‾	‿‿	‿	Failure rates higher in procedures requiring uterine instrumentation. Endometrial biopsy higher than hysteroscopy.[38,62,63,164]
Other	Minimal expertise required[62]	Extracavity / pelvic information[37]	Directed endometrial biopsies[134]	Advances in the technology and application of ultrasound[6,33,291] and other radiographic imaging techniques[168] gives this modality the greatest future potential in diagnosis

‿‿ invariably ‿ typically ‾ generally

Outpatient EB (Figure 1-1) is a blind procedure where the endometrium is sampled using small-diameter mechanical or suction devices, which can be easily introduced into the uterine cavity without the need for anaesthetic. There is concern however, surrounding the non-representative nature of these blind procedures, which may be related to the small proportion of the endometrial surface sampled[277] and the non-sampling of focal intrauterine lesions.[157]

The development of pelvic ultrasound scanning (transabdominal or transvaginal) has allowed high resolution imaging inside the uterus enabling measurement of the endometrial thickness. (Figure 1-2 to 1-4) [303] It has been shown that the endometrial thickness of normal atrophic uterus measures on average 2.3 mm[123,146,243,244]. However, advanced endometrial cancer has also been known to occur in cases without noticeable endometrial thickness on ultrasound[96] The expertise and availability of ultrasound to gynaecologists varies throughout the UK, Europe and North America. Consequently, radiologists or trained radiographers rather than gynaecologists often perform USS. In the United Kingdom this situation is likely to change as a result of the recent introduction of specialist gynecological training in USS.[280]

Hysteroscopy (Figures 1-5 and 1-7) is an endoscopic technique allowing visualisation of the endometrial cavity. Recent advances in instrumentation have allowed hysteroscopy to be performed in an outpatient setting, further increasing its use in gynecological practice.[296] Various macroscopic features have been suggested as indicative of endometrial disease. However, there is no consensus and visual interpretation is subjective and operator dependent.[56] Concerns surrounding the role and value of hysteroscopic diagnosis have therefore arisen.[5,25,164,232]

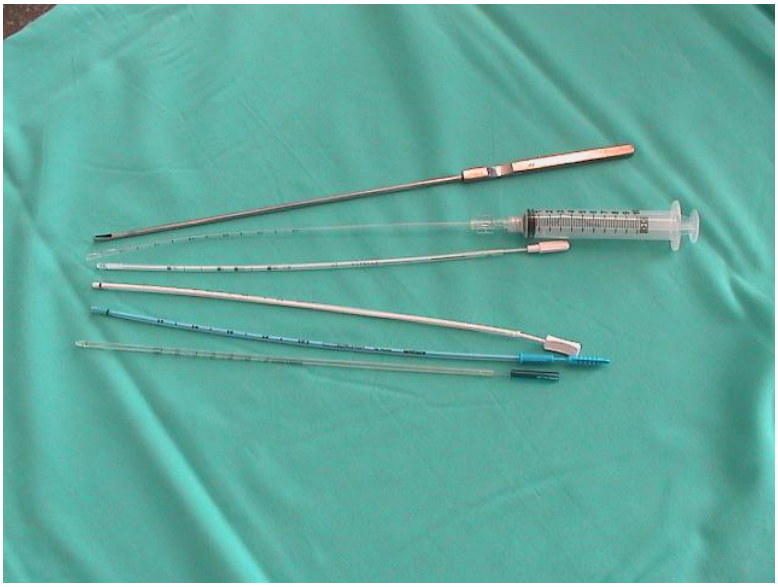
All the forgoing outpatient modalities are generally considered to be safe,[62,63] simple to use, [62,63] and acceptable to patients.[26,109,194,195] In addition, avoiding the need for an inpatient stay potentially reduces health resources utilisation. Such considerations have been examined in three published economic evaluations[257,167,119] (Appendix 2), which were based on imprecise data derived from small primary studies. The use of a single outpatient testing strategy in comparison to blind inpatient D&C was explored in each study. Two of the studies found

outpatient investigation using EB or OPH to be more cost-effective than inpatient D&C in terms of complications avoided and additional cases of cancer detected.[257,167] The study of highest quality found EB to be most cost-effective as measured by survival, compared to a policy of observation until bleeding recurred, D&C or immediate hysterectomy.[119] The relevance of these studies, is however, questionable given that endometrial assessment using D&C as a first-line is now outdated in clinical practice.[71] So, despite the widely accepted advantages of outpatient investigation, there is considerable debate regarding the best way to evaluate women with PMB for serious endometrial disease and consequently practice varies throughout the United Kingdom[3,59,251,272] Practice is largely dependent upon individual clinician preference and resources available to them.

Figure 1-1 Outpatient endometrial biopsy devices

A variety of outpatient endometrial biopsy devices exist and their common mode of action involves mechanically abrading and/or aspirating endometrium from the uterine cavity.

A) Panoramic view



B) Magnified view

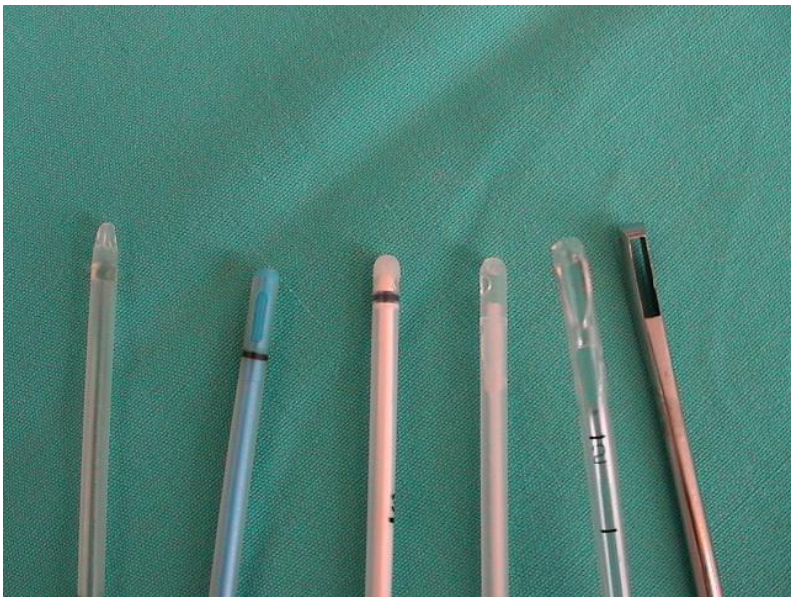
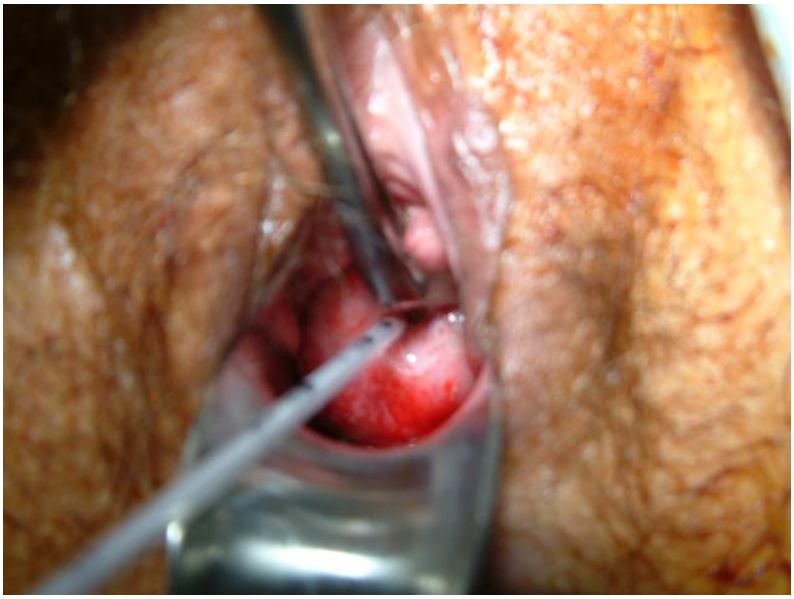


Figure 1-2 Outpatient endometrial biopsy

A) Insertion of endometrial biopsy device into the uterus



B) Endometrial tissue specimen

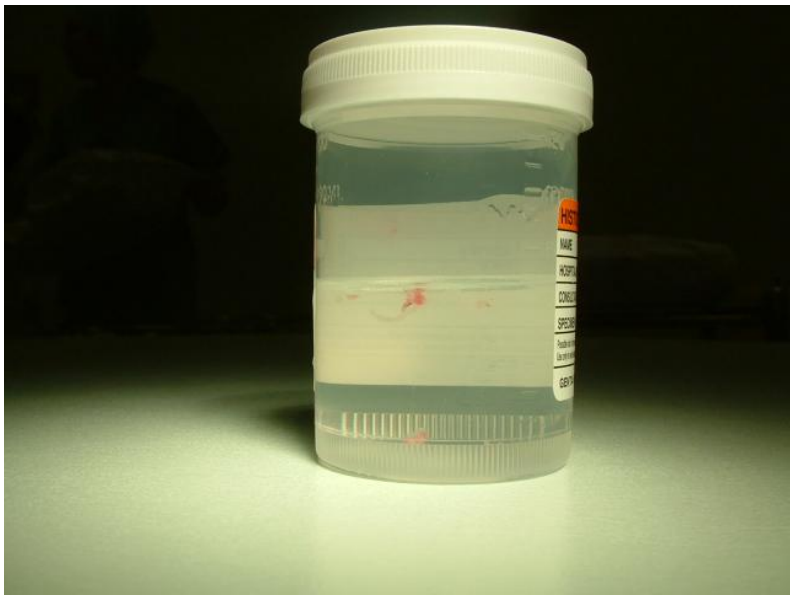
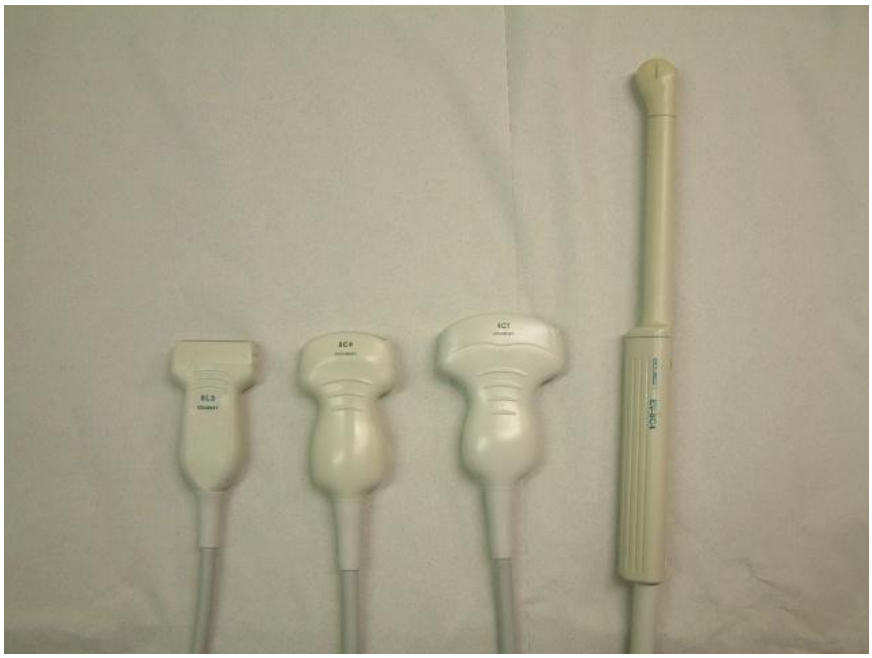


Figure 1-3 Pelvic ultrasound

A) Transducers suitable for gynaecologic pelvic ultrasound scans: Transabdominal and transvaginal probes



B) Transvaginal probe (magnified view).

Figure 1-4 Transvaginal ultrasound

The probe is gently inserted into the vagina with the patient in a semi-recumbent position and an empty bladder. The depth of tissue for ultrasound to penetrate is minimal using a transvaginal technique thereby allowing the use of higher frequency transducers with improved image resolution. A transabdominal scan often precedes the transvaginal approach.

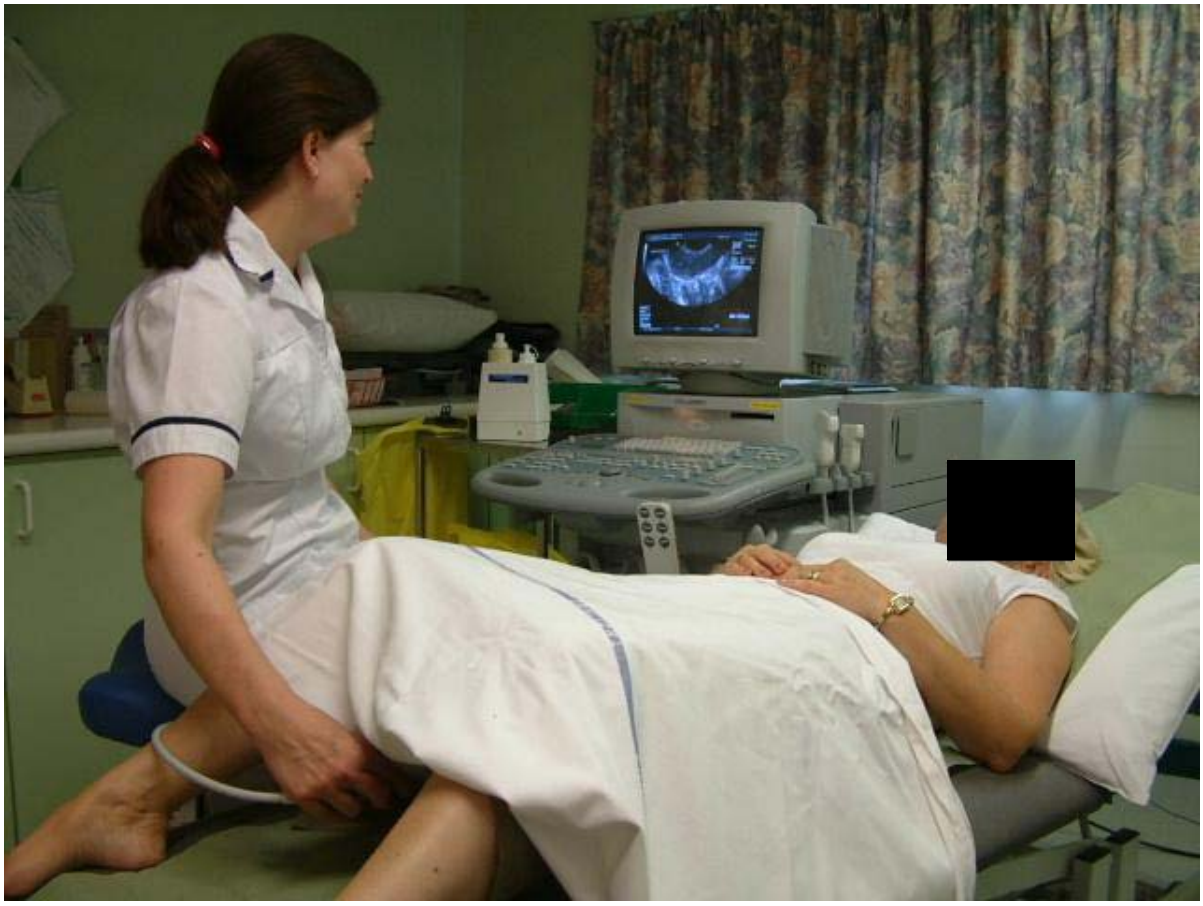
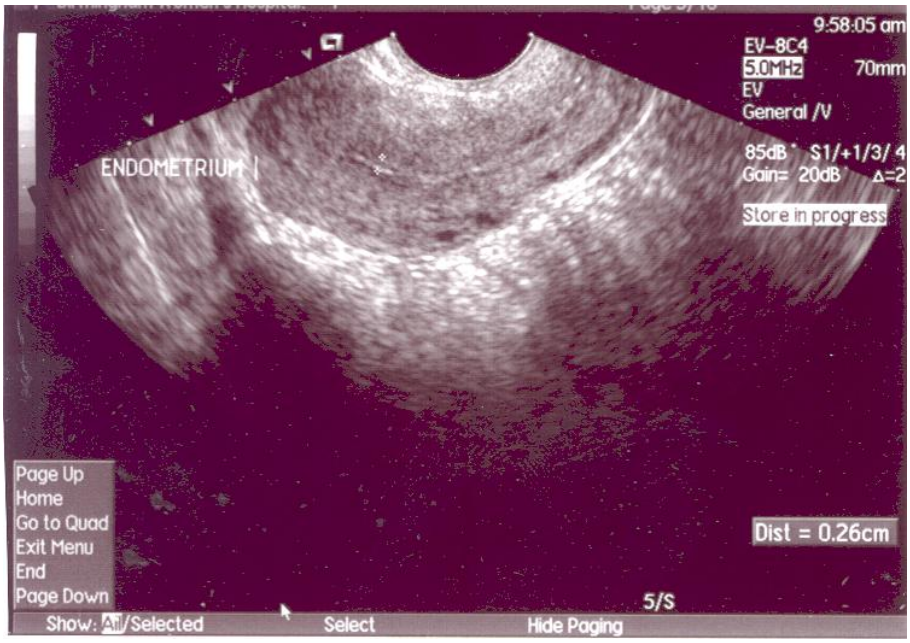


Figure 1-5 Endometrial thickness measured by transvaginal ultrasound scan

A) Normal, thin (atrophic) postmenopausal endometrium (3mm thickness)



B) Abnormal thickened postmenopausal endometrium (18mm thickness)

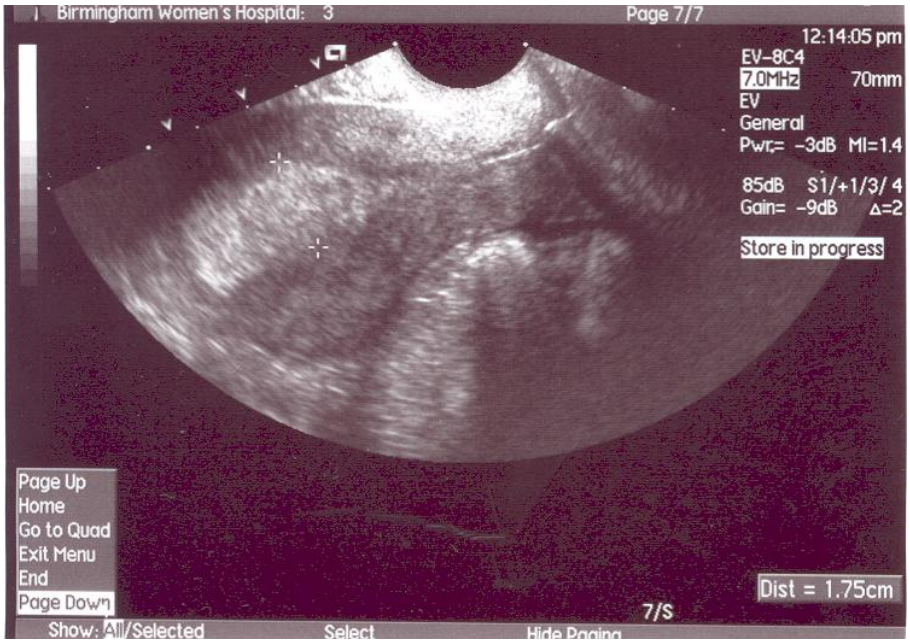


Figure 1-6 Hysteroscopy

Small diameter rigid or flexible endoscopes are used to image directly inside the uterine cavity (Reproduced with kind permission of *JAMA*) .

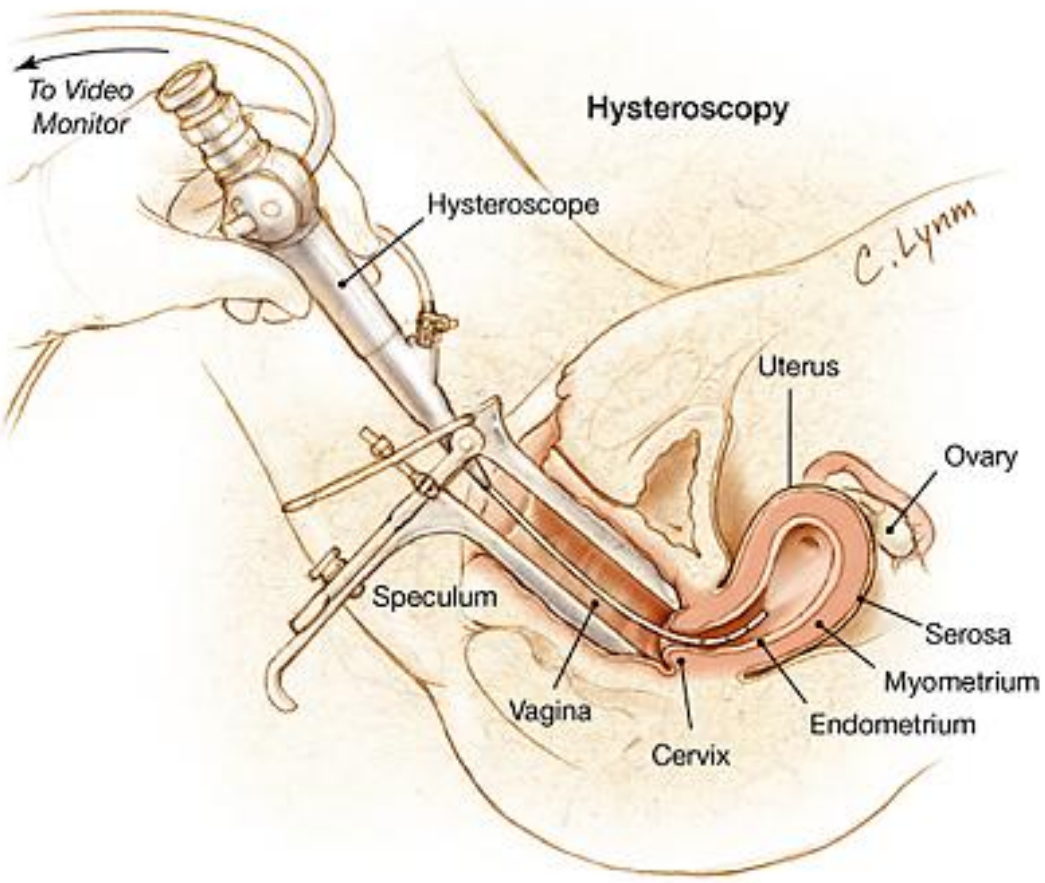
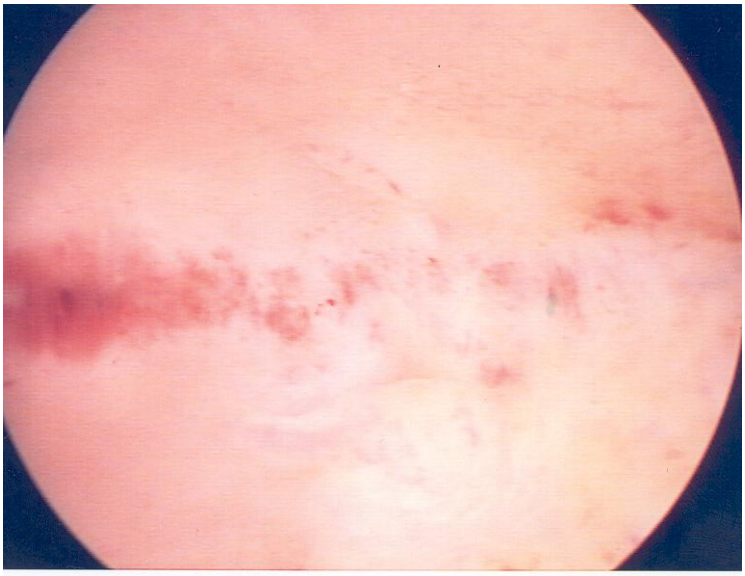


Figure 1-7 Semi-rigid 2.5mm diameter hysteroscopes

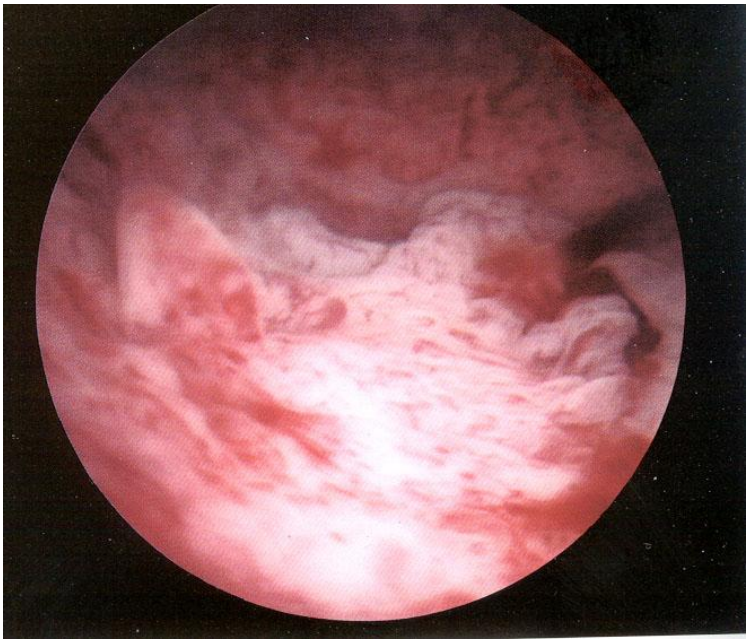
Miniaturisation of endoscopes has facilitated their use in the outpatient setting

Figure 1-8 Hysteroscopic views of the endometrium

A) Normal view showing thin, atrophic postmenopausal endometrium



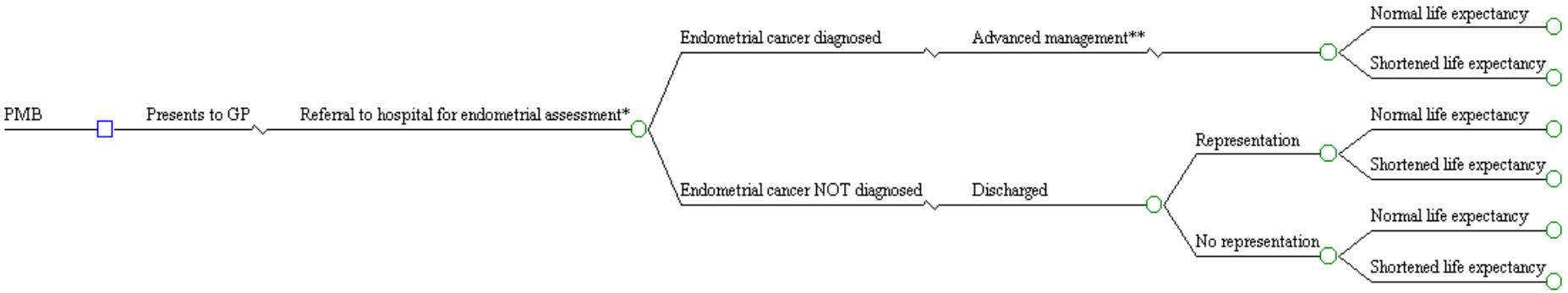
B) Abnormal view showing thickened, irregular and vascular endometrium.



1.3 Current service provision in the United Kingdom

Referral of all women presenting with PMB in the primary care setting for further investigation is mandatory[251] in order to exclude endometrial cancer. All women referred should be seen within 2 weeks.[251] Endometrial assessment is performed on referral, utilising the outpatient tests, EB, USS or OPH. This often takes place in a 'one stop' setting where the investigation(s) take place during a single consultation with no planned follow up unless test(s) fail or abnormal results are found. Negative findings result in discharge back to primary care, whereas a positive diagnosis leads to advanced treatment in most instances. Treatment for endometrial cancer varies, although in most instances hysterectomy and surgical staging is performed followed by adjuvant non-surgical treatments where necessary.[279,105] The typical event pathway is shown in Figure 1-9, which is the essential basis of any cost-effectiveness analyses.

Figure 1-9 Event pathway (current service provision) for the investigation and management of women with postmenopausal bleeding



PMB = postmenopausal bleeding, GP = General Practitioner
* Some combination of endometrial biopsy, pelvic ultrasound and hysteroscopy
** Surgery (hysterectomy) with or without adjuvant radiotherapy / chemotherapy

1.4 Existing evidence on accuracy of diagnostic tools

The bibliographic databases MEDLINE (1966-2001) and EMBASE (1982-2001) were searched for existing published evidence addressing the accuracy of investigative tools used in PMB. This showed that in the last decade, there have been many publications indicating that outpatient EB, ultrasound measurement of endometrial thickness and ambulatory hysteroscopy may be useful in predicting endometrial cancer and hyperplasia. However, individual studies addressing accuracy of these minimally invasive diagnostic tools, are small leading to imprecise and heterogeneous estimates of accuracy.[51] In addition, many studies have used measures of diagnostic accuracy that are not clinically intuitive. The generation of conflicting and confusing data has thus hampered clinical interpretation. The absence of a uniform strategy for the investigation of women with PMB has resulted because of a deficiency in the rigorous assessment of these newer diagnostic tools.

No systematic reviews of EB, USS or OPH were available at the outset of the research forming this thesis. However, during the course of my research program, two systematic reviews of USS and one of EB were published. The results and conclusions of all these reviews are of limited validity due to potential biases in their methodological approach as discussed later in the thesis (see section 4.4). I was unable to identify any systematic reviews addressing the diagnostic accuracy of hysteroscopy. Therefore the need to conduct comprehensive high quality reviews in this field was clear.

1.5 Existing economic evidence

The bibliographic databases MEDLINE (1966-2001) and EMBASE (1988-2001) were searched for existing published economic evidence addressing the cost-effectiveness of investigative tools currently used in PMB for detecting endometrial cancer. The search strategy used is shown in Appendix 1. In addition, the NHS Economic Evaluation Database (EED) held at the Centre for Reviews and Dissemination at the University of York and the Cochrane Library were also searched. Following the electronic searches of MEDLINE and EMBASE, there were 26 potentially eligible studies identified of which one[337] was selected after obtaining the full manuscripts. No manuscripts were selected from the EED out of 22 potentially eligible studies. No relevant studies were found from the Cochrane Library.

This study addressed outpatient investigation using USS or EB, and concluded that initial evaluation with USS was less costly than initial evaluation with EB in relation to test feasibility.[337] No study was identified that evaluated the cost-effectiveness of all contemporary outpatient modalities (i.e. EB, USS and OPH) used in sequence or combination for the investigation of postmenopausal bleeding for endometrial cancer (Appendix 2). Therefore there is a need to conduct a rigorous economic evaluation of diagnostic tools current used in investigating women with PMB for endometrial cancer.

1.6 Research questions

1.6.1 Questions addressed by this thesis

The following questions were posed in this thesis.

In women presenting with postmenopausal bleeding:

1. What is the accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer and hyperplasia and what are the rates of failure and complications?
2. What is the accuracy of outpatient endometrial ultrasound in the diagnosis of endometrial cancer and hyperplasia?
3. What is the accuracy of outpatient hysteroscopy in the diagnosis of endometrial cancer and hyperplasia and what are the rates of failure and complications?
4. Which of the above three tests and their combination is most cost effective in outpatient diagnosis of endometrial cancer?

1.6.2 Framing questions

Careful formulation of focussed research questions is necessary to aid the appropriate design of systematic reviews and cost-effectiveness analyses so that specific answers can be provided. The components of research questions in diagnosis are generally a *population*, a *test* and a *reference standard* against which the accuracy of the test will be measured. Some other *outcome* of interest may also be specified. Breaking down a question into these component parts facilitates the precise identification of problems needing to be addressed.[186] The factors considered when formulating the questions posed in this thesis are discussed below:

1.6.2.1 Question 1

What is the accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer and hyperplasia in women with postmenopausal bleeding and what are the rates of failure and complications?

Population:	Women with abnormal pre or postmenopausal uterine bleeding
Test:	Outpatient endometrial biopsy
Reference standard:	Histology of endometrial cancer and hyperplasia of a specimen obtained by an independent method (e.g. hysterectomy)
Other outcomes:	Failure to successfully complete the test Complications attributable to the test

Endometrial cancer and its precursor, endometrial hyperplasia, are the most important diagnoses to exclude in women with abnormal uterine bleeding. These conditions are more common in postmenopausal women, although they can occur in pre-menopausal women, where menstrual dysfunction is prevalent and also in perimenopausal women with unscheduled bleeding whilst taking hormone replacement therapy (HRT). Endometrial biopsy is performed in both pre and postmenopausal women and so in order to maximise the information about test accuracy, the population was not restricted to postmenopausal women. However, where possible, data was stratified according to menopausal status and HRT use.

Miniature endometrial biopsy devices have been designed for use in the conscious patient in an outpatient setting and various devices are now available. Although they can be used in the unconscious inpatient, they are almost always used in the conscious outpatient and therefore

the question of diagnostic performance was restricted to the outpatient setting, where it is most relevant. Both the test and reference standard (inpatient endometrial curettage or hysterectomy specimen) involve histological examination of obtained endometrial tissue. Therefore the disease outcomes of interest (endometrial cancer and hyperplasia) could be directly compared with one another facilitating ease of data abstraction. This also allowed the impact of the severity of endometrial hyperplasia on the diagnostic performance of endometrial biopsy to be examined, by stratifying data according to the presence or absence of abnormal cytology (atypical cells). Non-endometrial uterine malignancies were not considered in any of the reviews and where they occurred were excluded from analysis.

Good diagnostic performance depends upon test feasibility and safety in addition to diagnostic accuracy. This is especially true for tests designed for use in the outpatient setting, where patient factors may limit successful completion of the test. Unsuccessful sampling using outpatient endometrial biopsy was categorised as either failed procedures (i.e. failure to correctly position the device in the uterine cavity) or as histologically inadequate specimens (failure to obtain adequate endometrial tissue for histological diagnosis from a correctly sited device within the uterine cavity). Failed procedures may occur because of technical difficulties (usually unfavourable uterine anatomy) or pain resulting from the outpatient procedure. Histologically inadequate specimens are important because they may reflect the normal atrophic postmenopausal endometrial state where obtaining endometrial tissue would not necessarily be expected, rather than poor test performance. This consideration is important in clinical practice as it presents problems of interpretation. Failure to successfully complete the test was thus defined as both including and excluding histologically inadequate specimens (see data abstraction in chapter 3). Complications were categorised according to whether they

arose directly from the test procedure itself (e.g. visceral damage, haemorrhage, infection, vaso-vagal episodes) or indirectly (e.g. exacerbation of existing health problem such as angina) and by severity (potentially life threatening or not).

1.6.2.2 Question 2

What is the accuracy of pelvic ultrasound in the diagnosis of endometrial cancer and hyperplasia in women with postmenopausal bleeding?

Population:	Women with abnormal pre or postmenopausal uterine bleeding
Test:	Endometrial thickness measured by pelvic ultrasound
Reference standard:	Histological confirmation of endometrial cancer and disease (cancer + hyperplasia)

Measurement of endometrial thickness by pelvic ultrasound can be performed using transabdominal probes or more recently using transvaginal probes allowing better image resolution.[128] The procedure is rarely, if ever, required as an inpatient admission. Measurement of endometrial thickness is useful in postmenopausal women because oestrogen dependent endometrial thickening does not occur and so thin endometrium is considered normal. In contrast, thickened endometrium may represent the important diagnoses of cancer and hyperplasia as well as other benign conditions such as endometrial polyps. There is considerable debate regarding what constitutes an abnormally thickened endometrium and so various measurement cut-offs have been used.[160,303,319] Different methods for measuring endometrial thickness by ultrasound exist (e.g. single layer and double layer measurement)

and this has complicated the situation further. For the purposes of this review, all studies of symptomatic postmenopausal women undergoing pelvic ultrasound were included, but data were grouped according to the type of ultrasound probe, cut-off level for abnormality and measurement method used.

Pelvic ultrasound is not confined to use in postmenopausal women, but is widely employed in pre-menopausal women with abnormal menstrual bleeding. This is because patient acceptance is almost universal[128,303] and the modality allows the myometrium and ovaries to be imaged, in addition to the uterine cavity and endometrium. Consequently, the most commonly occurring gynaecologic pathology in women of reproductive age, uterine fibroids[340] and benign ovarian cysts,[28] can be diagnosed with a high degree of accuracy.[105,176] However, measurement of endometrial thickness to diagnose endometrial cancer or hyperplasia is of limited use in this population.[80,92,102,104,106,268] This is because a thickened endometrium is normally seen in pre-menopausal women as a result of ovarian oestrogen production and the extent of endometrial thickening varies in accordance with the stage of the menstrual cycle.[242] Furthermore, the prevalence of endometrial cancer is very low in premenopausal women with menstrual dysfunction[27,219,271] and benign endometrial polyps, which cause focal endometrial thickening, are far more common.[20,103] The population in my research question was therefore restricted to postmenopausal women with vaginal bleeding. Exogenous oestrogen given to postmenopausal women as part of HRT may cause endometrial proliferation to a varying, but lesser degree than in pre-menopausal women.[147] Thus, symptomatic postmenopausal women on HRT were also included in the population, although data was stratified according to HRT usage.

The review of endometrial biopsy was conducted first, where the diagnostic reference standard was endometrial histology obtained by *inpatient* sampling (endometrial curettage, directed biopsy, endometrial resection and hysterectomy specimens). However, a significant proportion of primary studies assessing diagnostic accuracy of ultrasound (and hysteroscopy) used outpatient endometrial biopsy devices to obtain histological samples. The results of the review of outpatient endometrial biopsy showed high diagnostic accuracy (see chapter IV). Bias due to misdiagnosis by endometrial biopsy, though considered unlikely to be a significant problem, was explored with subgroup analyses based on variation in histological reference standard (see chapter III). In contrast to the research question posed for endometrial biopsy, the condition of endometrial hyperplasia was not considered, but instead it was included together with endometrial cancer under the heading 'endometrial disease.' This approach was used because ultrasonic (and hysteroscopic) features of hyperplasia are not clearly distinct from those of endometrial cancer[56] and such an approach has previously been used.[134,303]

The safety of ultrasound has been well established[12] and a previous systematic review[303] has reported negligible failure rates and so these outcomes were not considered.

1.6.2.3 Question 3

What is the accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia in women with postmenopausal bleeding and what are the rates of failure and complications?

Population:	Women with abnormal pre or postmenopausal uterine bleeding
Test:	Hysteroscopy
Reference standard:	Histological confirmation of endometrial cancer and disease (cancer + hyperplasia)
Other outcomes:	Failure to successfully complete the test Complications attributable to the test

Hysteroscopy can be carried out as an inpatient test under general anaesthetic or as an outpatient test in the conscious patient. The research question relates to outpatient investigative tools in women with postmenopausal uterine bleeding. However, as with endometrial biopsy, hysteroscopy is performed in both pre and postmenopausal women and so in order to maximise the information about test accuracy, the population was not restricted to postmenopausal women. However, where possible, data was stratified according to the setting and menopausal status. Diagnosis of the conditions endometrial cancer or disease was considered (see question formulation for pelvic ultrasound – see section 1.6.2.2). Where cancer or hyperplasia was suspected within a focal abnormality, these were categorised under cancer and/or disease.

Hysteroscopic procedures failing to make a final diagnosis because of technical aspects (e.g. cervical stenosis, anatomical factors, structural abnormalities), inadequate visualization (e.g. obscured by bleeding, endometrial debris) or patient factors (e.g. pain, intolerance) were categorized as failed procedures. Complications were categorised in the same way as for endometrial biopsy (see section 1.6.2.1).

1.6.2.4 Question 4

What is the most cost-effective outpatient test or combination of outpatient tests for the diagnosis of endometrial cancer in women with postmenopausal bleeding?

Population:	Women with postmenopausal uterine bleeding
Test:	Diagnostic approaches utilising various combinations of outpatient endometrial biopsy, ultrasound and hysteroscopy
Clinical outcome:	Survival following diagnosis and treatment of endometrial cancer
Economic outcome:	Costs incurred in testing and in treating endometrial cancer (NHS hospital perspective)

Endometrial cancer is the most important diagnosis to exclude in women with abnormal uterine bleeding. This potentially life-threatening diagnosis is invariably made in association with postmenopausal bleeding (PMB), where endometrial cancer is found in 5-10% of such women.[16,146,149,251] Additional means of outpatient endometrial assessment is mandatory[251] (traditional investigation with inpatient dilatation and curettage as a first-line is considered outdated practice),[71] but which test or combination of tests is best to use is not established and consequently is the focus of clinical debate and the reason for eclectic hospital practice.[3,59,251,272] Endometrial hyperplasia is not considered to be premalignant unless found in association with abnormal cytology.[120,175,199] The hyperplastic process is usually reversed with simple hormonal treatment.[120,267,288,339] Endometrial cancer is the only diagnosis considered to significantly affect survival and therefore the management of this condition has been chosen for the cost-effectiveness analysis, where effectiveness is measured in terms of life years gained.

The benefits and costs of using an intervention to treat a disease depend upon whose perspective it is (i.e. patient, hospital, payer, society etc.) The societal perspective is the most comprehensive one (and encompasses all other perspectives), as it considers all costs and benefits irrespective of who pays and who benefits. This is of use to government and policy makers who are interested in allocating resources to improve population welfare.[231] However, our main concern related to maximising health (as opposed to welfare) in the symptomatic, postmenopausal female population undergoing mandatory investigation for abnormal uterine bleeding. For this reason we chose to take the perspective of the health service provider (NHS healthcare system) and considered direct medical costs appropriate to the NHS.

CHAPTER II

METHODS

This research presented in this thesis was undertaken with two aims:

(1) To summarise the current evidence on the diagnostic accuracy of outpatient endometrial evaluation using endometrial biopsy (EB), ultrasound scan (USS) and outpatient hysteroscopy (OPH) using systematic reviews

(2) To determine the most cost-effective combination of these tests for the investigation of women with post-menopausal bleeding (PMB) for endometrial cancer using decision-analytic modeling.

2.1 Systematic review methods

To determine the accuracy of the outpatient diagnostic tests used in PMB to predict endometrial cancer and hyperplasia, quantitative systematic reviews of endometrial biopsy (EB), pelvic ultrasound (USS) and hysteroscopy (OPH) were conducted. The methodology used was common to all three reviews, it was based on a prospective protocol considering widely recommended methods,[66,183,189] and followed the stages given below.

2.1.1 Identification of studies

General bibliographic databases, MEDLINE and EMBASE, were searched. Language restrictions were not applied. The electronic search strategies targeted the relevant diagnostic procedures exclusively, studies addressing the relevant clinical problem (abnormal uterine bleeding which encompasses both pre and postmenopausal bleeding) were then identified on completion of the initial search phase by examining all the retrieved citations. Pilot searches suggested that the chosen search strategies gave reasonable precision without compromising sensitivity. These search strategies are detailed in Appendices 3 to 5.

In addition, the Cochrane Library and relevant specialist registers of the Cochrane Collaboration were searched. Reference lists of all known reviews and primary studies were checked and direct contact with manufacturers of outpatient EB devices and hysteroscopes was also made.

2.1.2 Selection criteria

The reviews focused on prospective observational studies or comparative cross-sectional studies in which the results of the diagnostic test of interest were compared with the results of a reference standard. The following criteria were used to select articles for inclusion:

Population:	Women with abnormal pre or postmenopausal bleeding.
Diagnostic tests:	Outpatient endometrial biopsy, endometrial thickness measurement using ultrasound imaging and hysteroscopy.
Reference Standard:	Endometrial cancer and endometrial hyperplasia confirmed histologically.

Two reviewers identified the studies in a two-stage process independently (see Acknowledgments). The titles and abstracts identified as being potentially relevant from the computer database searches or inspection of bibliographies were scanned and provisionally included, unless they could definitely be excluded as not addressing the accuracy of EB, USS or OPH. The full texts of all provisionally included articles from the first stage were retrieved. The authors and journal titles were removed from the retrieved citations thereby blinding the reviewers. Final inclusion/exclusion decisions were made with reference to a checklist, the items of which were based on the selection criteria above. The checklists were piloted and the repeatability of their use tested and confirmed. The checklists used for each review are shown in Appendices 6 to 8. Disagreements about inclusion/exclusion were initially resolved by consensus and where this was not possible it was resolved using arbitration by a third reviewer (see Acknowledgements). The agreement statistics between reviewers were computed using percentage agreement and weighted kappa statistics.[67] The kappa statistic provides measurement of agreement obtained beyond chance and weights provide credit for partial agreement.[55]

2.1.3 Quality assessment

All papers meeting the eligibility criteria were assessed for their methodological quality. Quality was defined as the confidence that the study design, conduct and analysis minimized bias in the estimation of diagnostic accuracy. Based on existing checklists,[66,107,163,207,230] quality assessment involved scrutinizing study designs and the relevant features of population, intervention and outcome. These included method of data collection and patient selection, details relating to type of abnormal bleeding and menopausal status, description of the

diagnostic test and histological reference standard, and presence of verification bias and blinding (Table 2-1).[189] This approach is in line with the recently published STARD criteria for reporting test accuracy studies[34,35] and the recently developed 'QUADAS tool' for assessing quality of test accuracy studies (personal communication – see Chapter 4).

Table 2.1 Quality assessment and definitions

Feature	Quality assessment
Study design	Studies where the diagnostic test and reference standard were performed on the same occasion were defined as cross-sectional or simultaneous studies and considered ideal. Observational series where the intervention and reference standard were not carried out simultaneously were defined as sequential studies whereas case-control studies encompassed those studies where a subset of the population was already known to have endometrial cancer or hyperplasia. These latter designs were considered second best.
Data collection	Prospective collection of data from the study population was considered ideal whereas retrospective collection was considered second best.
Patient selection	Consecutive recruitment of eligible women was considered ideal and convenience sampling, i.e. arbitrary recruitment or non-consecutive recruitment was deemed second best. In the absence of any explicit information in the manuscript on the method of data collection or recruitment, the article was categorised as unclearly reported.
Population details	Population details were considered adequate if the menopausal status and type of abnormal uterine bleeding of women enrolled was reported and inadequate if not reported.
Population spectrum*	Population spectrum was considered wide if patients with and without Hormone Replacement Therapy (HRT) were included. Those excluding women on HRT were considered narrow and inadequate if not reported.
Definition of menopause*	Length of amenorrhoea indicating that the woman was menopausal was considered ideal if it was >/=12 months, and inadequate if it was < 12 months or unreported.
Diagnostic test: Endometrial biopsy	The description of the use of the outpatient biopsy device was considered ideal if the methodology was reported in sufficient detail to allow replication by other researchers. In the absence of the above information, the diagnostic intervention was considered as unclearly reported.
Ultrasound	The description of the ultrasound test was considered ideal if the method of obtaining the ultrasound image (i.e. transvaginal or transabdominal) was reported along with the frequency of the transducer used. Whether one or both layers of the endometrium were measured for thickness was also assessed. Information on the cut-off level for an abnormal test result was also sought. If the cut-off level for an abnormal result was determined *a priori* it was considered ideal. If any of the above information was not present then the diagnostic test was classified as unclearly reported.

Table 2-1 continued

Hysteroscopy	The description of the hysteroscopic technique and the definition of the hysteroscopic features constituting a diagnosis of endometrial disease were considered adequate if the methodology was reported in sufficient detail or referenced to allow replication by other researchers. For hysteroscopic technique to be deemed adequate the method used to inspect the uterine cavity had to be explicit in addition to describing the setting, type of hysteroscope, distension medium, and imaging system. In the absence of the above information, description of the diagnostic intervention was considered as inadequate.
Reference standard	For confirmation of diagnosis by a reference standard, histology obtained from inpatient endometrial sampling (hysterectomy, directed biopsy or D&C were considered ideal and histology obtained from blind outpatient sampling was considered second best (USS and OPH). For the reviews of EB confirmation of diagnosis by a reference standard, hysterectomy, directed biopsy and dilatation and curettage under anaesthesia were considered adequate, in that order of importance.
Verification bias†	Verification bias was considered to be present if the application of the reference test was dependent upon the result of the hysteroscopy (differential verification) or if <90% patients originally tested had diagnosis verified (incomplete or partial verification)
Timing of verification‡	The verification of diagnosis following the index test was either performed at the same time (simultaneous) or after a short delay (sequential). Simultaneous verification was considered ideal whereas sequential verification was considered second best.
Blinding	Blinding was considered present if it was clearly reported that the pathologists providing histological diagnoses were kept unaware of the test (endometrial biopsy, ultrasound or hysteroscopy) diagnosis. If the diagnosis following the test was divulged to the pathologists or in the absence of any such reporting, blinding was categorized as absent.
Follow up	Greater than 90% follow up of the original study population was considered ideal and less than 90% follow up as second best.

* Ultrasound review only
† Ultrasound and hysteroscopy reviews only
‡ Hysteroscopy review only

Analysis of these items was used to develop a hierarchy of evidence in diagnostic test studies, shown in Table 2-2.

Table 2.2 Hierarchy of evidence for primary research on diagnostic accuracy

Level	Description
1	An independent, blind comparison with reference standard among an appropriate population of consecutive patients.
2	An independent, blind comparison with reference standard among an appropriate population of non-consecutive patients or confined to a narrow population of study patients.
3	An independent, non-blind comparison with reference standard among an appropriate population of consecutive patients.
4	An independent, non-blind comparison with reference standard among an appropriate population of non-consecutive patients or confined to a narrow population of study patients.
5	An independent, blind comparison among an appropriate population of patients, but reference standard not applied to all study patients.
6	Reference standard not applied independently or expert opinion with no explicit critical appraisal, based on physiology, bench research or first principles.

Study levels 1-3 were considered to be high quality and levels 4-5 low quality. Level 6 studies were not eligible for inclusion in the reviews and were excluded. A piloted checklist was used to identify and record items of study quality. The assessment was performed independently, in duplicate for the reviews of EB and USS. In the hysteroscopy review, the assessment of English language papers was performed by one reviewer and foreign language papers by two reviewers independently following translation where necessary. Any disagreements were resolved by consensus.

2.1.4 Data abstraction

Data were extracted independently and in duplicate. Data abstraction forms are given in Appendices 6 to 8.

2.1.4.1 Diagnostic accuracy data extraction

Three outcomes were considered: endometrial cancer, endometrial hyperplasia and normal (functional or atrophic endometrium and benign focal abnormalities e.g. intrauterine polyps and fibroids) for the review of EB. As discussed in section 1.6.2.2, endometrial disease, defined as including cancer and/or hyperplasia, was examined rather than endometrial hyperplasia for the reviews of USS and hysteroscopy. Non-endometrial uterine malignancies were excluded from analysis.

Endometrial cancer was considered the most important diagnosis and, to analyse its prediction, data were abstracted as two by two tables of the diagnostic test under scrutiny, result (positive or negative for cancer) and the results of the reference standard histology (benign or cancer). Similarly contingency tables were produced for USS and hysteroscopy results and endometrial disease (benign or disease), and EB and endometrial hyperplasia (hyperplasia or non-hyperplasia). In the review of ultrasound measurement of endometrial thickness, different cut-off levels for an abnormal test result were adopted by the different selected studies and 2x2 tables were produced according to these cut-off levels (see also section 1.6.2.2).

To examine the impact of the severity of endometrial hyperplasia on the diagnostic performance of EB, endometrial hyperplasia data were stratified by the presence or absence of

atypical cells (abnormal cytology) as part of a secondary analysis (as discussed in section 1.6.2.1). This involved constructing two sets of 2x2 tables comparing EB and reference standard histology. The target disorder (histology) for the first table was hyperplasia without atypia (normal / negative test result being absence of hyperplasia) and in the second table the target disorder was hyperplasia with atypia (normal / negative test result being absence of hyperplasia with atypia). A final analysis was then conducted for endometrial cancer or precancer (complex or atypical hyperplasia). In this analysis, data were abstracted as 2x2 tables of the outpatient biopsy result (positive or negative for endometrial cancer + precancer) and the results of the reference standard histology (endometrial cancer/precancer or non-endometrial cancer/precancer).

2.1.4.2 Secondary outcomes data extraction

Data pertaining to complications, inadequate specimens (EB only) and failures associated with testing were recorded (see section 1.6). Failures were excluded from two by two tables, whereas inadequate specimens (precluding a definitive diagnosis following the reference test in the case of hysteroscopy) were used in sensitivity analyses including them along with negative results. This is because the inability to obtain a specimen is generally considered a negative result.[19,24] Information on menopausal status, the number of women recruited, and those whose outcome data were known was also sought from the manuscripts. In addition, the setting (outpatient or inpatient) and technical details pertaining to the hysteroscopic examination were sought.

2.1.5 Quantitative data synthesis

2.1.5.1 2x2 tables

The tables were constructed as detailed in section 2.1.4.1. True positive rate (sensitivity), false positive rate (1-specificity) and likelihood ratios (LRs) were calculated for each study along with their 95% confidence intervals (CIs). Where 2x2 tables contained zero cells, 0.5 was added to each cell to enable our calculations.[287]

2.1.5.2 Heterogeneity

Heterogeneity of results between different studies was formally assessed in all reviews graphically, using sensitivity and specificity plots in addition to the χ^2 test. In order to explore for clinical sources of heterogeneity, the potential explanatory variables were defined *a priori.*[64] In view of the potential influence of spectrum variability,[276,331] menopausal status and setting were considered to be important. In addition, examination of the impact of study quality on estimation of accuracy according to individual quality items (patient selection, reference standard, completeness of verification and blinding) and also according to an overall quality level (1-5) incorporating these items, was planned.[62]

2.1.5.2.1 Subgroup and meta-regression analysis

Statistical examination was performed to assess whether estimation of accuracy was different in the subgroups. This was done by examining if the impact of an explanatory variable on the log of diagnostic odds ratio (dOR), a measure which accommodates LRs for both positive and negative test results, in meta-regression analysis.[305,311] Univariable analyses were initially performed followed by multivariable modeling, which controlled for confounding between

variables.[305] In the review of ultrasound, meta-analyses were performed separately for subgroups of studies with the same cut-off level for abnormality and the same measurement techniques (single or both endometrial layers). The effect of HRT use on diagnostic accuracy was also evaluated by subgroup analysis. Sources of heterogeneity were explored for by univariate subgroup analyses according to the pre-specified possible explanatory variables population spectrum (HRT use) and study quality items. Additional subgroup analyses were performed, stratifying studies according to variation in specific study characteristics (e.g. population, intervention, and outcome).[82,305] Multivariable modeling was then performed as described for hysteroscopy below.

In the review of hysteroscopy, the models produced by multivariable analysis included menopausal status (postmenopausal vs. pre-menopausal and mixed population) and clinical setting (office vs. inpatient) as explanatory variables. The models were adjusted for the effect of study quality. For this quality was used as a binary variable (levels 1-3 vs. 4-5), which avoided problems of co-linearity between quality items. By testing only three variables in meta-regression analysis, it was hoped to avoid spurious results due to "overfitting". [311] This approach is in keeping with published recommendations, which advocate a cautious examination of potential reasons for heterogeneity by specification of a small number of subgroup analyses in advance. [64,69,82]

For the hysteroscopy review, additional *post hoc* analyses to explore for causes of heterogeneity were conducted alongside those planned in advance, when certain variables were considered to be informative or recommended by the peer reviewers. Following univariable analyses, multivariable meta-regression analyses were performed to evaluate the

effect of the explanatory variables on log dOR observed among individual studies.[305] The models produced by multivariable analysis included the independent variables description of test (adequate vs. inadequate), complications (present vs. absent), timing of verification (simultaneous vs. sequential), method of data collection (prospective vs. other) and completeness of follow up (greater than 90% vs. less than 90%), in addition to the variables defined *a priori*. The findings of these *post hoc* analyses were, however, considered in the context of hypothesis generation.

2.1.5.3 Meta-analysis

Meta-analysis to produce summary pooled estimates of sensitivity and specificity were performed if these measures were found to behave independently[83,170] as indicated by lack of statistical correlation between them. However, estimates of sensitivity and specificity have limited value in clinical interpretation.[86,162,174,283] Therefore summary likelihood ratios (LRs) were generated as the principal measures of diagnostic accuracy based on the recommendations of the various Evidence-based Medicine Groups.[82,84,86,150,173,174] The LRs indicate by how much a given hysteroscopy finding raises or lowers the probability of having endometrial cancer or disease.[21] This is important in clinical decision making because the estimated probability of disease (or not having disease) is a prime factor determining whether to withhold treatment, undertake further diagnostic testing or treat without further testing.[264] Thus the generation of LRs and post-test probabilities represents a more relevant method of establishing the utility of a test and reduces the risk of erroneous inferences being drawn.[162,185].

Pooling of LRs was performed by weighting the log LR from each study in inverse proportion to its variance. The clinical implications of the LRs generated for diagnostic accuracy were examined to determine post-test probabilities using Bayes' theorem using the formula: post-test probability = likelihood ratio x pre-test probability/[1-pre-test probability x (1-likelihood ratio)]. An estimate of pre-test probability was obtained by calculating the prevalence of pathology in the population studied. The post-test probability of endometrial pathology, in the presence of a particular test result, refers to the probability of this outcome being present conditional on this test result. In this way, a more clinically useful measure of the diagnostic performance of the test is obtained as it relates to the actual test result before the presence or absence of pathology is known. In order to deal with the uncertainty in the estimation, 95% confidence intervals (CI) around the point estimates were generated. Approximate variance for the post-test odds were obtained by adding the variances of the combined LRs and pre-test odds, enabling the calculation of its 95% CI. The 95% CIs for the post-test probabilities were then generated by converting the limits of the post-test odds to their respective probabilities. Inferences according to strength of evidence were generated considering estimate of accuracy, homogeneity of results and study quality.[188]

2.1.5.3.1 Fixed and random effects models

When heterogeneity was encountered within subgroup meta-analysis for hysteroscopy or ultrasound, results were initially pooled from individual studies using both a fixed effects and random effects model. In the presence of heterogeneity across studies, a random effects model may be considered preferable[64,69,82,91] in meta-analysis, as this approach produces wider CIs. However, this benefit has to be balanced against the potential disadvantage that by weighting smaller studies preferentially, it may produce biased point estimates of accuracy.[82]

Examination for such bias in meta-analyses was carried out and results reported with a fixed effects model where a random effects model was associated with higher estimates of accuracy. This allowed more conservative interpretation of the results. Furthermore, if heterogeneity remained within the pre-specified clinical subgroups, interpretations were based on inferences from high quality studies (levels 1-3).

2.1.5.4 Sensitivity analysis

In order to ascertain how uncertainty arising from underlying assumptions influence review results, sensitivity analyses were conducted where indicated. A sensitivity analysis was carried out in the review of hysteroscopy, considering inadequate histological specimens, precluding a definitive diagnosis following the reference test, as negative results. This is because insufficient tissue samples are generally taken to mean absence of pathology.[19,24] Intrauterine polyps were also excluded and fibroids as part of a sensitivity analysis, in order to examine whether the presence of these focal lesions affected estimates of diagnostic accuracy.

2.1.5.5 Publication bias

For all reviews, exploration for publication bias was carried out, by producing funnel plots (scatter plot of individual study accuracy against some measure of study information[186]) of diagnostic odds ration (dOR) against corresponding inverse of variance. When no publication bias is present the plots will be shaped like a funnel because studies of smaller size are expected to have increased variation in the estimates of accuracy.[318] The bigger the study variance, the lower the weighting of the study and the less information it provides. This means that in addition to small sample size of included primary studies, those studies reporting very

high accuracy (few false positive or negative diagnoses) will also have a relatively big variance and thus be weighted less. The adjusted rank correlation method was used to test the correlation between estimated LRs and their standard errors.[23,23]

2.2 Economic analysis methods

The cost-effectiveness analysis was based on modeling the costs and outcomes of patients with PMB investigated using various diagnostic strategies. Survival in terms of life years gained (LYG) was the outcome and cost per LYG was the measure of cost-effectiveness. This approach is widely used in health economics[137,231,262,327] and was conducted according to recommended methods.[99,111,231,240,253,301]

2.2.1 The model

A decision model[114,198,294] was constructed to reflect current service provision (Figure 2-1). As there is no consensus regarding how best to investigate women with PMB for endometrial cancer, initial investigation utilising all tests either alone or in combination were included in the model. For strategies involving USS, both 4mm and 5mm cut-offs were used to define abnormal endometrial thickening. This was done to address the ongoing clinical debate regarding what constitutes the best USS cut-off for abnormal endometrial thickening (4mm or 5mm) and also to reflect varying clinical practice.[160,303,319] A further option, of withholding immediate investigation at initial presentation and only instituting diagnostic work-up if PMB recurred, was also considered. Thus, 12 outpatient strategies for the clinical investigation of women with PMB for endometrial cancer were evaluated based on initial evaluation with:

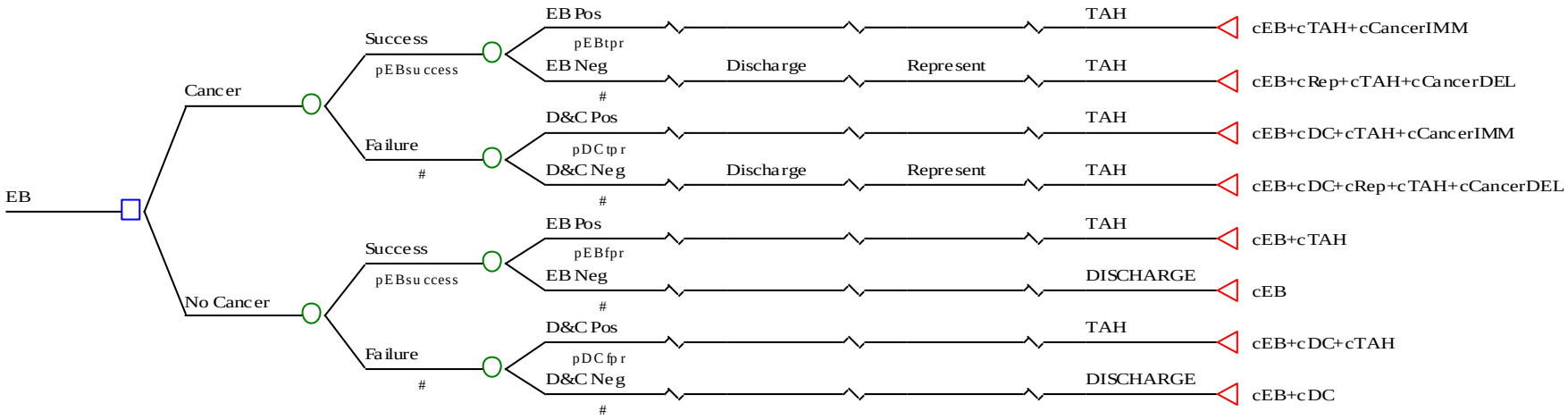
1. EB
2. USS (4mm)
3. USS (5mm)
4. OPH
5. USS (4mm) and OPH
6. USS (5mm) and OPH
7. USS (4mm) and EB
8. USS (5mm) and EB
9. EB and OPH
10. USS (4mm) and EB and OPH
11. USS (5mm) and EB and OPH
12. No initial evaluation

In cases of test failure, the default diagnostic procedure was inpatient evaluation of the endometrium under general anaesthetic utilising blind or directed dilatation of the cervix and curettage of the endometrium (D&C) (Figures 2-2 to 2-10). As discussed in section 1.2, initial endometrial assessment by inpatient D&C is outmoded, but is still employed when outpatient modalities fail.

The model used estimates of probabilities for various test results, life expectancy, direct medical cost and computed cost-effectiveness as a function of age cohorts (45 years, 55 years, 65 years, 75 years and greater than 80 years of age). Endometrial cancer was divided into

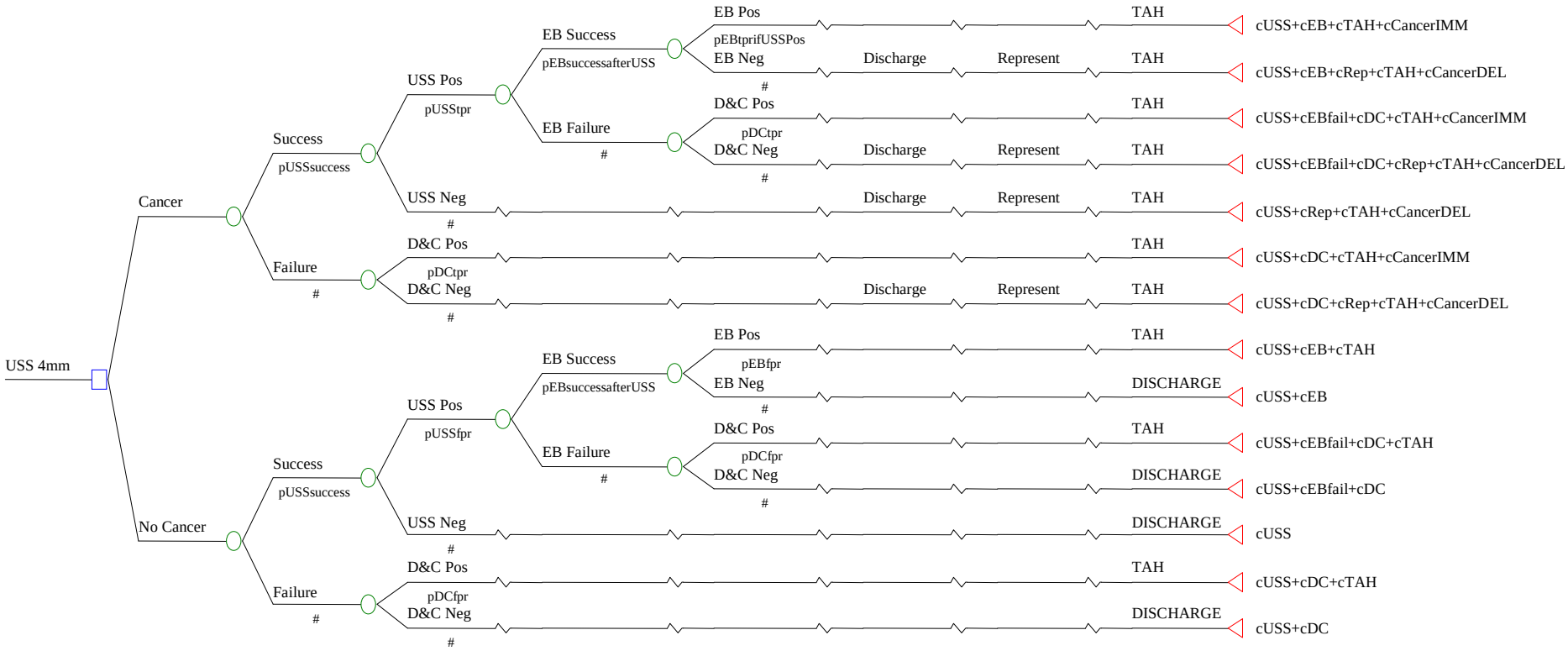
localised (FIGO stage I) and more advanced (FIGO stages II-IV) disease. The model also considered costs arising from morbidity associated with diagnosis by D&C.[152]

Figure 2-1 Decision analytic model: Strategy utilising initial evaluation with endometrial biopsy (EB) for the investigation of postmenopausal bleeding for endometrial cancer



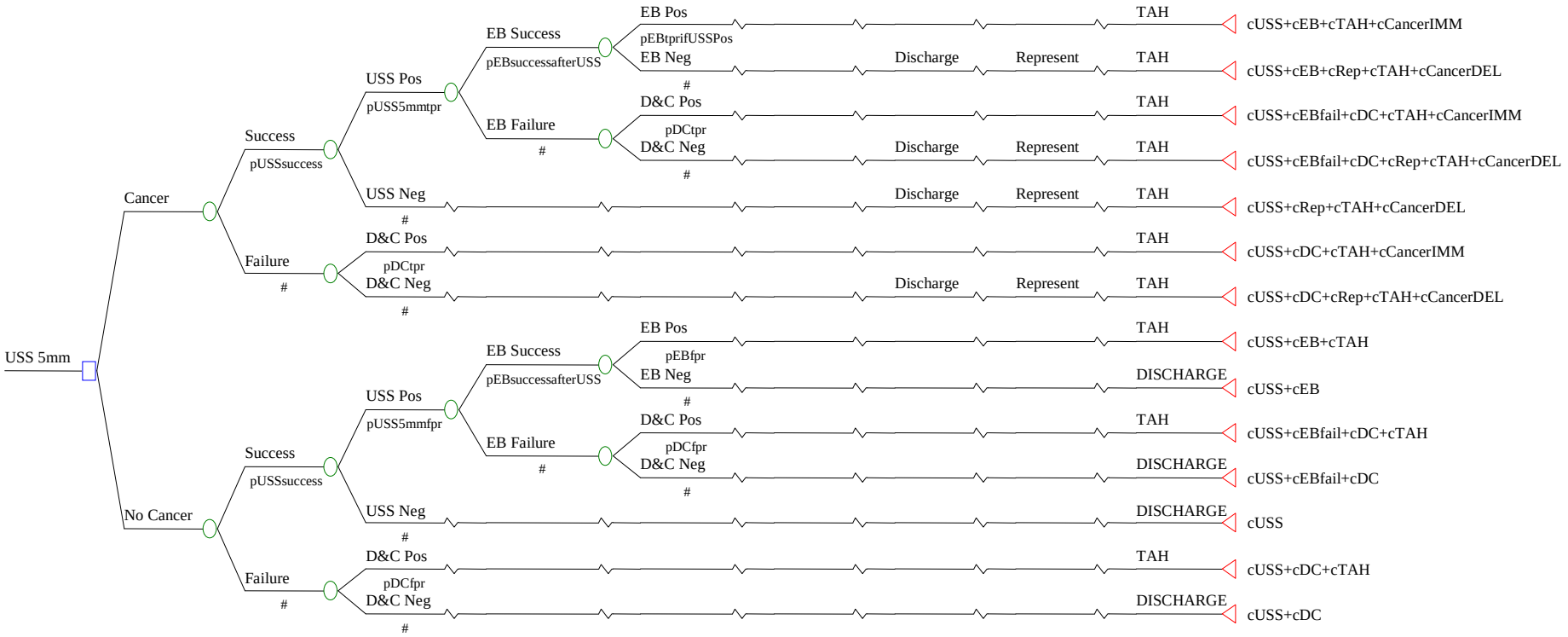
Cancer IMM = endometrial cancer treatment following immediate diagnosis, Cancer DEL = endometrial cancer treatment following delayed diagnosis, D&C or DC = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, Neg = negative test result, OPH =outpatient hysteroscopy, Pos = positive test result, PMB = postmenopausal bleeding, Rep = represent, TAH = total abdominal hysterectomy, tpr = true positive rate, USS = ultrasound scan.
Prefix c = cost, prefix p = probability, # = complementary probability
Represent = a combination of all three tests performed (USS and EB and OPH) – see text for details

Figure 2-2 Decision analytic model: Strategy utilising initial evaluation with pelvic ultrasound scan (USS) using a cut-off of 4mm to signify abnormal endometrial thickness for the investigation of postmenopausal bleeding for endometrial cancer



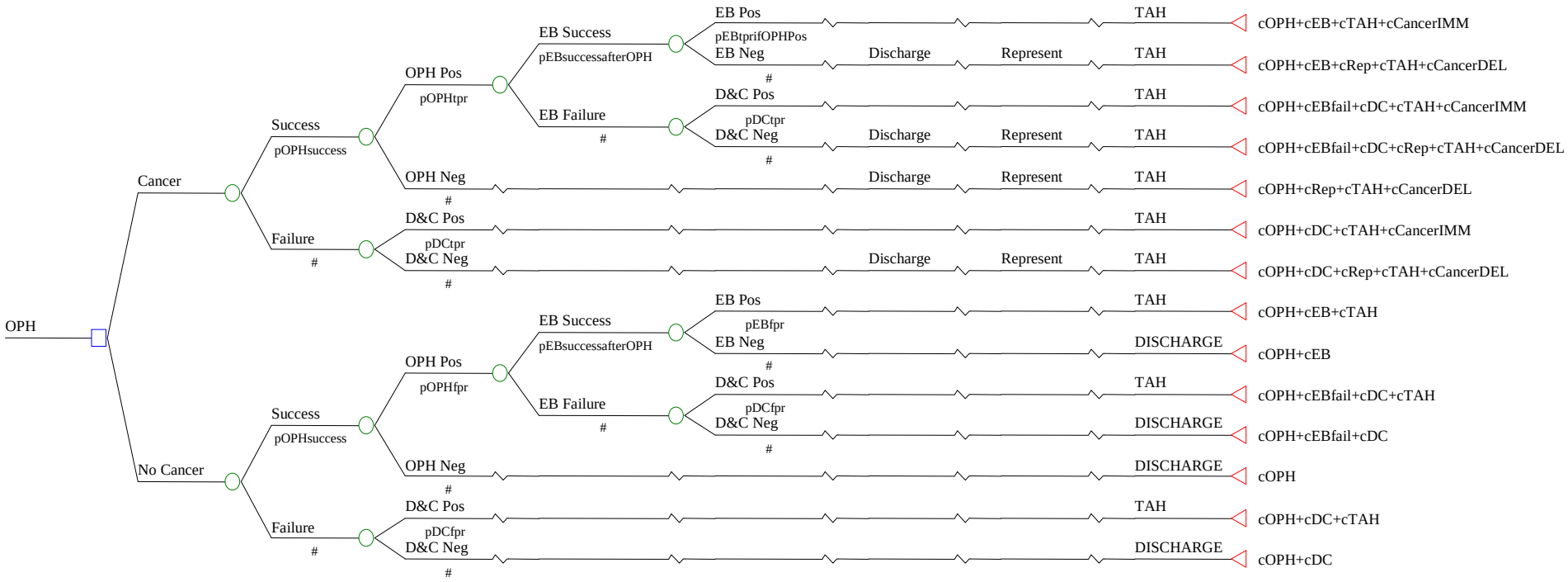
Cancer IMM = endometrial cancer treatment following immediate diagnosis, Cancer DEL = endometrial cancer treatment following delayed diagnosis, D&C or DC = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, Neg = negative test result, OPH =outpatient hysteroscopy, Pos = positive test result, PMB = postmenopausal bleeding, Rep = represent, TAH = total abdominal hysterectomy, tpr = true positive rate, USS = ultrasound scan.
Prefix c = cost, prefix p = probability., # = complementary probability, Represent = a combination of all three tests performed (USS and EB and OPH) – see text for details

Figure 2-3 Decision analytic model: Strategy utilising initial evaluation with pelvic ultrasound scan (USS) using a cut-off of 5mm to signify abnormal endometrial thickness for the investigation of postmenopausal bleeding for endometrial cancer



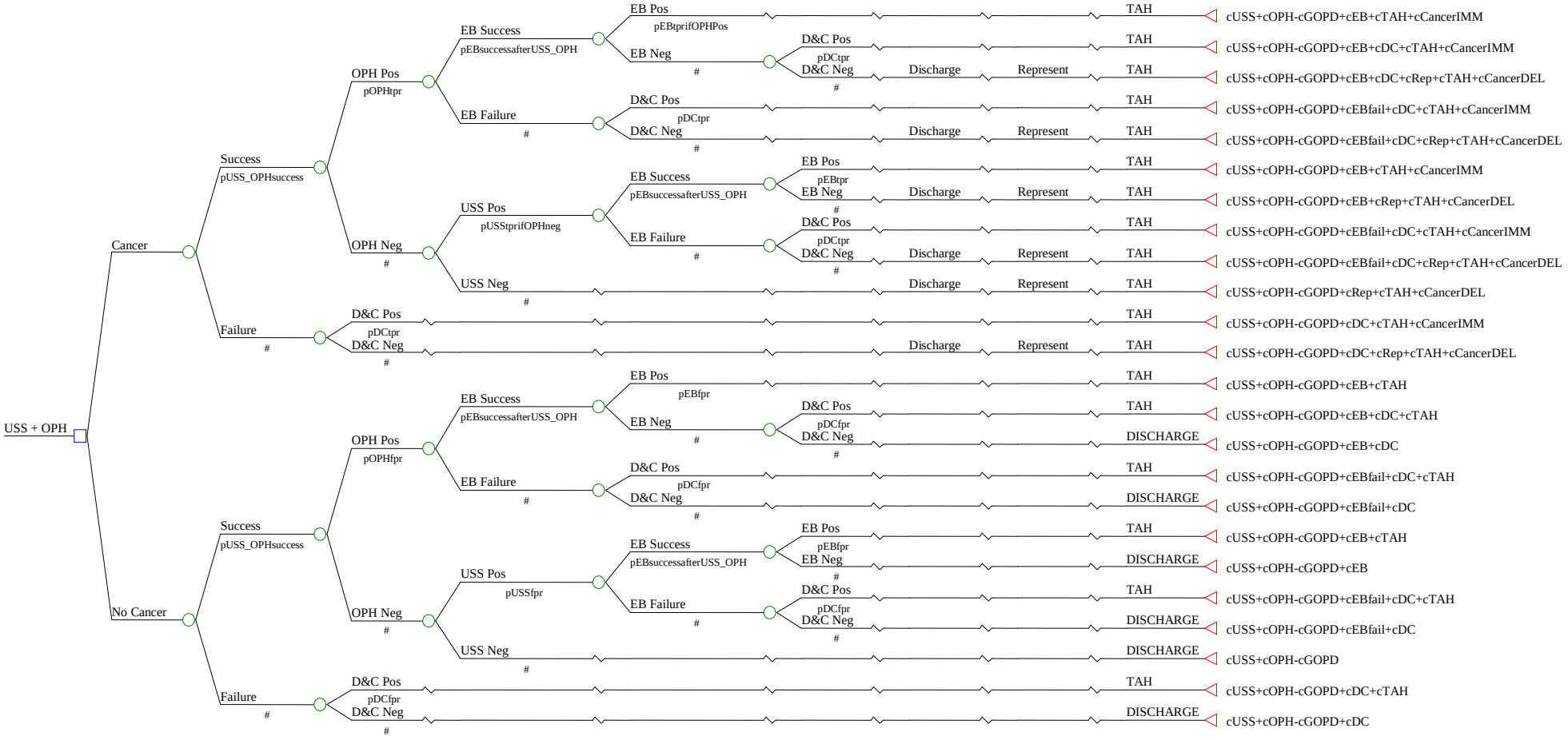
Cancer IMM = endometrial cancer treatment following immediate diagnosis, Cancer DEL = endometrial cancer treatment following delayed diagnosis, D&C or DC = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, Neg = negative test result, OPH =outpatient hysteroscopy, Pos = positive test result, PMB = postmenopausal bleeding, Rep = represent, TAH = total abdominal hysterectomy, tpr = true positive rate, USS = ultrasound scan.
Prefix c = cost, prefix p = probability, # = complementary probability.
Represent = a combination of all three tests performed (USS and EB and OPH) – see text for details

Figure 2-4 Decision analytic model: Strategy utilising initial evaluation with outpatient hysteroscopy (OPH) for the investigation of postmenopausal bleeding for endometrial cancer



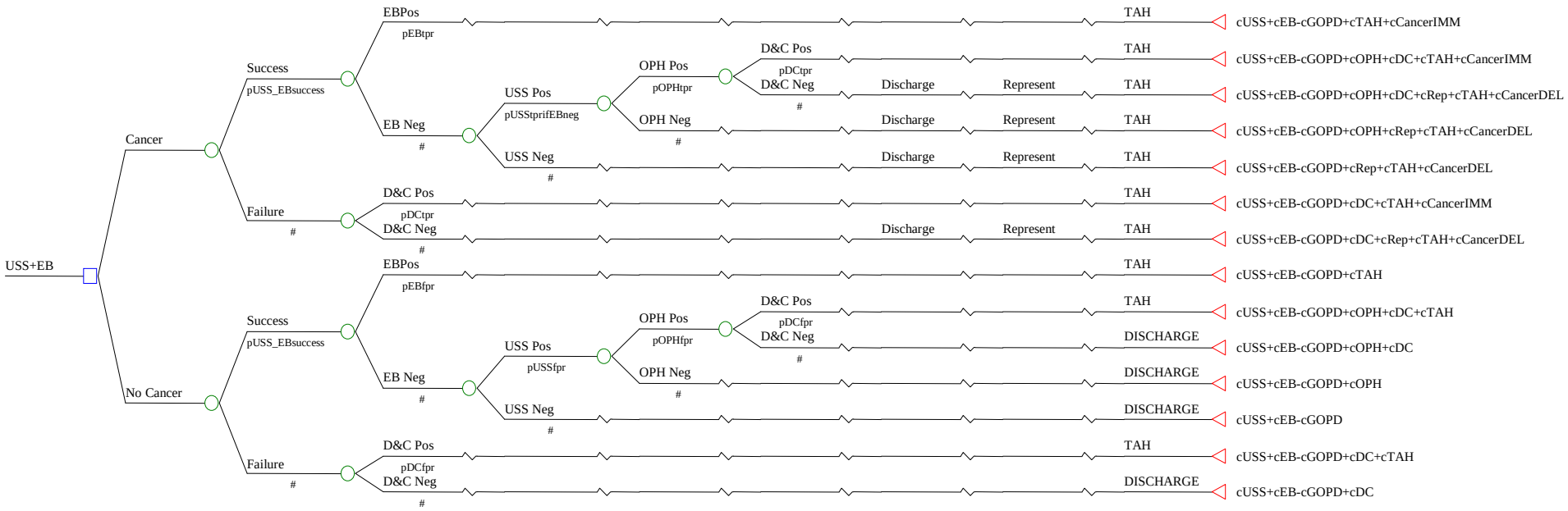
Cancer IMM = endometrial cancer treatment following immediate diagnosis, Cancer DEL = endometrial cancer treatment following delayed diagnosis, D&C or DC = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, Neg = negative test result, OPH =outpatient hysteroscopy, Pos = positive test result, PMB = postmenopausal bleeding, Rep = represent, TAH = total abdominal hysterectomy, tpr = true positive rate, USS = ultrasound scan.
Prefix c = cost, prefix p = probability, # = complementary probability.
Represent = a combination of all three tests performed (USS and EB and OPH) – see text for details

Figure 2-5 Decision analytic model: Strategy utilising initial evaluation with a combination of pelvic ultrasound and outpatient hysteroscopy (USS_OPH) for the investigation of postmenopausal bleeding for endometrial cancer (both 4mm and 5mm ultrasound cut-offs used to signify abnormal endometrial thickness)



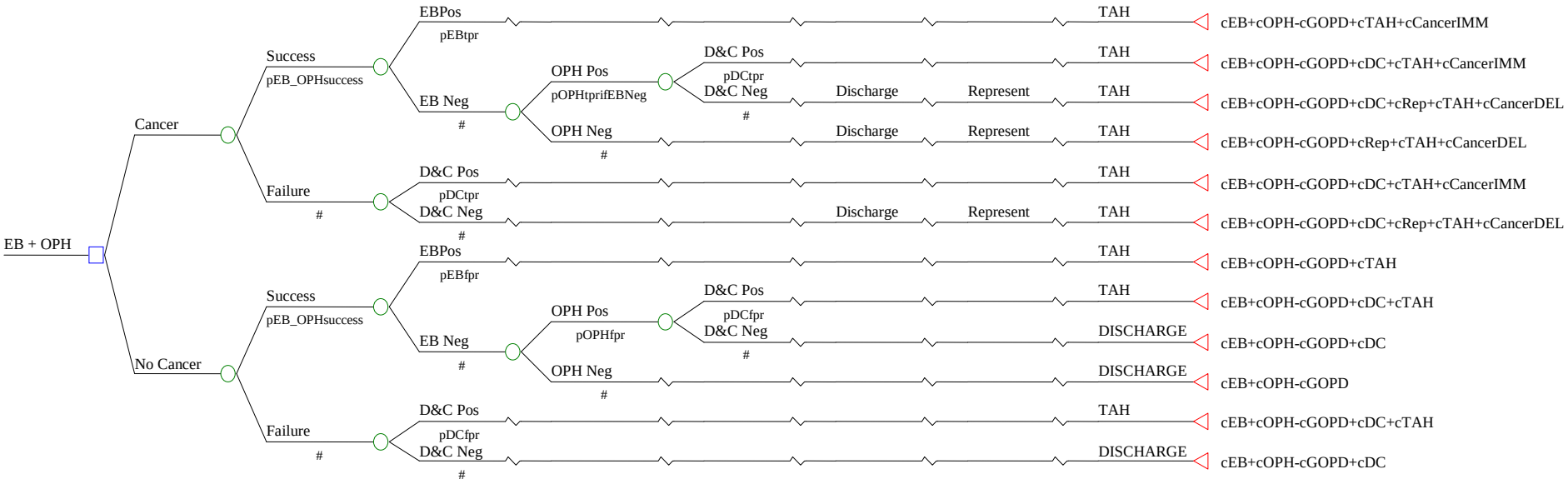
Cancer IMM = endometrial cancer treatment following immediate diagnosis, Cancer DEL = endometrial cancer treatment following delayed diagnosis, D&C or DC = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, GOPD = gynaecology outpateint department visit (additional), Neg = negative test result, OPH =outpatient hysteroscopy, Pos = positive test result, PMB = postmenopausal bleeding, Rep = represent, TAH = total abdominal hysterectomy, tpr = true positive rate, USS = ultrasound scan.
Prefix c = cost, prefix p = probability, # = complementary probability. Represent = a combination of all three tests performed (USS and EB and OPH) – see text for details

Figure 2-6 Decision analytic model: Strategy utilising initial evaluation with a combination of pelvic ultrasound and endometrial biopsy (USS_EB) for the investigation of postmenopausal bleeding for endometrial cancer (both 4mm and 5mm ultrasound cut-offs used to signify abnormal endometrial thickness)



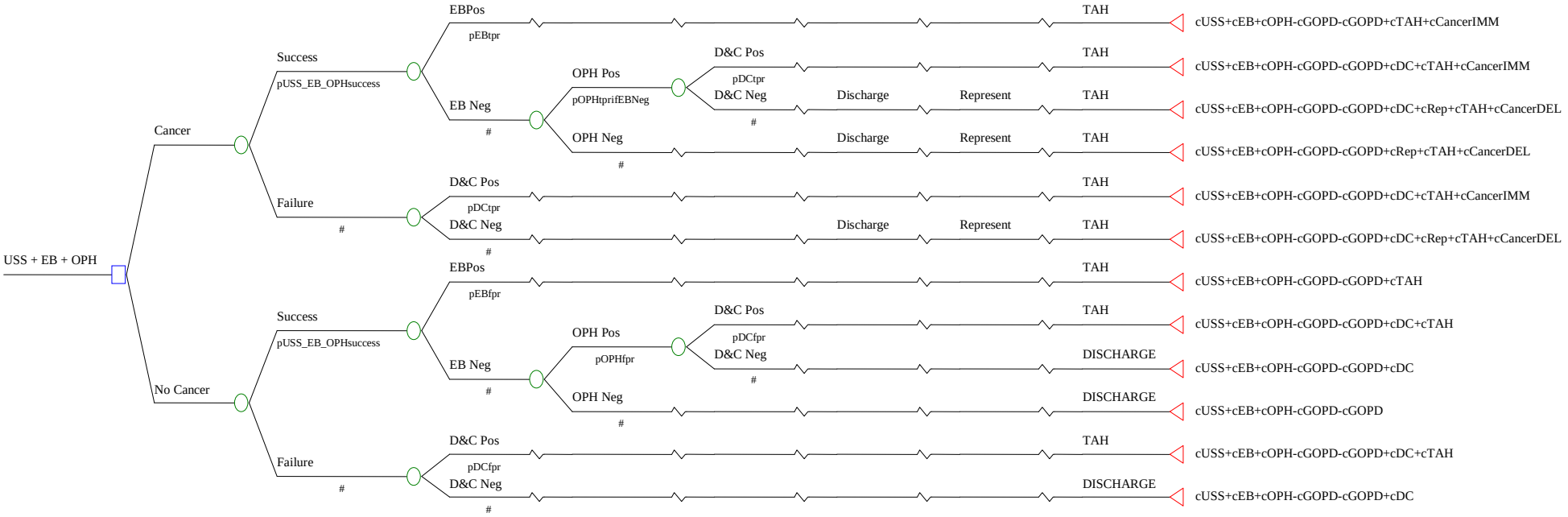
Cancer IMM = endometrial cancer treatment following immediate diagnosis, Cancer DEL = endometrial cancer treatment following delayed diagnosis, D&C or DC = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, GOPD = gynaecology outpateint department visit (additional), Neg = negative test result, OPH =outpatient hysteroscopy, Pos = positive test result, PMB = postmenopausal bleeding, Rep = represent, TAH = total abdominal hysterectomy, tpr = true positive rate, USS = ultrasound scan.
Prefix c = cost, prefix p = probability, # = complementary probability.
Represent = a combination of all three tests performed (USS and EB and OPH) – see text for details

Figure 2-7 Decision analytic model: Strategy utilising initial evaluation with a combination of endometrial biopsy and outpatient hysteroscopy (EB_OPH) for the investigation of postmenopausal bleeding for endometrial cancer



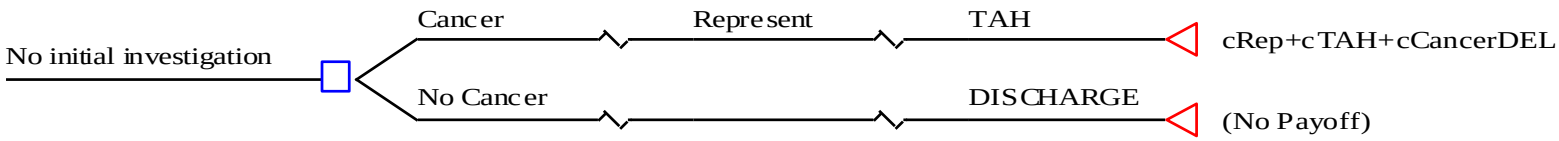
Cancer IMM = endometrial cancer treatment following immediate diagnosis, Cancer DEL = endometrial cancer treatment following delayed diagnosis, D&C or DC = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, GOPD = gynaecology outpateint department visit (additional), Neg = negative test result, OPH =outpatient hysteroscopy, Pos = positive test result, PMB = postmenopausal bleeding, Rep = represent, TAH = total abdominal hysterectomy, tpr = true positive rate, USS = ultrasound scan.
Prefix c = cost, prefix p = probability. # = complementary probability
Represent = a combination of all three tests performed (USS and EB and OPH) – see text for details

Figure 2-8 Decision analytic model: Strategy utilising initial evaluation with a combination of pelvic ultrasound, endometrial biopsy and outpatient hysteroscopy (USS_EB_OPH) for the investigation of postmenopausal bleeding for endometrial cancer (both 4mm and 5mm ultrasound cut-offs used to signify abnormal endometrial thickness)



Cancer IMM = endometrial cancer treatment following immediate diagnosis, Cancer DEL = endometrial cancer treatment following delayed diagnosis, D&C or DC = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, GOPD = gynaecology outpateint department visit (additional), Neg = negative test result, OPH =outpatient hysteroscopy, Pos = positive test result, PMB = postmenopausal bleeding, Rep = represent, TAH = total abdominal hysterectomy, tpr = true positive rate, USS = ultrasound scan.
Prefix c = cost, prefix p = probability. # = complementary probability
Represent = a combination of all three tests performed (USS and EB and OPH) – see text for details

Figure 2-9 Decision analytic model: Strategy of no initial evaluation (i.e. diagnostic work-up only if symptoms recurred) for the investigation of postmenopausal bleeding for endometrial cancer



Cancer DEL = endometrial cancer treatment following delayed diagnosis, Rep = represent, TAH = total abdominal hysterectomy,
Prefix c = cost,
Represent = a combination of all three tests performed (ultrasound, outpatient endometrial biopsy and hysteroscopy) – see text for details

2.2.2 Data sources and modeling assumptions for decision analysis

In the first instance it was assumed that the hypothetical presentation with postmenopausal bleeding represented the first episode. No postmenopausal woman was assumed to be less than 45 years old and no other significant aetiology (e.g. other genital tract malignancy) was considered. The woman was considered to be otherwise healthy with a normal age-adjusted life expectancy. The probability of endometrial cancer in women presenting with postmenopausal bleeding is between 5 and 10%[16,251] and women are most likely to present with this symptom in the seventh decade of life.[272] Therefore, a 65 year old woman presenting with PMB and a 5% prevalence of malignant disease were used for the base case analysis.

The initial investigation(s) used in each strategy were assumed to take place in a 'one stop' setting (i.e. one initial consultation only with no planned follow up unless test(s) failed or abnormal results were found). It was assumed that a consultant grade specialist performed all diagnostic and surgical procedures. For the base case analysis it was assumed that an additional return visit was required following a positive USS in order to perform endometrial sampling. The impact of performing EB following a positive USS at the same visit was examined as part of a sensitivity analysis, to reflect the practice of gynaecologists with expertise in ultrasound. Expert clinical opinion was then obtained independently about decision-making conditional upon positive or negative test results (i.e. the need for any further testing or therapeutic intervention). An expert clinical panel was then convened to reach consensus in cases of disagreement. In this manner a representative body of opinion was obtained regarding current management pathways in the diagnosis of PMB. It was agreed that invasive surgery (hysterectomy) for endometrial cancer would not be performed without

histological confirmation, whether by EB or inpatient sampling (D&C). Once the decision for hysterectomy had been made, additional pre-operative investigation by examination under anaesthesia, fractional curettage, cystoscopy, magnetic resonance imaging and other radiographic modalities was assumed not to have been necessary in accordance with current clinical practice.[279] Radiotherapy and chemotherapy were assumed to have been provided by the same medical oncologist.

2.2.2.1 Diagnostic Tests

Failed diagnostic procedures led to investigation by inpatient endometrial assessment under general anaesthesia (D&C). In the case of outpatient endometrial biopsy, failed procedures were considered to be cases where technical problems meant that an endometrial specimen could not be obtained. Histologically inadequate specimens were considered to be negative tests for both EB and D&C.[19,62] Inpatient D&C was assumed to have no technical failure rate.[219] Data for failure rates and estimates of diagnostic accuracy were obtained from high quality published systematic quantitative reviews of the diagnostic literature for EB, USS and OPH (presented in this thesis – Appendix 9).[62] Failure rates for initial strategies utilising test combinations were estimated by the consensus panel based on the definition of a failed strategy as any test making up the strategy failing and on available failure rate data from individual tests.[62 63,160,303] Similarly, failure rates were also adjusted for tests performed in a diagnostic strategy conditional on the success of preceding tests. The base case true positive rates for diagnostic tests carried out conditional on a preceding test result were also adjusted as part of a sensitivity analysis to take account of plausible changes in accuracy due to lack of complete test independence (Appendix 9).[16 57]As over 95% of women with endometrial cancer present with PMB,[250] it was assumed that all women who were erroneously discharged

following the initial presentation (i.e. false negatives) remained symptomatic. The interval to representation was thus taken to be short and all these women were then assumed to undergo reinvestigation with all outpatient tests where perfect test success and accuracy was assumed.

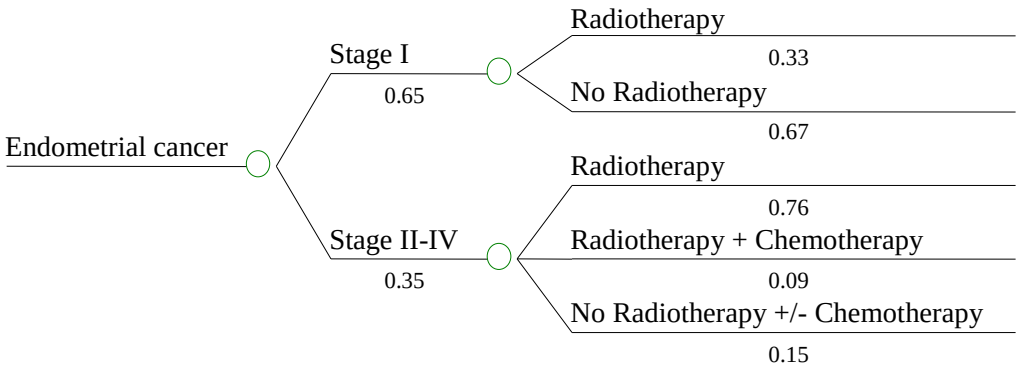
No serious morbidity was assumed to be associated with any of the ambulatory procedures (ultrasound, hysteroscopy and endometrial biopsy) based on evidence from systematic reviews of the available literature.[62,63,160,303] For D&C the major complication rate was assumed to be 1.4% (included haemorrhage 0.4%, infection 0.3%, perforation 0.6% and emergency laparotomy 0.1%).[152] Costs associated with morbidity arising from complications were incorporated into the model, but no adjustment to life expectancy was made (Appendix 10). Mortality rates were assumed to be negligible for all the diagnostic tests.[62,63,152,160,303] The mortality rate for abdominal hysterectomy in endometrial cancer was assumed to increase with age (0.4% in a woman aged 45 years, 0.8% at 55 years, 1.4% at 65 years and 3.5% at 75 years)[344] and adjustments to survival were made accordingly.

2.2.2.2 Treatment

For the base case analysis, it was assumed that all women not discharged underwent initial treatment by total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy with or without pelvic node sampling (i.e. all were fit for surgery and none had primary radical radiotherapy). All women were therefore assumed to be surgically staged.[72] There is some variation in practice in the treatment of endometrial cancer regarding the relative roles of surgery, radiotherapy / chemotherapy.[72,279] The treatment pathways in this model were based on published recommendations and reports of current practice.[2,245,251,279,309] All epidemiological statistics relating to endometrial cancer were taken from the latest annual

report from the International Federation of Obstetrics and Gynaecology (FIGO) of results of treatments of gynaecological cancers.[72] For the base case analysis, the cost of treating a woman correctly diagnosed with endometrial cancer on first presentation was based on the assumption that 70% of such women had localised (FIGO stage I) disease and 30% advanced (FIGO stages II-IV) disease.[72] To account for delayed diagnosis experienced by women with endometrial cancer who were erroneously discharged initially (false negatives) it was estimated that this group of women had a 5% increased probability of advanced stage endometrial cancer (stage II-IV) in the absence of relevant data (Appendix 9). Those with advanced disease (stages II, III or IV) underwent radiotherapy (adjuvant /palliative) and/or chemotherapy.[2,245,251,279] Women with stage Ic disease or poorly differentiated (histological grade 3) stage Ia or Ib disease were assumed to have adjuvant radiotherapy.[251] The proportion of women undergoing additional non-surgical treatment is shown in Figure 2-10.

Figure 2-10 Decision analytic model (common pathway for further treatment of endometrial cancer following initial hysterectomy)



Standardised radiotherapy and chemotherapy regimens were assumed regardless of disease stage, radiotherapy consisted of a 5-week course of external beam radiotherapy giving a total dose of 50-55 grays in 20-28 fractions. Chemotherapy consisted of standard cytotoxic and/or hormonal therapies.[2,245,251,279] Compliance with treatment was assumed to be 100%. It was assumed that hormonal treatment using long term oral progestogens was not employed given there is no evidence of benefit in terms of survival.[226] The 5 year survival rates were assumed to be 87% for stage I disease and 60% for advanced (stage II-IV) disease.[72]

2.2.3 Cost data

Costs were estimated from the perspective of my base National Health Service (NHS) hospital and from NHS data provided by the Department of Health. The analysis included all direct medical costs in UK pounds sterling (Appendix 10). Data for the base case and sensitivity analyses were obtained from local sources (Birmingham Women's Hospital data for uncomplicated procedures 2000-2001) and national sources (Department of Health, National Schedule of Reference Costs for the United Kingdom 2000[252] and Unit Costs of Health and Social Care 2000/2001[247]). Drug costs were obtained from the British National Formulary 2002. Costs for outpatient investigation included the clinic appointment and other hospital charges, the relevant procedures (endometrial biopsy, ultrasound scan or outpatient hysteroscopy) and the specialist(s) fee (consultant gynaecologist +/- consultant pathologist). Costs for inpatient endometrial assessment under general anaesthesia (hysteroscopy/D&C) took into account hospital costs for a day-case surgical procedure in addition to the specialists' fees for a consultant gynaecologist and anaesthetist. In addition, a cost associated with complications arising from D&C was estimated and incorporated (included costs of unexpected inpatient stay and antibiotic treatment for haemorrhage, uterine infection,

perforation and unplanned emergency laparotomy – see Appendix 10). The costs of reinvestigation by all three outpatient modalities incurred in those women representing after initial erroneous discharge were included in the model. Hysterectomy was classed as a complex major laparotomy and costed according to the base hospital charges taking into account uncomplicated inpatient hospital stay, operating theatre costs and specialist fees. Radiotherapy charges were estimated from charges for standard outpatient treatment charges (12-24 fractions of external beam radiotherapy) using national data.[252] Chemotherapy was costed according to national data for day-case treatment of the female reproductive system.[252] No adjustments to costs were made for the effects of inflation.

2.2.4 Clinical Outcomes

Baseline values of the probabilities of each test result and treatment outcome, together with the costs of each diagnostic intervention, were estimated and incorporated into the decision tree (DATA Professional 2001, Treeage software inc, 1075 Main Street, Williamstown, United States, MA 01267 [www.treeage.com]. The cost and effectiveness for each of the 12 strategies were calculated. The effectiveness of each competing diagnostic strategy was determined by comparing survival using the outcome measure cost per life year gained.[137,231,262]

Age specific life expectancies were calculated in the following way. For "true negative" results, normal actuarial age/sex specific death rates[177] were used to calculate life expectancy. For women with stage I or stage II-IV endometrial cancer, international 5-year survival data[72] were compared with the expected survival for the general population. The resulting hazard ratio was assumed to apply constantly over 12 years, after which survival is equivalent to the

normal population.[166] Finally, for "false positive" results, an age-specific immediate mortality was applied for the effect of the unnecessary hysterectomy[344], after which the general population life expectation was used. The base case analysis used an age of 65 years.[272] This age was chosen as endometrial cancer has its peak incidence in this decade.[272]

The costs, effect in terms of additional life year saved and average cost-effectiveness ratios (cost per additional life year saved) were determined for each diagnostic strategy.[137,231,262,327] Incremental cost-effectiveness ratios were then generated by using the ratio of cost compared to change in life expectancy relative to the cheapest strategy. In this way improvements in life expectancy per extra pound spent could be determined.[99,253,301] In accordance with Treasury guidelines, future years of life were discounted at 1.5% per year.[88,325] Discounting costs was not relevant as all costs were assumed to occur in the first year.

2.2.5 Sensitivity Analyses

Extensive sensitivity analyses were performed for all strategies found to be potentially cost-effective following the base case analysis. One-way analyses were performed over ranges of age at presentation, disease prevalence, test failure rates, estimates of diagnostic accuracy and upstaging of endometrial cancer due to delayed diagnosis to explore the robustness of the analytic model (Appendices 6 and 7). For treatment of endometrial cancer, the costs of local (FIGO Stage 1) and advanced (FIGO stage II-IV) disease were varied together.

CHAPTER III

RESULTS

3.1 Results of systematic review of endometrial biopsy

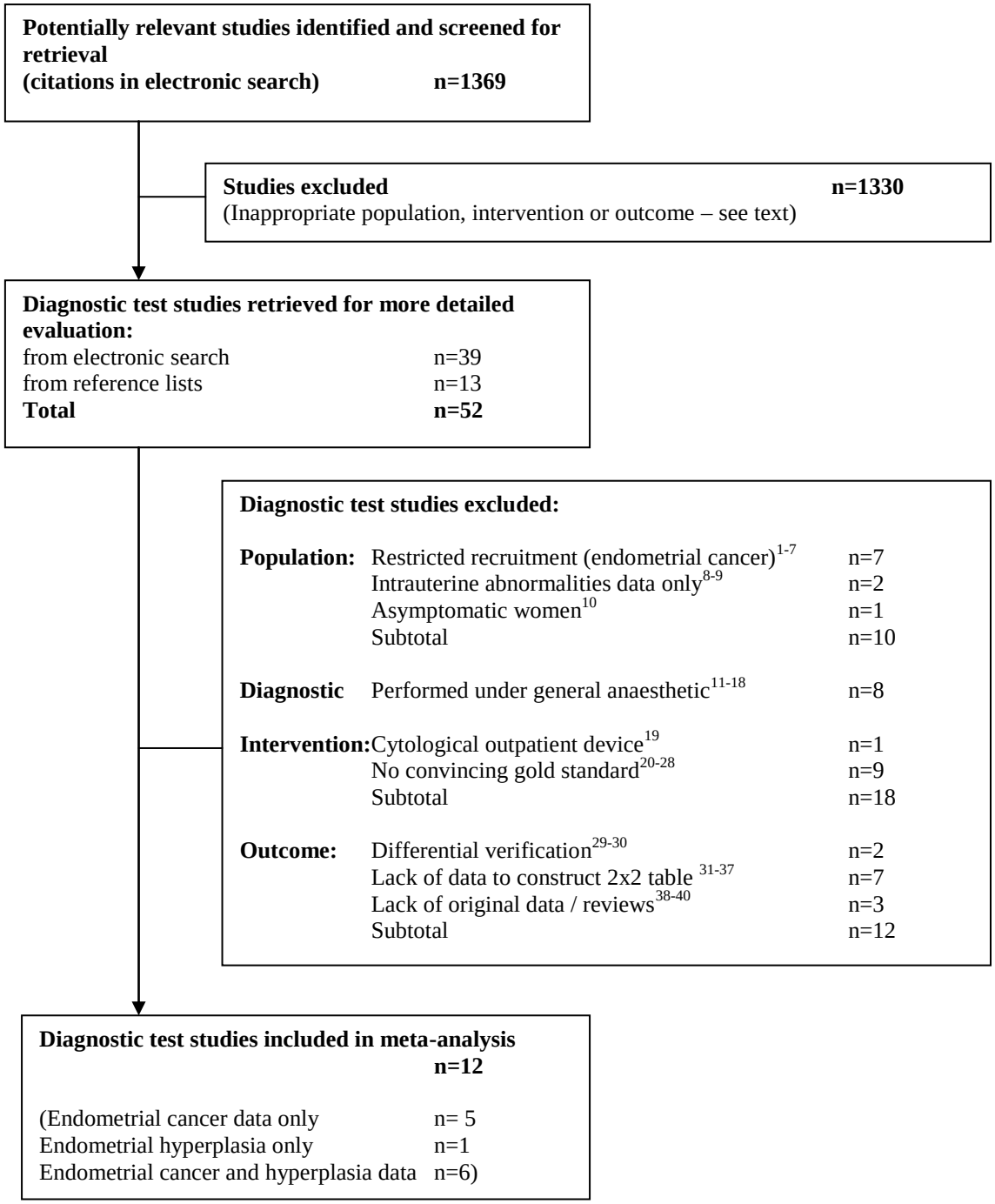
3.1.1 Question

What is the accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer and hyperplasia and what are the rates of failure and complications?

3.1.2 Study Selection

The electronic search generated 1369 citations and of these there were 39 articles[8,22,32,42,78,93,100,101,113,117,121,126,135,139,143,157,161,169,181,190,192,201,202,209,213,214,254,257,261,284,289,298,299,312,313,317,332,346,349] which both reviewers thought were relevant: 37 were published in English, one in French and one in Spanish. A further 13 articles[24,30,124,133,138,182,196,204,206,307,314,315,333] were identified through examination of the reference lists of the known primary publications and review articles. After independent review of the 52 manuscripts, 12 articles (11 English,[22,24,78,117,133,138,161,192,314,317,332] one French [284]) were considered to be eligible for inclusion in the review (Figure 3-1). Agreement regarding eligibility was 90% (weighted kappa 0.7). The lists of references supplied by the manufacturers contacted did not add anything to the above search. Excluded studies are listed in Appendix 11.

Figure 3-1 Study selection process for systematic review of outpatient EB



There were 1337 subjects in 14 diagnostic evaluations reported in 12 primary studies, which assessed the diagnostic accuracy of EB in detecting serious endometrial disease: 40 women in a single evaluation of the Accurette® device,[138] 70 women in a single evaluation of the Gynoscann® device,[317] 176 women in a single evaluation of the Novak® curette,[314] 865 women in 8 evaluations of the Pipelle® device,[22,24,78,133,161,192,284,332]
104 women in 2 evaluations of the Vabra® aspirator[138,314] and 77 women in a single evaluation of the Z-sampler®[117] device. Of the 12 included studies, 11 studies (1013 women) assessed the diagnosis of endometrial cancer. Seven of these evaluations contained data exclusively about postmenopausal women,[22,78,117,138,161,332] four about pre and postmenopausal women[24,192,284,317] and in three menopausal status was unclear[133,314]. Postmenopausal women represented 36% of the populations studied.

3.1.3 Study quality

The observer agreement for various items of study quality ranged from 73 to 100%. Kappa values were 0.5 for population enrolment, 1.0 for biopsy technique description, 0.9 for blinding of test results and 1.0 for description of outcomes. The methodological quality criteria of the studies selected for meta-analyses are detailed in Appendix 12 and summarised in Table 3-1.

Table 3.1 Methodological quality of outpatient EB studies included in meta-analyses

Quality Criteria	No. of Studies
Population	
Data Collection	
Adequate (prospective)	9/12 (75%)
Inadequate (retrospective)	3/12 (25%)
Patient Selection	
Adequate (consecutive)	4/12 (33%)
Inadequate (arbitrary/unreported)	8/12 (67%)
Population Details	
Complete	8/12 (67%)
Inadequate	4/12 (33%)
Intervention	
Biopsy technique description	
Adequate	9/12 (75%)
Inadequate	3/12 (25%)
Outcome	
***Reference standard**	
Hysterectomy	6/12
Directed Biopsy/Transcervical resection	2/12
D&C	10/12
Blinding of Test Results	
Adequate	2/12 (17%)
Unreported	10/12 (83%)
Use of reference standard regardless of test result	
Adequate (>90%)	12/12 (100%)

Study recruitment was prospective in nine (75%) of the studies, patient details were complete in 8 (67%) studies, but patient selection was consecutive in only 4 (33%) of the studies. The description of the interventions were adequate in 9 (75%) of the studies. The assessment of outcome data shows that in only 2 (17%) of the studies were the outpatient test results reported to be masked from the pathologist interpreting the reference standard. Thus 2 studies[22,78] (17%) were level 1, a further 2 studies[117,332] (17%) were level 3 and 8 studies[24,133,138,161,192,284,314,317] (66%) were level 4 in quality.

3.1.4 Data synthesis

3.1.4.1 Accuracy in predicting endometrial cancer

Amongst adequate specimens, outpatient EB failed to diagnose three endometrial cancers. Figure 3-2 presents the sensitivity and specificity of EB in the diagnosis of endometrial cancer. The overall pooled sensitivity was 94.1% (95% CI 83.8% to 98.8%) and specificity was 99.6% (95% CI 98.8% to 99.9%). In view of the lack of an association between sensitivity and specificity, a summary receiver operating characteristic curve was not generated.[83] The pooled LRs for endometrial cancer were 66.48 (95% CI 30.04-147.13) and 0.14 (95% CI 0.08-0.27) for positive and negative outpatient test results respectively. The pre-test probability increased from 6.3% (95% CI 4.7% to 8.2%) to 81.7% (95% CI 59.7% to 92.9%) with a positive result. It decreased to 0.9% (95% CI 0.4% to 2.4%) with a negative result (Table 3-2).

Figure 3-2 Sensitivity and specificity of endometrial biopsy in the diagnosis of endometrial cancer and hyperplasia

Results sorted according to estimated sensitivity and presented with 95% confidence interval

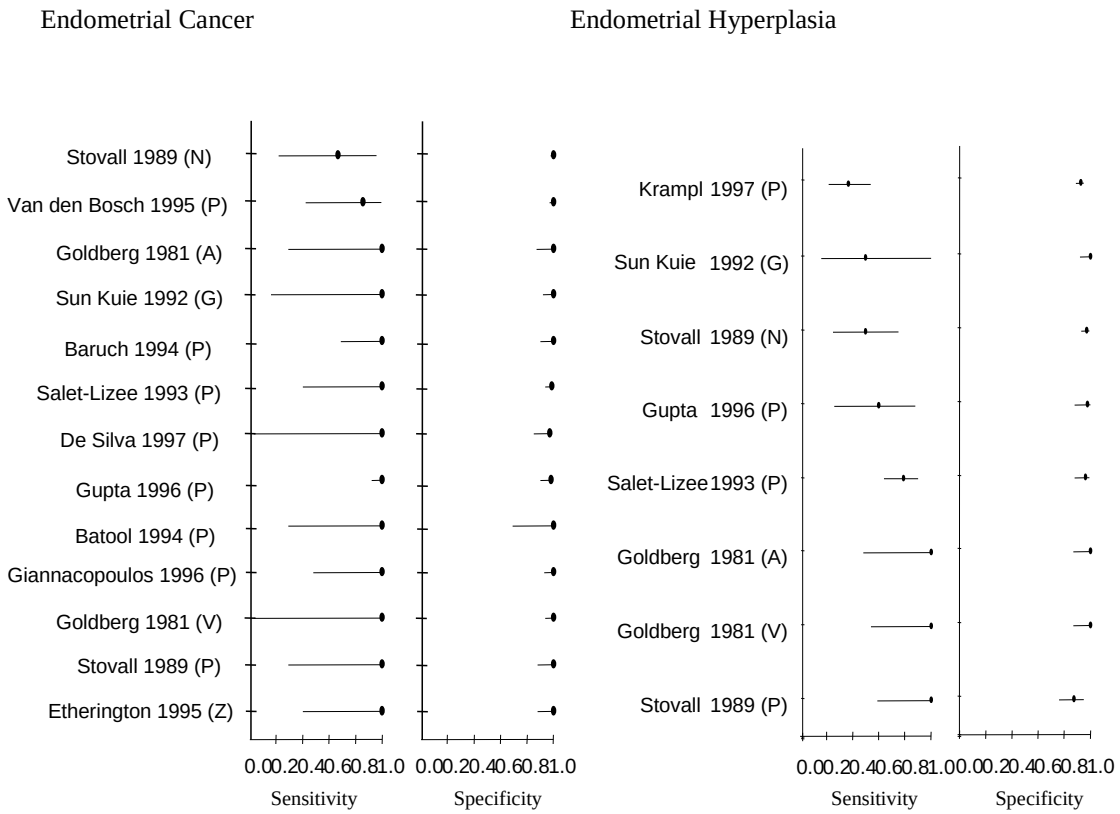


Table 3.2 Pooled estimates of pre-test probabilities, likelihood ratios and post-test probabilities for diagnostic accuracy of outpatient biopsy in detecting endometrial cancer in women with abnormal uterine bleeding

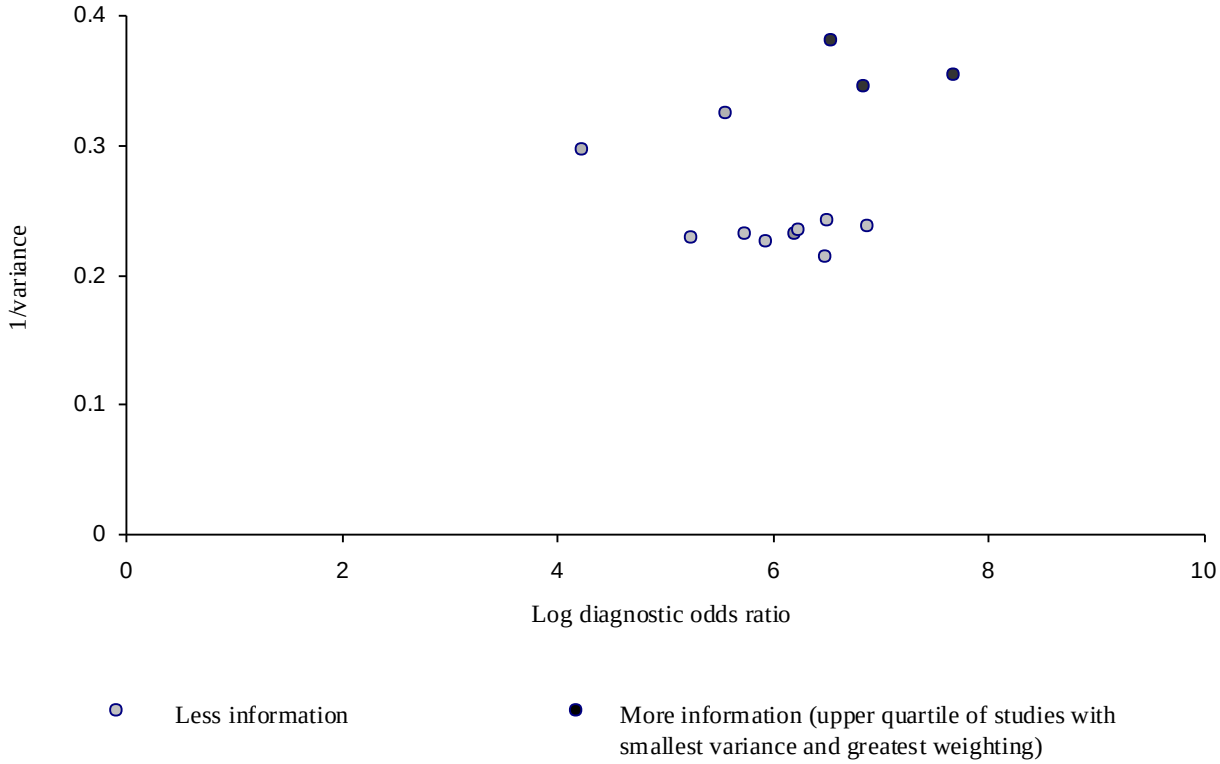
Device & Population	Pre-test Probability % (95% CI)	Post-test Probability % (range) Test +	Test –
All devices			
All Women	6.3 (4.7-8.2)	81.7 (59.7-92.9)	0.9 (0.4-2.4)
Postmenopausal Women	6.9 (4.4-10.1)	83.1 (58.0-94.3)	1.0 (0.4-2.9)
Pipelle©			
All Women	6.3 (4.7-8.2)	81.3 (52.4-94.4)	0.7 (0.2-2.4)
Postmenopausal Women	6.9 (4.4-10.1)	82.7 (50.7-95.5)	0.8 (0.2-3.1)

An estimate of the pre-test probability was obtained by calculating the prevalence of the outcome event in the population studied. The following equation was used for calculating post-test probability: post-test probability = likelihood ratio x pre-test probability / [1-pre-test probability x (1-likelihood ratio)], where Likelihood Ratios (95% CI) for all devices are LR+ 66.5 (30.0-147.1) / LR- 0.14 (0.1-0.3) and Likelihood Ratios (95% CI) for pipelle® device are LR+ 64.6 (22.3-187.1) / LR- 0.1 (0.04-0.28)
Ranges of post-test probability were calculated by using lower and upper limits of 95% confidence intervals of pre-test probabilities and likelihood ratios.

If inadequate samples were regarded as negative results then LRs for all devices were 87.24 (95% CI 38.87-195.79) and 0.15 (95% CI 0.08-0.27) for positive and negative outpatient test results respectively. In this case the pre-test probability increased from 5.50% (95% CI 4.13% to 7.15%) to 83.6% (95% CI 62.4% to 93.8%) with a positive result and decreased to 0.9% (95% CI 0.3% to 2.1%) with a negative result. Homogeneity of diagnostic performance was confirmed across all studies by a non-significant (p=0.99) χ^2 test. Subgroup analyses stratified for study quality did not affect the pooled LR estimates.

A funnel plot showing the distribution of effect sizes according to inverse of variance (Figure 3-3), indicated that larger studies tend to report better diagnostic test performance, though the correlation was not statistically significant (rank correlation r=0.4, p=0.17).

Figure 3-3 Funnel plot endometrial biopsy and cancer



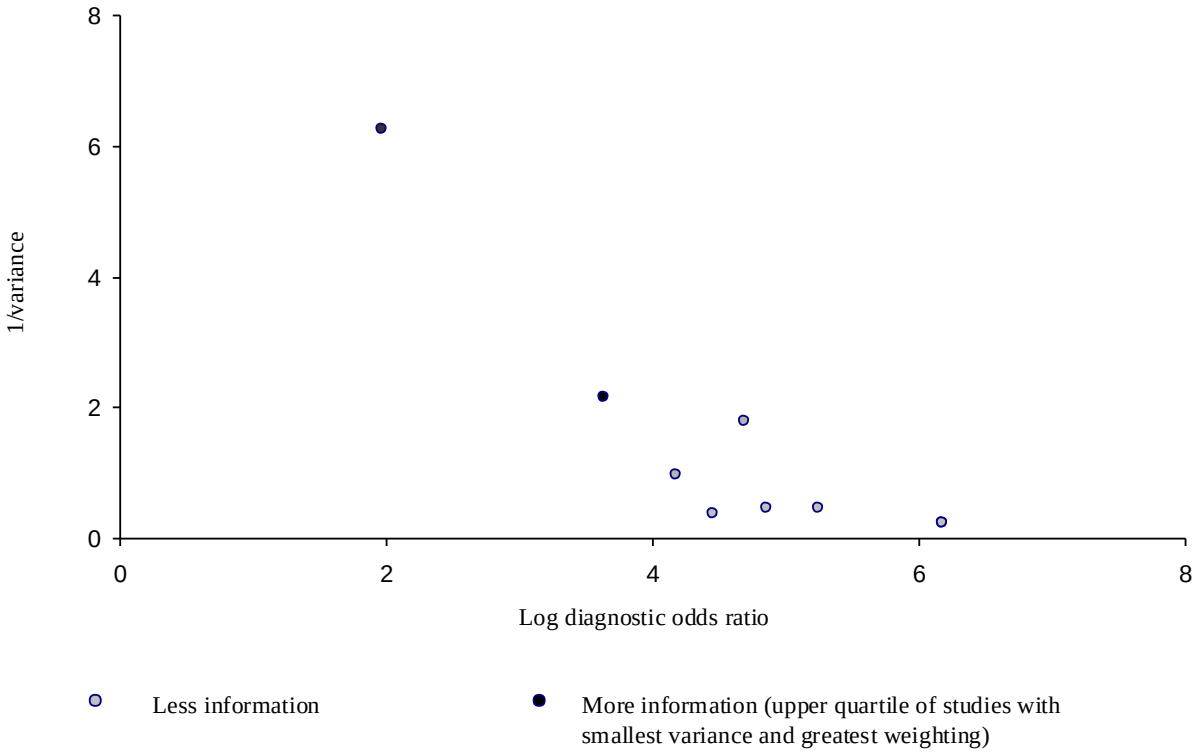
3.1.4.2 Accuracy in predicting endometrial hyperplasia

Diagnostic accuracy was lower for endometrial hyperplasia than endometrial cancer. The weighted overall sensitivity was 66.0% (95% CI 47.0% to 81.0%) and specificity was 95.0% (95% CI 91.0%to 98.0%). The pooled LRs for endometrial hyperplasia were 12.0 (95% CI 7.8-18.6) and 0.2 (95% CI 0.1-0.3) for positive and negative outpatient test results respectively (Table 3-3). The pretest probability increased from 10.2% (95% CI 8.2%-12.5% to 57.7% (95% CI 41.1% to 72.7%) with a positive result. It decreased to 2.2% (95% CI 0.9% to 4.1%) with a negative result. If inadequate samples were regarded as negative results then LRs were 15.7 (95% CI 9.7-25.5) and 0.4 (95% CI 0.3-0.5) for positive and negative EB

results respectively. In this case the pretest probability increased from 12.9% (95% CI 10.7% to 15.3%) to 70.0% (95% CI 53.7% to 82.2%) with a positive result and decreased to 5.6% (95% CI 3.7% to 8.1%) with a negative result. For studies of postmenopausal women, the pretest probability was increased from 14.3% (95% CI 8.6%-21.9%) to 66.7% (95% CI 42.3% to 83.9%) with a positive result and decreased to 3.2% (95% CI 0.9% to 7.8%) with a negative result.

Heterogeneity of diagnostic performance was confirmed across all studies for endometrial hyperplasia by a significant ($p = 0.0001$) χ^2 test. Sensitivity analyses stratified for items of study quality did affect the heterogeneity of diagnostic performance. Prospective recruitment ($p=0.9$), clear population details ($p=0.9$) and the exclusive use of one particular reference standard (D&C or hysterectomy, $p=0.9$) removed significant heterogeneity of diagnostic test performance and thereby provided a possible explanation for the overall observed heterogeneity. A funnel plot (Figure 3-4) indicated that smaller studies tend to report better diagnostic test performance (Spearman rank correlation $r= 0.83$, $p=0.02$) and publication bias is therefore likely.

Figure 3-4 Funnel plot endometrial biopsy and hyperplasia



3.1.4.2.1 Severity of endometrial hyperplasia

The data were separated for the presence of endometrial hyperplasia with or without atypia. Table 3-3 shows the pooled LRs, pre and posttest probabilities for positive and negative results for these subgroups along with the overall pooled result for comparison. Significant heterogeneity of diagnostic test performance was present. Possible explanations for this related to study design and type of reference standard as sensitivity analyses excluding retrospective studies and studies using more than one reference standard produced homogeneity of diagnostic performance. In addition the data was analysed to determine the diagnostic accuracy of outpatient biopsy in detecting premalignant (complex and atypical

hyperplasia) or malignant endometrial pathology. Homogeneity of diagnostic performance was confirmed across all studies by a non-significant ($p = 0.43$) χ^2 test.

3.1.5 Secondary outcomes

3.1.5.1 Failure rate and inadequate specimen rate

The overall failure rate for outpatient biopsy was 68/1337 representing 5% (95% CI 4%-6%) of all attempted biopsies. Pipelle®, the most frequently evaluated device, had a failure rate of 5% (43/870, 95% CI 4%-7%). Histologically inadequate samples (no specimen obtained or insufficient for adequate assessment) were reported in 148/1269 (12% 95% CI 10%-14%) samples overall and in 64/822 (8% 95% CI 6%-10%) of Pipelle® samples. Among the 7 evaluations of exclusively postmenopausal women, the failure rates and inadequate sampling rates were higher than that found in all studies combined. There were 58/486 (12% 95% CI 9%-15%) failures and 93/428 (22% 95% CI 17.9-25.9) inadequate samples. One case of cancer was found in all the inadequate specimens (Appendix 13).

3.1.5.2 Complication rate

No cases of potentially serious complications (e.g. life threatening haemorrhage or systemic illness, uterine trauma, visceral damage) were reported out of 1269 successful procedures. However, ascertainment of serious complications may be suboptimal as only 5/12 (42%) studies, which included 251 successful procedures, explicitly stated the intention to report or actually reported complications.

Table 3.3 Sensitivity analyses for meta-analysis of the diagnostic accuracy of outpatient endometrial biopsy in endometrial hyperplasia with or without atypia and its diagnostic accuracy in detecting endometrial cancer with or without premalignant complex/atypical endometrial hyperplasia

Device (No. Evaluations) &Study (Year published)	Positive test (Sensitivity)	Negative test (1-Specificity)	LR positive (95% CI)	LR negative (95% CI)	Pretest probability (95% CI)	Posttest probability +ve test (95% CI)	-ve test (95% CI)
Endometrial hyperplasia (all 8 evaluations)							
Total [21,26,40,44,61,66]	82/126	38/679	12.0 (7.8-18.6)	0.2 (0.1-0.3)	10.2% (8.%-12.5%)	57.7% (41.1 - 72.7%)	2.2% (0.9 to 4.1%)
Endometrial hyperplasia without atypia (4 evaluations)							
Total [21,26,40,44]	55/90	26/427	10.7 (6.1-18.9)	0.45 (0.35-0.57)	15.7% (12.6-19.1%)	86.7% (72.8 to 3.9%)	7.7% (4.8 to 11.9%)
Endometrial hyperplasia with atypia (1 evaluation)							
Total [44]	2/3	1/51	34 (4.2-277.4)	0.3 (0.07-1.7)	5.6 (1.2-15.4%)	66.9% (48.5 to 8.1%)	2.6% (0.4 to 9.4%)
Endometrial cancer +/- complex/atypical endometrial hyperplasia (8 evaluations)							
Total [21,26,40,44,61,66]	34/37	2/768	95.1 (41.2-219.4)	0.1 (0.07-0.3)	4.5% (3.2 to 6.1%)	81.8% (57.7 to 93.4%)	0.5% (0.2 to 1.9%)

3.2 Results of systematic review of endometrial thickness measurement by ultrasound

3.2.1 Question

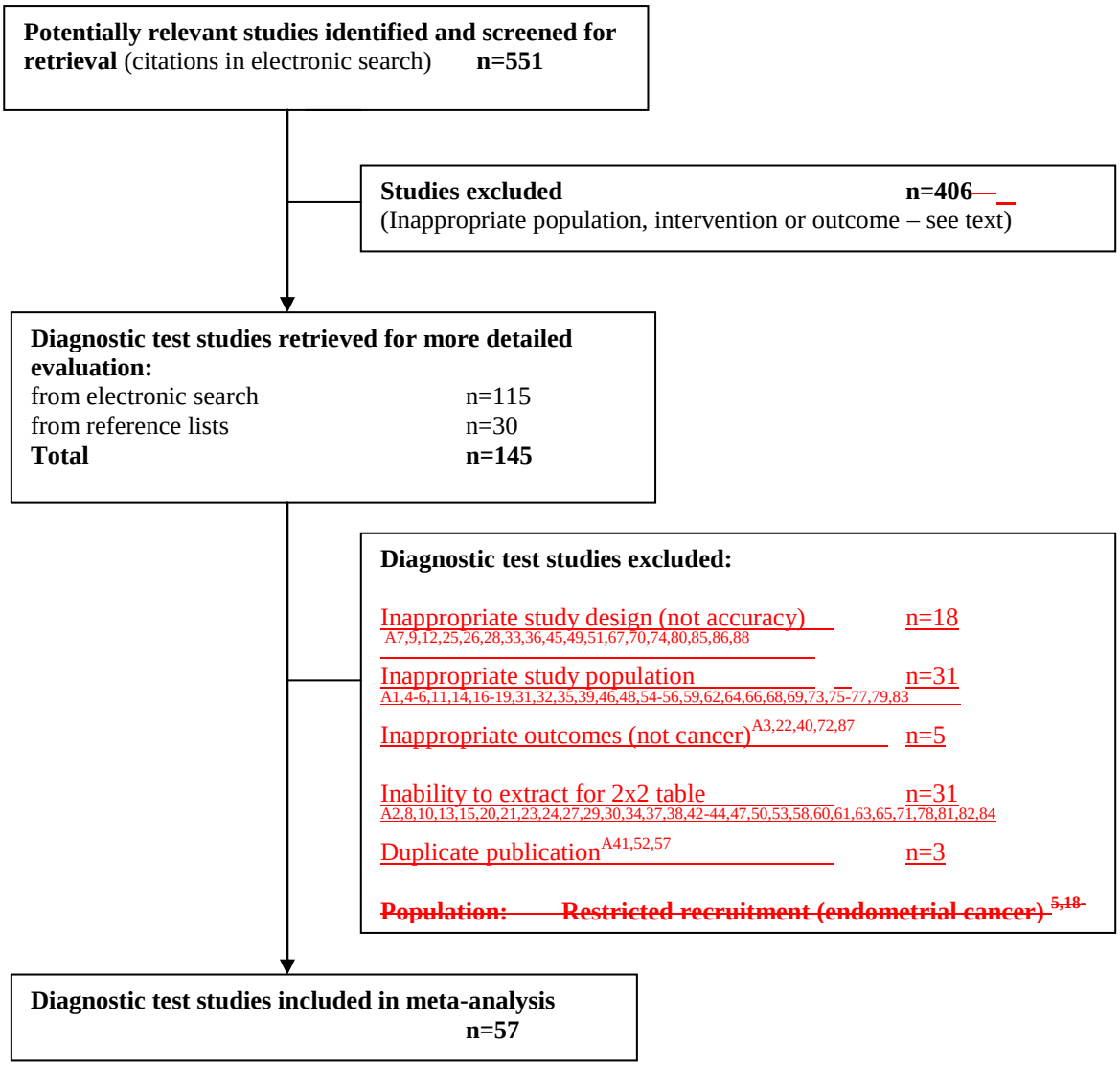
What is the accuracy of outpatient endometrial ultrasonography in the diagnosis of endometrial cancer and hyperplasia?

3.2.2 Study Selection

The initial electronic searches generated 551 citations, in which observer agreement was 518/551 (94%) with a kappa of 0.80. Eighty-two articles were thought to be relevant by both reviewers and 33 articles were considered relevant by one reviewer. The full manuscripts of these 115 articles were obtained for review. Another 30 articles were obtained from scanning the reference lists of known primary and review articles in my personal files. After reviewing the full manuscripts of a total of 145 articles, 35 English,[4,14,18,36,42,48,53,54,78,94,96,122,130,135,142,146,147,151,154,159,161,164,179,216,223,224,229,238,243,244,304,328,334,338,345] 7 German,[85,132,165,234,269,290,295] 4 Italian,[227,285,321,348] 2 French,[258,281] 2 Chinese,[155,205] 2 Bulgarian,[172,323] 1 Spanish,[237] 1 Polish,[316] 1 Turkish,[9] and 1 Dutch[43] articles were selected for inclusion in the overview. There were 6 articles in which the two reviewers initially disagreed on eligibility but this was resolved easily by consensus. These instances of disagreement were the result of an oversight by one of the reviewers. Agreement concerning eligibility was 96% (kappa = 0.91). Characteristics of the 57 studies selected for meta-analysis are shown in Appendix 14.

The reasons for excluding the remaining 88 manuscripts (Figure 3-5 and Appendix 15) included inappropriate study design (18 studies), inappropriate study population (31 studies), inappropriate clinical outcomes being reported (5 studies), and the inability to extract data precluding construction of 2x2 tables (31 studies). Three articles were also excluded due to duplicate publication.

Figure 3-5 Study selection process for systematic review of ultrasound scan



3.2.3 Study quality

The observer agreement for the various components of study quality was 89-100%, kappa values were 0.64 for population enrolment, 1.0 for description of amenorrhoea and HRT use, 1.0 for description of analytical test and cut-off level, 0.88 for number of endometrial layers used in the ultrasonic measurement of endometrial thickness, 0.69 for blinding of test results

and 1.0 for completeness of verification. The instances of disagreement were the result of an oversight on of one of the reviewers, and were resolved easily by consensus. The main features of the methodological qualities of those studies selected for meta-analysis are summarised in Table 3-4. A majority of the studies were quality level 4-5.

Table 3.4 Methodological quality of selected primary studies

Quality criteria*		Number of Studies (%)
Population		
Recruitment		
Consecutive		5/56 (9.0)
Arbitrary		2/56 (3.5)
Unclearly reported		49/56 (87.5)
Spectrum		
With and without HRT		13/56 (23.0)
Narrow		27/56 (48.0)
Unreported		16/56 (29.0)
Diagnostic test		
Determination of scanning method and transducer frequency		
Ideal		55/56 (98.2)
Unclearly reported		1/56 (1.8)
Determination of method of measuring endometrial thickness		
Ideal		48/56 (85.7)
Unclearly reported		8/56 (14.3)
Description of cut-off level for ≤ 4 mm only		
A priori		4/9 (44.4)
Post hoc		5/9 (55.6)
Description of cut-off level for ≤ 5 mm only		
A priori		7/21 (33.3)
Post hoc		14/21 (66.7)
Outcome		
Reference Standard		
1		0/56 (0)
2	Ideal	38/56 (67.8)
3		3/56 (5.4)
1,2		3/56 (5.4)
2,3	Non-ideal	10/56 (17.8)
1,2,3		2/56 (3.6)
Blinding of test results		
Blinded		7/56 (12.5)
Unclearly reported		49/56 (87.5)
Verification of diagnosis		
>90%		50/56 (89.4)
81-90%		3/56 (5.3)
<80%		3/56 (5.3)
Quality levels*		
1		0/56
2		5/56 (8.9)
3		1/56 (1.8)
4		45/56 (80.4)
5		5/56 (8.9)

HRT = hormone replacement therapy, Reference Standard: 1- Hysterectomy / directed biopsy under hysteroscopic vision, 2 - Inpatient Dilatation and Curettage (D&C), 3 - Outpatient biopsy e.g. Pipelle, Novak
*See Methods section for details

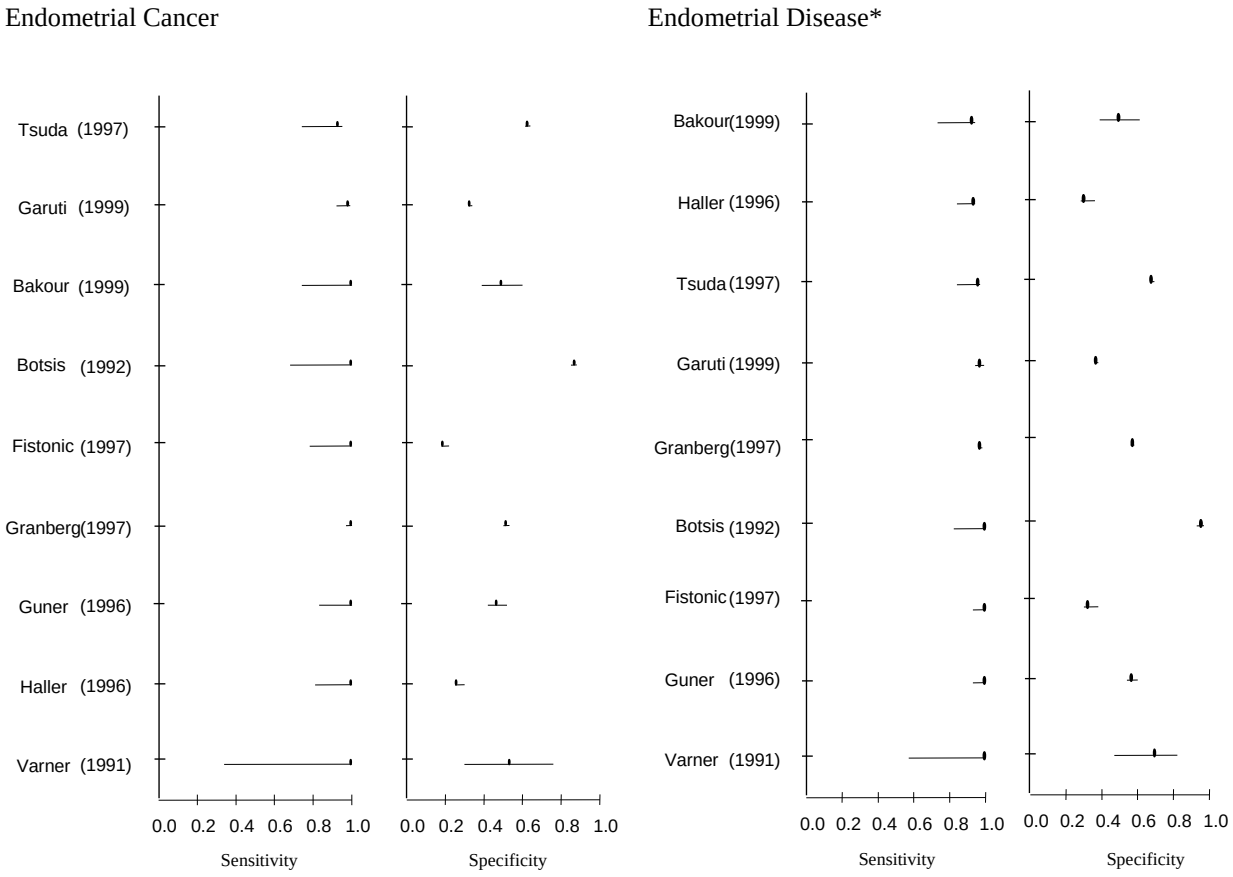
3.2.4 Data synthesis

3.2.4.1 Accuracy in predicting endometrial cancer

The commonest cut-off levels for abnormality were based on the measurement of both layers of endometrial thickness - 4 mm (9 studies) and 5 mm (21 studies). Figure 3-6 and 3-7 presents the sensitivity and specificity of ultrasound in the diagnosis of endometrial cancer using 4mm and 5mm cut-offs respectively. The overall sensitivity was 99.2% (95% CI 97.2% to 99.9%) and specificity was 48.6% (95% CI 46.4% to 50.8%) according to the 9 studies of ultrasound using an endometrial thickness cut-off for endometrial cancer of 4mm. Taking the 5mm cut-off, pooled sensitivity was 97.3% (95% CI 95.0% to 98.8%) and specificity was 55.2% (95% CI 52.9% to 57.4%) for endometrial cancer. In view of the lack of an association between sensitivity and specificity, a summary receiver operating characteristic curve was not generated.[83]

Figure 3-6 Sensitivity and specificity of ultrasound 4mm in the diagnosis of endometrial cancer and disease

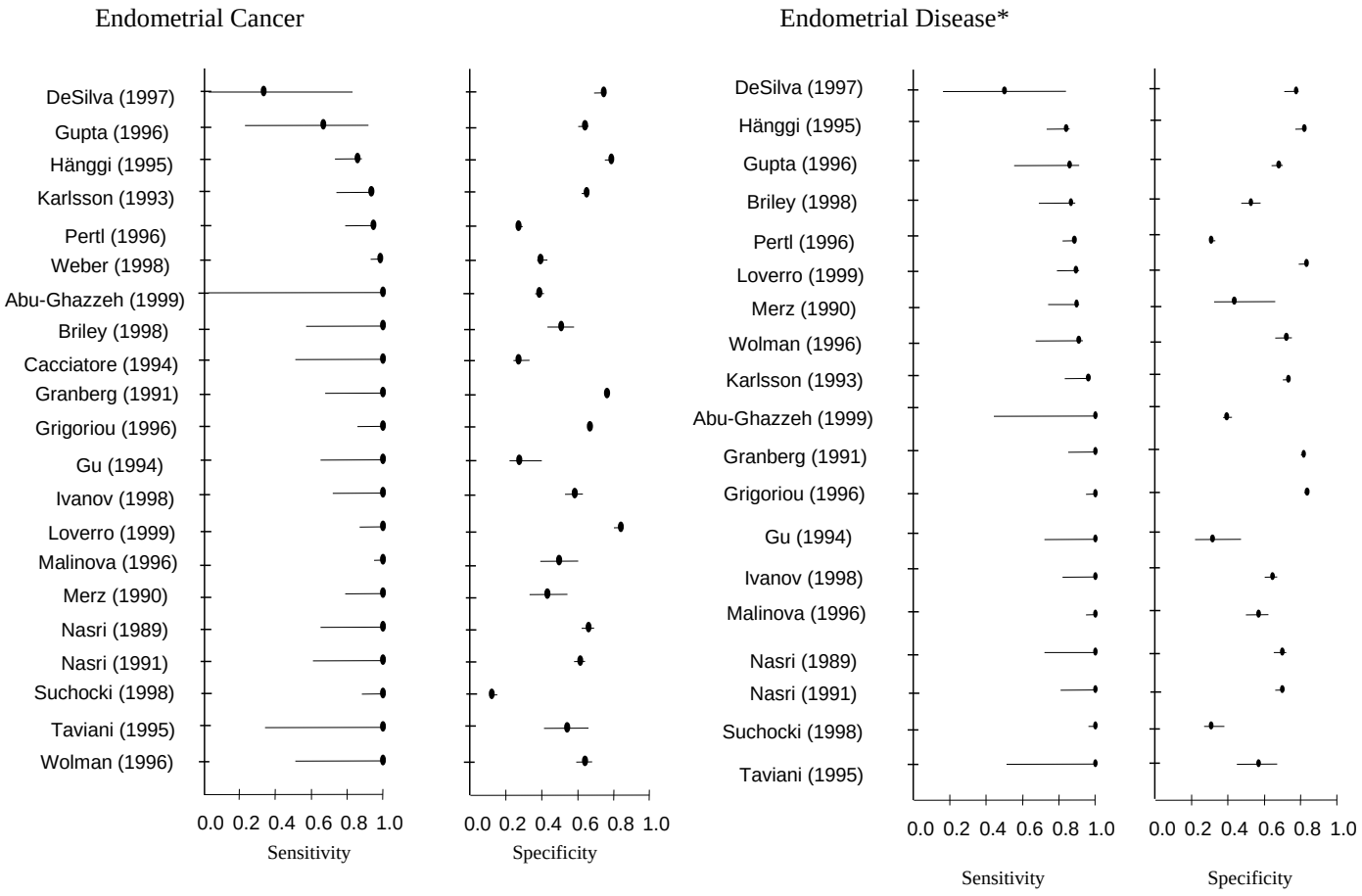
Results sorted according to estimated sensitivity and presented with 95% confidence interval



*Endometrial disease is endometrial cancer or endometrial hyperplasia (see section 1.6.2.2 for an explanation)

Figure 3-7 Sensitivity and specificity of ultrasound 5mm in the diagnosis of endometrial cancer and disease

Results sorted according to estimated sensitivity and presented with 95% confidence interval



*Endometrial disease is endometrial cancer or endometrial hyperplasia (see section 1.6.2.2 for an explanation)

Estimates of LRs for individual studies for the various reported cut-off levels are shown in Appendix 16. Pooled estimates of pre-test probability, LRs and post-test probability are shown in Table 3-5. There were 1243 cases of endometrial cancer among 8890 patients giving a pre-test probability of 14.0% (95% CI 13.3 – 14.7%). As shown in Table 3-5, a negative test result reduced the post-test probability of cancer to 1.2% (95% CI 0.4-2.9) at ≤ 4

mm and 2.3% (95% CI 1.2-4.8) at ≤ 5 mm. The pooled estimates for ≤ 4 mm negative results were homogeneous (p=0.65), although none of the 9 studies using the ≤ 4 mm cut-off level were of good quality. The pooled estimates of LRs for ≤ 5 mm were heterogeneous (p=0.0001 and p=0.02 for positive and negative test respectively), sensitivity analyses failed to produce an explanation as the confidence intervals of the LRs for the various subgroups overlapped (Table 3-6). The pre-specified subgroups population spectrum and patient selection were found to be significant explanatory variables for heterogeneity in univariable analyses. A narrow population spectrum (i.e. not explicitly including postmenopausal women on HRT) and the quality item non-consecutive patient selection were associated with significantly higher accuracy of ultrasound. Of the additional exploratory variables, a lower ultrasound probe transducer frequency (giving reduced image resolution) and a ≤ 5 mm cut-off level for abnormal endometrial thickening defined *post hoc* in advance were also predictive of higher accuracy. However, the effect of these features on diagnostic accuracy was not confirmed with multivariable analysis (Table 3-7). There were only 4 studies out of the 21 studies using the ≤ 5 mm cut-off level that employed the best quality criteria. Using the pooled estimates from these 4 studies only, a negative test result reduced the post-test probability of cancer to 2.5% (95% CI 0.9-6.4).

Table 3.5 Pooled estimates of pre-test probability, likelihood ratio and post-test probability for ultrasound measurement of endometrial thickness in predicting endometrial cancer

Method of measurement and cut-off level for abnormality	Pre-test probability % (95% CI)	Likelihood ratio (95% CI)	Post-test probability % (95% CI)
Measurement of both layers ET thickness			
3 mm (n = 2 studies)			
Positive test result	14.0 (13.3-14.7)	2.1 (1.9-2.3)	25.3 (22.8-27.9)
Negative test result	14.0 (13.3-14.7)	0.04 (0.01-0.19)	0.7 (0.2-3.2)
4 mm (n = 9 studies)			
Positive test result	14.0 (13.3-14.7)	1.96 (1.60-2.4)*	24.2 (19.7-29.2)
Negative test result	14.0 (13.3-14.7)	0.08 (0.03-0.17)	1.2 (0.4-2.9)
5 mm (n = 21 studies)			
Positive test result	14.0 (13.3-14.7)	2.17 (1.75-2.68)*	26.1 (21.1-31.6)
Negative test result	14.0 (13.3-14.7)	0.15 (0.08-0.29)*	2.3 (1.2-4.8)
6 mm (n = 2 studies)			
Positive test result	14.0 (13.3-14.7)	2.5 (2.0-3.1)	28.5 (23.1-34.5)
Negative test result	14.0 (13.3-14.7)	0.2 (0.08-0.5)	3.2 (1.2-7.9)
8 mm (n = 1 study)			
Positive test result	14.0 (13.3-14.7)	2.0 (1.0-4.0)	24.6 (13.3-40.8)
Negative test result	14.0 (13.3-14.7)	0.3 (0.02-4.55)	5.1 (0.3-4.4)
15 mm (n = 1 study)			
Positive test result	14.0 (13.3-14.7)	7.0 (3.7-13.4)	53.4 (36.2-69.8)
Negative test result	14.0 (13.3-14.7)	0.2 (0.06-0.7)	3.3 (0.9-11.0)
Single layer ET measurement			
2 mm (n = 3 studies)			
Positive test result	14.0 (13.3-14.7)	2.4 (2.0-3.0)	28.4 (23.5-33.8)
Negative test result	14.0 (13.3-14.7)	0.15 (0.1-0.3)	2.4 (1.1-5.2)
3 mm (n = 6 studies)			
Positive test result	14.0 (13.3-14.7)	1.9 (1.7-2.2)*	24.0 (20.5-27.9)
Negative test result	14.0 (13.3-14.7)	0.3 (0.2-0.5)*	5.1 (3.0-8.5)
4 mm (n = 2 studies)			
Positive test result	14.0 (13.3-14.7)	1.8 (1.6-2.0)	22.8 (20.0-25.6)
Negative test result	14.0 (13.3-14.7)	0.08 (0.02-0.27)	1.3 (0.3-4.5)
10 mm (n = 1 study)			
Positive test result	14.0 (13.3-14.7)	29.2 (4.1-208.0)	82.6 (38.6-97.3)
Negative test result	14.0 (13.3-14.7)	0.17 (0.03-1.0)	2.7 (0.5-15.1)
Unreported number of layers for ET measurement			
4 mm (n = 4 studies)			
Positive test result	14.0 (13.3-14.7)	1.9 (1.8-2.1)	23.9 (21.6-26.4)
Negative test result	14.0 (13.3-14.7)	0.1 (0.06-0.2)	1.6 (0.9-2.9)
5 mm (n = 2 studies)			
Positive test result	14.0 (13.3-14.7)	2.3 (1.8-3.1)*	27.4 (21.2-34.6)
Negative test result	14.0 (13.3-14.7)	0.04 (0.01-0.2)*	0.7 (0.2-3.5)
6 mm (n = 1 study)			
Positive test result	14.0 (13.3-14.7)	3.3 (2.5-4.2)	34.7-28.0-41.9)
Negative test result	14.0 (13.3-14.7)	0.04 (0.00-0.6)	0.7 (0.1-9.2)
7 mm (n = 1 study)			
Positive test result	14.0 (13.3-14.7)	2.7 (1.9-3.7)	30.1 (22.8-38.7)
Negative test result	14.0 (13.3-14.7)	0.04 (0.00-0.6)	0.7 (0.0-9.8)

ET = endometrial thickness, *heterogeneity P<0.05 (chi-squared test for heterogeneity used)

Table 3.6 Sensitivity analyses: Studies of ultrasound measurement of both layers ≤ 4 mm or ≤ 5 mm endometrial thickness for endometrial cancer or disease with pooled LRs stratified according to study characteristics and quality

	Cancer				Disease (hyperplasia and/or cancer)			
	≤ 4 mm		≤ 5 mm		≤ 4 mm		≤ 5 mm	
Quality Criteria*	**n**	**Positive test LR (95% CI)**	**n**	**Positive test LR (95% CI)**	**Negative test LR (95% CI)**	**n**	**Positive test LR (95% CI)**	**n**	**Positive test LR (95% CI)**	**Negative test LR (95% CI)**
POPULATION										
Recruitment										
Consecutive	0	-	2	3.5 (2.4-5.6)	0.3 (0.1-0.6)	0	-	2	4.0 (2.5-6.4)	0.3 (0.2-0.6)
Arbitrary	0	-	0	-	-	0	-	0		
Unclearly reported	9	1.83 (1.76-1.9)	19	1.9 (1.8-2.1)	0.08 (0.05-0.14)	9	2.1 (1.95-2.2)	17	2.5 (2.3-2.9)	0.1 (0.06-0.2)
Length of amenorrhoea										
≥ 12 months	3	1.5 (1.4-1.6)	7	1.8 (1.6-2.1)	0.1 (0.03-0.2)	3	1.7 (1.6-1.8)	6	2.4 (2.0-2.9)	0.15 (0.1-0.4)
< 12 months	2	2.0 (1.9-2.1)	3	2.1 (2.0-2.3)	0.1 (0.07-0.2)	2	2.3 (2.2-2.5)	3	2.6 (2.3-2.8)	0.1 (0.1-0.2)
Unreported	4		11			4		10		
Spectrum										
With and without HRT	4	1.8 (1.75-1.9)	5	1.8 (1.6-2.0)	0.2 (0.1-0.4)	4	2.0 (1.9-2.1)	5	1.9 (1.7-2.2)	0.2 (0.1-0.3)
Narrow	4	1.8 (1.6-2.0)	10	2.0 (1.8-2.1)	0.06 (0.03-0.12)	4	2.1 (1.9-2.4)	9	2.9 (2.6-3.3)	0.06 (0.03-0.1)
Unreported	1	1.9 (1.6-2.2)	6	2.6 (2.1-3.1)	0.2 (0.1-0.4)	1	2.3 (1.9-2.8)	5	2.8 (2.4-3.4)	0.2 (0.1-0.3)
DIAGNOSTIC TEST										
Cut-off level for abnormality										
A priori	4	1.46 (1.37-1.54)	7	2.0 (1.8-2.3)	0.1 (0.05-0.2)	4	1.5 (1.4-1.7)	6	2.9 (2.4-3.5)	0.16 (0.1-0.3)
Post-hoc	5	2.2 (2.0-2.3)	14	2.0 (1.8-2.1)	0.1 (0.06-0.2)	5	2.5 (2.3-2.7)	13	2.5 (2.2-2.7)	0.1 (0.07-0.2)
OUTCOME										
Reference Standard										
1		0	0			0	-	0	-	-
2	Ideal	4	15	1.9 (1.8-2.0)	0.12 (0.07-0.2)	4	2.3 (2.2-2.5)	14	2.5 (2.3-2.7)	0.1 (0.08-0.2)
1,2		0	3			0	-	2		
3		1	1			1		1		
2,3	Non-ideal	4	1	3.6 (2.8-4.5)	0.05 (0.01-0.2)	4	1.7 (1.6-1.9)	1	3.0 (2.4-3.7)	0.1 (0.06-0.3)
1,2,3		0	1			0	-	1		

Table 3-6 continued

	Cancer					Disease (hyperplasia and/or cancer)				
	≤ 4 mm		≤ 5 mm			≤ 4 mm		≤ 5 mm		
Quality Criteria*	**n**	**Positive test LR (95% CI)**	**n**	**Positive test LR (95% CI)**	**Negative test LR (95% CI)**	**n**	**Positive test LR (95% CI)**	**n**	**Positive test LR (95% CI)**	**Negative test LR (95% CI)**
Blinding of test results										
Blinded	0	-	3	2.9 (2.4-3.4)	0.1 (0.02-0.3)	0	-	3	5.0 (3.9-6.4)	0.03 (0.01-0.1)
Unclearly reported	9	1.83 (1.76-1.9)	18	1.9 (1.8-2.0)	0.1 (0.07-0.2)	9	2.1 (1.95-2.2)	16	2.2 (2.0-2.4)	0.015 (0.1-0.2)
Verification of diagnosis										
>90%	9	1.83 (1.76-1.9)	17	2.0 (1.9-2.1)	0.1 (0.05-0.2)	9	2.1 (1.95-2.2)	15	2.9 (2.6-3.2)	0.1 (0.05-0.1)
81-90%	0	-	2	2.0 (1.7-2.3)	0.2 (0.1-0.4)	0	-	2	1.9 (1.7-2.2)	0.2 (0.1-0.4)
<80%	0	-	2			0	-	2		
Quality Level										
I-III	0	-	4	2.8 (2.3-3.3)	0.16 (0.06-0.4)	0	-	4	4.7 (3.7-6.0)	0.08 (0.03-0.2)
IV-VI	9	1.83 (1.76-1.9)	17	1.9 (1.8-2.1)	0.09 (0.05-0.2)	9	2.1 (1.95-2.2)	15	2.2 (2.0-2.4)	0.13 (0.09-0.2)
Reference Standard and Quality Level										
Ideal and I-III	0	-	4	2.8 (2.3-3.3)	0.16 (0.06-0.4)	0	-	4	4.7 (3.7-6.0)	0.08 (0.03-0.2)
Ideal and IV-VI	4	2.0 (1.9-2.1)	14	1.8 (1.6-1.9)	0.1 (0.06-0.2)	4	2.3 (2.2-2.5)	12	2.05 (1.9-2.3)	0.1 (0.09-0.2)
Non-ideal and IV-VI	5	1.6 (1.5-1.7)	3	3.6 (2.8-4.5)	0.05 (0.01-0.2)	5	1.7 (1.6-1.9)	3	3.0 (2.4-3.7)	0.1 (0.06-0.3)

Reference Standard: 1- Hysterectomy / directed biopsy under hysteroscopic vision, 2 - Inpatient D&C (D&C), 3 - Outpatient biopsy e.g. Pipelle, Novak, *see Methods section for details

Table 3.7 Exploration of heterogeneity in estimation of accuracy of ultrasound (≤5mm double layer endometrial thickness) for diagnosis of endometrial cancer and disease: Results of meta-regression analysis

Outcome ***Explanatory variables***	**Univariable analysis**		**Multivariable analysis I (Hypothesis testing)**		**Multivariable analysis II (Hypothesis generating)**	
	Coefficient (standard error)†	P value	Coefficient (standard error)†	P value	Coefficient (standard error)†	P value
ENDOMETRIAL CANCER						
Clinical features						
Population spectrum (Wide vs. narrow)*	-0.34 (0.14)	0.02	-0.06 (0.25)	0.80	-0.37 (0.80)	0.65
Study quality‡						
Items:						
Patient selection (Consecutive vs. non-consecutive)	-0.48 (0.15)	0.01	-	-	-	-
Reference standard (Outpatient biopsy vs. other)	1.17 (0.91)	0.21	-	-	-	-
Complete verification (Present vs. absent)	0.38 (0.14)	0.02	-	-	-	-
Blinding (Blind vs. not blind)	0.14 (0.24)	0.56	-	-	-	-
Levels: (1-3 vs. 4-5)	0.08 (0.20)	0.69	-0.13 (0.32)	0.68	-0.28 (0.99)	0.78
Ultrasonic procedure						
Transducer frequency(high (>5MHz) vs. low (≤5MHz))	-0.35 (0.14)	0.02	-	-	-0.43 (0.75)	0.57
Additional items of study quality						
Length of amenorrhoea (Adequate vs. inadequate)[#]	0.11 (0.17)	0.53	-	-	-0.13 (0.80)	0.88
Definition of abnormal result (5mm) (*A-priori vs. post hoc*)	-0.34 (0.14)	0.02	-	-	0.13 (0.91)	0.89

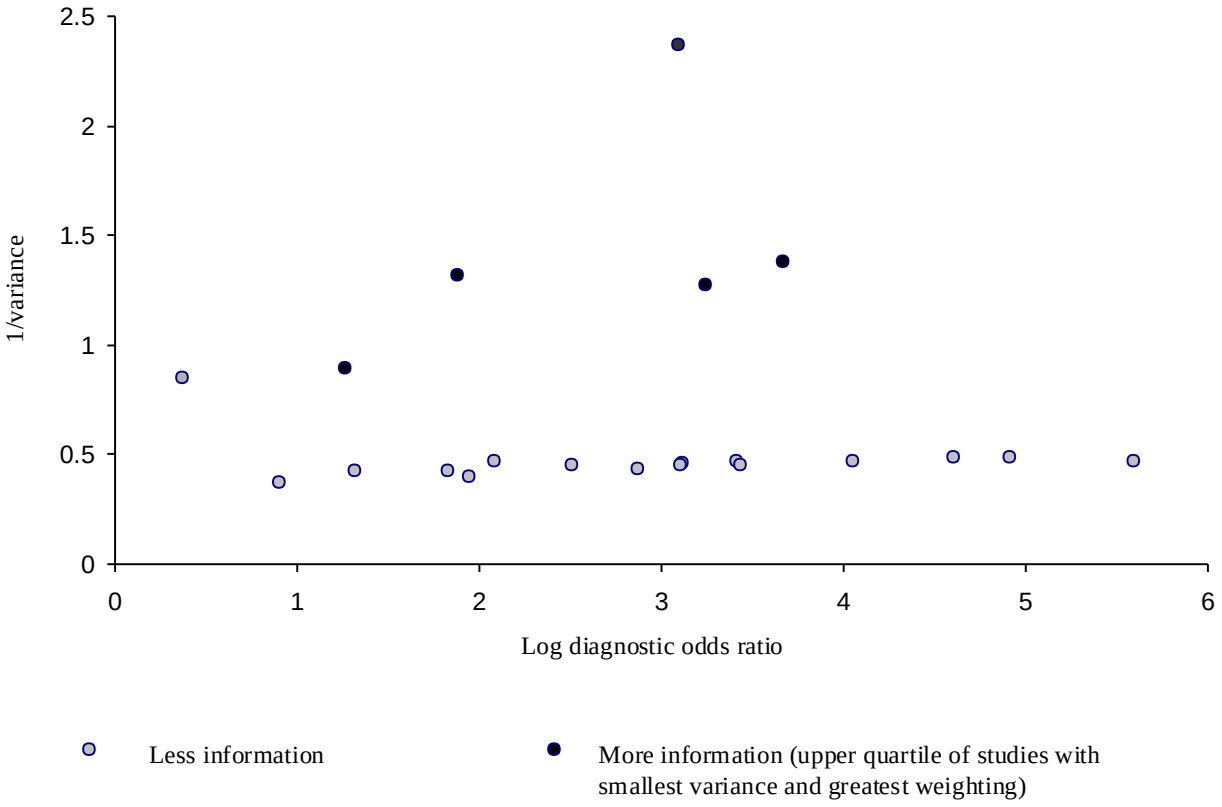
Table 3-7 continued

Outcome ***Explanatory variables***	**Univariable analysis**		**Multivariable analysis I (Hypothesis testing)**		**Multivariable analysis II (Hypothesis generating)**	
	Coefficient (standard error)†	P value	Coefficient (standard error)†	P value	Coefficient (standard error)†	P value
ENDOMETRIAL DISEASE						
Clinical features						
Population spectrum (Wide vs. narrow)*	-0.98 (0.60)	0.12	-0.22 (0.83)	0.80	-0.57 (0.93)	0.54
Study quality‡						
Items:						
Patient selection (Consecutive vs. non-consecutive)	-0.33 (0.82)	0.69	-	-	-	-
Reference standard (Outpatient biopsy vs. other)	0.40 (0.77)	0.61	-	-	-	-
Complete verification (Present vs. absent)	1.17 (0.58)	0.06	-	-	-	-
Blinding (Blind vs. not blind)	1.24 (1.07)	0.26	-	-	-	-
Levels: (1-3 vs. 4-5)	-0.04 (0.89)	0.96	0.30 (0.94)	0.75	0.12 (1.07)	0.91
Ultrasonic procedure						
Transducer frequency(high (>5MHz) vs. low (≤5MHz))	0.40 (0.64)	0.54	-	-	0.55 (0.87)	0.52
Additional items of study quality						
Length of amenorrhoea (Adequate vs. inadequate)†	0.57 (0.82)	0.50			-0.52 (0.87)	0.55
Definition of abnormal result (5mm) (***A-priori vs. post hoc***)	0.55 (0.65)	0.41			-0.50 (1.03)	0.63

* Wide population spectrum meant that the study population included postmenopausal women on HRT, whereas studies categorised as having a narrow population spectrum did not include postmenopausal women on HRT or where the use of HRT was unreported.
†The dependent variable is the log diagnostic odds ratio, a positive coefficient means that the diagnostic accuracy as measured by the odds ratio is increased and a negative coefficient means that it is reduced in relation to the variable. P values <0.05 considered statistically significant.
‡ Quality levels (1-5) rather than individual quality items used for multivariable analysis[62] (see text)
# The length of amenorrhoea indicating that the woman was menopausal was considered ideal if it was ≥ 12 months, and inadequate if it was < 12 months or unreported.

Statistical tests (rank correlation) to explore for publication and related biases, found that funnel plot asymmetry (Figure 3-8) was not statistically significant (p=0.82)

Figure 3-8 Funnel plot of ultrasound (≤ 5 mm double layer) and endometrial cancer



3.2.4.2 Accuracy in predicting endometrial disease

Estimates of LRs for individual studies are shown in Appendix 17. Pooled estimates of pretest probability, LRs and posttest probability are shown in Table 3-8. There were 1887 cases of endometrial disease among 7270 patients giving a pretest probability of 26.0% (95% CI 25.0 – 27.0%). The commonest cut-off levels for abnormality were based on the

measurement of both layers of endometrial thickness - 4 mm (9 studies) and 5 mm (19 studies). As shown in Table 3-8, a negative test result reduced the posttest probability of cancer to 2.4% (95% CI 1.3-3.9) at ≤ 4 mm and 5.0% (95% CI 2.9-9.1) at ≤ 5 mm. The pooled estimates for ≤ 4 mm negative results were homogeneous. However, none of the 9 studies using the ≤ 4 mm cut-off level were of good quality. Although the pooled estimates of LRs for ≤ 5 mm were heterogeneous ($p<0.05$), sensitivity analyses failed to produce an explanation as the confidence intervals of the LRs for the various subgroups overlapped (Table 3-6). An explanation for heterogeneity was not provided by the population spectrum or items of study quality (Table 3-7) when examined using both univariable and multivariable analysis. Similarly, the other potential explanatory variables considered did not appear to influence diagnostic accuracy. There were only 4 studies out of the 21 studies using the ≤ 5 mm cut-off level that employed the best quality criteria. Using the pooled estimates from these 4 studies only, a negative test result reduced the posttest probability of endometrial disease to 2.7% (95% CI 0.9-6.9).

Table 3.8 Pooled estimates of pretest probability, likelihood ratio and posttest probability for ultrasound measurement of endometrial thickness in predicting endometrial disease (hyperplasia and/or cancer)

Method of measurement and cut-off level for normality	Pretest probability % (95% CI)	Likelihood ratio (95% CI)	Posttest probability % (95% CI)
Measurement of both layers ET thickness			
3 mm (n = 1 study)			
Positive test result	26.0 (25.0-27.0)	2.5 (1.95-3.2)	46.7 (39.4-54.0)
Negative test result	26.0 (25.0-27.0)	0.03 (0.0-0.4)	1.0 (0.0-12.9)
4 mm (n = 9 studies)			
Positive test result	26.0 (25.0-27.0)	2.17 (1.73-2.73)*	43.3 (36.6-46.7)
Negative test result	26.0 (25.0-27.0)	0.07 (0.04-0.11)	2.4 (1.3-3.9)
5 mm (n = 19 studies)			
Positive test result	26.0 (25.0-27.0)	2.62 (2.03-3.38)*	47.9 (40.4-55.6)
Negative test result	26.0 (25.0-27.0)	0.15 (0.09-0.27)*	5.0 (2.9-9.1)
6 mm (n = 2 studies)			
Positive test result	26.0 (25.0-27.0)	1.4 (1.0-1.9)*	32.8 (25.4-41.3)
Negative test result	26.0 (25.0-27.0)	0.8 (0.6-1.0)*	21.3 (16.4-27.0)
Single layer ET measurement			
2 mm (n = 3 studies)			
Positive test result	26.0 (25.0-27.0)	2.6 (2.0-3.4)	47.9 (40.5-55.4)
Negative test result	26.0 (25.0-27.0)	0.14 (0.07-0.27)	4.7 (2.3-9.1)
3 mm (n = 5 studies)			
Positive test result	26.0 (25.0-27.0)	2.1 (1.9-2.6)	43.7 (38.1-49.3)
Negative test result	26.0 (25.0-27.0)	0.3 (0.2-0.4)*	9.0 (6.5-12.6)
4 mm (n = 2 studies)			
Positive test result	26.0 (25.0-27.0)	1.9 (1.7-2.2)	40.5 (36.7-44.5)
Negative test result	26.0 (25.0-27.0)	0.07 (0.02-0.2)	2.4 (0.7-6.9)
10 mm (n = 1 study)			
Positive test result	26.0 (25.0-27.0)	21.9 (1.3-364.1)	88.5 (30.6-99.3)
Negative test result	26.0 (25.0-27.0)	0.6 (0.4-0.9)	17.4 (11.8-25.2)
Unreported number of layers for ET measurement			
4 mm (n = 3 studies)			
Positive test result	26.0 (25.0-27.0)	2.7 (2.1-3.4)	48.5 (41.4-55.6)
Negative test result	26.0 (25.0-27.0)	0.08 (0.05-0.1)	2.7 (1.6-4.9)
5 mm (n = 2 studies)			
Positive test result	26.0 (25.0-27.0)	2.3 (1.8-2.9)	44.4 (37.2-51.6)
Negative test result	26.0 (25.0-27.0)	0.03 (0.0-0.15)	1.0 (0.0-5.3)
6 mm (n = 1 study)			
Positive test result	26.0 (25.0-27.0)	4.7 (3.4-6.7)	62.4 (52.8-71.1)
Negative test result	26.0 (25.0-27.0)	0.02 (0.0-0.3)	0.7 (0.0-9.4)

ET = endometrial thickness, *heterogeneity P<0.05 (chi-squared test for heterogeneity used)

3.3 Results of systematic review of hysteroscopy

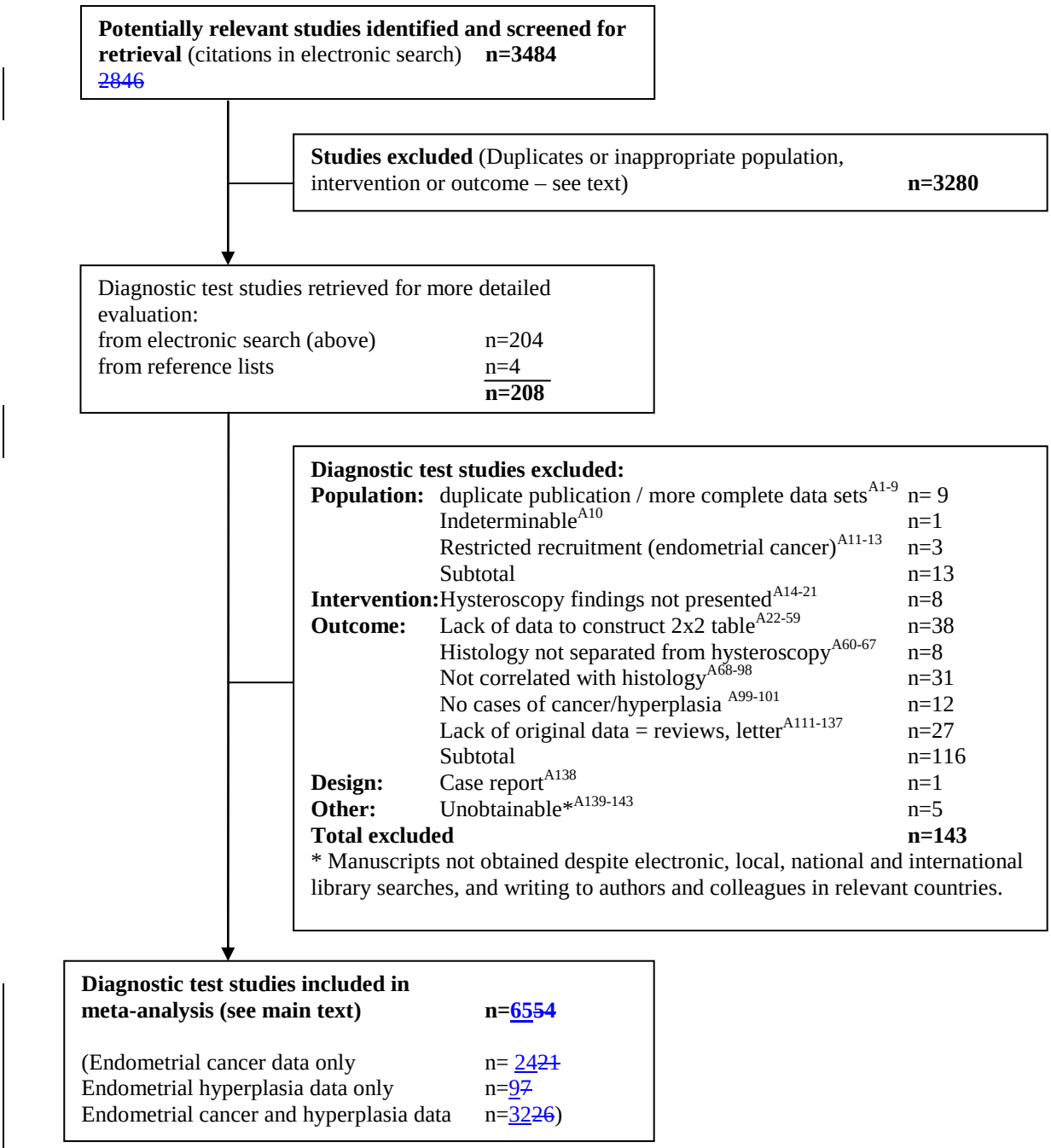
3.3.1 Question

What is the accuracy of outpatient hysteroscopy in the diagnosis of endometrial cancer and hyperplasia and what are the rates of failure and complications?

3.3.2 Study selection

A total of 65 primary studies (20 non-English studies), including 26,346 women, assessed the diagnostic accuracy of hysteroscopy in detecting serious endometrial disease and met the criteria for inclusion (Figure 3-9 and Appendix 18).

Figure 3-9 Study selection process for systematic review of hysteroscopy



Agreement regarding eligibility was 96% (weighted kappa 0.8). Of the 65 included studies, 56 studies (24,649 women) assessed the diagnosis of endometrial cancer. Postmenopausal women represented 29% of the populations studied.

3.3.3 Study quality

Details of the participants, interventions, outcomes and study quality criteria of the studies selected for meta-analyses are summarized in Appendices 19 and 20. There was a single study of the highest methodological quality (level 1), one study was classified as level 2, ten studies (15%) were level 3, 42 studies (65%) were level 4 and 11 studies (17%) were level 5 in quality.

3.3.4 Data synthesis

3.3.4.1 Accuracy in predicting endometrial cancer

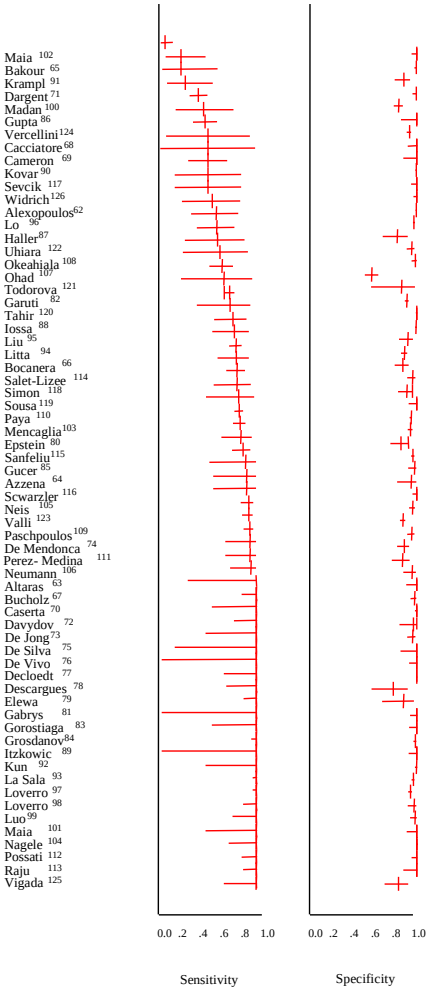
Figure 3-10 presents the sensitivity and specificity of hysteroscopy in the diagnosis of endometrial cancer. The variations in sensitivity were much greater than the variations in specificity and there was no significant association between sensitivity and specificity (Spearman's correlation coefficient r=-0.06, P=0.65). Weighted by the number of cases, the overall sensitivity was 86.4% (95% CI 84.0% to 88.6%) and specificity was 99.2% (95% CI 99.1% to 99.3%) according to 56 studies of hysteroscopy for endometrial cancer. In view of the lack of an association between sensitivity and specificity, a summary receiver operating characteristic curve was not generated.[83]

Figure 3-10 Sensitivity and specificity of hysteroscopy in the diagnosis of endometrial cancer and disease

Results sorted according to estimated sensitivity and presented with 95% confidence interval.

Endometrial Cancer

Endometrial Disease*



*Endometrial disease is endometrial cancer or endometrial hyperplasia (see section 1.6.2.2 for an explanation)

The pooled LRs for endometrial cancer are shown in Table 3-9. The pretest probability (prevalence) increased from 3.9% (95% CI 3.7%-4.2%) to 71.8% (95% CI 67.0%-76.6%) with a positive result and decreased to 0.6 % (95% CI 0.5%-0.8%) with a negative result.

Heterogeneity of diagnostic performance between studies was present as confirmed by a statistically significant $\chi 2$ test and this remained within the pre-specified clinical subgroups (setting and menopausal status). An explanation for heterogeneity was not provided by the study setting, menopausal status or study quality (Table 3-10). Neither did the other potential explanatory variables defined *post hoc* significantly influence diagnostic accuracy. The reported occurrence of complications was associated with reduced accuracy on univariable analysis, but this was not confirmed on multivariable analysis.

Statistical tests (rank correlation) to explore for publication and related biases, found that funnel plot asymmetry (Figure 3-11) was not statistically significant (p=0.34)

Table 3.9 Pooled estimates of pretest probabilities, likelihood ratios and posttest probabilities for diagnostic accuracy of hysteroscopy in detecting endometrial cancer and disease in women with abnormal uterine bleeding

Outcome (pretest probability with 95% CI) Population sub group (number of studies)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	Posttest Probability % (range) Test +	 Test –
ENDOMETRIAL CANCER (3.9% (3.7%-4.2%))				
All studies (61)	60.9 (51.2-72.5)	0.15 (0.13-0.18)	71.8 (67.0-76.6)	0.6 (0.5-0.8)
Quality (High vs. low quality)*				
High quality studies (11)	34.8 (25.6-47.3)	0.21 (0.15-0.28)	58.6 (49.6-67.5)	0.8 (0.6-1.2)
Low quality studies (50)	73.5 (59.5-90.8)	0.14 (0.12-0.17)	74.9 (69.6-79.9)	0.6 (0.5-0.7)
Setting (Outpatient vs. inpatient)				
Outpatient setting (31)	82.5 (64.9-105.0)	0.13 (0.10-0.16)	77.0 (71.4-82.2)	0.5 (0.4-0.7)
High quality studies (4)	119.2 (63.0-225.7)	0.16 (0.11-0.24)	82.8 (70.7-90.8)	0.7 (0.4-1.0)
Low quality studies (27)	76.5 (59.0-99.2)	0.12 (0.09-0.15)	75.6 (69.4-81.3)	0.5 (0.3-0.7)
Inpatient setting (16)	21.9 (15.9-30.2)	0.28 (0.21-0.37)	47.1 (37.9-57.0)	1.1 (0.8-1.6)
High quality studies (5)	8.6 (5.4-13.6)	0.36 (0.23-0.54)	25.8 (17.2-37.4)	1.4 (0.9-2.3)
Low quality studies (11)	58.6 (33.5-102.7)	0.25 (0.17-0.35)	70.4 (56.3-81.8)	1.0 (0.7-1.5)
Menopausal status (Postmenopausal vs. mixed)				
Postmenopausal women (16)	38.3 (26.1-56.1)	0.13 (0.09-0.18)	60.9 (50.1-71.1)	0.5 (0.4-0.8)
High quality studies (2)	45.4 (9.7-211.5)	0.09 (0.02-0.44)	64.8 (27.2-90.3)	0.4 (0.08-1.9)
Low quality studies (14)	37.8 (25.5-56.0)	0.13 (0.09-0.19)	60.5 (49.5-71.1)	0.5 (0.3-0.8)
Pre/post menopausal women (45)	72.5 (59.7-88.1)	0.16 (0.13-0.19)	74.6 (69.6-79.4)	0.6 (0.5-0.8)
High quality studies (9)	34.0 (25.1-46.1)	0.22 (0.16-0.29)	58.0 (49.1-66.9)	0.9 (0.6-1.3)
Low quality studies (36)	104.7 (80.7-135.9)	0.14 (0.12-0.18)	81.0 (75.6-85.6)	0.6 (0.5-0.7)

Table 3-9 continued

Outcome (pretest probability with 95% CI) Population sub group (number of studies)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	Posttest Probability % (range) Test +	 Test –
ENDOMETRIAL DISEASE (10.6% (10.2%-11.0%))				
All studies (71)	10.4 (9.7-11.1)	0.24 (0.22-0.25)	55.2 (52.4-57.8)	2.8 (2.4-3.0)
Quality (High vs. low quality)*				
High quality studies (12)	5.5 (4.8-6.3)	0.31 ((0.27-0.37)	39.4 (35.3-43.8)	3.5 (3.0-4.4)
Low quality studies (59)	12.6 (11.5-13.7)	0.22 (0.1-0.24)	59.9 (56.6-62.3)	2.5 (1.1-2.9)
Setting (Outpatient vs. inpatient)				
Outpatient setting (36)	13.9 (12.6-15.3)	0.21 (0.19-0.23)	62.2 (58.9-65.4)	2.4 (2.1-2.8)
High quality studies (4)	8.3 (6.9-10.1)	0.29 (0.24-0.35)	49.6 (43.9-55.5)	3.3 (2.7-4.2)
Low quality studies (32)	16.2 (14.5-18.2)	0.20 (0.17-0.22)	65.7 (62.2-69.2)	2.3 (1.9-2.7)
Inpatient setting (18)	4.6 (4.0-5.3)	0.39 (0.34-0.44)	35.3 (31.2-39.6)	4.4 (3.7-5.2)
High quality studies (5)	2.4 (2.0-2.9)	0.45 (0.34-0.59)	22.1 (18.5-26.4)	5.1 (3.7-6.8)
Low quality studies (13)	7.0 (5.6-8.6)	0.37 (0.32-0.43)	45.4 (38.9-51.5)	4.2 (3.5-5.1)
Menopausal status (Postmenopausal vs. mixed)				
Postmenopausal women (18)	20.4 (15.7-26.6)	0.14 (0.11-0.19)	70.8 (64.1-76.7)	1.6 (1.2-2.3)
High quality studies (2)	71.5 (9.8-522.9)	0.09 (0.02-0.41)	89.5 (52.7-98.5)	1.1 (0.2-4.8)
Low quality studies (16)	19.6 (15.0-25.6)	0.15 (0.11-0.19)	69.9 ((63.0-76.0)	1.8 (1.2-2.3)
Pre/post menopausal women (53)	9.6 (9.0-10.4)	0.25 (0.23-0.27)	53.2 (50.1-56.2)	2.9 (2.6-3.2)
High quality studies (10)	5.2 (4.6-6.0)	0.28 (0.23-0.34)	38.1 (34.3-42.6)	3.2 (2.6-4.0)
Low quality studies (43)	11.8 (10.8-12.9)	0.20 (0.18-0.22)	58.3 (55.1-61.5)	2.3 (2.0-2.7)

An estimate of the pretest probability was obtained by calculating the prevalence of the outcome event in the overall population in the 65 included studies.
The following equation was used for calculating post-test probability: posttest probability = likelihood ratio x pretest probability/[1-pretest probability x (1-likelihood ratio)].
Ranges of posttest probability were calculated by using lower and upper limits of 95% confidence intervals of pretest probabilities and likelihood ratios.
* High quality studies (levels 1-3), low quality studies (levels 4-5) – see Methods section for details

Table 3.10 Exploration of heterogeneity in estimation of accuracy of hysteroscopy for diagnosis of endometrial cancer and disease: Results of meta-regression analysis

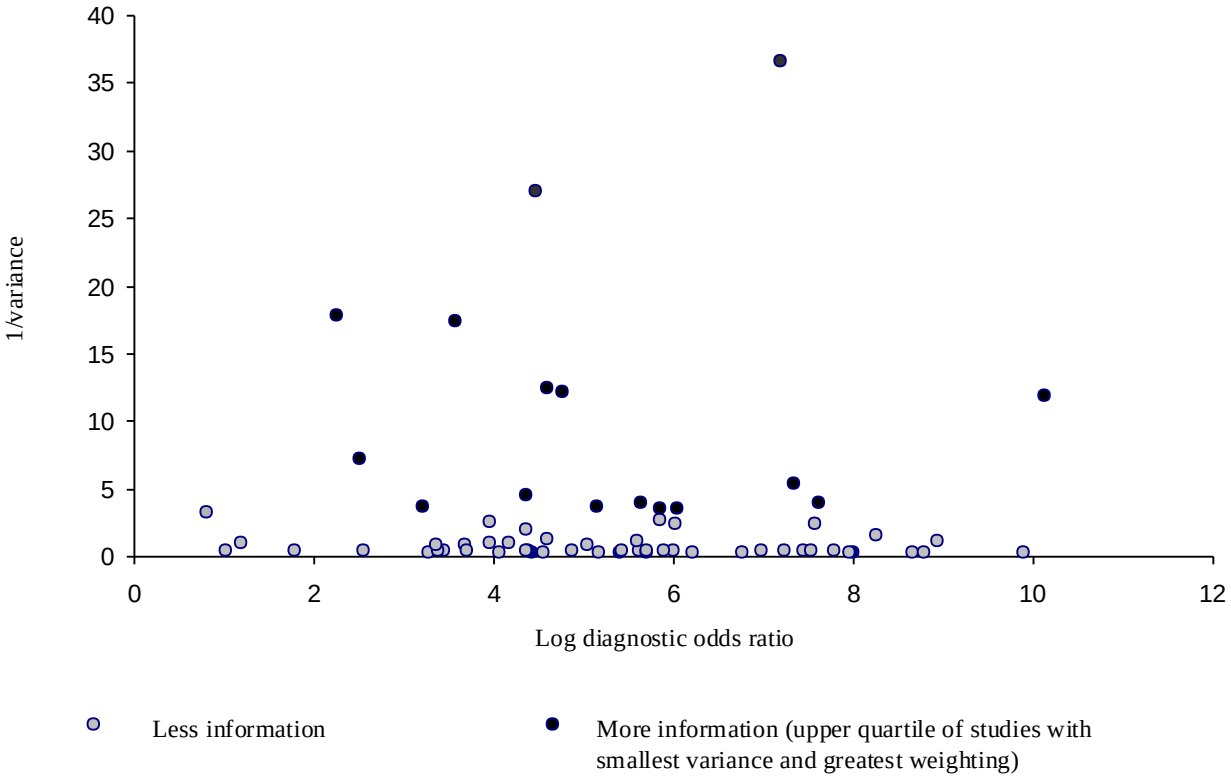
Outcome ***Explanatory variables***	**Univariable analysis**		**Multivariable analysis I (Hypothesis testing)**		**Multivariable analysis II (Hypothesis generating)**	
	Coefficient (standard error)†	P value	Coefficient (standard error)†	P value	Coefficient (standard error)†	P value
ENDOMETRIAL CANCER						
Defined a priori						
Clinical features						
Setting (Outpatient vs. inpatient)	0.60 (0.44)	0.18	0.52 (0.47)	0.26	0.89 (0.51)	0.09
Menopausal status (Postmenopausal vs. mixed)	-0.64 (0.69)	0.36	-0.41 (0.72)	0.57	-0.55 (0.75)	0.47
Study quality‡						
Items:						
Patient selection (Consecutive vs. non-consecutive)	-0.08 (0.46)	0.86	-	-	-	-
Reference standard (Outpatient biopsy vs. other)	0.45 (0.61)	0.46	-	-	-	-
Complete verification (Present vs. absent)	-0.14 (0.47)	0.77	-	-	-	-
Blinding (Blind vs. not blind)	-0.39 (2.1)	0.85	-	-	-	-
Levels: (1-3 vs. 4-5)	-0.18 (0.52)	0.73	-0.12 (0.52)	0.82	-0.35 (0.70)	0.62
Defined post hoc						
Hysteroscopic procedure						
Description of diagnostic test (Adequate vs. inadequate)	-1.11 (0.57)	0.06	-	-	-1.02 (0.77)	0.19
Complications (Present vs. absent)	-1.71 (0.67)	0.01	-	-	-1.28 (0.87)	0.15
Items of study quality						
Timing of verification (Sequential vs. simultaneous)	0.13 (0.48)	0.78	-	-	0.07 (0.66)	0.91
Data collection (Prospective vs. other)	-0.36 (0.55)	0.52	-	-	0.01 (0.60)	0.99
Follow up (>90% vs. < 90%)	-0.28 (0.99)	0.98	-	-	0.35 (1.03)	0.73

Table 3-10 continued

Outcome ***Explanatory variables***	**Univariable analysis**		**Multivariable analysis I (Hypothesis testing)**		**Multivariable analysis II (Hypothesis generating)**	
	Coefficient (standard error)†	P value	Coefficient (standard error)†	P value	Coefficient (standard error)†	P value
ENDOMETRIAL DISEASE						
Defined a priori						
Clinical features						
Setting (Outpatient vs. inpatient)	1.18 (0.37)	0.002	1.25 (0.33)	0.001	0.54 (0.38)	0.15
Menopausal status (Postmenopausal vs. mixed)	1.41 (0.69)	0.045	1.54 (0.60)	0.013	1.05 (0.56)	0.06
Items of study quality‡						
Items:						
Patient selection (Consecutive vs. non-consecutive)	-1.08 (0.38)	0.005	-	-	-	-
Reference standard (Outpatient biopsy vs. other)	0.36 (0.50)	0.48	-	-	-	-
Complete verification (Present vs. absent)	0.57 (0.46)	0.22	-	-	-	-
Blinding (Blind vs. not blind)	1.81 (2.77)	0.52	-	-	-	-
Levels: (1-3 vs. 4-5)	-1.10 (0.41)	0.009	-1.28 (0.37)	0.001	-1.69 (0.60)	0.006
Defined post hoc						
Hysteroscopic procedure						
Description of diagnostic test (Adequate vs. inadequate)	1.61 (0.82)	0.05	-	-	1.22 (0.73)	0.10
Complications (Present vs. absent)	-2.12 (0.64)	0.001	-	-	-1.15 (0.73)	0.12
Items of study quality						
Timing of verification (Sequential vs. simultaneous)	0.002 (0.43)	1.0	-	-	0.88 (0.57)	0.13
Data collection (Prospective vs. other)	0.82 (0.52)	0.12	-	-	0.58 (0.43)	0.19
Follow up (>90% vs. < 90%)	1.59 (0.53)	0.004	-	-	1.78 (0.52)	0.001

* Results are based on data from 61 data points presented in the 56 studies of endometrial cancer and 71 data points presented in the 65 studies of endometrial disease. In some studies, data could be extracted for both postmenopausal and premenopausal women, thus, there are more data points than studies.
†The dependent variable is the log diagnostic odds ratio, a positive coefficient means that the diagnostic accuracy as measured by the odds ratio is increased and a negative coefficient means that it is reduced in relation to the variable. P values <0.05 considered statistically significant.
‡ Quality levels (1-5) rather than individual quality items used for multivariable analysis (see Methods section for details)

Figure 3-11 Funnel plot of hysteroscopy and endometrial cancer



3.3.4.2 Accuracy in predicting endometrial disease

As observed with endometrial cancer, the variation in sensitivity was much greater than the variation in specificity and there was no significant association between sensitivity and specificity (correlation coefficient r=0.05, P= 0.70). Diagnostic accuracy was lower for endometrial disease than endometrial cancer. The weighted overall sensitivity was 78.0% (95% CI 76.3% to 79.6%) and specificity was 95.8% (95% CI 95.6% to 96.1%). The summary LRs for endometrial disease are also shown in Table 3-9. The pretest probability

increased from 10.6% (95% CI 10.2%-11.0%) to 55.2% (95% CI 52.4%-57.8%) with a positive result and decreased to 2.8% (95% CI 2.4%-3.0%) with a negative result (Table 3-9).

There was heterogeneity in the overall and subgroup meta-analyses (Table 3-9). Clinical setting and menopausal status were significant explanatory variables for heterogeneity in univariable analyses as was the quality item, patient selection (Table 3-10). Poor study quality, the office setting and postmenopausal women were associated with significantly higher accuracy of hysteroscopy. The effect of these features on diagnostic accuracy was confirmed with multivariable analysis (Table 3-10). Of the variables defined post hoc, only follow up greater than 90% was associated with higher accuracy on both univariable and multivariable analyses (Table 3-10).

3.3.5 Sensitivity analysis

In 12 (18%) studies it was not possible to determine the rate of inadequate specimen due to a lack of clear reporting and the rate was assumed to be zero for the purpose of analysis. This gave an inadequate specimen rate on the reference test of 1196/25409 (4.7%, 95% CI 4.5%-5.0%). The pooled LRs were not altered if inadequate samples were regarded as negative results. There were 4622 focal lesions (intrauterine polyps of fibroids) detected in 25409 hysteroscopies (prevalence 18%) reported in 55/65 primary studies. In 152 of the 4622 focal anomalies (prevalence 3%) endometrial cancer (17) or hyperplasia (135) was present. Estimates of accuracy for endometrial cancer were not affected when focal abnormalities were excluded as part of a sensitivity analysis (LR for positive and negative test 59.3 (49.2-71.6) and 0.14 (0.12-0.16).

3.3.6 Secondary outcomes

3.3.6.1 Failure rate

Failure rates were clearly reported in 36/65 (55%) studies. The overall failure rate was 937/26346 (3.6%, 95% CI 3.3%-3.8%) when considering all studies and 937/19323 (4.9%, 95% CI 4.6-5.2%) when studies with unclear reporting were excluded. In those studies performed exclusively in one setting, the failure rate for an ambulatory procedure was 755/18126 (4.2%, 95% CI 3.9-4.5%) compared to 86/2526 (3.4%, 95% CI 2.7-4.2%) for an inpatient procedure. However, the underlying reasons for failure varied between settings. Failed hysteroscopies in the office setting resulted from technical problems (e.g. cervical stenosis, anatomical factors, structural abnormalities) or patient factors (e.g. pain, intolerance) more often than in inpatient setting (79% v 9%). By contrast, inadequate visualization (e.g.

obscured by bleeding, debris) was more common in the inpatient setting as a reason for failure (3% v 0.7%). Endometrial cancer was found in 8/927 (0.8%, 95% CI 0.4%-1.7%) failed procedures reported in the 56 cancer studies and endometrial disease was found in 25/937 (2.7%, 95% CI 1.7%-3.9%) failures reported in all included studies. In those studies where data for postmenopausal women could be separated, the failure rate of hysteroscopy (67/1948, 3.4%, 95% CI 2.7%-4.4%) was comparable to the overall rate (Appendix 20).

3.3.6.2 Complication rate

Eight cases of potentially serious complications (pelvic infection, uterine perforation (4), bladder perforation, and precipitation of a hypocalcaemic crisis and an anginal episode) were reported out of 25,409 successful procedures. However, ascertainment of serious complications may be suboptimal as only 19/65 (29%) studies, which included 9413 successful procedures, explicitly stated the intention to report or actually reported complications.

3.4 Results of economic analysis

3.4.1 Question

Which of the three available tests (EB, USS and OPH) and their combinations is most cost effective in outpatient diagnosis of endometrial cancer?

3.4.2 Base case results

Life expectancies adjusted for age, surgery and presence of endometrial cancer are shown in Appendix 21. All strategies for diagnostic work-up were associated with improved survival when compared with a strategy of undertaking no initial investigation of women with PMB. However, there was little difference in expected survival between diagnostic strategies. The strategies OPH, EB + OPH and USS+EB+OPH were dominated by other strategies (i.e. in each case there was an alternative strategy that was both cheaper and more effective – Appendix 22). Incremental cost-effectiveness ratios (ICERs) comparing the cost-effectiveness of strategies with no initial investigation are shown in Table 3-11.

Table 3.11 Investigation of postmenopausal bleeding: Incremental cost-effectiveness ratios for diagnostic strategies, compared in each case to no initial investigation

Strategy	**Incremental cost** (£)	**Life Years Gained** (LYG)	**Average days extra survival/ patient**	**ICER (£/LYG)***
USS 5mm	211.94	0.018477	6.74	11,470
USS 4mm	225.57	0.018839	6.88	11,974
EB	231.89	0.018845	6.88	12,305
OPH	239.32	0.016647	6.08	14,376
USS 5mm+EB	371.69	0.019706	7.19	18,862
USS 4mm+EB	383.07	0.019724	7.20	19,422
USS 5mm+OPH	386.91	0.019853	7.25	19,489
EB+OPH	399.06	0.019731	7.20	20,225
USS 4mm+OPH	399.07	0.019883	7.26	20,071
USS+EB+OPH	453.06	0.019731	7.20	22,962

Survival discounted at a rate of 1.5%
*The incremental cost-effectiveness ratios are calculated in each case by comparison with no initial investigation.
EB = endometrial biopsy, ICER = incremental cost-effectiveness ratio, £/LYG = UK pound sterling per life year gained, OPH = outpatient hysteroscopy, USS = transvaginal ultrasound.

The strategy based on USS using a 5mm cut-off was the least expensive. Incremental cost-effectiveness ratios (ICERs) comparing the cost-effectiveness of non-dominated strategies with USS 5mm are shown in Table 3-12.

Table 3.12 Investigation of postmenopausal bleeding: Incremental cost-effectiveness ratios for the non-dominated strategies, compared in each case to a strategy of ultrasound (5mm cut-off)

Strategy	**Incremental cost** (£)	**Life Years Gained** (LYG)	**Average days extra survival/patient**	**ICER (£/LYG***
USS 4mm	13.63	0.000362	0.13	37,652
EB	19.95	0.000368	0.13	54,212
OPH	27.38	-0.00183	-0.67	D
USS 5mm+EB	159.76	0.001229	0.45	129,992
USS 4mm+EB	171.13	0.001246	0.45	137,343
USS 5mm+OPH	174.97	0.001376	0.50	127,158
EB+OPH	187.12	0.001254	0.46	149,219
USS 4mm+OPH	187.13	0.001405	0.51	133,189

Survival discounted at a rate of 1.5%
*The incremental cost-effectiveness ratios are calculated in each case by comparison with a strategy of initial investigation with ultrasound using a 5mm endometrial thickness cut-off.
D=dominated, EB = endometrial biopsy, ICER = incremental cost-effectiveness ratio, £/LYG = UK pound sterling per life year gained, OPH = outpatient hysteroscopy, USS = transvaginal ultrasound.

The ICERs compared to no initial investigation reduced for USS 5mm (£11,470), USS 4mm (£11,974) and OPH (£12,305) strategies when the model was altered to allow for EB to be performed following a positive test on the same visit, rather than a subsequent one. In these circumstances, the ICERs compared to USS 5mm, increased for all diagnostic strategies apart from USS 4mm (£27,873) (Appendix 23).

3.4.3 Other age-groups

Table 3-13 shows the ICERs of diagnostic strategies compared to USS 5mm for women presenting at different ages. At older ages of presentation, more strategies became dominated. The ICERs increased for all strategies that remained non-dominated with increasing age. The

general patterns of dominance were the same when survival effects were not discounted although ICERs were generally lower (Appendix 24).

Table 3.13 Investigation of postmenopausal bleeding at different ages of presentation: Incremental cost-effectiveness ratios of strategies compared to ultrasound (5mm cut-off)

Strategy	ICER compared to USS5mm for starting age (years)				
	45	55	65	75	80+
USS 4mm	24,940	26,401	37,652	75,493	191,431
EB	24,336	29,039	54,212	D(USS5)	D(USS5)
OPH	D(USS5)	D(USS5)	D (USS5)	D(USS5)	D(USS5)
USS 5mm+EB	78,078	85,417	129,992	375,287	D(USS5)
USS 4mm+EB	82,616	90,324	137,343	392,722	D(USS5)
USS 5mm+OPH	D(USS+EB)	91,993	127,158	222,326	428,949
EB+OPH	89,786	98,171	149,219	D (USS5+OPH)	D(USS5)
USS 4mm+OPH	D(EB+OPH)	95,407	133,189	D (USS5+OPH)	D (USS5+OPH)

Survival discounted at a rate of 1.5%
EB = endometrial biopsy, OPH = outpatient hysteroscopy, USS = transvaginal ultrasound.
D(USS5) = dominated by USS 5mm cut-off. D(USS+EB) = dominated by USS+OPH strategy. D(EB+OPH) = dominated by EB+OPH strategy. D(U5+OPH) = dominated by USS 5mm cut-off+OPH strategy.

3.4.4 Results of sensitivity analyses

Univariate sensitivity analyses for the strategies involving two initial tests applied over ranges of diagnostic feasibility, accuracy and disease prevalence had little effect on overall cost-effectiveness. However, the assumed effect of delayed diagnosis on increasing disease stage from local (FIGO stage I) to advanced (FIGO stages II-IV) endometrial cancer ("upstaging") did reduce the ICERs for all strategies substantially (See Table 3-14). The ICERs for the strategies based on initial investigation with USS 4mm or EB reduced to under £30,000 per

life year gained when the probability of upstaging endometrial cancer following delay was 6% and 8% respectively.

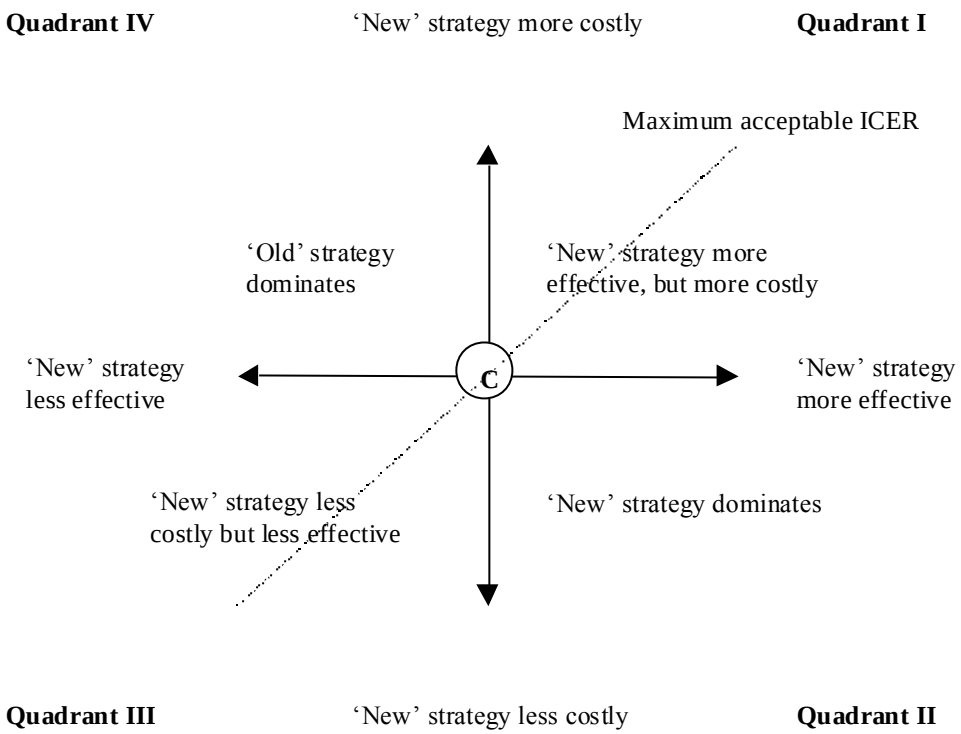
Table 3.14 Sensitivity analysis: The effect of delayed diagnosis on the incremental cost-effectiveness ratios of combination strategies compared to ultrasound (5mm cut-off)

Strategy	**ICERs** (£/LYG) **stratified according to the probability of upstaging endometrial cancer as a result of delayed diagnosis**	
	0.05	0.3
USS 5mm+EB	129,992	18,909
USS 4mm+EB	137,343	20,005
USS5mm +OPH	127,158	20,946
EB+OPH	149,219	21,747
USS 4mm+OPH	133,189	21,662

0.05 assumes a 5% increase in stage of endometrial cancer as a result of delayed diagnosis following erroneous initial discharge, 0.3 assumes a 30% 'upstage' of disease.
EB = endometrial biopsy, OPH = outpatient hysteroscopy, USS = transvaginal ultrasound.
ICER (£/LYG) = incremental cost-effectiveness ratio (£/life year gained).

The potentially most cost-effective strategies were those based on initial investigation with USS (4 and 5mm) or EB alone. Factors influencing the cost and effectiveness of these three diagnostic strategies were varied in order to determine how sensitive the base case results were to changes in the underlying assumptions. Figure 3-12 shows the four quadrants of the cost-effectiveness plane[11,31,41] and the results of the sensitivity analyses comparing USS 4mm, USS 5mm and EB are shown graphically in this format (Figures 3-13 to 3-15, tabulated data is given in Appendices 25 to 27). These results show that there is not yet sufficient data to determine which of these strategies is preferred on cost-effectiveness grounds (data points appear in all four quadrants of the respective graphs).

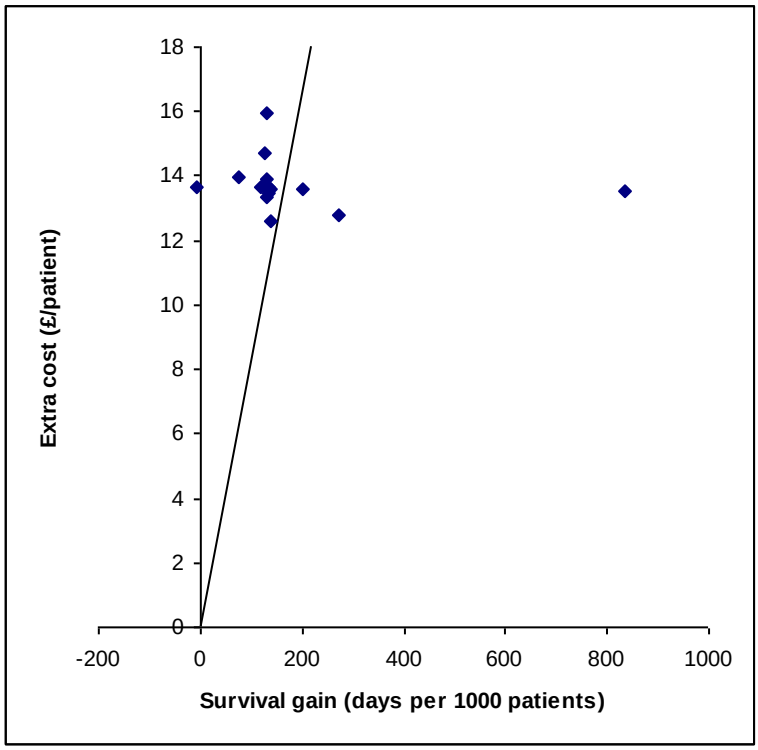
Figure 3-12 The cost-effectiveness plane



The cost-effectiveness space is incremental such that the comparison strategy (**C**) is the origin in the figure and the horizontal and vertical axes relate to effect and cost differences respectively

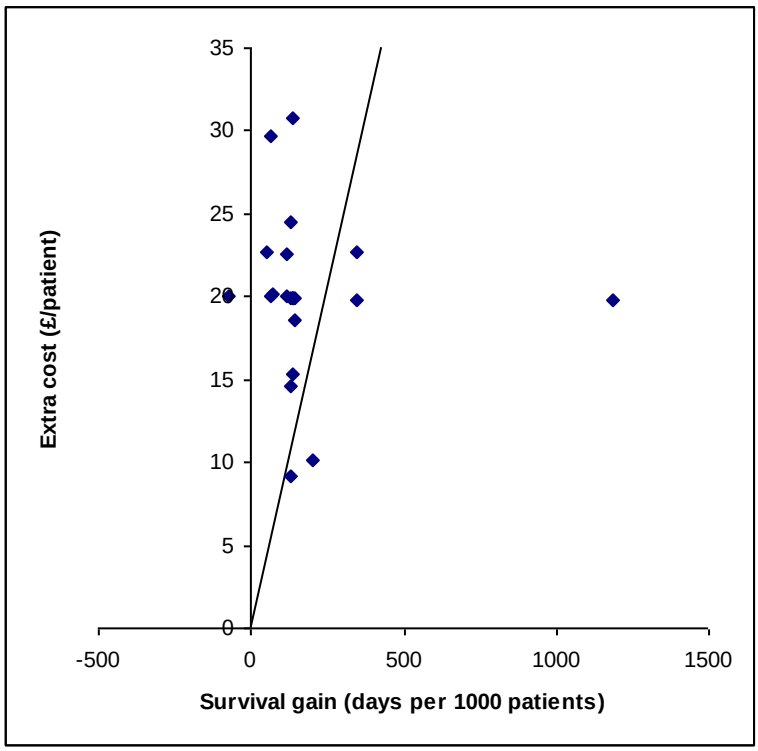
Quadrants I and III represent the situation where one of the strategies is both more effective and more costly. The decision regarding cost-effectiveness is unclear and a judgement must be made concerning whether the additional costs of the more expensive strategy are justified by the additional effectiveness associated with the particular strategy. A maximum acceptable incremental cost-effectiveness ratio (ICER) can be explicitly set to aid decision making. This is represented by the dashed line. Datapoints to the right of the line suggest that strategy in question is cost-effective, while points to the left of the line are associated with cost-ineffective strategies.[41]

Figure 3-13 Results of univariate sensitivity analysis on extra cost and survival of USS 4mm compared to USS 5mm



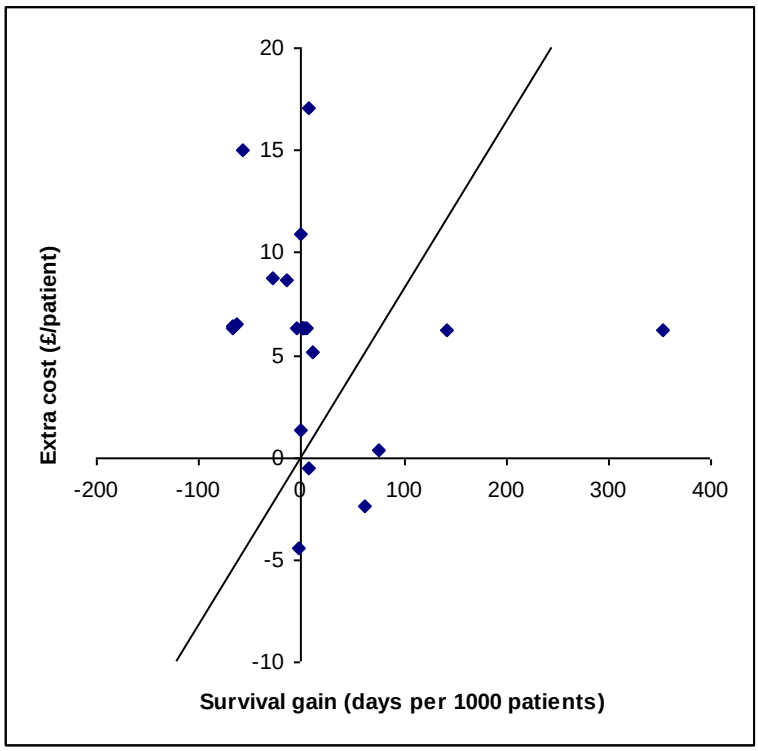
Each datapoint represents one parameter change, all others remaining at base case values. Parameters varied were test failure rates, test accuracy estimates for true and false positive rate, the adjustments to true positive rates conditional on previous test results and the probability of upstaging endometrial cancer due to delayed diagnosis.
Line represents £30,000/additional life year gained threshold.[274] The strategy USS 4mm may be considered potentially cost-effective compared with USS 5mm when the data points (representing increased upstaging probability to 30%, endometrial cancer prevalence increased to 10% and true positive rate of USS 5mm reduced to 94%) are to the right of the line. The strategy USS5mm dominates when no endometrial cancer upstaging is assumed.

Figure 3-14 Results of univariate sensitivity analysis on extra cost and survival of EB compared to USS 5mm



Each datapoint represents one parameter change, all others remaining at base case values. Parameters varied were test failure rates, test accuracy estimates for true and false positive rate, the adjustments to true positive rates conditional on previous test results and the probability of upstaging endometrial cancer due to delayed diagnosis.
Line represents £30,000/additional life year gained threshold.[274] The strategy EB may be considered potentially cost-effective compared with USS 5mm when the data points (representing increased upstaging probability to 30%, endometrial cancer prevalence increased to 10%, true positive rate of USS 5mm reduced to 94%, and false positive rate and failure rate of EB reduced to 0% and 9% respectively) are to the right of the line. The strategy USS5mm dominates when no endometrial cancer upstaging is assumed.

Figure 3-15 Results of univariate sensitivity analysis on extra cost and survival of EB compared to USS 4mm



Each datapoint represents one parameter change, all others remaining at base case values. Parameters varied were test failure rates, test accuracy estimates for true and false positive rate, the adjustments to true positive rates conditional on previous test results and the probability of upstaging endometrial cancer due to delayed diagnosis.
Line represents £30,000/additional life year gained threshold.[274] These results show that there is not yet sufficient data to determine which of these strategies is preferred on cost-effectiveness grounds (data points appear in all four quadrants of the graph).

3.5 Summary of Results

3.5.1 Summary of results of systematic reviews

- The literature was of relatively poor methodological quality.

- There was statistical heterogeneity in pooling of likelihood ratios, for USS and OPH, but an explanation for this could not be found in spectrum composition and study quality.

- A positive test result on EB diagnosed endometrial cancer with a pooled LR of 66.48 (95% CI 30.04-147.13) while a negative test result had a pooled LR of 0.14 (95% CI 0.08-0.27).

- The commonest USS cut-offs to define abnormal endometrial thickness were 4mm and 5mm, measuring both endometrial layers. Using a 4mm cut-off, a positive test result on USS diagnosed endometrial cancer with a pooled LR of 1.96 (95% CI 1.6-2.4) while a negative test result had a pooled LR of 0.08 (95% CI 0.03-0.17). The LRs for positive and negative ultrasound results for diagnosing endometrial cancer using a 5mm cut-off were 2.17 (95% CI 1.75-2.68) and 0.15 (95% CI 0.08-0.29) respectively.

- A positive test result on OPH diagnosed endometrial cancer with a pooled LR of 60.9 (95% CI 51.2-72.5) while a negative test result had a pooled LR of 0.15 (95% CI 0.13-0.18).

3.5.2 Summary of results of economic analysis

- Life expectancies were comparable for all diagnostic strategies, but costs varied.

- For all ages economic modeling indicated that the strategy based on initial diagnosis with USS was the least expensive for the investigation of women with PMB.

- Strategies based on initial investigation with OPH or all tests combined were dominated by other strategies, in that in each case there was an alternative strategy that was cheaper and more effective.

- When compared to initial investigation with USS 5mm for a woman aged 65 (base case - decade of peak incidence of endometrial cancer), the ICERs for the non-dominated strategies ranged between £37,652 for the initial strategy USS 4mm and £149,219 for the strategy EB + OPH per additional LYG.

- The ICERs increased when considering older ages at presentation and reduced for lower ages. However, the ICERs were still well above generally recognised thresholds for all strategies with the exception of USS 4mm and EB under the age of 65 years.

- Initial investigation with EB is potentially a cost-effective strategy (ICER reduced below £30,000 per LYG)) compared to USS, if EB performs at the more favourable estimates of accuracy and USS at the least favourable estimates of accuracy. Similarly, the ICER

reduced for EB compared to USS 4mm or 5mm as the probability of upstaging of endometrial cancer with delayed diagnosis increased.

- The strategies involving initial evaluation with two tests (combination strategies) could become more cost-effective if the effect on life expectancy of a delayed diagnosis is much greater than is assumed in the base case.

Table 3.15 Summary of results of economic evaluation: cost-effectiveness of each strategy compared with ultrasound scan (5mm cut-off)

Comparator	**Ultrasound scan (5mm cut-off)**
No initial investigation	A
Ultrasound scan (4mm cut-off)	I
Endometrial biopsy	I
Outpatient hysteroscopy	G
Ultrasound scan + outpatient hysteroscopy	I
Ultrasound scan + endometrial biopsy	I
Endometrial biopsy + outpatient hysteroscopy	I
Ultrasound scan + endometrial biopsy + outpatient hysteroscopy	I

Possible permutations for results of economic evaluation[82]

A	Trade off	Higher costs but better outcomes (incremental cost-effectiveness analysis required)
B	Reject	Higher costs and no difference in outcomes
C	Reject	Higher costs and poorer outcomes
D	Accept	No difference in costs and improved outcomes (partial dominance)
E	Neutral	No difference in costs and no difference in outcomes
F	Reject	No difference in costs and poorer outcomes
G	Accept	Lower costs and improved outcomes (extended dominance)
H	Accept	Lower costs and no difference in outcomes (partial dominance)
I	Trade off	Lower costs but poorer outcomes (incremental cost-effectiveness analysis required)

CHAPTER IV

DISCUSSION AND CONCLUSIONS

4.1 Diagnostic reviews

4.1.1 Test accuracy in the diagnosis of endometrial cancer

The reviews of diagnostic hysteroscopy and endometrial biopsy show them to be safe procedures with a low incidence of serious complications.[62,63] Although the review of ultrasound did not record this data, primary studies have not reported these procedures to be associated with significant side effects.[12] When the uterine cavity is adequately visualised, hysteroscopy is highly accurate, and thereby clinically useful in the diagnosis of endometrial cancer. Moreover, performance of the test does not appear to be significantly altered by the clinical setting or menopausal status. Endometrial biopsy is also highly accurate when adequate specimens are obtained. For both these diagnostic tests, a positive test result is highly accurate but a negative test result is of more limited accuracy and thereby only moderately useful.[21,174] As the diagnosis of endometrial cancer is very important, the high likelihood ratio for a positive test should raise most pre-test probabilities over any threshold for advanced management.[264] In contrast, the likelihood ratio for a negative test may not be low enough to negate the need for further diagnostic testing (i.e. malignant pathology can be missed by outpatient biopsy and hysteroscopy), thereby reducing the utility of outpatient biopsy or hysteroscopy in isolation for excluding cancer.

In contrast, these results suggest that ultrasonic measurement of endometrial thickness has limited diagnostic prediction for endometrial cancer but is a good test for exclusion of malignancy. A ≤ 4 mm or ≤ 5 mm cut-off level measuring both layers, can be used to rule out endometrial cancer with good certainty, as a negative test result reduced the post-test probability substantially (less than 0.5% using 4mm and less than 1% using 5mm, assuming a 5% pre-test probability). The marginally greater reduction in post-test probability, and the statistical homogeneity of the pooled LR for a negative test result, may favour use of the ≤ 4mm double layer cut-off level. However, all 9 included studies at this cut-off were of poor methodological quality. The tangible reduction in post-test probability of endometrial cancer observed at a ≤ 5 mm cut-off level remained (4.2% assuming a 5% prevalence) when pooling only the best quality studies, although no explanation for heterogeneity was found. As the exclusion of endometrial cancer is very important, one should be wary of relying on the pooled estimates of only 4 studies, despite them being of good quality. This illustrates the poor methodological quality of the majority of primary studies on this topic. These findings concur with a recent Consensus Conference statement, which has also concluded that, an endometrial thickness greater than 5 mm should be considered as abnormal,[141] similar to a previous systematic review[303] (see below).

4.1.2 Test accuracy in the diagnosis of endometrial disease

Abnormal postmenopausal endometrial thickening is a feature of endometrial hyperplasia as well as endometrial cancer. It is not surprising therefore, that the diagnostic performance of ultrasound is similar for both conditions and the inferences remain the same i.e. ultrasonic measurement of endometrial thickness has limited diagnostic prediction for endometrial hyperplasia or cancer but it is a good test for exclusion of endometrial pathology. However,

the diagnostic accuracy of EB and OPH is reduced in endometrial disease (cancer and/or hyperplasia) compared with estimates of accuracy for endometrial cancer. The modest estimates of accuracy in diagnosing endometrial disease reduce the usefulness of these two outpatient modalities in informing clinical decision-making.[21] Further testing will be indicated, especially if symptoms persist or intrauterine structural abnormalities are suspected, as endometrial disease cannot be ruled in or excluded with a high level of certainty.

Items of poor study quality (retrospective recruitment, unclear reporting) appear to explain the observed heterogeneity of diagnostic test performance of EB in hyperplasia. Separating the data for the presence of atypia changed the estimates of diagnostic accuracy, although not significantly. Diagnostic accuracy was reduced for endometrial hyperplasia without atypia and increased when atypical cells were present. The presence of complex hyperplasia with atypia is important in clinical practice, because approximately 33% will progress to malignancy.[199] Simple hyperplasia on the other hand, rarely progresses and the hyperplastic process can be reversed with local or systemic progestogens.[125] Moreover, this review demonstrates that outpatient endometrial biopsy is highly accurate in diagnosing either premalignant or malignant endometrial pathology. A positive test result was more accurate than a negative test result. It is encouraging that the more clinically significant the endometrial pathology, the better the diagnostic accuracy of outpatient endometrial biopsy and hence the more clinically useful the test. In contrast to the findings for endometrial cancer, hysteroscopy is more accurate for the diagnosis of endometrial disease in postmenopausal women and when undertaken in the office setting. In this review (OPH), statistically significant differences between these clinical subgroups are quantitative rather than qualitative. Invariably such differences only explain part of the heterogeneity. Therefore,

it may be argued that the overall average estimates may provide the best summary of the available evidence.[347] However, cautious interpretation would demand that one considers the test's performance to vary according to setting and menopausal status. Therefore, inferences are based on these clinical subgroups and methodological quality in the case of endometrial disease.

4.1.3 Test feasibility

The results of these systematic reviews show outpatient endometrial biopsy and hysteroscopy to be successful procedures.[62,63] Ultrasonography is the least invasive investigation and has previously been shown to be associated with a negligible failure rate.[303] Failure rates and inadequate sampling rates were higher for EB in postmenopausal women compared with premenopausal women. Inadequate endometrial samples, despite successful outpatient procedures, may result from poor patient compliance or biopsy technique, inherent problems with non-representative sampling, varied pathological interpretation or be consistent with the underlying atrophic endometrial state. The review of EB found that single cases of cancer and hyperplasia were found in inadequate EB specimens, although sensitivity analysis showed that the effect of these missed cases on overall accuracy estimates was minimal. However, further means of endometrial evaluation should be considered, particularly when endometrial imaging or menopausal status is inconsistent with the finding of inadequate tissue. Hysteroscopy is a successful procedure in both pre and postmenopausal women although the lack of an effect of menopausal status may be the result of reporting bias, as recording of failures was unclear in some studies. The office setting appears to have a marginally higher failure rate compared to the inpatient setting. This is attributable to anatomical and patient factors rather than inadequate visualization, which is more common in the inpatient setting.

The failure rate of office hysteroscopy may represent an underestimate because of more favourable patient selection. However, selection bias is unlikely to have affected diagnostic performance in endometrial disease because the ease of visualisation, and hence diagnosis, is not readily predictable prior to hysteroscopy. Furthermore, the trend towards improved diagnostic performance was confirmed on multivariable analysis, which adjusted for menopausal status. Technical failure in performing the EB or OPH should lead to other means of endometrial assessment.

4.2 Validity of reviews

The strength of this overview is based on its compliance with criteria for performing rigorous systematic reviews.[66,170,235,260] The study focused on explicit research questions and a clear prospective protocol was formulated. The search strategies were broad and data that were subject to duplicate publication were excluded from the reviews. Articles were included that were published in non-English languages. Furthermore, the assessment of methodological quality and data extraction was performed in a valid[107,207] and reproducible fashion. The evidence was quantitatively summarised and summary LRs were used based on the recommendations of the various Evidence-based Medicine Working Group's.[84,86,150,174] Using LRs and Bayes' theorem allowed the generation of clinically meaningful post-test probabilities thereby facilitating clinical decision making.[174] Since the completion of the reviews included in this thesis, recommendations have been published for the optimal reporting of primary studies of diagnostic accuracy.[34,35] The vast majority of information advocated in this 'STARD' statement has been extracted and presented.

4.2.1 Heterogeneity

Sensitivity analyses were performed to investigate for possible sources of heterogeneity, which were planned *a priori.* Heterogeneity relates to the presence of differences in results between individual studies. Homogeneity of results from study to study is one of the criteria for meta-analysis, but presence of inconsistency itself does not always invalidate a meta-analysis. In this situation, it is important to consider possible reasons for heterogeneity and so try and explain it. Exploration for sources of heterogeneity was performed as thoroughly as possible in accordance with published guidelines,[69,82,91] taking into account differences in methodological quality and study characteristics, using both univariable and multivariable analytic techniques. However, this approach did not explain the observed variation in the reviews of ultrasound and hysteroscopy. Such analyses are often restricted due to the number of available studies.[322,341] Although the reviews included numerous studies, the exploration of underlying sources of heterogeneity may be limited without access to individual patient data.[110] Cautious interpretation of the pooled findings for hysteroscopy and ultrasound is recommended in this situation. However, in view of the lack of satisfactory explanations for heterogeneity between studies it may be reasonable to base inferences on the overall pooled results.[347]

The methodological quality of the primary studies included in the reviews were generally poor. Frequent methodological shortcomings included non-consecutive population enrolment and unclear reporting of patient's menopausal status. Another potential source of bias in the review of ultrasound was the manner in which the cut-off level for abnormal endometrial thickness was determined. In a majority of studies using the ≤ 4 and ≤ 5 mm cut-off level, this

was determined *post hoc* i.e. retrospectively following the conduct of the test and outcome examinations. This would explain the large number of studies in which there was no incidence of endometrial cancer in the presence of a negative test result. Ideally, the cut-off level at which a test will perform most optimally should be determined prior to conducting a study to assess its diagnostic performance.[148] Such potential biases may contribute to heterogeneity, but in this review they did not account for the inconsistency of the results across studies.

4.2.2 Sources of bias

4.2.2.1 Reference standard

In the reviews of USS and OPH, choice of histological reference standard and lack of blinding in its assessment could potentially introduce bias. Hysterectomy specimens are regarded as the 'gold' standard for verification of endometrial disease, but the exclusive use of this reference standard in a diagnostic test study is not feasible. Therefore it is not surprising that many studies included in these reviews obtained endometrial tissue using other methods. It is worth noting that any test applied in clinical practice to finally direct patient management can serve as a reference standard. However, evaluating diagnostic tests compared to reference tests instead of a 'gold' standard (in this case hysterectomy), will generally underestimate diagnostic accuracy as a result of misclassification on true disease status by the reference test chosen.[236] Bias due to misdiagnosis by these methods is however, unlikely to be a significant problem in this thesis. This is because outpatient endometrial sampling methods are considered to be highly accurate for endometrial cancer.[61,62] Moreover, both subgroup analyses did not show the type of reference standard or blinding to be significant predictors

for diagnostic performance. Blinding in this overview may be less important than in other diagnostic test studies. This is because the histological diagnosis of endometrial cancer, the primary outcome measure, is an objective one[215] and consequently not as susceptible to expectation bias.

4.2.2.2 Publication bias

The impact of publication bias is another important consideration in all systematic reviews, as diagnostic accuracy may be overestimated as a result. Here studies with negative or non-significant results may have been less likely to be published. However, this was only suggested by funnel plot asymmetry[82,306] in the review of EB in endometrial hyperplasia. Removal of the smaller studies that reported the highest estimates of diagnostic accuracy as part of a sensitivity analysis did not materially alter the results although it did reduce the estimates of accuracy slightly, suggesting that the pooled results are reliable.

4.3 Comparison with other reviews and guidelines

4.3.1 Reviews

Two systematic reviews of ultrasound and one review of EB have been recently published.[303,319] Methodological deficiencies arising from the review of EB[95] compromise the internal and external validity of their review findings. These deficiencies include the use of a limited search and the inappropriate inclusion of data derived from studies restricted to women known to have endometrial cancer, asymptomatic women, cytological devices and procedures carried out under general anaesthetic in overall data synthesis. Estimates of

diagnostic performance are thus likely to be affected to an unknown degree. However, despite these limitations, the pooled detection rates and false positive rates for endometrial cancer were comparable with those derived from the EB review included in this thesis (95% and 0.5% vs. 94% and 1% respectively). The reviews of ultrasound[303,319] also had methodological problems such as restricting the searching to just one database, which is associated with literature retrieval bias[306] and lack of study quality assessment.[207] One of the USS reviews[303] suggested that an endometrial thickness of ≤ 5 mm can reliably exclude endometrial pathology in postmenopausal women (detection rate 96% for a 39% false positive rate compared with 97% and 45% respectively for the review in this thesis). They recommended that a negative test result avoided the need for endometrial sampling for histological examination. However, the potential biases in the review process raised concerns that this conclusion was over optimistic and therefore required testing as part of a decision analysis (see below).

In contrast, the other recently published USS review[319] recommended that histological sampling (D&C) was still required following a negative USS (detection rate 96% for a 50% false positive rate). The authors used individual patient data from a few centres to demonstrate that the median USS endometrial thickness in postmenopausal women with and without endometrial cancer varied between them. They argued that a universal, optimum endometrial thickness cut-off was not appropriate, but such cut-offs should be individualized according to local data. The findings of this review are potentially biased because of a narrow and outdated search restricted to the English language, use of a small data sample and lack of any attempt to explore the reasons for variation in endometrial thickness measurements (the reproducibility of this measurement has been demonstrated by others[116]) and accuracy

between centres. Indeed, 9 of the 11 included centres reported median endometrial thickness of ≤ 5 mm for unaffected women and all reported median endometrial thickness greater than this for endometrial cancer, in keeping with the findings of both Smith-Bindman et al[303] and the USS review included in this thesis. Applying the accuracy estimates from all three USS reviews, assuming a 5% pre-test probability of cancer and USS endometrial thickness cut-offs of 4 or 5mm, the posterior probability of cancer following a negative USS is between 0.4 and 0.8%. Thus, the inference that USS is a good test for exclusion of endometrial malignancy in PMB remains regardless of which pooled estimate of accuracy is applied. I was unable to identify any systematic reviews addressing the diagnostic accuracy of hysteroscopy.

4.3.2 Guidelines

The Scottish Intercollegiate Guidelines Network (SIGN) published a clinical guideline for the investigation of post-menopausal bleeding in September 2002.[293] No other such guideline was identified following searches of electronic bibliographic databases and relevant internet health sites. This guideline favoured the use of transvaginal ultrasound because of the *"…..greater quantity and higher quality of evidence supporting its use compared with other methods."* Although the guideline was developed using a standard methodology,[292] the acquisition of evidence was incomplete and important recommendations have been made without due regard to the supporting evidence, thereby undermining the strength of contained recommendations. For example, the findings from systematic reviews of pelvic ultrasound[160,303] were included in the SIGN guideline, but those of endometrial biopsy were not.[61,62,95] Furthermore, the review of hysteroscopy presented in this thesis[63] was not published until the month following publication of the SIGN guideline. These omitted reviews show there to be an even greater quantity of available primary research for other outpatient modalities compared with

transvaginal ultrasound that is of a similar quality. The SIGN guideline recommended using ultrasound as the first-line investigation in PMB, taking a 3mm cut-off (unless on sequential hormone replacement therapy where a 5mm cut-off was taken as the pre-test risk of cancer was assumed to be lower). Endometrial tissue sampling combined with hysteroscopy was recommended following a positive ultrasound result. This recommendation was based on a high pre-test risk of endometrial cancer (10%) and accuracy data obtained from the ultrasound review presented as part of this thesis.[160] However, only two studies assessed ultrasound diagnostic performance using a 3mm double-layer endometrial thickness cut-off (Table 3-8). The recommendations of the SIGN guideline may therefore be prone to bias toward the use of ultrasound.

4.4 Applicability of reviews

The prevalence of endometrial cancer in women with postmenopausal bleeding has been reported to be between 3 and 10% in Europe and North America.[16,146,149,251] Although there is controversy, likelihood ratios are generally considered to be less affected by disease prevalence than other measures of accuracy[282] and therefore the accuracy estimated derived from these reviews can be cautiously translated into other settings where disease prevalence may differ. For a postmenopausal woman with vaginal bleeding with a 5% pre-test probability of endometrial cancer, her probability of cancer is approximately 80% following a positive EB or OPH and approximately 0.5% following a negative USS using a 4mm cut-off (0.8% using a 5mm cut-off). This is illustrated graphically in Figures 4-1 to 4-3.

The pre-test probability can be individualised in the presence of factors obtained from earlier in the clinical process. These will include adverse historical features (e.g. unopposed endogenous or exogenous oestrogen exposure, severity and duration of bleeding, family history) and adverse examination findings (e.g. obesity, immobile uterus).[272] However, the absolute effect of such factors is unknown and thus difficult to quantify without further research (see section 4-10).

Figure 4-1 Pooled estimates of pretest probabilities, likelihood ratios and posttest probabilities for accuracy of outpatient endometrial biopsy in diagnosing endometrial cancer in women with postmenopausal bleeding (Nomogram reproduced with permission)[118]

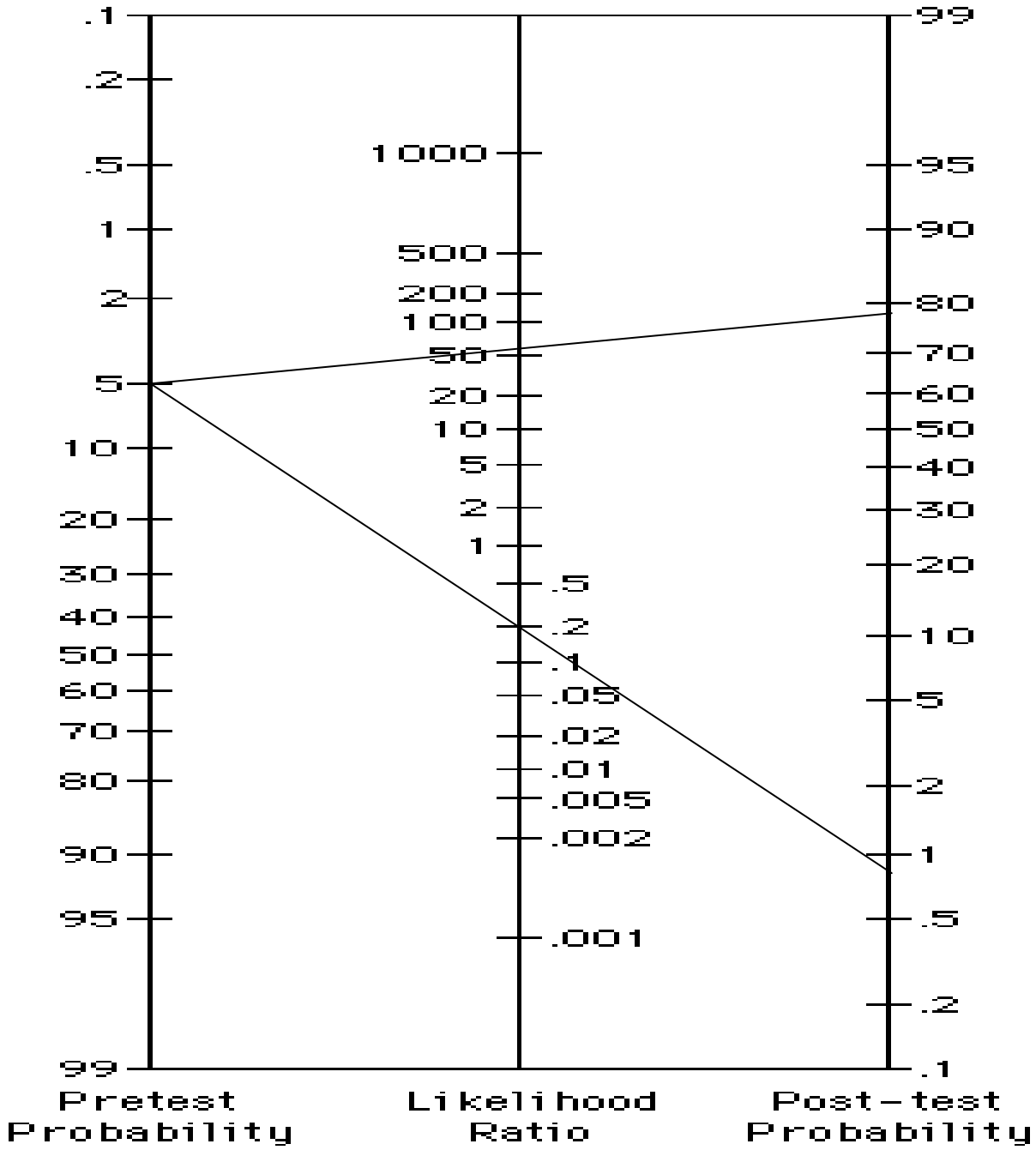


Figure 4-2 Pooled estimates of pretest probabilities, likelihood ratios and posttest probabilities for accuracy of endometrial thickness measurement by pelvic ultrasound, using both a 4mm and 5mm cut-offs, in diagnosing endometrial cancer in women with postmenopausal bleeding. (Nomogram reproduced with permission)[118]

4mm cut-off ———— 5mm cut-off ---------

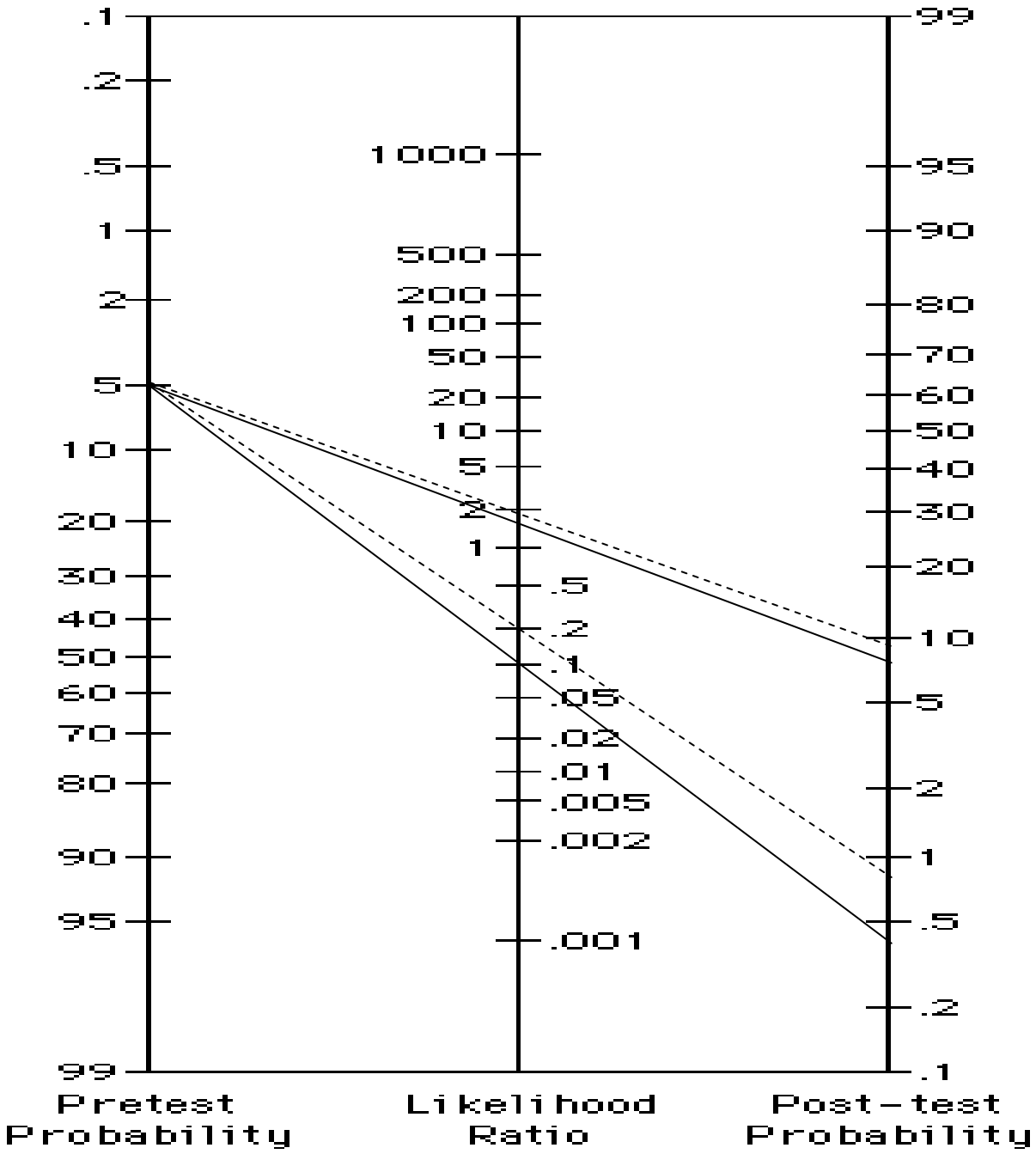
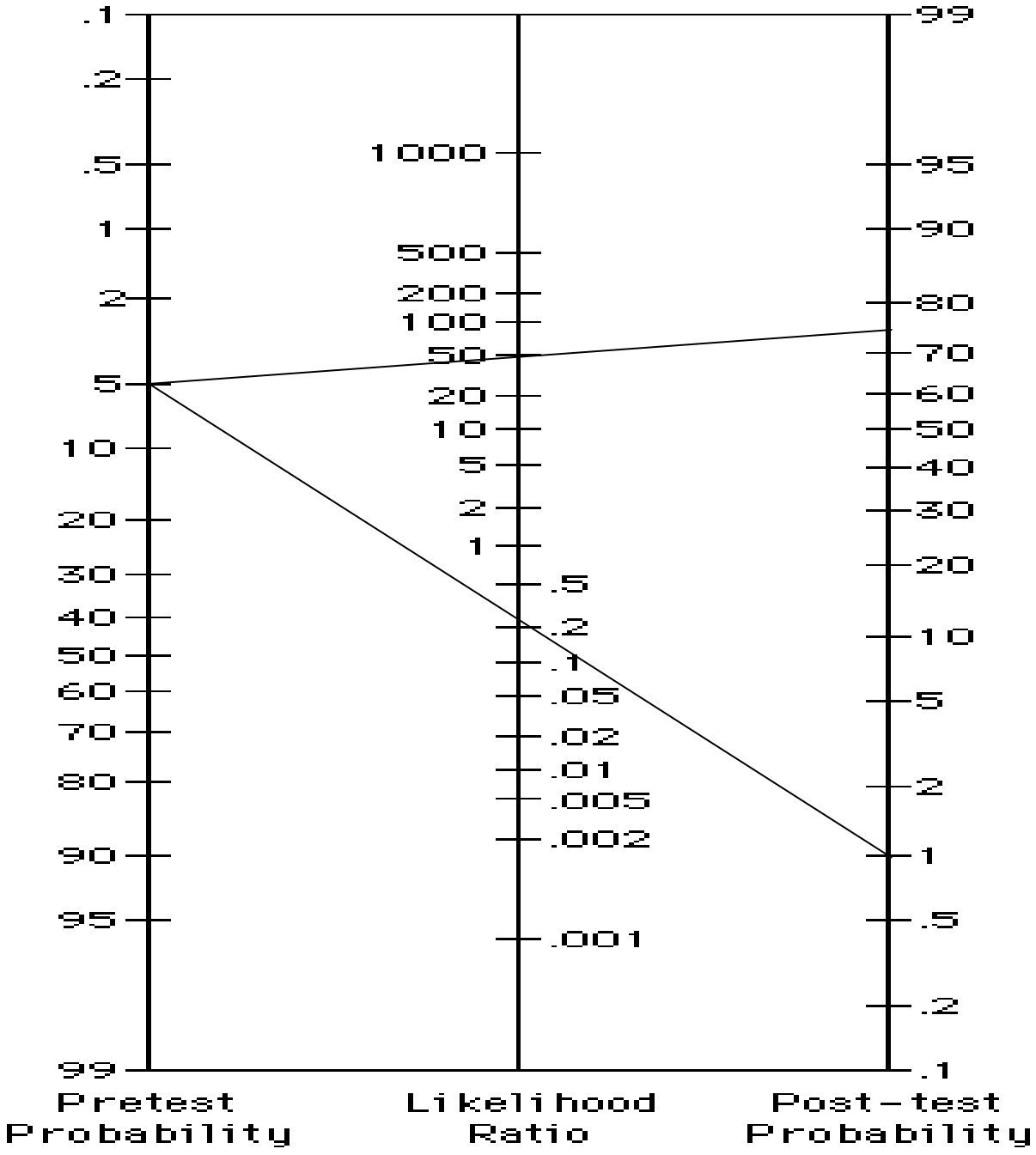


Figure 4-3 Pooled estimates of pretest probabilities, likelihood ratios and posttest probabilities for accuracy of hysteroscopy in diagnosing endometrial cancer in women with postmenopausal bleeding (Nomogram reproduced with permission)[118]



4.5 Economic evaluation

These quantitative reviews provide precise estimates of accuracy of EB, USS and OPH in the diagnosis of endometrial cancer facilitating comparison between diagnostic performance. In order to further define the roles of respective tests and resolve the debate regarding the best sequence and combination of tests,[44] a decision analysis was conducted based on this data.[114,198,294] The results of this economic approach show that survival is similar regardless of which initial diagnostic strategy is selected for the investigation of women with PMB for endometrial cancer. In contrast, costs varied between strategies, being more expensive when utilising combinations of tests from the outset. Postmenopausal bleeding is a common condition associated with high resource use,[1,89,310] and under such circumstances, small differences in costs and outcome can be expected to affect healthcare expenditure and disease burden substantially.

The balance between clinical benefit and economics (cost per life year gained) will influence recommendations for practice (see Figure 3-12).[40,65] Cost-effectiveness analysis is an aid to decision making. As cost-effectiveness is relative, judicious interpretation involves describing competing interventions as being more or less cost-effective than others.[300] No clear decision rule exists for cost-effectiveness analyses and therefore absolute statements about the cost-effectiveness of a particular intervention should be viewed with caution. [40] However, absolute 'threshold' values for determining cost-effectiveness that represent the willingness of society to pay for additional units of health benefit, are often used to make rationale decisions regarding the implementation of particular health care strategies.[41,65,73,203,249,274]

4.5.1 Base case analysis

One such approach is to consider that a strategy is not cost-effective if the ICER is above a threshold, generally taken to be £30,000 per life-year gained.[274] Application of this standard threshold suggests that all strategies are cost-effective compared to a policy of undertaking no initial investigation for first episode of PMB. Of the diagnostic modalities available, initial investigation with USS using a 5mm cut-off was the least expensive and no other strategy was found to be cost-effective compared to USS at this cut-off. However, the ICERs for USS 4mm (£37,652) and EB (£53,212) were close to the £30,000 ceiling. Compared to combination test strategies, initial investigation with USS 5mm alone remained the most cost-effective strategy for the diagnosis of endometrial cancer regardless of age at presentation. In women less than 65 years of age, however, initial investigation with USS at a lower 4mm cut-off or EB may be considered cost-effective, although the additional cost is still over £20,000 to gain one additional year of life for the very young (aged 45 years) postmenopausal woman.

4.5.2 Sensitivity analysis

Sensitivity analyses showed that initial investigation with USS 4mm or EB were potentially cost-effective strategies compared to USS 5mm, if they performed at their most favourable estimates of diagnostic performance (accuracy and success). Despite obtaining precise estimates of diagnostic performance from high quality secondary research,[61-63,160,303] the base case results were sensitive to small changes in these variables limiting the strength of any inferences regarding comparison of these three testing protocols. Variation in the prevalence of endometrial cancer also had an important influence of cost-effectiveness. At higher disease prevalence (10%), a strategy based on initial testing with EB was potentially more cost-effective than strategies based on USS (ICER for EB strategy reduced to £1633 and £23,730

compared with USS 4mm and 5mm respectively). In contrast, at cancer prevalences below 5% assumed in the base case analysis, USS strategies became more favourable on cost-effectiveness grounds. The choice between initial testing with EB or USS at a 4 or 5mm cut-off will therefore depend upon the nature of the clinician's practice (including the prevalence of endometrial cancer in the local population), the availability of high quality USS and patient preference[140]

In contrast, the base case findings for combination strategies were robust to changes in the underlying model assumptions apart from if the effect on life expectancy of a delayed diagnosis was considered to be much greater than assumed in the base case. This is an example of uncertainty arising from the evaluative process[39] i.e. the need to extrapolate from a clinical outcome (false negative diagnosis resulting in erroneous discharge) to a health outcome (reduced survival resulting from upstaging of endometrial cancer due to delayed diagnosis). However, it is doubtful that the additional proportion of women presenting with advanced extrauterine disease (i.e. greater than stage I localised disease), as a consequence of delayed diagnosis, would be significantly greater than 5%. This is because endometrial cancer presents with PMB in almost all cases and this alarming symptom will persist with an untreated endometrial tumour. Time to representation following erroneous discharge is therefore likely to be short, even when taking into account the impact of initial false reassurance, and so the effect of this delay on disease progression would be limited.

In addition to its cost-effectiveness in terms of survival, there is consistent qualitative evidence showing ultrasound to be less invasive, better tolerated and preferred by women when compared with EB and OPH.[26,140,320] Furthermore, the base case analysis assumed that an additional return visit was required following a positive USS in order to perform

endometrial sampling. However, USS is increasingly being performed by the consulting gynaecologist[280] (this is common in much of Europe[46,180]) rather than radiologists or radiographers, and in such circumstances return visits for histological testing would not be necessary. This favours the initial independent USS strategies further as a result of reduced costs and convenience. This was confirmed by sensitivity analysis, where the ICER for the EB strategy was in excess of £100,000. An initial strategy employing USS is therefore recommended for the investigation of women with postmenopausal bleeding. There is insufficient data however, to recommend whether a 4 or 5mm endometrial thickness cut-off is preferred. In practice, the choice between initial testing with EB or USS at a 4 or 5mm cut-off will depend upon the nature of the clinician's practice, the availability of high quality USS and patient preference[140]

4.6 Validity of economic evaluation

An analytic approach was used to quantify decisions made within the clinical process for the diagnostic work up of women with PMB. This involved developing a clear decision making framework based on contemporary clinical practice.[114] The design and reporting of the decision analysis is in keeping with current recommendations for a rigorous economic analysis.[87,98,99,111,253,300,301] The research question, study design and perspective of analysis[47,225] were clearly stated and the decision model described incorporating all alternate strategies.[99] Outcomes of interest were identified and all supporting assumptions and estimates of test performance and costs comprehensively stated. A basic set of base case test results (discounted and non-discounted)[49] including incremental cost-effectiveness ratios were

presented for all alternate non-dominated strategies[40,300] and key sensitivity analyses presented to assess the stability of data assumptions.[39,99]

Previous economic analyses evaluating the investigation of PMB have been of limited value because they have used imprecise and heterogeneous estimates of accuracy derived from particular primary studies published in the medical literature, in addition to evaluating outmoded tests.[119,167,257,337] The economic analysis presented in this thesis used data on feasibility, accuracy and safety obtained from high quality systematic reviews[62,63,160,303] and survival data from a recognised international source.[72] In the few areas where explicit data to populate the decision tree was unavailable from the literature, probabilities of relevant outcomes (conditional estimates of test failure and accuracy) were independently estimated followed by consensus where disagreements arose. In this way it was hoped to represent the mainstream view.

4.6.1 Limitations of economic analysis

My approach could be criticised firstly in respect of test accuracy assessment. This stems from the fact that most published accuracy data looks at tests in isolation, but does not take into account the whole clinical context, such as information available from the preceding clinical history and examination. Consequently the usefulness of diagnostic tests may be overestimated[16,57] increasing cost-effectiveness ratios to an unknown degree. Furthermore, without access to precise individual patient data, the accuracy of tests had to be estimated when used in combination as well as the changes in accuracy, which would be anticipated when conditional on a prior test result. Another potential limitation relates to the assumption that women with endometrial cancer who were erroneously discharged (false negatives) all

remained symptomatic and all represented within a short time frame where the error was always detected. Endometrial cancer presents with PMB in the vast majority of cases[250] and so the assumption of persistent symptoms appears to be reasonable. However, the effect of false reassurance on the likelihood and timing of representation is unknown. We tried to account for this delay by assuming that some of these women would represent with higher stage disease. This approach has been used before.[119] Sensitivity analysis around the proportion of women 'upstaged' in this way increased costs. The strategies involving initial evaluation with EB or any two tests combined became more favourable in terms of cost-effectiveness if the effect of a delayed diagnosis was assumed to have a greater impact on survival.

A third area for possible criticism surrounds the identification, measurement and valuation of costs.[111,273] Precise and comprehensive economic data is not readily available and so the best routine data that could be acquired from local and national sources was used.[247,252]
It was felt reasonable to disregard indirect costs (e.g. patient transportation, time off work) as the viewpoint of this analysis was that of the hospital provider of health care within the United Kingdom National Health Service (NHS).[231] Furthermore, all diagnostic strategies were based on outpatient investigation with comparably short 'recovery times' and treatment following diagnosis (and thereby costs) were common to all strategies. Although microcosting was used to some extent, gross costing was used in most instances in keeping with available data sources (e.g. hospital costs at the level of healthcare resource groups).[252] Where local costs were used, these often reflected charges as distinct from real costs.[273] Potential litigation costs were not included for those women erroneously discharged. However, legal proceedings are likely to continue increasing in the future within the United Kingdom NHS and so such

costs may need to be taken into account. However, inferences are unlikely to be altered in such circumstances because USS has the lowest rate of false negative diagnosis.

Uncertainty in parameters other than costs results from the fact that data are obtained from finite samples, and is therefore statistically uncertain. Data for the parameters diagnostic performance and treatment outcomes, were based upon precise confidence interval data derived from systematic reviews[62,63,160] and high quality international cancer registry data respectively (FIGO).[72] In contrast, unit costs for procedures at individual centres are likely to be known with reasonable certainty, but costs will vary between centres. Thus, it is appropriate to consider variation in cost parameters in a different way from uncertainty in other parameters. In effect, there is a new "base case" result for each centre, which is itself subject to sensitivity analysis on other parameters.

The main results here apply to centres whose patterns of costs are similar to those at the Birmingham Women's Hospital (BWH). If the patterns of costs at another centre are substantially different, the analysis must be re-run. For examples of this, we ran the analysis for one centre whose costs were always at the bottom of the range given in Appendix 10, and separately for a centre whose costs were consistently at the top of the range. In each case, using the base case values for other parameters, the results show that EB dominates USS4mm, although this is not the case for the costs based on BWH. Similarly, the strategy EB dominated USS 5mm assuming high costs, but was also very cost-effective at low costs (£962/LYG). The ICER for USS 4mm compared with USS 5mm decreased (£26,129) at low assumed costs and increased slightly assuming high costs (£42,365). It should also be appreciated that a best (minimum costs) or worst (maximum costs) case scenario is likely to

overestimate any uncertainty associated with the results of economic evaluation, because cost components are unlikely to be perfectly correlated. [39,41] In view of the aforementioned, sensitivity analyses around cost data were not presented. As the results of this economic evaluation are limited to the NHS perspective, their use outside this setting would only be appropriate if the findings are maintained after application of more relevant local cost data (see section 4.7). This is also true for NHS centres with markedly different patterns of costs to those used in the base case analysis.

4.7 Comparison with other economic evaluations and guidelines

No study was identified that evaluated the cost-effectiveness of all contemporary outpatient modalities (i.e. EB, USS and OPH) used in sequence or combination for the investigation of postmenopausal bleeding for endometrial cancer (see section 1.5). The only identified guideline for the investigation of PMB (SIGN guideline)[293] highlighted the need for a cost-effectiveness analysis of different sequences of investigation using available tests and the effect of using different ultrasound endometrial thickness cut-offs.

4.8 Applicability of economic evaluation

The applicability of findings from this evaluation are limited geographically given that the perspective of this analysis is that of the United Kingdom National Health Service (NHS).[97,253] However, one would expect that the twelve strategies defined within this decision

algorithm would encompass most clinical practices from Europe and North America.[3,59,70,99,251,296,326] The application of more relevant local cost data to this model will facilitate translation of findings to different healthcare settings.[99,145]

This analysis is confined to the initial investigation of women with PMB for endometrial cancer and did not look at women presenting with recurrent episodes of PMB. A recently published cohort study followed up women for 10 years or more that had been discharged after original presentation for PMB.[158] They found that a quarter of the original cohort of 252 women developed further PMB during this time. Of these symptomatic women, 11% had an underlying endometrial cancer, which is similar to the 5-10% prevalence generally quoted for endometrial cancer in first episode PMB.[16,146,149,251] Reassuringly, no woman with endometrial cancer had an endometrial thickness less than 5mm on transvaginal ultrasound and no asymptomatic women developed endometrial cancer during the period of follow up.[158] The interval of recurrent bleeding was wide (2 months to 10 years), stages at diagnosis of the seven endometrial cancers were not given and data were missing in 14% of the original cohort. Thus inferences must be cautious. However, as longer periods before representation are more likely to signify new rather than existing pathology, it appears reasonable to consider women who develop a recurrent episode of PMB at an interval of at least 6 months or more to be at similar risk of endometrial cancer as if they presented with a first episode. The findings of the analysis are thus likely to be generalisable to recurrent PMB in this set of circumstances.

The baseline estimates of accuracy cannot be reliably extrapolated to include those postmenopausal women with unscheduled bleeding on hormone replacement therapy (HRT).

However, such women bleeding on combined HRT regimens have a lower prior risk of endometrial cancer[16] thereby more in keeping with the lower range of cancer prevalence (3%) used as part of a sensitivity analysis. This would appear to favour the use of USS, as competing strategies become less cost-effective at lower disease prevalence compared to those based on USS. However, optimal cut-offs for endometrial thickness measurement in women taking HRT are less well defined (false-positive rates are higher)[303 140,160] and so alternative or additional testing with EB or OPH is likely to be necessary in the presence of this uncertainty. The accuracy of endometrial thickness measurement by USS is also less well defined in symptomatic women at risk of endometrial cancer due to tamoxifen therapy[29,108] and so additional testing is recommended[68] In most cases, however, PMB results from benign endometrial or intra-cavity pathology,[60,278,342] which does not require treatment unless symptoms persist.

This analysis did not consider those women with less common malignant causes of PMB, such as non-uterine pelvic masses (vulvar, vaginal, cervical and ovarian cancers). More commonly these conditions are diagnosed after presentation with other symptoms such as pain or urinary and bowel problems.[251] However, one should recommend a clinical gynaecologic examination in all women with PMB regardless of which diagnostic tests are used. The place of ultrasound is further strengthened as it is the only modality that has the advantage of allowing assessment of other pelvic organs[68] and in particular opportunistic ovarian screening.

4.9 Recommendations for practice

- Women presenting for the first time with PMB should undergo initial evaluation with pelvic ultrasound as this represents the most cost-effective strategy for excluding endometrial cancer. A threshold of 4mm or 5mm with double layer endometrial thickness may be used to define abnormal results on pelvic ultrasound. Different approaches to enable the generation of practice recommendations exist, based on the methodological strength of evidence and the clinical outcomes and associated costs.[73,203,228,274] Applying one such approach (the basis for recommendations about the use of interventions, treatments or services employed by the West Midlands Health Technology Assessment Collaboration) would rate the recommendation from this thesis as Evidence level II – Supported (£3000-£20,000 per life year). Details of this basis for recommendation are given in Appendix 28.

- Clinical guidelines should be developed and disseminated based on the results from this analysis.[208] This should facilitate more effective and efficient delivery of gynaecological cancer services in line with current recommendations.[251] I have prepared a West Midlands Health Technology Assessment Report for dissemination within the region (see Appendix 29).

4.10 Recommendations for future research

The remit of any research has to be specified at the outset if it is to be successfully realised. Time restraints and the availability of resources limit the extent of research undertaken. Consequently, potentially important areas of research may be left unexplored. For example, in the reviews included as part of this thesis, it was not feasible to contact authors to acquire individual patient data. This would have strengthened the reviews by providing clinical data relating to patient history and examination findings, as well as data pertaining to individual tests and those used in combination. This would have allowed a more rigorous exploration of variation in results and more precisely determine the pre-test probability of endometrial cancer for a particular individual, which may then impact on the usefulness of tests in specific circumstances. Similarly, the economic analysis would have benefited from acquiring quality of life data so that non-monetary units of valuation could have been generated (quality adjusted life years or QALY).[137,253,324] This would have then allowed a cost-per-QALY analysis to be performed taking into account quantitative and qualitative aspects of health. [225] Moreover this approach enables the comparison of diverse competing health care interventions (allocative efficiency).[262] A further improvement would have involved the acquisition of data about resource use associated with the treatment of endometrial cancer,[309] especially the follow up of women with advanced endometrial cancer, as this would have facilitated more precise estimation of costs.

4.10.1 Diagnostic accuracy

- Future research should be aimed at generating estimates of diagnostic test accuracy of test combinations from individual patient meta-analyses. Such analyses should take into account the whole clinical process so that the additional information provided by diagnostic testing is more accurately quantified in the clinical context.[16,57,183] The analysis should be updated in the future to take into account the use of new diagnostic tools, such as 3D ultrasonography.[178]

- The decision to treat or withhold treatment is determined by the estimated probability of disease (or not having disease) and the costs and benefits of subsequent clinical action.[236,264] In clinical practice these factors are implicitly integrated into the clinical decision making process. Synthesizing the available diagnostic evidence in a clinician-friendly manner[185] (generation of pre and post-test probabilities) enables therapeutic recommendations to be made by explicit consideration of the available evidence, obviating the need for intuition. However, even in the presence of robust evidence about disease probability and treatment costs and consequences, the threshold at which treatment decisions are made will vary between individual clinicians.[184] Research determining the relative values assigned to these outcomes by clinicians will allow relevant decision frameworks to be produced for application in specific settings.

4.10.2 Economic evaluation

- Future decision-models may be improved by incorporation of new diagnostic tools and collecting data about resource use in treatment follow up and palliative care. The effect of staging endometrial cancer clinically (e.g. using magnetic resonance imaging), as opposed to surgically, on therapeutic outcomes may need to be explored if this method of staging becomes more established.[127,239] If the ongoing Medical Research Council ASTEC trial shows benefit from routine pelvic node dissection, then the effects of this approach on costs and survival will need to be incorporated into the model.[239] The design of disease specific quality of life instruments[58] for women with PMB and endometrial cancer will allow the collection of meaningful utility data. This will improve the sensitivity of the model and the effects of a particular diagnostic and consequent therapeutic intervention will be more usefully and individually quantified in a cost-utility analysis.[208]

APPENDICES

Appendix 1 Search strategy for economic evidence

Medline (1966 – May 2002) and Embase (1982 – May 2002)

PMB (tw)
Endometrium [pathology]
Endometrial neoplasms [diagnosis,economics]
Uterine haemorrhage [diagnosis,economics]
1 or 2 or 3 or 4
Decision support techniques (tw)
Costs
Cost analysis (tw)
Cost-benefit analysis (tw)
Economics (tw)
Economic evaluation (tw)
Cost effectiveness
Outcome assessment (health care) [economics]
6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
5 and 14

Cochrane Library issue 3 (CCTR)

Postmenopausal bleeding or endometrial cancer or cost-effectiveness or decision analysis

NHS Economic Effectiveness Database, Centre for Reviews and Dissemination (NHS EED, June 2002) [**Available at http://www1.york.ac.uk/inst/crd/welcome.htm Accessibility verified 13 June 2002]**

Postmenopausal bleeding or endometrial cancer or cost-effectiveness or decision analysis

Appendix 2 Economic evaluations in the diagnosis of endometrial cancer in postmenopausal bleeding

Author (Year)	Study and Comparison	Economic analysis	Limitations
*Ong et al[257] (1997)	Retrospective non-randomised study with concurrent controls. *Population*: 498 women with suspected endometrial cancer. *Intervention*: EB vs. D&C. *Outcome*: rate of detection of endometrial cancer, benign abnormalities and complications	Cost-effectiveness analysis *Measure of benefit:* complications avoided and additional cases of endometrial cancer detected. *Finding:* EB was found to be the dominant strategy (cheaper and associated with less complications) therefore a synthesis of benefits and costs not provided	Selection bias (retrospective observational design). Failure rates of EB not accounted for (not intention to treat analysis). Short term (< 2 year), incomplete follow up – maybe undetected false negatives. No sensitivity analyses, discounted rates or cost data reported.
*Hidlebaugh[167] (1996)	Retrospective cohort study with concurrent controls. *Population*: 568 women with abnormal uterine bleeding *Intervention*: OPH+ EB vs. IPH + D&C *Outcome*: adequacy of tissue sampling, clinical outcomes and success rates and complications	Cost-effectiveness analysis *Measure of benefit:* additional successful cases and cases with adequate tissue sampling, complications avoided. *Finding:* OPH + EB found to be dominant strategy therefore a synthesis of benefits and costs not provided	Selection bias (retrospective observational design). No estimates of diagnostic accuracy. Unclear length of follow up – maybe undetected false negatives. Not intention to treat analysis casting doubt over estimates of benefit. No sensitivity analyses.
*Feldman et al[119] (1993)	Computer-based recursive decision tree model based on retrospective review of pathology reports *Population:* 287 women with PMB *Intervention:* Management pathways based on EB, D&C, TAH or observation at initial presentation *Outcome:* correct diagnosis of endometrial cancer or complex hyperplasia (with or without atypia).	Cost-effectiveness analysis. *Measure of benefit:* life expectancy of the various strategies and their cost-effectiveness as a function of patient age and combined risk of cancer or complex hyperplasia. Sensitivity analyses performed. *Finding:* initial evaluation with EB was found to be the most cost-effective strategy. Cost, but not effectiveness (life expectancy) did vary markedly as a function of the strategy chosen.	Diagnostic strategies did not include USS or OPH.
Weber et al[337] (1998)	Comparison of two diagnostic algorithms *Population:* Computer simulation *Intervention*: Algorithms based on EB vs. USS at initial presentation *Outcome*: probability of non-diagnostic test and abnormal result (endometrial cancer, hyperplasia and benign abnormalities).	Cost-analysis. *Measure of benefit:* Mean cost/completed diagnostic algorithm. No clinical benefits reported. Sensitivity analyses performed around these performance characteristics *Finding:* initial evaluation with USS was less costly than EB in the evaluation of women with PMB.	Relative performance characteristics of EB and USS vary widely in the literature, often based on poor quality studies, which influence estimates of benefit. No estimates of diagnostic accuracy, complications or effectiveness data incorporated in the algorithms.

*Less relevant study because a single outpatient strategy was compared with blind D&C, which is now outdated

Appendix 3 Search strategy for Endometrial biopsy evidence

Medline (1966 – December 1999)

Endometrial biopsy
Endometrial biop$.tw
1 or 2
Exp diagnosis
Diagnos$.tw
di.fs.
4 or 5 or 6
3 and 7
limit 8 to human

Embase (1982 – December 1999)

Endometrial biopsy
Endometrial biop$.tw
1 or 2
Exp diagnosis
Diagnos$.tw
di.fs.
4 or 5 or 6
3 and 7
limit 8 to human

Cochrane Library issue 3 (CCTR)

Endometrial biopsy

Hand searching

Reference lists of included primary studies and review articles

Appendix 4 Search strategy for ultrasound endometrial thickness evidence

Medline (1966 – December 2000)

Ultrasound
Sonography
1 or 2
Endometrial thickness
3 and 4
limit 5 to human

Embase (1982 – December 1999)

Ultrasound
Sonography
1 or 2
Endometrial thickness
3 and 4
limit 5 to human

Cochrane Library issue 3 (CCTR)

Ultrasound or sonography

Hand searching

Reference lists of included primary studies and review articles

Appendix 5 Search strategy for hysteroscopy evidence

Medline (1966 – December 2001)

Exp hysteroscopy/
Hysteroscop$.ti,ab.
Exp diagnosis
Diagnos$.ti,ab.
di.fs.
or/ 1-2
or/ 3-5
6 and 7
animal/ not human
8 not 9

Embase (1982 – December 2001)

Exp hysteroscopy/
Hysteroscop$.ti,ab.
Exp diagnosis
Diagnos$.ti,ab.
di.fs.
or/ 1-2
or/ 3-5
6 and 7
animal/ not human
8 not 9

Cochrane Library issue 4 (CCTR)

Hysteroscopy

Hand searching

Reference lists of included primary studies and review articles
Specialist journal *Gynaecological Endoscopy*

Appendix 6 Data collection checklist for review of outpatient endometrial biopsy

Reviewer ID:…… PaperNo:……

Selection or rejection: (must have all four as yes)

a) population- (at risk of abnormal endometrial histology)	Y/N
b) outpatient biopsy- test	Y/N
c) histology- gold standard (obtained by method other than OPBx)	Y/N
d) can you construct 2x2 table (Ca vs. nonCa) (test vs. gold standard)	Y/N

Select this diagnostic test study? Y/N

if this is Y – complete the form

if N must describe why not selected

……..……

<u>Data Collection</u> (if more than one population subgroups fill additional forms)

Total number of patients recruited (n) ……..

Risk factors reported for population (n) a) PMB (…….)
b) premenopausal (…….)
c) not described (…….)

Patient enrolment: consecutive/ arbitrary/ unreported/ other

Description of diagnostic test: a) pipelle
b) vabra
c) other (state)……..

Blinding of test results from outcome: yes/ no/ unreported

Verification by reference standard (complete/partial/differential)

Completeness of follow-up: ……. (>90/81-90/<81%)

Legitimate exclusions: ……..

Number of patients with data available: ……

Failure rate of O/P Bx = (…….)

Insufficient sample of O/P Bx = (…….)

Cancer in insufficient samples = (…….)

Hyperplasia in insufficient samples = (…….)

Complications= (…….)

Endometrial cancer

Test (=O/P BX)	Cancer present	Cancer absent	Total
POSITIVE			
NEGATIVE			
TOTAL			

Endometrial hyperplasia

Test (=O/P BX)	Hyperplasia present	Hyperplasia absent	Total
POSITIVE			
NEGATIVE			
TOTAL			

Appendix 7 Data collection checklist for review of pelvic ultrasound

Reviewer:	Paper No:
Type of study:	Diagnostic Yes/No
	If so Cohort/Case-control
Ultrasound measurement of ET	Yes/No
	If yes: Single layer/Double layer/Unreported
If both yes:	
Total number recruited:_____	No of recruited patients on HRT: _____/unreported
Inclusion criteria:	
Exclusion criteria:	
Patient enrollment:	Consecutive/Arbitrary/Unreported
Description of diagnostic test:	Trans-vaginal ultrasound Trans-abdominal ultrasound Transducer frequency_____ Hz Unreported
Cut-off point for normality:	≤ _____ mm is normal
Risk factors for endometrial carcinorma reported for study population:	Yes/No
	If yes: Obesity/Diabetes mellitus/Hypertension
Endometrial specimen obtained by:	D + C/Pipelle/Hysteroscopy/Hysterectomy
Blinding of test results from outcome:	Yes/No/Unreported
Verification of pathology results:	Yes/No/Unreported

Appendix 7 continued

Number of patients with data available: _____

Number of legitimate exclusions: _____

Follow-up rate: > 90%/ 81-90%/ <80%

CUT-OFF VALUE_____ MM

Endometrial cancer

TEST RESULT	**ENDOMETRIAL CA PRESENT**	**ENDOMETRIAL CA ABSENT**	**TOTAL**
POSITIVE			
NEGATIVE			
TOTAL			

Endometrial disease (i.e. endometrial cancer + all types of endometrial hyperplasia but excluding endometrial polyp and pyometra)

TEST RESULT	**ENDOMETRIAL DIS PRESENT**	**ENDOMETRIAL DIS ABSENT**	**TOTAL**
POSITIVE			
NEGATIVE			
TOTAL			

Appendix 8 Data collection checklist for review of hysteroscopy

Reviewer …… **Paper No. ……**

Selection criteria (diagnostic test

i) population - abnormal uterine bleeding yes / no
ii) intervention – hysteroscopy yes / no
iii) reference standard – histology yes / no
iv) 2x2 table construction possible yes / no

Select this diagnostic test study (i-iv inclusive) yes / no ***if no reject & specify reason***

……

……

Data Retrieval:

Population:

Study Design Cohort / Cross-sectional / Case control / Other……

Data Collection Prospective / Retrospective / Unreported / Other…….

Patient Enrolment Consecutive / Arbitrary / Unreported / Other……..

Study Design Hierarchy 1 2 3 4 5 6

No. patients recruited

A original population n=……

B Pre-enrolment exclusions n=……
(reasons eg population characteristics)……

C actually recruited (**A-B**) n=……

D post-enrolment exclusions n=……
(reasons eg missing data etc)…..……

E analysable data **(C-D)** n=……

Completeness of Follow up (%) >90 / 81-90 / <81 (FU% = **E/C** x 100% **=…… %)**

Menopausal status (no. & %) PMB n=…… HRT n=……
Pre-men n=…… Unreported =……

Appendix 8 continued

Intervention:

Description of technique Adequate / Inadequate

Setting outpatient yes/no (dilatation n=…..anal/anaesn=…../…..)
inpatient yes/no

type rigid…… flexible…… Other……

manufacturer ……..

diameter ……..

angle ……..

Medium (specify) gas……. fluid…… Unreported…….

Video monitor yes / no / unreported

Menstrual phase not timed / proliferative / secretory / preparation - (specify…)

Complications (specify) major n=….. …… minor n=……

Levels of test abnormality([) Cancer …….
Hyperplasia …… (specify if Atypia…Complex…Simple…)
Other ……

test positive cases n=……
test negative cases n=……

Reference standard:

Method inpatient (specify hyst…. Dir Bx…. D&C…. OP device….)
outpatient (specify OP Device…Directed Bx… Other….)

Partial verification yes / no (if yes specify & give %……)

Differential verification yes / no
verification in test positive cases n =… % (>90 / 81-90 / <81)
verification in test negative cases n= …% (>90 / 81-90 / <81)

Blinding of test result yes / no / unreported

Levels of Reference abnormality([) Cancer …
Hyperplasia … (specify Atypia…Complex…Simple…)
Other …

Appendix 8 continued

Outcome:

Failure Rate	n / **E** =…..	
Specify reason for failure	Technical n=….. Patient factor n=…..	Inadequate view n=…..
Failed hysteroscopies	Cancer n=……	Hyperplasia n=……
Insufficient histology	n=……	

Appendix 8 continued

2x2 Contingency tables (INcluding insufficient histology):

Endometrial Cancer

Reference Histology→ Hysteroscopy↓	Cancer present	Cancer absent	Total
Positive			
Negative			
Total			

Endometrial Hyperplasia

ReferenceHistology→ Hysteroscopy↓	Hyperplasia present	Hyperplasia absent	Total
Positive			
Negative			
Total			

Endometrial Cancer + Hyperplasia

ReferenceHistology→ Hysteroscopy↓	Ca +H present	Ca + H absent	Total
Positive			
Negative			
Total			

NB. If level of abnormality is different (ie more or less specific) from the above, then complete this table and specify the level

ReferenceHistology→ Hysteroscopy↓	Positive […….]	Negative […….]	Total
Positive […….]			
Negative […….]			
Total			

Appendix 8 continued

2x2 Contingency tables (EXcluding insufficient histology):

Endometrial Cancer

Reference Histology→ Hysteroscopy↓	Cancer present	Cancer absent	Total
Positive			
Negative			
Total			

Endometrial Hyperplasia

ReferenceHistology→ Hysteroscopy↓	Hyperplasia present	Hyperplasia absent	Total
Positive			
Negative			
Total			

Endometrial Cancer + Hyperplasia

ReferenceHistology→ Hysteroscopy↓	Ca +H present	Ca + H absent	Total
Positive			
Negative			
Total			

NB. If level of abnormality is different (ie more or less specific) from the above, then complete this table and specify the level

ReferenceHistology→ Hysteroscopy↓	Positive [……]	Negative [……..]	Total
Positive [……]			
Negative [……..]			
Total			

Appendix 9 Probability estimates used and data sources for the decision tree used for the investigation of postmenopausal bleeding

Variable	Baseline	Sensitivity analysis (range)	Source
Failure rates			
Endometrial biopsy	0.12	(95% CI 0.09-0.15)	SR[62]
Ultrasound scan	0.0	(95% CI 0.0-0.02)	SR[303]
Outpatient hysteroscopy	0.05	(95% CI 0.04-0.07)	SR[63]
Ultrasound scan + outpatient hysteroscopy	0.04	(95% CI 0.03-0.06)	EP
Ultrasound scan + endometrial biopsy	0.12	(95% CI 0.09-0.17)	EP
Ultrasound scan + endometrial biopsy + outpatient hysteroscopy	0.12	(95% CI 0.09-0.17)	EP
Endometrial biopsy after successful outpatient hysteroscopy	0.07	(95% CI 0.05-0.10)	EP
Endometrial biopsy after successful ultrasound scan	0.12	(95% CI 0.09-0.15)	EP
Complication Rates			
Outpatient diagnostic procedures (EB, USS, OPH)	-	-	SRs[61,63,160,303]
Dilatation and curettage	0.014	-	NR[152]
True Positive Rates			
Endometrial biopsy	0.94	(95% CI 0.84-0.99)	SR[62]
Ultrasound scan 4mm	0.99	(95% CI 0.97-1.0)	SR[160]
Ultrasound scan 5mm	0.97	(95% CI 0.94-0.98)	SR[160]
Outpatient hysteroscopy	0.86	(95% CI 0.84-0.89)	SR[63]
Dilatation and curettage	0.96	(95% CI 0.82-1.0)	EP
Conditional True Positive Rates			
Endometrial biopsy if outpatient hysteroscopy positive	0.94	(95% CI 0.93-0.97)	EP
Endometrial biopsy if ultrasound positive	0.94	(95% CI 0.94-0.95)	EP
Outpatient hysteroscopy if endometrial biopsy negative	0.86	(95% CI 0.83-0.87)	EP
Outpatient hysteroscopy if ultrasound positive	0.86	(95% CI 0.86-0.87)	EP
Ultrasound scan 4mm if endometrial biopsy negative	0.99	(95% CI 0.82-0.99)	EP
Ultrasound scan 4mm if outpatient hysteroscopy negative	0.99	(95% CI 0.92-0.99)	EP
Ultrasound scan 5mm if endometrial biopsy negative	0.97	(95% CI 0.80-0.99)	EP
Ultrasound scan 5mm if outpatient hysteroscopy negative	0.97	(95% CI 0.91-0.99)	EP
False Positive Rates			
Endometrial biopsy	0.01	(95% CI 0.0-0.02)	SR[62]
Ultrasound scan 4mm	0.51	(95% CI 0.49-0.54)	SR[160]
Ultrasound scan 5mm	0.45	(95% CI 0.43-0.47)	SR[160]
Outpatient hysteroscopy	0.01	(95% CI 0.0-0.06)	SR[63]
Dilatation and curettage	0.01	(95% CI 0.0-0.03)	EP
Prevalence	0.05	(95% CI 0.03-0.10)	PL[16,251]
Surgical stage at hysterectomy (FIGO)			
Probability of stage I (First presentation)	0.7	0.6-0.8	FIGO[72]
Probability of stage II-IV (First presentation)	0.3	0.2-0.4	FIGO[72]
Probability of stage I (Representation)	0.65	0.4-0.7	EP
Probability of stage II-IV (Representation)	0.35	0.3-0.6	EP

EB = endometrial biopsy, EP = expert panel, FIGO = International Federation of Gynecology and Obstetrics, NR = narrative review, OPH = outpatient hysteroscopy, PL = published literature, SR = systematic review, USS = ultrasound scan

Appendix 10 Direct medical costs used and data sources for decision tree for the investigation of postmenopausal bleeding (base case and sensitivity analyses)

Variable	Baseline (£)[$]	Source	Range (£)*	Source
Diagnosis				
Pelvic ultrasound scan	115	BWH	93-219	DoH
Outpatient hysteroscopy	225	BWH	143-247	DoH
Endometrial biopsy	186	BWH	126-195	DoH
Pelvic ultrasound scan + outpatient hysteroscopy	279	BWH	191-395	DoH†
Pelvic ultrasound scan + endometrial biopsy	240	BWH	174-343	DoH†
Outpatient hysteroscopy + endometrial biopsy	350	BWH	224-371	DoH†
Pelvic ultrasound scan + outpatient hysteroscopy + endometrial biopsy	404	BWH	272-519	DoH†
Day-case hysteroscopy/D&C	360[#]	BWH	317-493	DoH
GOPD FU	61	DoH	45-71	DoH
Failed endometrial biopsy**	111	BWH	75-116	DoH
Treatment				
Complex hysterectomy	2123	BWH	926-2773	DoH
External beam radiotherapy	845	DoH	504-1756	DoH
Chemotherapy	258	DoH	167-327	DoH
Complications‡				
Co-amoxiclav 375mg tds (7 day course)	3.30	BNF	-	-
Inpatient stay (1 day)	620	BWH		
Unplanned laparotomy	2123	BWH	1121-2008	DoH

*used for sensitivity analyses, ranges represent interquartile spread from National Schedule of Reference Costs (November 2000), Department of Health. Includes cost of outpatient appointment (first visit)
†adapted from national schedule of reference costs[252] (November 2000), Department of Health, Interquartile ranges summed.
‡ Incidence of major complications associated with Dilatation and curettage (D&C) applied to these costs and cost of inpatient hysteroscopy/D&C altered accordingly. See text)
# includes £10 additional cost to account for complications incidence and cost i.e.
cost of complication (infection, haemorrhage and perforation) x incidence = 623.3x1.3% + cost of unplanned laparotomy + incidence = 2123x0.1% = £8 therefore rounded up to £10 additional cost (£350 increased to £360)
$ Where two diagnostic modalities used, the cost = sum of individual costs - £61 (cost of outpatient appointment), where three diagnostic modalities used, the cost = sum of individual costs - £61x2 (cost of outpatient appointments)
** Minus histopathological examination of endometrial specimen costs
BWH = Birmingham Women's Hospital standard charges for uncomplicated procedures 2000
DoH = Department of Health, National Schedule of Reference Costs (November 2000)[252]
BNF = British National Formulary

Appendix 11 Reference list of excluded studies from systematic reviews of e endometrial biopsy

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Appendix 12 Diagnostic accuracy of outpatient endometrial biopsy in detecting endometrial cancer and hyperplasia in women at risk of abnormal endometrial histology

Study (Year Published)	Population						Intervention	Outcome		
				Menopausal Status (%)						
	Data Collection	Patient Selection	Quality Level	Post	Pre	Unclear	Description of Technique	Reference Standard	‡Level of test result reported	Blinding of Results
Accurette®										
Goldberg[138] (1981)	Prospective	Arbitrary	4	30 (100)	-	-	Adequate	†D&C	H	Unreported
Gynoscann®										
Sun-Kuie[317] (1992)	Prospective	Arbitrary	4	*5 (11)	41 (89)	-	Adequate	†D&C	C, H, N	Unreported
Novak Curette®										
Stovall[314] (1989)	Retrospective	Arbitrary	4	-	-	165(100)	Adequate	Hyst	C. H	Unreported
Pipelle®										
Baruch[24] (1994)	Retrospective	Arbitrary	4	*23 (52)	9 (20)	112 (28)	Adequate	†D&C/Hyst	C	Unreported
Krampl[192] (1997)	Retrospective	Unreported	4	37 (12)	247(77)	35 (11)	Adequate	†TCRE/Hyst	H, N	Unreported
Salet-Lizee[284] (1993)	Prospective	Arbitrary	4	*41 (42)	57 (58)	-	Inadequate	†D&C	C, H, N	Unreported
De Silva[78] (1997)	Prospective	Consecutive	1	35 (100)	-	-	Adequate	†D&C	C	Yes
Van den Bosch[332] (1995)	Prospective	Consecutive	3	138 (100)	-	-	Adequate	Biopsy/Hyst	C	Unreported
Gupta[161] (1996)	Prospective	Arbitrary		54 (100)	-	-	Inadequate	†D&C	C, H, N, A	Unreported
Batool[22] (1994)	Prospective		1	13 (100)	-	-	Adequate	†D&C	C	Yes
Giannacopoulos[133](1996)	Prospective	Arbitrary		-	-	57 (100)	Inadequate	†D&C/Hyst	C	Unreported
Vabra Aspiration®										
Goldberg[138] (1981)	Prospective	Arbitrary	4	31 (100)	-	-	Adequate	†D&C	C, H	Unreported
Stovall[314] (1989)	Retrospective	Arbitrary	4	-	-	62 (100)	Adequate	Hyst	C, H	Unreported
Z-sampler®										
Etherington[117] (1995)	Prospective	Consecutive	3	34 (100)	-	-	Adequate	†D&C	C	Unreported

*Numbers of patients within respective menopausal status groups following exclusions for inadequate endometrial samples calculated from initial proportion of patients within these groups before such exclusions

†D&C = dilatation of cervix and curettage of uterine cavity under anaesthesia, Hyst = hysterectomy, TCRE = transcervical resection of the endometrium

‡ Level of test reported: H= hyperplasia, N= non-atypical hyperplasia, A= atypical hyperplasia

Appendix 13 Procedure feasibility and diagnostic accuracy of outpatient endometrial biopsy in endometrial cancer and hyperplasia.

Device (No. Evaluations) & Study (Year Published)	*Failure rate (95% CI)	Inadequate rate (95% CI)	Disease in failed biopsy 95% CI Ca	Hyp	Cancer Cases: +ve test Sensitivity	-ve test 1-Specificity	Likelihood ratio for a positive test (95% CI)	Likelihood ratio for a negative test (95% CI)	Disease Cases: +ve test Sensitivity	-ve test 1-Specificity	Likelihood ratio for a positive test (95% CI)	Likelihood ratio for a negative test (95% CI)
Accurette®												
Goldberg[138] (1981)	5/40 (13%)	5/35 (14%)	0	1	3/3 (1.0)	0/27 (0.0)	49.0 (3.1-783.4)	0.1 (0.01-1.7)	5/5 (1.0)	0/25 (0.0)	47.6 (3.0-749.9)	0.1 (0.01-1.2)
Gynoscann®												
Sun-Kuie[317] (1992)	8/70 (11%)	16/62 (26%)	0	0	2/2 (1.0)	0/44 (0.0)	75.0 (4.6-1236.4)	0.2 (0.01-2.1)	2/4 (0.5)	0/42 (0.0)	43.0 (2.4-775.1)	0.5 (0.2-1.3)
Novak Curette®												
Stovall[314] (1989)	0/176 (0%)	11/176 (6%)	0	0	4/6 (0.67)	0/159 (0.0)	205.7 (12.2-3458)	0.3 (0.1-1.0)	8/16 (0.5)	4/149 (0.03)	18.6 (6.3-55.1)	0.5 (0.3-0.8)
Pipelle®												
Baruch[24] (1994)	0/45 (0%)	1/45 (2%)	0	-	10/10 (1.0)	0/34 (0.0)	66.8 (4.3-1050.5)	0.1 (0.00-0.7)	-	-	-	-
Krampl[192] (1997)	0/324 (0%)	5/324 (2%)	-	0	-	-	-	-	14/35 (0.4)	24/284 (0.0)	4.7 (2.7-8.3)	0.7 (0.5-0.9)
Salet-Lizee[284] (1993)	0/98 (0%)	0/98 (0%)	0	0	4/4 (1.0)	1/94 (0.01)	94.0 (13.4-660.4)	0.1 (0.01-1.41)	34/43 (0.8)	2/55 (0.02)	21.7 (5.5-85.5)	0.2 (0.1-0.4)
De Silva[78] (1997)	9/50 (18%)	6/41 (15%)	1	-	1/1 (1.0)	1/34 (0.03)	34.0 (1.7-666.1)	0.5 (0.1-0.9)	-	-	-	-
Van den Bosch[332] (1995)	2/140 (1%)	0/138 (0%)	0	-	6/7 (0.86)	0/131 (0.0)	214.5 (13.2-3480)	0.1 (0.02-0.9)	-	-	-	-
Gupta[161] (1996)	15/69 (22%)	0/54 (0%)	0	0	2/2 (1.0)	1/52 (0.0)	52.0 (7.5-362.2)	0.2 (0.01-2.15)	6/10 (0.6)	1/44 (0.02)	26.4 (3.6-195.6)	0.4 (0.2-0.9)
Batool[22] (1994)	15/70 (21%)	42/55 (76%)	0	-	3/3 (1.0)	0/10 (0.0)	19.3 (1.3-296.2)	0.1 (0.01-1.8)	-	-	-	-
Giannacopoulos[133] (1996)	2/74 (3%)	15/72 (21%)	0	-	5/5 (1.0)	0/52 (0.0)	97.2 (6.1-1549.5)	0.1 (0.01-1.2)	-	-	-	-
Total	43/546 (8%)	64/503 (13%)	1	0	-	-	64.6 (22.3-187.1)	0.1 (0.04-0.28)	54/88 (0.6)	27/383 (0.07)	9.9 (5.5-17.6)	0.5 (0.4-0.6)

Appendix 13 continued

Device (No. Evaluations) & Study (Year Published)	*Failure rate (95% CI)	Inadequate rate (95% CI)	Disease in failed biopsy 95% CI Ca	Hyp	Cancer Cases: +ve test Sensitivity	-ve test 1-Specificity	Likelihood ratio for a positive test (95% CI)	Likelihood ratio for a negative test (95% CI)	Disease Cases: +ve test Sensitivity	-ve test 1-Specificity	Likelihood ratio for a positive test (95% CI)	Likelihood ratio for a negative test (95% CI)
Vabra Aspiration®												
Goldberg[138] (1981)	0/64 (0%)	2/64 (3%)	0	0	1/1 (1.0)	0/61 (0.0)	93.0 (5.3-1647.3)	0.3 (0.02-2.8)	6/6 (1.0)	0/25 (0.0)	48.3 (3.1-757.4)	0.1 (0.01-1.1)
Stovall[314] (1989)	5/40 (13%)	4/35 (11%)	0	0	3/3 (1.0)	0/28 (0.0)	50.8 (3.2-812.1)	0.1 (0.01-1.7)	7/7 (1.0)	7/55 (0.13)	18.6 (6.3-55.1)	0.1 (0.0-1.1)
Total	5/104 (5%)	6/99 (6%)	0	0	-	-	59.4 (6.8.-518.6)	0.2 (0.03-1.0)	13/13 (1.0)	7/80 (0.09)	12.6 (5.6-28.1)	0.1 (0.01-0.5)
Z-sampler®												
Etherington[117] (1995)	7/77 (9%)	36/70 (51%)	0	-	4/4 (1.0)	0/30 (0.0)	55.8 (3.5-886.0)	0.1 (0.01-1.4)	-	-	-	-
Endometrial cancer (13)	**68/1013 6.7% (5.2-8.4%)**	**138/945 14.6% (12.4-17%)**	**1/138 0.7% (0.02-4.0%)**	**-**	**48/51 (0.94)**	**3/756 (0.004)**	**66.5 (30.0-147.1)**	**0.14 (0.1-0.3)**	**-**	**-**	**-**	**-**
Endometrial hyperplasia (8)	**33/881 3.7% (2.6-5.2%)**	**43/848 5.1% (3.7-6.8%)**	**-**	**1/43 2.3% (0.06-12.3 %)**	**-**	**-**	**-**	**-**	**82/126 (0.65)**	**38/679 (0.06)**	**12.0 (7.8-18.6)**	**0.4 (0.3-0.5)**

Ca = endometrial cancer, hyp = endometrial hyperplasia

Appendix 14 Studies included in systematic review of ultrasound measurement of endometrial thickness for predicting endometrial cancer and hyperplasia

Study	Population			Diagnostic Test		Outcome			Quality Level*
	Patient selection	Length of amenorrhoea	Number of HRT users	Method of scanning	Transducer frequency	Blinding of results	Outcome measures	Verification	
Measurement of both layers endometrial thickness									
3 mm									
Auslender et al[14] 1993	Consecutive	12 months	None	TVS	6.5 MHz	Unreported	Eca, Ehyp	> 90%	4
Zannoni et al[348] 1994	Unreported	6 months	None	TVS	5-6.5 MHz	Unreported	Eca	> 90%	4
4 mm									
Bakour et al[18] 1999[a]	Unreported	6 months	46/96	TVS	6.5 MHz	Unreported	Eca, Ehyp	> 90%	4
Botsis et al[36] 1992[p]	Unreported	Unreported	None	TVS	Unreported	Unreported	Eca, Ehyp	> 90%	4
Fistonic et al[122] 1997[a]	Unreported	12 months	None	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Garuti et al[130] 1999[a]	Unreported	12 months	51/419	TVS	7.5 MHz	Unreported	Eca, Ehyp	> 90%	4
Granberg et al[147] 1997[p]	Unreported	Unreported	351/1168	TVS	5-7.5 MHz	Unreported	Eca, Ehyp	> 90%	4
Guner et al[159] 1996[p]	Unreported	Unreported	Unreported	TVS	5-7.5 MHz	Unreported	Eca, Ehyp	> 90%	4
Haller et al[164] 1996[a]	Unreported	Unreported	None	TVS	5.5 MHz	Unreported	Eca, Ehyp	> 90%	4
Tsuda et al[328] 1997[p]	Unreported	12 months	None	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Varner et al[334] 1991[p]	Unreported	6 months	9/15	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
5 mm									
Abu-Ghazzeh et al[4] 1999[a]	Unreported	6 months	Unreported	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Briley et al[42] 1998[a]	Unreported	Unreported	Unreported	TVS	5, 7.5 MHz	Unreported	Eca, Ehyp	< 80%	4
Cacciatore et al[48] 1994[p]	Unreported	Unreported	Unreported	TVS	5-6.5 MHz	Unreported	Eca	> 90%	4
DeSilva et al[78] 1997[p]	Consecutive	Unreported	6/50	TVS	7.5 MHz	Unreported	Eca, Ehyp	> 90%	3
Granberg et al[146] 1991[p]	Unreported	Unreported	30/205	TVS	7 MHz	Unreported	Eca, Ehyp	> 90%	4
Grigoriou et al[151] 1996[p]	Unreported	Unreported	None	TVS	5 MHz	Yes	Eca, Ehyp	> 90%	2
Gu et al[155] 1994[p]	Unreported	12 months	None	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Gupta et al[161]1996[p]	Unreported	12 months	None	TVS	6.5 MHz	Yes	Eca, Ehyp	> 90%	2
Hänggi et al[165] 1995[a]	Consecutive	Unreported	Unreported	TVS	6.5 MHz	No	Eca, Ehyp	< 80%	5
Ivanov et al[172] 1998[p]	Unreported	6 months	None	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4

Appendix 14 continued

Study	Population			Diagnostic Test		Outcome			Quality Level*
	Patient selection	Length of amenorrhoea	Number of HRT users	Method of scanning	Transducer frequency	Blinding of results	Outcome measures	Verification	
Karlsson et al[179] 1993[a]	Unreported	Unreported	Unreported	TVS	7 MHz	Unreported	Eca, Ehyp	> 90%	4
Loverro et al[216] 1999[p]	Unreported	Unreported	None	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Malinova et al[224] 1996[a]	Unreported	24 months	None	TVS	7.5 MHz	Unreported	Eca, Ehyp	> 90%	4
Merz et al[234] 1990[p]	Unreported	Unreported	> 8	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Nasri et al[243] 1989[p]	Unreported	12 months	None	ABS	3.5 MHz	Yes	Eca, Ehyp	> 90%	2
Nasri et al[244] 1991[p]	Unreported	6 months	3/103	TVS	5 MHz	Unreported	Eca, Ehyp	81-90%	5
Pertl et al[269] 1996[p]	Unreported	Unreported	35/169	TVS	5 MHz	Unreported	Eca, Ehyp	81-90%	5
Suchocki et al[316] 1998[p]	Unreported	Unreported	None	TVS+ABS	5, 6, 7.5 MHz	Unreported	Eca, Ehyp	> 90%	4
Taviani et al[321] 1995[p]	Unreported	12 months	Unreported	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Weber et al[338] 1998[a]	Unreported	12 months	None	TVS	5, 7.5 MHz	Unreported	Eca	> 90%	4
Wolman et al[345] 1996[a]	Unreported	12 months	None	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
6 mm									
Moreles et al[237] 1998	Unreported	12 months	Unreported	TVS	5, 6, 7.5 MHz	Unreported	Eca, Ehyp	< 80%	5
Rudigoz et al[281] 1993	Unreported	Unreported	None	TVS	5-7.5 MHz	Unreported	Eca, Ehyp	> 90%	4
8 mm									
Todorova et al[323] 1998	Unreported	Unreported	Unreported	TVS	7.5 MHz	No	Eca	> 90%	4
15 mm									
Gruboeck et al[154] 1996	Unreported	6 months	None	TVS	7.5 MHz	Unreported	Eca	> 90%	4
Single Layer endometrial thickness measurement									
2 mm									
Chan et al[54] 1994	Unreported	12 months	None	TVS	5 MHz	Unreported	Eca, Ehyp	81-90%	5
Degenhardt et al[85] 1991	Unreported	Unreported	2/137	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Dijkhuizen et al[94] 1996	Consecutive	12 months	None	TVS	5 MHz	Yes	Eca, Ehyp	> 90%	2
3 mm									
Brolmann et al[43] 1993	Arbitrary	Unreported	11/65	TVS	5 MHz	Yes	Eca, Ehyp	> 90%	4

Appendix 14 continued

Study	Population			Diagnostic Test		Outcome			Quality Level*
	Patient selection	Length of amenorrhoea	Number of HRT users	Method of scanning	Transducer frequency	Blinding of results	Outcome measures	Verification	
Ceccini et al[53] 1996	Unreported	12 months	Unreported	TVS+ABS	6, 3.5 MHz	Unreported	Eca	> 90%	4
Masearetti et al[227] 1993	Unreported	24 months	Unreported	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Mortakis et al[238] 1997	Unreported	12 months	None	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Schramm et al[290] 1995	Unreported	Unreported	None	TVS	5-7.5 MHz	Yes	Eca, Ehyp	> 90%	4
Smith et al[304] 1991	Arbitrary	Unreported	Unreported	TVS	5 MHz	Yes	Eca, Ehyp	> 90%	2
4 mm									
Osmers et al[258] 1992	Unreported	24 months	None	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Seelbach-Göbel et al[295] 1995	Unreported	6 months	Unreported	TVS	5-7.5 MHz	Unreported	Eca, Ehyp	> 90%	4
10 mm									
Altuncu et al[9] 1992	Unreported	Unreported	13/68	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Unreported number of layers for endometrial thickness measurement									
4 mm									
Archer et al[13] 1999	Unreported	Unreported	38/38	TVS	5-7.5 MHz	Unreported	Ehyp	> 90%	4
Dorum et al[96] 1993	Consecutive	12 months	Unreported	TVS	7 MHz	Unreported	Eca	> 90%	4
Gerber et al[132] 1999	Unreported	Unreported	None	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
Li et al[205] 1997	Unreported	12 months	None	TVS	3.5 MHz	Unreported	Eca, Ehyp	> 90%	4
Salmaggi et al[285] 1997	Unreported	Unreported	Unreported	TVS + ABS	3.5, 5 MHz	Unreported	Eca, Ehyp	> 90%	4
5 mm									
Goldstein et al[142] 1990	Unreported	Unreported	18/30	TVS	5, 7.5 MHz	Unreported	Eca, Ehyp	> 90%	4
Malinova et al[223] 1995	Unreported	24 months	None	TVS	7.5MHz	Unreported	Eca, Ehyp	> 90%	4
6 mm									
Mateos et al[229] 1997	Unreported	6 months	None	TVS	5 MHz	Unreported	Eca, Ehyp	> 90%	4
7 mm									
Guisa-Chiferi et al[135] 1996	Unreported	Unreported	Unreported	TVS	5 MHz	Unreported	Eca	> 90%	4

TVS = transvaginal USS, ABS = abdominal USS, HRT = hormone replacement therapy, Eca = endometrial cancer, Ehyp = endometrial hyperplasia, [a] = cut-off for abnormality determined *a priori*, [p] = cut-off for abnormality determined *post hoc*, * see Methods section for details of quality

Appendix 15 Reference list of excluded studies from systematic reviews of ultrasound

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Appendix 16 Likelihood ratios (LR) for predicting endometrial cancer in primary studies

Method of measurement and cut-off level for abnormality	Positive test results			Negative test results		
	TPR	FPR	LR (95% CI)	FNR	TNR	LR (95% CI)
Measurement of both layers of endometrial thickness						
3 mm						
Auslender et al[14] 1993	16/16	55/113	2.05 (1.70-2.48)	0/16	58/113	0.06 (0.00-0.88)
Zannoni et al[348] 1994	55/56	331/705	2.09 (l.92-2.28)	1/56	374/705	0.03 (0.00-0.24)
4 mm						
Bakour et al[18] 1999	11/11	43/85	1.98 (l.60-2.44)	0/11	42/85	0.08 (0.01-1.28)
Botsis et al[36] 1992	8/8	14/112	8.00 (4.90-13.06)	0/8	98/112	0.06 (0.00-0.94)
Fistonic et al[122] 1997	14/14	72/89	1.24 (l.12-1.37)	0/14	17/89	0.17 (0.01-2.70)
Garuti et al[130] 1999	59/60	240/359	1.47 (l.36-1.59)	1/60	119/359	0.05 (0.01-0.35)
Granberg et al[147] 1997	114/114	480/996	2.08 (l.95-2.21)	0/114	516/996	0.01 (0.00-0.13)
Guner et al[159] 1996	19/19	92/173	1.88 (l.64-2.16)	0/19	81/173	0.05 (0.00-0.83)
Haller et al[164] 1996	16/16	48/65	1.35 (l.17-1.56)	0/16	17/65	0.11 (0.01-1.75)
Tsuda et al[328] 1997	14/15	56/151	2.52 (l.96-3.22)	1/15	95/151	0.11 (0.02-0.71)
Varner et al[334] 1991	2/2	6/13	2.17 (l.20-3.90)	0/2	7/13	0.31 (0.02-4.09)
5 mm						
Abu-Ghazzeh et al[4] 1999	1/1	60/97	1.62 (l.38-1.89)	0/1	37/97	0.65 (0.06-7.30)
Briley et al[42] 1998	5/5	85/172	2.02 (1.74-2.35)	0/5	87/172	0.16 (0.01-2.35)
Cacciatore et al[48] 1994	4/4	30/41	1.37 (l.14-1.64)	0/4	11/41	0.37 (0.03-5.30)
DeSilva et al[78] 1997	1/3	12/47	1.31 (0.24-6.96)	2/3	35/47	0.90 (0.40-2.03)
Granberg et al[146] 1991	8/8	47/197	4.19 (3.27-5.38)	0/8	150/197	0.07 (0.00-1.08)
Grigoriou et al[151] 1996	24/24	75/226	3.01 (2.50-3.63)	0/24	151/226	0.03 (0.00-0.47)
Gu et al[155] 1994	7/7	16/22	1.38 (l.06-1.78)	0/7	6/22	0.22 (0.01-3.50)
Gupta et al[161] 1996	2/3	26/72	1.85 (0.78-4.35)	1/3	46/72	0.52 (0.10-2.61)
Hänggi et al[165] 1995	18/21	15/70	4.00 (2.47-6.47)	3/21	55/70	0.18 (0.06-0.52)
Ivanov et al[172] 1998	10/10	31/74	2.39 (l.83-3.12)	0/10	43/74	0.08 (0.01-1.18)
Karlsson et al[179] 1993	14/15	31/88	2.65 (l.94-3.63)	1/15	57/88	0.10 (0.02-0.69)
Loverro et al[216] 1999	25/25	13/81	6.23 (3.79-10.25)	0/25	68/81	0.02 (0.00-0.36)
Malinova et al[224] 1996	69/69	43/85	2.35 (l.75-3.14)	0/69	42/85	0.02 (0.00-0.24)
Merz et al[234] 1990	14/14	24/42	1.75 (l.35-2.27)	0/14	18/42	0.08 (0.00-1.21)
Nasri et al[243] 1989	7/7	19/56	2.95 (2.05-4.25)	0/7	37/56	0.10 (0.01-1.40)
Nasri et al[244] 1991	6/6	32/83	2.59 (l.98-3.40)	0/6	51/83	0.12 (0.01-1.69)
Pertl et al[269] 1996	18/19	96/131	1.29 (1.11-1.50)	1/19	35/131	0.20 (0.03-1.36)
Suchocki et al[316] 1998	28/28	89/101	1.13 (l.06-1.22)	0/28	12/101	0.14 (0.01-2.31)
Taviani et al[321] 1995	2/2	18/39	2.17 (l.54-3.04)	0/2	21/39	0.31 (0.02-3.96)
Weber et al[338] 1998	61/62	59/97	1.62 (l.37-1.90)	1/62	38/97	0.04 (0.01-0.29)
Wolman et al[345] 1996	4/4	18/50	2.78 (l.92-4.02)	0/4	32/50	0.16 (0.01-2.19)
6 mm						
Moreles et al[237] 1998	20/22	70/178	2-31 (l.85-2.90)	2/22	108/178	0.15 (0.04-0.56)
Rudigoz et al[281] 1993	7/9	12/46	2.98 (l.64-5.43)	2/9	34/46	0.30 (0.09-1.03)
8 mm						
Todorova et al[323] 1998	2/2	4/8	2.00 (l.00-4.00)	0/2	4/8	0.33 (0.02-4.55)

Appendix 16 continued

Method of measurement and cut-off level for abnormality	Positive test results			Negative test results		
	TPR	FPR	LR (95% CI)	FNR	TNR	LR (95% CI)
15 mm						
Gruboeck et al[154] 1996	9/11	10/86	7.04 (3.69-13.42)	2/11	76/86	0.21 (0.06-0.72)
Single layer endometrial thickness measurement						
2 mm						
Chan et al[54] 1994	17/17	19/50	2.63 (l.85-3.75)	0/17	31/50	0.04 (0.00-0.70)
Degenhardt et al[85] 1991	32/37	33/96	2.52 (l.86-3-41)	5/37	63/96	0.21 (0.09-0.47)
Dijkhuizen et al[94] 1996	8/8	31/61	1.97 (l.54-2.52)	0/8	30/61	0.11 (0.01-1.69)
3 mm						
Brolmann et al[43] 1993	10/10	26/55	2.12 (l.60-2.80)	0/10	29/55	0.09 (0.01-1.31)
Ceccini et al[53] 1996	15/16	101/352	3.27 (2.65-4.02)	1/16	251/352	0.09 (0.01-0.59)
Masearetti et al[227] 1993	3/3	8/19	1.98 (l.60-2.44)	0/3	11/19	0.01 (0.00-0.23)
Mortakis et al[238] 1997	7/7	30/71	2.37 (l.80-3.11)	0/7	41/71	0.11 (0.01-1.60)
Schramm et al[290] 1995	18/29	83/166	1.24 (0.90-1.71)	11/29	83/166	0.76 (0.46-1.24)
Smith et al[304] 1991	4/4	19/41	2.16 (l.55-3.00)	0/4	22/41	0.19 (0.01-2.63)
4 mm						
Osmers et al[258] 1992	27/27	103/206	2.00 (l.74-2.29)	0/27	103/206	0.04 (0.00-0.56)
Seelbach-Göbel et al[295] 1995	37/39	109/193	1.68 (l.45-1-94)	2/39	84/193	0.12 (0.03-0.46)
10 mm						
Altuncu et al[9] 1992	5/6	1/35	29.17 (4.09-208.03)	1/6	34/35	0.17 (0.03-1.03)
Unreported number of layers for endometrial thickness measurement						
4 mm						
Dorum et al[96] 1993	11/13	35/87	2.10 (l.49-2.97)	2/13	52/87	0.26 (0.07-0.93)
Gerber et al[132] 1999	148/154	375/725	1.86 (l.72-2.01)	6/154	350/725	0.08 (0.04-0.18)
Li et al[205] 1997	59/62	56/130	2.21 (l.80-2.71)	3/62	74/130	0.09 (0.03-0.26)
Salmaggi et al[285] 1997	4/4	13/21	1.62 (l.15-2.26)	0/4	8/21	0.26 (0.02-3.78)
5 mm						
Goldstein et al[142] 1990	1/1	16/27	1.69 (1.23-2.31)	0/1	11/27	0.61 (0.05-6.99)
Malinova et al[223] 1995	57/57	26/61	2.38 (l.40-4.02)	0/57	35/61	0.22 (0.02-2.99)
6 mm						
Mateos et al[229] 1997	18/18	43/140	3.26 (2.54-4.18)	0/18	97/140	0.04 (0.00-0.59)
7 mm						
Guisa-Chiferi et al[135] 1996	19/19	23/61	2.65 (l.92-3.66)	0/19	38/61	0.04 (0.00-0.63)

LR = likelihood ratio, CI = confidence interval,
TPR = True positive rate, FPR = False positive rate, FNR = False negative rate, TNR = True negative rate

Appendix 17 Likelihood ratios (LR) for predicting endometrial disease (hyperplasia and/or cancer) in primary studies

Method of measurement and cut-off level for abnormality	Positive test results			Negative test results		
	TPR	FPR	LR (95% CI)	FNR	TNR	LR (95% CI)
Measurement of both layers of endometrial thickness						
≤ 3 mm						
Auslender et al[14] 1993	32/32	39/97	2.49 (l.95-3.17)	0/32	58/97	0.03 (0.00-0.40)
≤ 4 mm						
Bakour et al[18] 1999	13/14	41/82	1.86 (l.43-2.41)	1/14	41/82	0.14 (0.02-0.96)
Botsis et al[36] 1992	18/18	4/102	25.50 (9.76-66.64)	0/18	98/102	0.03 (0.00-0.42)
Fistonic et al[122] 1997	51/51	35/52	1.49 (l.23-1.80)	0/51	17/52	0.03 (0.00-0.47)
Garuti et al[130] 1999	103/106	196/313	1.55 (l.42-1.70)	3/106	117/313	0.08 (0.02-0.23)
Granberg et al[147] 1997	220/226	374/884	2.30 (2.12-2.49)	6/226	510/884	0.05 (0.02-0.10)
Guner et al[159] 1996	50/50	61/142	2.33 (l.93-2.81)	0/50	81/142	0.02 (0.00-0.27)
Haller et al[164] 1996	30/32	34/49	1.35 (1.10-1.66)	2/32	15/49	0.20 (0.05-0.83)
Tsuda et al[328] 1997	26/27	44/139	3.04 (2.36-3.93)	1/27	95/139	0.05 (0.01-0.37)
Varner et al[334] 1991	5/5	3/10	3.33 (l.29-8.59)	0/5	7/10	0.12 (0.01-1.79)
≤ 5 mm						
Abu-Ghazzeh et al[4] 1999	3/3	58/95	1.64 (l.39-1.92)	0/3	37/95	0.32 (0.02-4.33)
Briley et al[42] 1998	13/15	77/162	1.82 (l.41-2.36)	2/15	85/162	0.25 (0.07-0.93)
DeSilva et al[78] 1997	3/6	10/44	2.20 (0.84-5.79)	3/6	34/44	0.65 (0.29-1.46)
Granberg et al[146] 1991	21/21	34/184	5.41 (4.00-7.33)	0/21	150/184	0.03 (0.00-0.43)
Grigoriou et al[151] 1996	69/69	30/181	6.03 (4.35-8.37)	0/69	151/181	0.01 (0.00-0.14)
Gu et al[155] 1994	10/10	13/19	1.46 (l.08-1.98)	0/10	6/19	0.14 (0.01-2.26)
Gupta et al[161] 1996	6/7	22/68	2.65 (l.68-4.19)	1/7	46/68	0.21 (0.03-1.31)
Hänggi et al[165] 1995	21/25	12/66	4.62 (2.69-7.92)	4/25	54/66	0.20 (0.08-0.48)
Ivanov et al[172] 1998	17/17	24/67	2.79 (2.03-3.85)	0/17	43/67	0.04 (0.00-0.67)
Karlsson et al[179] 1993	24/25	21/78	3.57 (2.45-5.18)	1/25	57/78	0.05 (0.01-0.38)
Loverro et al[216] 1999	25/28	13/78	5.36 (3.21-8.94)	3/28	65/78	0.13 (0.04-0.38)
Malinova et al[224] 1996	80/80	32/74	2.31 (l.78-3.00)	0/80	42/74	0.01 (0.00-0.17)
Merz et al[234] 1990	17/19	21/37	1.58 (l.14-2.17)	2/19	16/37	0.24 (0.06-0.95)
Nasri et al[243] 1989	10/10	16/53	3.31 (2.20-4.99)	0/10	37/53	0.07 (0.00-0.99)
Nasri et al[244] 1991	16/16	22/73	3.32 (2.34-4.71)	0/16	51/73	0.04 (0.00-0.65)
Pertl et al[269] 1996	46/52	68/98	1.27 (l.08-1.50)	6/52	30/98	0.38 (0.17-0.85)
Suchocki et al[316] 1998	90/90	27/39	1.44 (l.17-1.78)	0/90	12/39	0.02 (0.00-0.29)
Taviani et al[321] 1995	4/4	16/37	2.31 (1.60-3.35)	0/4	21/37	0.18 (0.01-2.49)
Wolman et al[345] 1996	10/11	12/43	3.26 (l.95-5.45)	1/11	31/43	0.13 (0.02-0.82)
≤ 6 mm						
Moreles et al[237] 1998	24/59	66/141	0.87 (0.61-1.24)	35/59	75/141	1.12 (0.86-1.45)
Rudigoz et al[281] 1993	17/19	2/36	16.1 (4.15-62.48)	2/19	34/36	0.11 (0.03-0.41)
Single layer endometrial thickness measurement						
≤ 2 mm						
Chan et al[54] 1994	23/23	13/44	3.38 (2.14-5.34)	0/23	31/44	0.03 (0.00-0.47)
Degenhardt et al[85] 1991	39/46	26/87	2.84 (2.01-4.00)	7/46	61/87	0.22 (0.11-0.44)
Dijkhuizen et al[94] 1996	15/15	24/54	2.25 (l.67-3.03)	0/15	30/54	0.06 (0.00-0.87)

Appendix 17 continued

Method of measurement and cut-off level for abnormality	Positive test results			Negative test results		
	TPR	FPR	LR (95% CI)	FNR	TNR	LR (95% CI)
≤ 3 mm						
Brolmann et al[43] 1993	11/12	25/53	1.94 (l.39-2.71)	1/12	28/53	0.16 (0.02-1.05)
Masearetti et al[227] 1993	5/6	6/16	2.22 (l.07-4.60)	1/6	10/16	0.27 (0.04-1.66)
Mortakis et al[238] 1997	11/12	26/66	2.33 (l.65-3.28)	1/12	40/66	0.14 (0.02-0.91)
Schramm et al[290] 1995	68/103	33/92	1.84 (l.35-2.50)	35/103	59/92	0.53 (0.39-0.72)
Smith et al[304] 1991	8/8	15/37	2.47 (l.67-3.64)	0/8	22/37	0.09 (0.01-1.41)
≤ 4 mm						
Osmers et al[258] 1992	35/35	95/198	2.08 (l.80-2.41)	0/35	103/198	0.03 (0.00-0.42)
Seelbach-Göbel et al[295] 1995	59/62	87/170	1.86 (l.59-2.18)	3/62	83/170	0.10 (0.03-0.30)
≤ 10 mm						
Altuncu et al[9] 1992	6/15	0/26	21.94 (l.32-364.10)	9/15	26/26	0.60 (0.40-0.91)
Unreported number of layers for endometrial thickness measurement						
≤ 4 mm						
Gerber et al[132] 1999	203/213	320/666	1.98 (l.82-2.16)	10/213	346/666	0.09 (0.05-0.17)
Li et al[205] 1997	77/80	38/112	2.84 (2.18-3.69)	3/80	74/112	0.06 (0.02-0.17)
Salmaggi et al[285] 1997	7/7	10/18	1.80 (l.19-2.72)	0/7	8/18	0.14 (0.01-2.14)
≤ 5 mm						
Goldstein et al[142] 1990	4/4	13/24	1.85 (l.28-2.67)	0/4	11/24	0.22 (0.02-3.12)
Malinova et al[223] 1995	64/64	19/54	2.84 (l.98-4.08)	0/64	35/54	0.01 (0.00-0.19)
≤ 6 mm						
Mateos et al[229] 1997	35/35	26/123	4.73 (3.36-6.66)	0/35	97/123	0.02 (0.00-0.28)

LR = likelihood ratio, CI = confidence interval
TPR = True positive rate, FPR = False positive rate, FNR = False negative rate, TNR = True negative rate

Appendix 18 Reference list of excluded studies from systematic reviews of hysteroscopy

A1. Valli E, Zupi E, Marconi D, Dini M-L, Di Felice M, Romanini C. A new score for endometrial lesions based on hysteroscopic parameters: Preliminary results. *Gynae Endosc* 1994, 3(3):185-188.

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A3. La Sala GB, Sacchetti F, Dessanti L. Ambulatory diagnostic hysteroscopy: our experience with Hamou's microhysteroscopy in 676 patients. *Ann Ostet Ginecol Med Perinat* 1984, 105(5):300-307.

A4. La Sala GB, Sacchetti F, Dessanti L, Torelli MG, Sartori F. Panoramic diagnostic microhysteroscopy: Analysis of results obtained from 976 patients. *Acta Eur Fertil* 1986, 17(5):369-375.

A5. Garuti G, Sambruni I, Cellani F, Garzia D, Alleva P, Luerti M. Hysteroscopy and transvaginal ultrasonography in postmenopausal women with uterine bleeding. *Int J Gynaecol Obstet* 1999, 65(1):25-33.

A6. Mencaglia L, Perino A. Diagnostic hysteroscopy today. *Acta Eur Fertil* 1986, 17(6):431-439.

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A9. Alexopoulos ED, Simonis CD, Kidsley S, Fay TN. The value of outpatient hysteroscopy in the management of postmenopausal bleeding: A review of 862 cases. *Gynaecol Endosc* 2000, 9(2):107-112.

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A15. Conoscenti G, Meir YJ, Fischer-Tamaro L, Maieron A, Natale R, D'Ottavio et al. Endometrial assessment by transvaginal sonography and histological findings after D & C in women with postmenopausal bleeding. *Ultrasound Obstet G*ynecol 1995, 6(2):108-115.

A16. Mortakis AE, Mavrelos K. Transvaginal ultrasonography and hysteroscopy in the diagnosis of endometrial abnormalities. *J Am Assos Gynecol Laparosc* 1997, 4(4):449-452.

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A23. Finikiotis G. Hysteroscopy: an analysis of 523 patients. *Aust NZ J Obstet Gynaecol* 1989, 29(3 Pt 1):253-255.

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Appendix 19 Diagnostic accuracy of hysteroscopy in detecting endometrial cancer and hyperplasia in women at risk of abnormal endometrial histology: Methodological details

Study (Year Published)	Data Collection	Patient Selection	Study Quality Level	Bleeding Type / Menopausal Status (%)				Method(s) of obtaining endometrial histology (Reference Standard)	Timing of Verification§	Completeness of Verification	Follow Up
				Post	HRT	Pre	†Other				
Alexopoulos[7](1999)	Unreported	Unreported	5	861 (33)	40 (2)	1647(64)	33 (1)	OB	Simultaneous	Partial 49%	>90
Altaras[8] (1993)	Prospective	Unreported	4	39 (100)	-	-	-	OB	Simultaneous	Complete	>90
Azzena[15] (1999)	Prospective	Unreported	2	*9 (18)	-	11 (22)	30 (60)	DB	Sequential	Complete	>90
Bakour[17] (1999)	Prospective	Unreported	4	35 (14)	77 (31)	136 (45)	-	D&C, OB	Simultaneous	Complete	>90
Bocanera[32] (1994)	Unreported	Consecutive	5	72 (46)	-	84 (54)	-	Hyst / D&C / OB	Sequential	Complete‡	<81
Bucholz[45] (1988)	Retrospective	Unreported	4	168(100	-	-	-	D&C	Simultaneous	Complete	>90
Cacciatore[48] (1994)	Prospective	Unreported	4	25 (56)	20 (44)	-	-	D&C	Simultaneous	Complete	>90
Cameron[50] (2001)	Unreported	Unreported	4	*12 (35)	21 (65)	-	-	Hyst / OB	Sequential	Complete	81-90
Caserta[52] (1999)	Unreported	Unreported	4	-	-	-	222 (100)	DB	Simultaneous	Complete	>90
Dargent[74] (1983)	Unreported	Unreported	4	63 (33)	-	143 (75)	-	OB	Simultaneous	Complete	>90
Davydov[75] (1989)	Unreported	Unreported	4	46 (100)	-	-	-	D&C	Simultaneous	Complete	>90
De Jong[76] (1990)	Unreported	Unreported	5	62 (39)	-	87 (54)	11 (7)	D&C/OB	Simultaneous	Partial 74%	>90
De Mendonca[77] (1994)	Unreported	Unreported	4	158(100	-	-	-	Unreported	Simultaneous	Complete	>90
De Silva[78] (1997)	Prospective	Consecutive	3	44 (88)	6 (12)	-	-	Hyst / D&C	Sequential	Complete	>90
De Vivo[79] (1986)	Unreported	Unreported	4	-	-	18 (36)	32 (64)	Unreported	Unreported	Unreported	>90
Decloedt[81] (1999)	Retrospective	Unreported	4	204 (30)		-	469 (70)	OB	Sequential	Complete	>90
Descargues[90] (2001)	Prospective	Consecutive	4	8 (21)	1 (3)	29 (76)	-	DB / D&C / OB	Simultaneous	Complete	>90
Elewa[112](2001)	Unreported	Unreported	4	20 (40)			30 (60)	DB / D&C	Simultaneous	Complete	>90
Epstein[115] (2001)	Prospective	Consecutive	3	#77(73)	28 (27)	-	-	Hyst / DB / D&C	Sequential	Complete	>90
Gabrys[129] (1994)	Unreported	Unreported	4				63 (100)	DB	Simultaneous	Complete	>90
Garuti[131] (2001)	Retrospective	Consecutive	3	*523(34	-	607 (41)	370 (25)	Hyst/DB/D&C/OB	Sequential	Complete	>90
Gorostiaga[144] (2001)	Prospective	Consecutive	3	100(100	-	-	-	OB	Simultaneous	Complete	>90
Grosdanov[153] (1988)	Unreported	Unreported	4	-	-	-	631 (100)	DB	Unreported	Complete	>90
Gucer[156] (1996)	Unreported	Unreported	4	74 (72)	13 (13)	16 (15)	-	D&C	Simultaneous	Complete	>90
Gupta[161] (1996)	Prospective	Unreported	4	73 (100)	-	-	-	D&C	Simultaneous	Complete	>90
Haller[164] (1996)	Prospective	Unreported	4	81 (100)	-	-	-	D&C	Simultaneous	Complete	>90
Iossa[169] (1991)	Retrospective	Consecutive	5	-	-	-	815 (100)	D&C / OB	Simultaneous	Partial 37%	>90

Appendix 19 continued

Study (Year Published)	Data Collection	Patient Selection	Study Quality Level	Bleeding Type / Menopausal Status (%)				Method(s) of obtaining endometrial histology (Reference Standard)	Timing of Verification§	Completeness of Verification	Follow Up
				Post	HRT	Pre	†Other				
Itzkowic[171] (1990)	Unreported	Consecutive	3	6 (12)	-	43 (86)	1 (2)	OB	Simultaneous	Complete	>90
Kovar[191] (2000)	Retrospective	Unreported	4	*391(36	206 (19)	495 (45)	-	D&C	Simultaneous	Complete	>90
Krampl[193] (2001)	Prospective	Consecutive	3	5 (5)	6 (6)	89 (89)	-	DB	Simultaneous	Complete	>90
#Kun[197] (1999)	Prospective	Consecutive	3	63 (20)	-	180 (80)	-	D&C / DB	Simultaneous	Complete	>90
La Sala[200] (1987)	Unreported	Unreported	5	317 (33)	-	415 (43)	244 (25)	Hyst / DB / OB	Sequential	Partial 38%	>90
Litta[210] (1996)	Unreported	Unreported	4	251 (40)	-	378 (60)	-	DB	Simultaneous	Complete	>90
Liu[211] (1995)	Unreported	Unreported	4	130(100	-	-	-	Unreported	Sequential	Complete	>90
Lo[212] (2000)	Retrospective	Unreported	4	503 (31)	-	950 (59)	147 (10)	DB / D&C / OB	Simultaneous	Partial 74%	>90
Loverro[217] (1996)	Unreported	Unreported	4	455 (46)	-	525 (54)	-	DB / OB	Simultaneous	Complete	>90
Loverro[216] (1999)	Prospective	Unreported	4	106(100	-	-	-	DB / OB	Simultaneous	Complete	>90
Luo[218] (1989)	Unreported	Unreported	4	125(100	-	-	-	D&C	Sequential	Complete	>90
Madan[220] (2001)	Retrospective	Unreported	4	76 (13)	-	480 (77)	64 (10)	D&C	Simultaneous	Complete	81-90
Maia[221] (1996)	Unreported	Unreported	4	16 (34)	15 (32)	-	16 (32)	OB	Simultaneous	Complete	>90
Maia[222] (1998)	Retrospective	Unreported	4	-	143(100)	-	-	Hyst / DB / OB	Sequential	Complete	>90
Mencaglia[233] (1987)	Unreported	Unreported	5	NR	NR	NR	638(100) NS	OB	Simultaneous	Partial 33%	>90
Nagele[241] (1996)	Unreported	Unreported	5	202 (8)	-	1925(77)	373 (15)	DB / OB	Simultaneous	Partial 68%	>90
Neis[246] (1986)	Prospective	Unreported	4	NR	NR	NR	307(100) NS	D&C	Sequential	Complete	<81
Neumann[248] (1994)	Unreported	Unreported	4	54	-	31	-	D&C	Simultaneous	Complete	>90
Ohad[255] (1998)	Retrospective	Consecutive	3	173 (46)	-	-	200(54) NS	D&C	Simultaneous	Complete	>90
Okeahialam[256] (2001)	Retrospective	Unreported	4	-	190(100)	-	-	DB / OB	Simultaneous	Complete	>90
Paschpoulos[263] (1997)	Prospective	Unreported	4	-	-	-	235(73) NS 89 (37)	DB	Simultaneous	Complete	>90
Paya[265] (1998)	Retrospective	Unreported	4	866 (54)	109 (6)	641 (40)	-	Unreported	Simultaneous	Complete	>90
Perez-Medina[266] (1994)	Prospective	Unreported	4	*80 (65)	-	53 (35)	-	D&C / DB	Sequential	Complete	>90
Possati[270] (1994)	Unreported	Unreported	4	78 (78)	-	-	22 (22)	Unreported	Simultaneous	Complete	>90
Raju[275] (1986)	Unreported	Unreported	4	49 (70)	7 (10)	14 (20)	-	DB / D&C	Simultaneous	Complete	>90
Salet-Lizee[284] (1993)	Prospective	Unreported	4	43 (24)	32 (18)	103 (58)	-	D&C	Simultaneous	Complete	>90
Sanfeliu[286] (1990)	Retrospective	Unreported	4	127 (26)	-	482 (74)	-	OB	Unreported	Complete	>90

Appendix 19 continued

Study (Year Published)	Data Collection	Patient Selection	Study Quality Level	Bleeding Type / Menopausal Status (%)				Method(s) of obtaining endometrial histology (Reference Standard)	Timing of Verification§	Completeness of Verification	Follow Up
				Post	HRT	Pre	†Other				
Scwarzler[291] (1998)	Unreported	Consecutive	3	29 (30)	-	69 (70)	-	D&C	Simultaneous	Complete	>90
Sevcik[297] (1998)	Unreported	Unreported	4	34 (47)	-	-	39 (53)	DB / D&C	Simultaneous	Complete	>90
Simon[302] (1993)	Retrospective	Unreported	4	*15 (14)	-	-	91 (86)	Hyst	Sequential	Complete	<81
Sousa[308] (2001)	Prospective	Consecutive	1	75 (85)	13 (15)	-	-	Hyst/DB/OB	Sequential	Complete	>90
Tahir[320] (1999)	Prospective	Consecutive	3	123 (31)	-	277 (69)	-	D&C / OB	Simultaneous	Complete	>90
Todorova[323] (1998)	Prospective	Unreported	4	10 (50)	-	10 (50)	-	Unreported	Simultaneous	Complete	>90
Uhiara[329] (1999)	Retrospective	Unreported	5	*61 (32)	8 (5)	81 (43)	38 (20)	OB	Simultaneous	Partial 36%	>90
Valli[330] (1995)	Prospective	Unreported	5	*162(17)	-	233 (25)	538 (58)	DB	Simultaneous	Partial 26%	>90
Vercellini[335] (1997)	Unreported	Consecutive	5	-	-	793(100)	-	OB	Simultaneous	Partial 98%	>90
Vigada[336] (1995)	Unreported	Unreported	4	49 (58)	-	23 (28)	12 (14)	OB	Simultaneous	Complete	>90
Widrich[343] (1995)	Prospective	Unreported	5	29 (22)	5 (4)	88 (68)	8 (6)	OB/surgery - NS	Sequential	Partial 49%	>90

*Numbers calculated from initial proportion of patients within these groups before missing outcome data or duplicate testing was excluded
† Other refers to proportion of women included in the study who did not have abnormal uterine bleeding as an indication for hysteroscopy
‡ Incomplete reporting of endometrial cancer (i.e. not all histologically confirmed cases included in study analysis)
§Timing of verification of diagnosis refers to when verification of diagnosis following hysteroscopy was performed, at the same time (simultaneous) or after a short delay sequential).
¶ Proportion of successful hysteroscopies for which outcome data was available
# All patients had endometrium thickness >5mm on transvaginal ultrasound
NS = not specified (refers to proportion of women included in the study where the type of abnormal uterine bleeding was not specified)
D&C = dilatation of the cervix and curettage of the endometrium, DB = directed biopsy, OB = outpatient biopsy (blind), Hyst = hysterectomy specimen

Appendix 20 Procedure feasibility and diagnostic accuracy of hysteroscopy in endometrial cancer and endometrial disease (cancer and hyperplasia)

Study (Year published)	*Failure rate	Disease in failed Hysteroscopy		Inadequate rate	Cancer Cases:		Disease Cases:	
		Cancer	Hyper		+ve test (Sensitivity)	-ve test (1-Specificity)	+ve test (Sensitivity)	-ve test (1-Specificity)
Alexopoulos[7](1999)	83/2581	0	-	165/2498	6/11 (0.55)	13/2322 (0.006)	6/11 (0.55)	13/2322 (0.006)
Altaras[8] (1993)	0/39	0	-	0/39	3/3 (1.0)	0/36 (0.0)	3/3 (1.0)	0/36 (0.0)
Azzena[15](1999)	3/50	-	0	0/47	-	-	9/10 (0.9)	2/37 (0.05)
Bakour[17] (1999)	†0/248	-	0	0/248	-	-	4/14 (0.29)	1/230 (0.004)
Bocanera[32] (1994)	7/156	0	3	6/149	10/11 (0.91)	0/132 (0.0)	23/29 (0.79)	15/114 (0.13)
Bucholz[45] (1988)	0/168	0	0	0/168	12/12 (1.0)	4/156 (0.03)	23/23 (1.0)	3/145 (0.02)
Cacciatore[48] (1994)	2/45	0	-	0/43	2/4 (0.50)	0/39 (0.0)	2/4 (0.50)	0/39 (0.0)
Cameron[50] (2001)	3/33	-	0	0/30	-	-	1/2 (0.50)	0/28 (0.0)
Caserta[52] (1999)	0/222	0	-	0/222	6/6 (1.0)	0/216 (0.0)	6/6 (1.0)	0/216 (0.0)
Dargent[74] (1983)	0/191	0	-	31/191	4/15 (0.27)	1/145 (0.007)	4/15 (0.27)	1/145 (0.007)
Davydov[75] (1989)	0/46	0	0	0/46	11/11 (1.0)	0/35 (0.0)	14/14 (1.0)	1/32 (0.03)
De Jong[76] (1990)	8/160	1	-	19/152	5/5 (1.0)	5/128 (0.04)	5/5 (1.0)	5/128 (0.04)
De Mendonca[77] (1994)	0/158	0	-	0/158	14/15 (0.93)	17/143 (0.12)	14/15 (0.93)	17/143 (0.12)
De Silva[78] (1997)	1/50	1	-	25/49	2/2 (1.0)	0/22 (0.0)	2/2 (1.0)	0/22 (0.0)
DeVivo[79](1986)	0/50	-	0	0/50	-	-	1/1 (1.0)	0/49 (0.0)
Decloedt[81] (1999)	37/673	0	-	0/636	9/9 (1.0)	0/627 (0.0)	9/9 (1.0)	0/627 (0.0)
Descargues[90] (2001)	1/38	0	0	0/37	2/2 (1.0)	1/35 (0.03)	10/10 (1.0)	6/27 (0.22)
Elewa[112](2001)	0/50	0	0	0/50	3/3 (1.0)	0/47 (0.0)	26/26 (1.0)	3/24 (0.13)
Epstein[115] (2001)	0/105	0	-	0/105	21/25 (0.84)	12/80 (0.15)	21/25 (0.84)	12/80 (0.15)
Gabrys[129] (1994)	0/63	0	-	5/63	1/1 (1.0)	0/57 (0.0)	1/1 (1.0)	0/57 (0.0)
Garuti[131] (2001)	†‡0/1050	0	0	43/1457	85/102 (0.83)	7/1355 (0.005)	208/287 (0.73)	91/869 (0.09)
Gorostiaga[144] (2001)	4/100	0	-	41/96	6/6 (1.0)	0/49 (0.0)	6/6 (1.0)	0/49 (0.0)
Grosdanov[153] (1988)	0/461	0	-	0/461	67/67 (1.0)	6/394 (0.02)	67/67 (1.0)	6/394 (0.02)
Gucer[156] (1996)	5/103	0	-	0/98	8/9 (0.89)	2/89 (0.02)	8/9 (0.89)	2/89 (0.02)
Gupta[161] (1996)	4/73	-	0	35/69	-	-	5/11 (0.46)	0/23 (0.0)
Haller[164] (1996)	5/81	1	4	0/76	8/15 (0.53)	0/61 (0.0)	16/27 (0.59)	9/49 (0.18)
Iossa[169] (1991)	196/2007	1	-	26/1811	22/29 (0.76)	13/1756 (0.007)	22/29 (0.76)	13/1756 (0.007)
Itzkowic[171] (1990)	2/50	0	-	1/48	1/1 (1.0)	0/46 (0.0)	1/1 (1.0)	0/46 (0.0)

Appendix 20 continued

Study (Year published)	*Failure rate	Disease in failed Hysteroscopy		Inadequate rate	Cancer Cases:		Disease Cases:	
		Cancer	Hyper		+ve test (Sensitivity)	-ve test (1-Specificity)	+ve test (Sensitivity)	-ve test (1-Specificity)
Kovar[191] (2000)	0/1092	0	-	0/690	13/26 (0.50)	6/1174(0.005)	13/26 (0.50)	6/1174(0.005)
Krampl[193] (2001)	1/100	0	0	0/99	1/1 (1.0)	0/98 (0.0)	2/9 (0.22)	11/90 (0.12)
Kun[197] (1999)	1/318	0	-	2/317	5/5 (1.0)	1/310 (0.003)	5/5 (1.0)	1/310 (0.003)
La Sala[200] (1987)	87/976	0	0	0/889	32/33 (0.97)	4/856 (0.005)	105/105 (1.0)	26/784 (0.03)
Litta[210] (1996)	†0/629	0	0	0/629	35/42 (0.83)	0/587 (0.0)	128/162 (0.79)	54/467 (0.12)
Liu[211] (1995)	0/130	0	0	24/130	9/11 (0.82)	4/95 (0.04)	17/22 (0.77)	7/84 (0.08)
Lo[212] (2000)	132/1600	3	-	0/1468	10/17 (0.59)	38/1451 (0.03)	10/17 (0.59)	38/1451 (0.03)
Loverro[217](1996)	0/980	-	0	90/980	-	-	102/102 (1.0)	47/788 (0.06)
Loverro[216] (1999)	0/106	0	-	0/106	25/25 (1.0)	2/81 (0.03)	25/25 (1.0)	2/81 (0.03)
Luo[218] (1989)	0/125	0	-	0/125	13/13 (1.0)	2/112 (0.02)	13/13 (1.0)	2/112 (0.02)
Madan[220] (2001)	39/556	0	10	82/517	2/7 (0.29)	2/428 (0.005)	49/122 (0.40)	53/313 (0.17)
Maia[221] (1996)	0/47	0	-	5/47	5/5 (1.0)	0/37 (0.0)	5/5 (1.0)	0/37 (0.0)
Maia[222](1998)	0/143	-	0	2/143	-	-	4/69 (0.06)	0/72 (0.0)
Mencaglia[233] (1987)	20/638	0	0	0/618	59/60 (0.98)	7/558 (0.01)	124/149 (0.83)	28/469 (0.06)
Nagele[241] (1996)	91/2500	0	-	392/2409	11/11 (1.0)	0/2006 (0.0)	11/11 (1.0)	0/2006 (0.0)
Neis[246] (1986)	0/307	0	0	0/307	44/48 (0.92)	0/259 (0.0)	70/76 (0.92)	9/231 (0.04)
Neumann[248] (1994)	4/89	0	0	0/85	4/5 (0.80)	0/80 (0.0)	17/18 (0.94)	3/67 (0.04)
Ohad[255] (1998)	25/373	0	0	33/348	2/10 (0.20)	0/305 (0.0)	42/65 (0.65)	105/250 (0.42)
Okeahialam[256] (2001)	0/190	0	0	37/190	2/3 (0.66)	5/150 (0.03)	5/8 (0.63)	2/181 (0.01)
Paschpoulos[263] (1997)	12/324	0	0	0/312	12/12 (1.0)	0/300 (0.0)	119/128 (0.93)	9/184 (0.05)
Paya[265] (1998)	30/1616	0	0	0/1586	84/85 (0.99)	2/1501 (0.001)	256/311 (0.82)	69/1275 (0.05)
Perez-Medina[266] (1994)	5/123	1	0	28/118	8/9 (0.89)	0/81 (0.0)	14/15 (0.93)	10/75 (0.13)
Possati[270](1994)	0/100	-	0	0/100	-	-	23/23 (1.0)	0/77 (0.0)
Raju[275] (1986)	0/70	0	0	17/70	14/14 (1.0)	0/39 (0.0)	25/25 (1.0)	0/28 (0.0)
Salet-Lizee[284] (1993)	0/195	0	0	0/195	7/8 (0.88)	2/187 (0.01)	56/70 (0.8)	5/125 (0.04)
Sanfeliu[286] (1990)	0/609	0	0	0/609	14/15 (0.93)	1/594 (0.001)	51/59 (0.86)	20/550 (0.04)
Scwarzler[291] (1998)	0/98	0	0	0/98	3/3 (1.0)	0/95 (0.0)	9/10 (0.9)	0/88 (0.0)
Sevcik[297] (1998)	0/73	0	0	0/73	1/4 (0.25)	0/69 (0.0)	4/8 (0.5)	0/65 (0.0)
Sousa[308] (2001)	15/84	0	0	12/69	8/9 (0.89)	1/48 (0.02)	9/11 (0.82)	0/46 (0.0)
Simon[302] (1993)	0/106	0	0	0/106	6/8 (0.75)	0/98 (0.0)	16/20 (0.8)	8/86 (0.09)

Appendix 20 continued

Study (Year published)	*Failure rate	Disease in failed Hysteroscopy		Inadequate rate	Cancer Cases:		Disease Cases:	
		Cancer	Hyper		+ve test (Sensitivity)	-ve test (1-Specificity)	+ve test (Sensitivity)	-ve test (1-Specificity)
Tahir[320] (1999)	7/400	0	-	30/393	8/11 (0.73)	0/352 (0.0)	8/11 (0.73)	0/352 (0.0)
Todorova[323] (1998)	0/20	-	0	0/20	-	-	4/6 (0.67)	2/14 (0.14)
Uhiara[329] (1999)	14/188	0	0	0/174	1/2 (0.50)	0/172 (0.0)	6/10 (0.6)	8/164 (0.05)
Valli[330] (1995)	47/933	0	0	18/886	18/18 (1.0)	9/850 (0.01)	95/103 (0.92)	99/765 (0.13)
Vercellini[335] (1997)	23/793	0	0	17/770	2/2 (1.0)	0/751 (0.0)	32/68 (0.47)	48/685 (0.07)
Vigada[336] (1995)	13/84	0	0	10/71	1/2 (0.5)	0/59 (0.0)	9/9 (1.0)	9/52 (0.17)
Widrich[343] (1995)	10/130	0	0	0/120	1/1 (1.0)	0/119 (0.0)	4/8 (0.5)	0/112 (0.0)
Endometrial disease studies (65)	**937/26346 3.6% (3.3-3.8%)**	**25/937 2.7% (1.7-3.9%)**		**1196/25409 4.7% (4.5-5.0%)**	**-**	**-**	**2004/2570**	**900/21643**
Endometrial cancer studies (56)	**927/24649 3.8% (3.6-4.0%)**	**8/927 0.8% (0.4-1.7%)**		**1069/23722 4.5% (4.3-4.8%)**	**768/889**	**167/21764**	**-**	**-**

* Failed outpatient hysteroscopic procedures included technical aspects (e.g. cervical stenosis, anatomical factors), inadequate visualization (e.g. obscured by bleeding) or patient factor (e.g. pain)
†Failed outpatient hysteroscopies, which were successfully performed subsequently as an inpatient NOT included in the failure rates
‡ 128 'unsatisfactory hysteroscopies' but all included in results

Appendix 21 Life expectancies of United Kingdom women stratified by age, surgery and presence of endometrial cancer

Life Expectancy	Age 45 years	Age 55 years	Age 65 years	Age 75 years	Age 80+ years
General					
Non-discounted	36.11	26.94	18.51	11.40	8.49
Discounted	27.37	21.68	15.76	10.22	7.79
General + abdominal hysterectomy					
Non-discounted	36.11	26.92	18.45	11.31	8.39
Discounted	27.37	21.66	15.72	10.14	7.70
Endometrial Cancer (Immediate Diagnosis)					
Non-discounted	30.00 (18.02)	19.95 (16.02)	13.54 (8.02)	9.26 (4.80)	5.48 (2.31)
Discounted	22.98 (14.33)	16.33 (13.32)	11.73 (7.23)	8.38 (4.53)	5.13 (2.25)
Endometrial Cancer (Delayed Diagnosis)					
Non-discounted	29.19 (17.59)	19.23 (15.47)	13.04 (7.79)	8.97 (4.71)	5.33 (2.28)
Discounted	22.40 (14.01)	15.77 (12.89)	11.32 (7.03)	8.14 (4.45)	5.00 (2.23)

The values were derived from United Kingdom life tables for females[177], data from the International Federation of Gynaecology and Obstetrics (FIGO),[72] the West-Midlands Cancer Intelligence Unit (WMCIU) and Wingo et al.[344] Discounted values are shown at 1.5% per year. Survival times for delayed diagnosis relate to times from initial investigation. The lower ranges of values used in sensitivity analyses are shown in parentheses. See text for further details.

Appendix 22 Investigation of postmenopausal bleeding: Base-case results for the decision model with a starting age of 65 years

Strategy	Average cost per patient (£)	Expected survival per patient (years)*	Dominated by
No investigation	146.27	15.538200	
USS 5mm	358.20	15.556677	
USS 4mm	371.84	15.557039	
EB	378.16	15.557045	
OPH	385.58	15.554847	USS (either) or EB
USS5+EB	517.96	15.557906	
USS4+EB	529.33	15.557924	
USS5+OPH	533.18	15.558053	
EB+OPH	545.32	15.557931	USS5mm+OPH
USS4+OPH	545.34	15.558083	
USS+EB+OPH	599.32	15.557931	USS+OPH

EB = endometrial biopsy, OPH = outpatient hysteroscopy, USS = transvaginal ultrasound.
*It is not claimed that the model can predict even a population average survival accurately to 6 decimal places, the numbers are quoted in that form to show how little difference the various strategies make to the expected survival.

Appendix 23 Incremental cost-effectiveness ratios for diagnostic strategies, compared to ultrasound (5mm cut-off) assuming endometrial biopsy is performed at the same visit following a positive ultrasound or outpatient hysteroscopy

Strategy	Incremental cost (£)	Life Years Gained (LYG)	Average days extra survival per patient	ICER (£/LYG)
USS 4mm	10.09	0.000362	0.13	27,873
EB	48.99	0.000368	0.13	133,125
OPH	53.37	-0.00183	-0.67	D
USS 5mm+EB	188.79	0.001229	0.45	153,613
USS 4mm+EB	200.17	0.001246	0.45	160,650
USS 5mm+OPH	204.01	0.001376	0.50	148,263
EB+OPH	216.15	0.001254	0.46	172,368
USS 4mm+OPH	216.17	0.001405	0.51	153,858
USS 4mm+EB+OPH	270.15	0.001254	0.46	215,431

Survival discounted at a rate of 1.5%
D = dominated by alternate strategy

Appendix 24 Investigation of postmenopausal bleeding at different ages of presentation: Non-discounted incremental cost-effectiveness ratios of strategies compared to ultrasound (5mm cut-off)

Strategy	ICER compared to USS5mm for starting age (years)				
	45	**55**	**65**	**75**	**80+**
USS 4mm	17,858	20,434	31,195	61,407	161,595
EB	17,426	21,848	D(USS4mm)	D(USS5mm)	D(USS5mm)
OPH	D(USS5mm)	D(USS5mm)	D(USS5mm)	D(USS5mm)	D(USS5mm)
USS5+EB	55,907	65,615	110,317	290,752	D(USS5mm)
USS4+EB	59,157	69,395	116,442	304,691	D(USS5mm)
USS5+OPH	D(USS5mm+EB)	D(USS4mm+EB)	104,050	183,487	370,562
EB+OPH	64,291	75,422	D(USS5mm+OPH)	D(USS5mm+OPH)	D(USS5mm)
USS4+OPH	D(EB+OPH)	74,049	109,302	D(EB+OPH)	D(USS5mm+OPH)

D(X) = dominated by strategy X

Appendix 25 Sensitivity analysis for the diagnostic strategy ultrasound using a 4mm cut-off compared to ultrasound using a 5mm cut-off

(When varying the test characteristics for ultrasound, low and high values were taken for both cut-off points simultaneously)

Variable	Value	Survival gain (days per 1000 patients	Extra cost (£ per patient)
Base		132	13.63
Adjustment for conditional probability EBtpr after USS*	0	-8	13.65
Probability of upstaging cancer	0.3	834	13.51
Probability D&C fpr	0	133	13.49
Probability D&C fpr	0.03	130	13.92
Probability D&C tpr	0.82	130	13.64
Probability D&C tpr	1	133	13.63
Probability EB fpr	0	139	12.57
Probability EB fpr	0.02	125	14.7
Probability EB tpr	0.84	119	13.66
Probability pEB tpr	0.99	139	13.62
Probability USS fpr	low	132	13.63
Probability USS fpr	high	131	15.93
Probability USS tpr	low	202	13.57
Probability USS tpr	high	132	13.63
Probability USS success	0.98	129	13.36
Probability pUSS success	1	132	13.63
Probability of endometrial cancer (prevalence)	0.03	76	13.97
Probability of endometrial cancer (prevalence)	0.1	273	12.78

* Adjustment made to account for lack of complete test independence
Survival discounted at a rate of 1.5%
D&C = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, OPH = outpatient hysteroscopy, tpr = true positive rate, USS = transvaginal ultrasound.

Appendix 26 Sensitivity analysis for the diagnostic strategy endometrial biopsy compared to ultrasound using a 5mm cut-off

Variable	Value	Survival gain (days per 1000 patients	Extra cost (£ per patient)
Base case		134	19.95
Adjustment for conditional probability EBtpr after USS*	0.01	69	20.12
Probability of upstaging cancer	0	-76	19.98
Probability Upstage	0.3	1187	19.78
Probability D&C fpr	0	143	18.62
Probability D&C fpr	0.03	116	22.62
Probability D&C tpr	0.82	130	19.96
Probability D&C tpr	1	135	19.95
Probability EB fpr	0	201	10.19
Probability EB fpr	0.02	67	29.71
Probability EB tpr	0.84	115	20.00
Probability pEB tpr	0.99	144	19.93
Probability USS fpr	0.43	131	24.54
Probability USS fpr	0.47	137	15.37
Probability USS tpr	0.94	345	19.76
Probability USS tpr	0.98	64	20.02
Probability EB success	0.85	139	30.74
Probability EB success	0.91	130	9.16
Probability USS success	0.98	129	14.64
Probability pUSS success	1	134	19.95
Probability of endometrial cancer (prevalence)	0.03	48	22.69
Probability of endometrial cancer (prevalence)	0.1	349	22.69

* Adjustment made to account for lack of complete test independence
Survival discounted at a rate of 1.5%
D&C = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, OPH = outpatient hysteroscopy, tpr = true positive rate, USS = transvaginal ultrasound.

Appendix 27 Sensitivity analysis for the diagnostic strategy endometrial biopsy compared to ultrasound using a 4mm cut-off

Variable	Value	Survival gain (days per 1000 patients	Extra cost (£ per patient)
Base		2	6.32
Adjustment for conditional probability EBtpr after USS*	0.01	-63	6.49
Probability of upstaging cancer	0	-68	6.33
Probability Upstage	0.3	353	6.26
Probability D&C fpr	0	10	5.14
Probability D&C fpr	0.03	-14	8.7
Probability D&C tpr	0.82	1	6.32
Probability D&C tpr	1	3	6.32
Probability EB fpr	0	62	-2.37
Probability EB fpr	0.02	-58	15.01
Probability EB tpr	0.84	-4	6.34
Probability pEB tpr	0.99	5	6.31
Probability USS fpr	0.49	-1	10.91
Probability USS fpr	0.54	6	-0.56
Probability USS tpr	0.97	143	6.19
Probability USS tpr	1	-68	6.39
Probability EB success	0.85	7	17.11
Probability EB success	0.91	-2	-4.47
Probability USS success	0.98	0	1.29
Probability pUSS success	1	2	6.32
Probability of endometrial cancer (prevalence)	0.03	-27	8.72
Probability of endometrial cancer (prevalence)	0.1	76	0.34

* Adjustment made to account for lack of complete test independence
Survival discounted at a rate of 1.5%
D&C = dilatation and curettage, EB = endometrial biopsy, fpr = false positive rate, OPH = outpatient hysteroscopy, tpr = true positive rate, USS = transvaginal ultrasound.

Appendix 28 Basis for recommendations about the use of interventions, treatments or service

THE UNIVERSITY OF BIRMINGHAM

Code for categorising the quality of the evidence*:

I At least one properly designed randomised controlled trial

(High quality studies with a blind comparison of test to reference standard in an appropriate population spectrum)*

II Well-designed controlled trials or well-designed cohort or case-control analytic studies, preferably from more than one centre or research group or multiple time-series or dramatic results in uncontrolled experiments

(Any one of the following is present in the study: narrow population spectrum, differential use of reference standard, reference standard not blind, case-control design)*

III Opinions of respected authorities based on clinical evidence, descriptive studies or reports of expert committees

(Any three or more of the above)*

IV Evidence inadequate owing to problems of methodology (e.g. sample size, length or comprehensiveness of follow up) or conflicts of evidence

(Expert opinion)*

Appendix 28 continued

Evidence	<£3000 per QALY	£3000 - £20,000 per QALY	£20,000 - £30,000 per QALY	>£30,000 per QALY	Negative QALYs
I	Strongly Supported	Strongly Supported	Supported	Borderline	Not Supported
II	Strongly Supported	Supported	Borderline	Borderline	Not Supported
III	Supported	Borderline	Borderline	Borderline	Not Supported
IV	Not Proven	Not Proven	Not Proven	Not Proven	Not Proven

* The levels of evidence are not suitable for assessing test accuracy studies, so a grading system devised by the NHS Centre for Reviews and Dissemination[187] has been used to adapt the code for categorising the quality of evidence.

Appendix 29 Publications from the thesis

1. Clark TJ, Mann CH, Shah N, Song F, Khan KS, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial hyperplasia: A systematic review. *Acta Obstet Gynecol Scand* 2001; 80(9): 784-793.

2. Clark TJ, Mann CH, Shah N, Song F, Khan KS, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial cancer: A systematic review. *Br J Obstet Gynecol* 2002; 109: 313-321.

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7. Clark TJ, Gupta JK. Endometrial sampling of gynaecological pathology. *Obstetrician and Gynaecologist* 2002;4:169–174.

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9. Bachmann LM, Clark TJ, ter Riet G, Gupta JK, Khan KS. Probability analysis for diagnosis of endometrial hyperplasia and cancer in postmenopausal bleeding: An approach for a rational diagnostic workup. *Acta Obstet Gynecol Scand* 2003; 82: 1-6.

10. Clark TJ, Barton PM, Gupta JK, Khan KS. Ambulatory diagnosis of endometrial cancer in women with postmenopausal bleeding. (ISBN) *West Midlands Health Technology Assessment Collaboration Report* 2003University of Birmingham [in press, will be available at http://www.publichealth.bham.ac.uk]

11. Clark TJ, Khan KS, Ter Riet G, Gupta JK. Bias associated with delayed verification in test accuracy studies: Accuracy of tests for endometrial hyperplasia may be much higher than we think! *BMC Med Res Methodol* 2003 (submitted)

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