# National Institute for Health and Care Excellence

# Heavy menstrual bleeding (update)

## A: Evidence reviews for diagnostic test accuracy in investigation for women presenting with heavy menstrual bleeding

*NICE guideline 88*

*Evidence reviews*

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*Final*

*These evidence reviews were developed by National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists*

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# Abbreviations

| Abbreviation | Definition |
|---|---|
| 2D | Two-dimensional |
| 2D-TAUS | Two-dimensional transabdominal ultrasound scan |
| 2D-TVUS | Two-dimensional transvaginal ultrasound scan |
| 3D | Three-dimensional |
| 3D-TAUS | Three-dimensional transabdominal ultrasound scan |
| 3D-TVUS | Three-dimensional transvaginal ultrasound scan |
| AUC | Area under the curve |
| BSGE | British Society for Gynaecological Endoscopy |
| CI | Confidence interval |
| D&C | Dilatation and curettage |
| EBx | Endometrial biopsy |
| EQ-5D | EuroQol five dimensions questionnaire |
| FN | False negative |
| FP | False positive |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HMB | Heavy menstrual bleeding |
| HRQoL | Health-related quality of life |
| HSROC | Hierarchical summary receiver operating characteristic |
| LNG-IUS | Levonorgestrel-releasing intrauterine system |
| LR+ | Positive likelihood ratio |
| LR- | Negative likelihood ratio |
| MRI | Magnetic resonance imaging |
| N/A | Not applicable |
| NGA | National Guideline Alliance |
| NHS | National Health Service |
| NICE | National Institute of Health and Care Excellence |
| NMA | Network meta-analysis |
| NMB | Net monetary benefit |
| OPH | Outpatient hysteroscopy |
| PSA | Probabilistic sensitivity analysis |
| QALY | Quality-adjusted life year |
| QUADAS-2 | A quality assessment tool for diagnostic accuracy studies |
| RCOG | Royal College of Obstetricians and Gynaecology |
| RCT | Randomised controlled trial |
| RPOC | Retained products of conception |
| Sens | Sensitivity |
| SIS | Saline infusion sonography |
| Spec | Specificity |
| TAUS | Transabdominal ultrasound scan |
| TN | True negative |
| TP | True positive |
| TVUS | Transvaginal ultrasound scan |

# Diagnosis of heavy menstrual bleeding

## Review questions

Review question 1. What is the diagnostic accuracy of ultrasound and hysteroscopy for investigation of women presenting with heavy menstrual bleeding?

Review question 2. What is the most clinically effective imaging strategy for diagnosing adenomyosis in women with heavy menstrual bleeding?

## Introduction

Many women presenting to primary care with heavy menstrual bleeding (HMB) will only ever require simple treatment without the need for further investigations.  However, some women with HMB may have an underlying pathology, which is often not apparent from the woman's history or examination and further investigations to identify the cause may be needed. The aim of investigation is to identify structural abnormalities such as submucosal fibroids, endometrial polyps, larger fibroids, or adenomyosis, and to also detect rare and potentially serious pathologies such as endometrial hyperplasia or carcinoma.

The identification of structural, focal or histological abnormalities enables targeted treatment, which should result in more effective management. Whilst the cause of HMB will not always be apparent from the investigation, women may also gain reassurance in knowing that no serious pathology is causing their symptoms, and that no focal treatable lesion was missed that make simple treatments less effective.

## Review question 1. What is the diagnostic accuracy of ultrasound and hysteroscopy for investigation of women presenting with heavy menstrual bleeding?

### Introduction

Ultrasound scan has been the technique most commonly used to investigate causes of heavy menstrual bleeding. Over time, diagnostic hysteroscopy techniques have improved, which has also enabled the development of 'see-and-treat' services. Furthermore, new evidence is available on the clinical and cost-effectiveness of different diagnostic techniques in the investigation of women presenting with heavy menstrual bleeding.

The aim of this review was to determine the diagnostic accuracy of hysteroscopy and ultrasound in investigation of women presenting with heavy menstrual bleeding, also taking into account patient acceptability and satisfaction as well as the cost-effectiveness of these approaches.

### Summary of the protocol

Please see Table 1 for a summary of the characteristics of this review including population, index tests, reference standard, outcomes and target conditions.

**Table 1: Summary of the protocol**

| | |
|---|---|
| **Population** | Premenopausal women with heavy menstrual bleeding (HMB).<br><br>At least 66% of the population should be women with heavy menstrual bleeding. |
| **Index test(s)** | • Transvaginal ultrasound scan (TVUS)<br>  ○ Two-dimensional (2D)<br>  ○ Three-dimensional (3D)<br>• Transabdominal ultrasound scan (TAUS)<br>  ○ 2D<br>  ○ 3D<br>• Hysteroscopy<br>  ○ Inpatient/day case (under general anaesthesia/sedation or spinal/epidural anaesthesia)<br>  ○ Outpatient vaginoscopy[1]<br>  ○ Outpatient all other cases<br>• Transvaginal ultrasound followed by hysteroscopy if needed |
| **Reference standard** | • Histopathology<br>• Ultrasound scan (when compared with hysteroscopy)<br>• Inpatient hysteroscopy (when compared with outpatient hysteroscopy) |
| **Outcomes** | • Sensitivity (sens)<br>• Specificity (spec)<br>• Positive likelihood ratio (LR+)<br>• Negative likelihood ratio (LR-)<br>• Area under the curve (AUC) if meta-analysis can be conducted<br>• Patient satisfaction and acceptability |
| **Target condition** | Examples: submucosal fibroids, fibroids less than 3 cm in diameter, fibroids larger than 3 cm in diameter, endometrial polyps, endometrial hyperplasia, cancer,abnormal uterine thickness, synechiae, endometritis, retained products of conception (RPOC), congenital abnormalities. |

*2D: two-dimensional; 3D: three-dimensional; AUC: area under the curve; HMB: heavy menstrual bleeding; LR+: positive likelihood ratio; LR-: negative likelihood ratio; RPOC: retained products of conception; sens: sensitivity; spec: specificity; TAUS: transabdominal ultrasound scan; TVUS: transvaginal ultrasound scan*
*1 Vaginoscopy approach to hysteroscopy is a technique where the hysteroscope is inserted into the vagina and through the cervical canal and into the uterine cavity without a vaginal speculum or cervical instrumentation.*

For full details see review protocol in Appendix A – Review protocols.

## Clinical evidence

Histopathology was considered as the reference standard to which the diagnostic accuracy of ultrasound and hysteroscopy were compared. Histopathology was derived from surgery specimen from hysterectomy, hysteroscopy-guided biopsy, or dilatation and curettage (D&C). No evidence was found comparing the diagnostic accuracy of hysteroscopy to ultrasound as a reference standards, however, studies that compared the diagnostic accuracy of ultrasound to hysteroscopy as the reference standard were considered instead.

The target conditions in which the diagnostic accuracy of these tests were studied included endometrial polyps, fibroids, endometrial hyperplasia, endometrial carcinoma, and any abnormal finding.

A combined literature search was undertaken for this review question together with the review question on the diagnostic accuracy of imaging techniques in detecting adenomyosis in women presenting with heavy menstrual bleeding.

In addition, relevant studies included in NICE guideline on Heavy menstrual bleeding: assessment and management (CG44) published in 2007 were assessed and included if they fitted the inclusion criteria in the current protocol.

Due to the limited evidence available when the population was restricted only to women presenting with heavy menstrual bleeding, the committee agreed that one third of the population could be women without heavy menstrual bleeding and these results could be extrapolated to women presenting with heavy menstrual bleeding as long as the indirectness of the population was accounted for when assessing the quality of the evidence. Since most studies did not report the exact proportion of women presenting with heavy menstrual bleeding, studies which included premenopausal women with abnormal uterine bleeding were still included with the assumption that heavy menstrual bleeding is likely to be a common presentation of abnormal uterine bleeding in these women. Again, the indirectness of the population was accounted for when assessing the quality of evidence and the confidence in the evidence using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

No evidence was found on the diagnostic accuracy of three-dimensional transvaginal ultrasound scan (3D-TVUS) or transabdominal ultrasound scan (TAUS).

Meta-analysis was conducted when appropriate with a minimum of 5 studies. In the presence of heterogeneity, potential reasons for heterogeneity were explored and subgroup analyses were conducted when possible according to pre-specified groups in the protocol.

Test sensitivity or specificity was considered high when sensitivity or specificity was 90% or higher, and moderate when sensitivity or specificity was between 75% and 89%. A positive likelihood ratio (LR+) of 10 or higher was considered to indicate that the test was very useful in 'ruling in' the condition, and a LR+ between 5 and 9.9 was considered moderately useful in 'ruling in' the condition. A negative likelihood ratio (LR-) of 0.1 or lower was considered to indicate that the test was very useful in 'ruling out' the condition, and a LR- between 0.1 and 0.2 was considered to indicate that the test was moderate useful in 'ruling out' the condition.

**Included studies**

Nineteen studies (n=3501) were included in the review (Abd Elkhalek 2016; Abe 2008; Alborzi 2007; Cicinelli 1995; Critchley 2004; Dasgupta 2011a; Dasgupta 2011b; Dueholm 2001a; Erdem 2007; Fakhar and Mahmud 2010; Krampl 2001; Mukhopadhayay 2007; Najeeb 2010; Nanda 2002; Soguktas 2012; Taylor 2001; Vercellini 1997; Williams and Marshburn 1998; Yildiz 2009). Of these 1 study investigated patient acceptability and satisfaction of ultrasound and hysteroscopy (Critchley 2004), the other studies investigated the diagnostic accuracy of these tests.

Fifteen studies provided evidence on the diagnostic accuracy of two-dimensional transvaginal ultrasound scan (2D-TVUS) (Abe 2008; Alborzi 2007; Cicinelli 1995; Dasgupta 2011a; Dasgupta 2011b; Dueholm 2001a; Erdem 2007; Krampl 2001; Mukhopadhayay 2007; Najeeb 2010; Nanda 2002; Soguktas 2012; Taylor 2001; Vercellini 1997; Williams and Marshburn 1998). Six studies provided evidence on the diagnostic accuracy of hysteroscopy (Abd Elkhalek 2016; Cicinelli 1995; Fakhar and Mahmud, 2010; Mukhopadhayay 2007; Soguktas 2012; Yildiz 2009).

The studies came from the following countries: Denmark (Dueholm 2001a); Egypt (AbdElkhalek 2016); India (Dasgupta 2011a; Dasgupta 2011b; Mukhopadhayay 2007; Nanda 2002); Iran (Alborzi 2007); Italy (Cicinelli 1995; Vercellini 1997); Japan (Abe 2008); Norway

(Krampl 2001); Pakistan (Fakhar and Mahmud 2010; Najeeb 2010); Turkey (Erdem 2007; Soguktas 2012; Yildiz 2009); UK (Critchley 2004); and US (Williams and Marshburn 1998).

Evidence from these are presented in Appendix G – GRADE tables.

See also Appendix D – Clinical evidence study selection, Appendix H – Forest plots and hierarchical summary receiver operating characteristic (HSROC) plots, and Appendix F – Clinical evidence tables.

## Excluded studies

Studies not included in this review with reasons for their exclusions are provided in Appendix I – Excluded studies.

## Summary of clinical studies included in the evidence review

Table 2 and Table 3 provide a brief summary of the included studies.

**Table 2: Summary of included studies on diagnostic accuracy**

| Study | Population | Index test | Reference standard | Target condition (prevalence) |
|---|---|---|---|---|
| Abd Elkhalek 2016 (Egypt) | N=50 women with abnormal uterine bleeding and normal endometrial lining on 2D-TVUS, age range 25-45 years<br>Proportion with HMB not reported.<br>Exclusions: bleeding secondary to obvious pelvic infection; cervical and adnexal pathologies | Hysteroscopy (under general anaesthetic) following 2D-TVUS | Histopathology (hysteroscopy-guided biopsy) | • Polyp or fibroid (64%) |
| Abe 2008 (Japan) | N=213 premenopausal women with abnormal uterine bleeding, less than 50 years of age<br>Proportion with HMB not reported.<br>Exclusions: presence of cervical polyps or neoplasm; hormone replacement therapy; cases with TVUS with indeterminate results | 2D-TVUS | Histopathology (vacuum biopsy) | • Any abnormal finding (69%) |

| Study | Population | Index test | Reference standard | Target condition (prevalence) |
|---|---|---|---|---|
| Alborzi 2007 (Iran) | N=81 women with abnormal uterine bleeding<br>Proportion with HMB not reported.<br>Exclusions: none specified | 2D-TVUS | Histopathology (hysteroscopy-guided biopsy) | • Polyp (40%)<br>• Fibroid (28%) |
| Cicinelli 1995 (Italy) | N=52 premenopausal women who underwent hysterectomy<br>67% with HMB<br>Exclusions: none specified | • 2D-TVUS<br>• Hysteroscopy (outpatient) | Histopathology (hysterectomy) | • Polyp (2%)<br>• Fibroid (19%) |
| Dasgupta 2011a (India) | N=274 women with abnormal uterine bleeding for at least 3 months, age range 40-50 years of which N=252 included in final analysis<br>Proportion with HMB not reported.<br>Exclusions: uterus larger than that at 12 weeks' gestation; hormone therapy within the last 6 months; previous abnormal endometrial biopsy; positive pregnancy test; cervical pathology on speculum examination; abnormal cervical Pap smear; active pelvic infection | 2D-TVUS | Histopathology (hysteroscopy-guided biopsy) | • Polyp (12%)<br>• Submucosal fibroid (18%) |
| Dasgupta 2011b (India) | N=100 perimenopausal (40-55 years old) women with abnormal uterine bleeding who had been on oral progesterone therapy for at least 10 days of which n=83 were included in final analysis | 2D-TVUS | Histopathology (hysteroscopy-guided biopsy) | • Any abnormal finding (65%)<br>• Polyp (13%)<br>• Fibroid (16%) |

| Study | Population | Index test | Reference standard | Target condition (prevalence) |
|---|---|---|---|---|
| | Proportion with HMB not reported. Exclusions: uterus larger than that at 12 weeks' gestation; previous abnormal endometrial biopsy; cervical lesion on speculum examination; abnormal Pap smear; active pelvic infection; adnexal mass on clinical examination or during ultrasound scan; positive pregnancy test | | | |
| Dueholm 2001a (Denmark) | N=452 women less than 55 years of age with abnormal uterine bleeding Proportion with HMB not reported. Exclusions: hormone replacement therapy and indefinite menopausal status with duration of hormone replacement therapy less than 3 years | 2D-TVUS | Histopathology (hysteroscopy-guided biopsy or hysterectomy) | • Polyp or fibroid (62%) |
| Erdem 2007 (Turkey) | N=133 women with abnormal uterine bleeding of which n=122 in final analysis 78% premenopausal, 22% postmenopausal Proportion with HMB not reported. Exclusions: bleeding due to pregnancy or pelvic infections; premenopausal | 2D-TVUS | Histopathology (hysterectomy, hysteroscopy-guided biopsy, or D&C) | • Polyp (50%)<br>• Submucosal fibroid (16%)<br>• Abnormal endometrial thickness/endometrial hyperplasia (3%) |

| Study | Population | Index test | Reference standard | Target condition (prevalence) |
|---|---|---|---|---|
| | women who had received hormonal therapy | | | |
| Fakhar and Mahmud 2010 (Pakistan) | N=290 women 35 years old or more with abnormal uterine bleeding of which n=223 included in final analysis 66.2% with HMB. Exclusions: refusal of procedure; incomplete follow-up; positive pregnancy test; recent cervicitis, vaginitis, endometritis, pelvic infection, or uterine perforation; non-availability of histopathology reports | Hysteroscopy (mostly outpatient) | Histopathology (hysteroscopy-guided biopsy) | • Adenocarcinoma (1%) <br> • Retained products of conception (2%) <br> • Polyp (9%) <br> • Hyperplasia (12%) <br> • Endometritis (20%) |
| Krampl 2001 (Norway) | N=100 women with abnormal uterine bleeding 89% premenopausal Proportion with HMB not reported. Exclusions: an endometrial biopsy within the past 1 year; large multiple fibroid causing discomfort; patients considered medically unfit for general or spinal anaesthesia | • 2D-TVUS <br> • Hysteroscopy (under spinal or general anaesthetic) | Histopathology (hysteroscopy-guided biopsy) | • Abnormal endometrial thickness (double-layer endometrium 12 mm or thicker and single-layer endometrium 6 mm or thicker) (10%) <br> • Focal pathology (polyp or fibroid) (24%) |
| Mukhopadhyay 2007 (India) | N=85 perimenopausal women aged 40-55 years with abnormal uterine bleeding Proportion with HMB not reported. Exclusions: active bleeding per vagina; atrophic | • 2D-TVUS <br> • Hysteroscopy (under general anaesthetic) | Histopathology (hysteroscopy-guided biopsy or D&C) | • Polyp (17%) <br> • Hyperplasia (17%) |

| Study | Population | Index test | Reference standard | Target condition (prevalence) |
|---|---|---|---|---|
| | vaginitis; carcinoma cervix; cervical polyp; bleeding following trauma; varicose vein | | | |
| Najeeb 2010 (Pakistan) | N=141 perimenopausal women with abnormal uterine bleeding aged 40-47 years Proportion with HMB not reported. Exclusions: any form of hormonal treatment; known gynaecological malignancy; endocrinological disorder | 2D-TVUS | Histopathology (D&C) | • Polyp (23%)<br>• Fibroid (4%) |
| Nanda 2002 (India) | N=50 women with abnormal uterine bleeding, aged 30-50 years, undergoing hysterectomy Proportion with HMB not reported. Exclusions: none specified | 2D-TVUS | Histopathology (hysterectomy) | • Submucosal fibroid (38%)<br>• Polyp (6%) |
| Soguktas 2012 (Turkey) | N=93 premenopausal women with abnormal uterine bleeding related to uterine cavity abnormality of which n=89 were included in final analysis Proportion with HMB not reported. Exclusions: pelvic infection; pregnancy; abnormal uterine bleeding without iuterine cavity abnormality | • 2D-TVUS<br>• Hysteroscopy (under general anaesthetic) | Histopathology (hysteroscopy-guided biopsy or D&C) | • Polyp (38%)<br>• Submucosal fibroid (5%)<br>• Hyperplasia (8%)<br>• Endometrial carcinoma (2%)<br>• Any abnormal finding (53%) |
| Taylor 2001 (UK) | N=264 premenopausal women with abnormal uterine bleeding | 2D-TVUS | Hysteroscopy or hysteroscopy-guided biopsy | • Polyp (17%)<br>• Suspicious focal thickening (3%) |

| Study | Population | Index test | Reference standard | Target condition (prevalence) |
|---|---|---|---|---|
| | Proportion with HMB not reported. Exclusions: none specified | | | |
| Vercellini 1997 (Italy) | N=793 women with HMB Exclusions: women with IUD; hormonal treatment in the last 3 months (6 months for GnRh); women who had already undergone D&C or diagnostic or operative hysteroscopy | 2D-TVUS | Hysteroscopy | • Any abnormal finding (58%) |
| Williams and Marshburn 1998 (US) | N=47 women with abnormal uterine bleeding that had not responded to medical treatment of which n=39 included in final analysis 92% premenopausal Proportion with HMB not reported. Exclusions: inability to undergo endovaginal ultrasonography; refusal to undergo hysteroscopy; interval pregnancy; suspected current cervical, uterine or tubal infection; suspected anovulatory (dysfunctional) bleeding; active menstrual bleeding | 2D-TVUS | Hysteroscopy or histopathology from hysterectomy | • Any abnormal finding (31%) |
| Yildiz 2009 (Turkey) | N=86 women with abnormal uterine bleeding 84% premenopausal 65.1% of total sample with menometrorrhagia | Hysteroscopy (under general, local or no anaesthetic) | Histopathology (hysteroscopy-guided biopsy or hysterectomy) | • Any abnormal finding (81%) |

| Study | Population | Index test | Reference standard | Target condition (prevalence) |
|---|---|---|---|---|
| | Exclusions: genital malignancy; pregnancy | | | |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; 3D-TVUS: three-dimensional transvaginal ultrasound scan; D&C: dilatation and curettage; GA: general anaesthesia; HMB: heavy menstrual bleeding;*

### Table 3: Summary of included studies on patient satisfaction and acceptability

| Study | Population | Test(s) | Outcomes | Comments |
|---|---|---|---|---|
| Critchley 2004 (UK) | n=326 premenopausal women aged 40 years or more, or aged less than 40 years with risk factors, 68% with HMB<br><br>(Total N=683 women with abnormal uterine bleeding in three groups based on level of risk of endometrial cancer:<br><br>High risk group: n=200 postmenopausal women (not of interest to this review)<br><br>Moderate risk group: n=326 premenopausal women aged 40 years or more, or aged less than 40 years with risk factors, 68% with HMB<br><br>Low risk group: n=157 premenopausal women aged less than 40 years without risk factors, 57% with HMB (not of interest to this review)) | • Blind endometrial biopsy<br>• Hysteroscopy<br>• TVUS or TAUS | • Found procedure 'markedly unpleasant'<br>• Abdominal discomfort<br>• Experiences about the clinic visit and health 1 day, 10 months, and 24 months after investigation | • Unblinded trial (due to the nature of investigations)<br>• Only descriptive reporting of evidence on patient satisfaction/acceptability<br>• All women underwent biopsy |

*HMB: heavy menstrual bleeding; TAUS: transabdominal ultrasound scan; TVUS: transvaginal ultrasound scan*

See Appendix F – Clinical evidence tables for full evidence tables.

## Quality assessment of clinical studies included in the evidence review

Studies providing evidence on the diagnostic accuracy of ultrasound and hysteroscopy in investigating women presenting with heavy menstrual bleeding were individually assessed using the QUADAS-2 checklist. QUADAS-2 assesses the risk of bias in the study and the applicability of the study for the review question.

The quality of each piece of evidence, whether from meta-analysis or from individual studies was then assessed using adapted GRADE methodology. See Appendix G – GRADE tables for full GRADE tables.

The quality of the study providing evidence on the patient acceptability and satisfaction of ultrasound and hysteroscopy was assessed using the Cochrane Collaboration's tool for assessing risk of bias. The tool assesses the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. The overall quality of the evidence was based on the assessment of all of these.

For more details on the quality assessment of clinical studies in the evidence review, please see Methods chapter.

## Economic evidence

### Included studies

One cost-effectiveness analysis (Cooper 2014) was found for inclusion in this review, see Table 4. A narrative review of this study is provided in the Health cconomics chapter.

### Excluded studies

There were no excluded economic studies relating to the diagnosis of heavy menstrual bleeding.

## Summary of studies included in the economic evidence review

**Table 4: Summary of studies included in the economic evidence review**

| Study | Limitations | Applicability | Other comments | Costs | Effects | Inc. cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| Cooper 2014 (UK)<br><br>Population: Women with HMB, a mean age of 45 years and referred from primary care<br><br>Interventions:<br>1. LNG-IUS alone<br>2. hysterectomy alone<br>3. OPH<br>4. TVS<br>5. EBx<br>6. SIS<br>7. OPH and EBx<br>8. TVS and EBx<br>9. SIS and EBx<br>10. OPH and SIS<br>11. OPH and TVS<br>12. SIS, OPH and EBx | Potentially serious [a, b] | Directly [c] | Decision trees developed for 13 investigation strategies.. Estimated that a woman's QoL is reduced by 0.5 for the 1 week per month of heavy menses ~ HMB is associated with a reduction of 0.125 QALYs in any year. Analyses on PMB also undertaken. Parameter inputs were derived from systematic reviews, individual patient data and focused searches and in the absence of estimates, the consensus view of an expert clinical panel was obtained. | Total cost per patient over 1 year:<br>LNG-IUS alone £1067<br>OPH alone £1078<br>SIS alone £1083<br>TVUS alone £1085<br>TVUS+OPH £1139<br>OPH+EBx £1149<br>SIS+OPH £1170<br>EBx alone £1209<br>SIS+EBx £1223<br>TVUS+OPH+EBx £1227<br>TVUS+EBx £1231<br>SIS+OPH+EBx £1256<br>Hysterectomy alone £3182 | Satisfaction (0 to 100% scale) at 1 year:<br>LNG-IUS alone 0.933327<br>OPH alone 0.964122<br>SIS alone 0.962914<br>TVUS alone 0.955106<br>TVUS+OPH 0.964382<br>OPH+EBx 0.967421<br>SIS+OPH 0.96445<br>EBx alone 0.945963<br>SIS+EBx 0.964271<br>TVUS+OPH+EBx 0.964933<br>TVUS+EBx 0.953851<br>SIS+OPH+EBx 0.965028<br>Hysterectomy alone 0.9335 | OPH alone and OPH+EBx remain non-dominated by alternative empirical treatment or diagnostic testing strategies.<br>OPH alone dominates the testing strategies SIS alone and TVUS alone. The combination testing strategy TVUS + OPH is excluded by extended dominance between OPH alone and OPH + EBx. The remaining 7 alternative strategies are dominated by OPH + EBx.<br>ICER (to gain an extra woman satisfied following treatment for HMB):<br>The most effective strategy is the OPH+EBx, generating an ICER of £21,500 compared with OPH alone and an ICER of £21,859 when compared with LNG-IUS alone. OPH alone is less effective than OPH+EBx, but is less costly with an ICER of £360.<br>Estimate that an ICER of £21,000 per case satisfied is approximately equivalent to an ICER of £26,500 per QALY, which falls within the £20,000–30,000 per QALY threshold range. Hence, OPH+EBx maybe cost-effective compared to OPH alone. | In PSA OPH remained more cost-effective than the LNG-IUS even at relatively low WTP thresholds. OPH+EBx also remained stable, to be at least 70% certain that it was a more cost-effective alternative than OPH alone, the WTP threshold would need to be £40,000 per patient satisfied (~£50,000 per QALY). Deterministic SA and additional PSA also performed [d]. |

| Study | Limitations | Applicability | Other comments | Costs | Effects | Inc. cost-effectiveness | Uncertainty |
|---|---|---|---|---|---|---|---|
| 13. TVS, OPH and EBx. | | | | | | | |

EBx: endometrial biopsy; OPH: outpatient hysterectomy; SIS: saline infusion sonography; TVUS: transvaginal ultrasound scan; PMB: postmenopausal bleeding; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay

(a) 1-year time horizon may not be sufficiently long to reflect all important differences in costs and outcomes

(b) Unclear if all important outcomes have been captured using 'satisfaction' as the measure of effect

(c) This study does not use the preferred measure of effects (QALYs) as the primary measure of effects, but is still thought to be useful for decision making given that all other criteria are applicable and an approximation to QALYs is provided

(d) Sensitivity analysis  (non-dominated strategies): women being managed during multiple clinic appointments (LNG-IUS alone, SIS alone, OPH+EBx), prior treatment with the levonorgestrel-releasing intrauterine system (OPH alone, TVUS+EBx), women wishing to preserve their fertility (LNG-IUS alone, SIS alone, OPH alone, SIS+OPH)

## Economic model

A cost utility analysis was developed to compare the cost-effectiveness of a range of diagnostic and management strategies. A Markov (state transition) model was developed to evaluate the costs and health related quality of life (HRQoL), measured in Quality Adjusted Life Years (QALYs), over a 5-year time frame.

The entry point for the model was women aged 42 years, presenting with heavy menstrual bleeding in an NHS primary care setting. The model could be run for up to 5 diagnostic strategies, including strategies involving treatment without any prior investigation:

- levonorgestrel-releasing intrauterine (LNG-IUS) alone
- hysterectomy alone
- outpatient hysteroscopy
- TVUS
- endometrial biopsy.

The decision analytic framework follows the approach used in a previous health economic evaluation (Cooper 2014) and the structure for one of the diagnostic strategies is illustrated in Figure 1.

**Figure 1: An example decision tree to illustrate model structure for the diagnosis of underlying pathology in women with heavy menstrual bleeding**
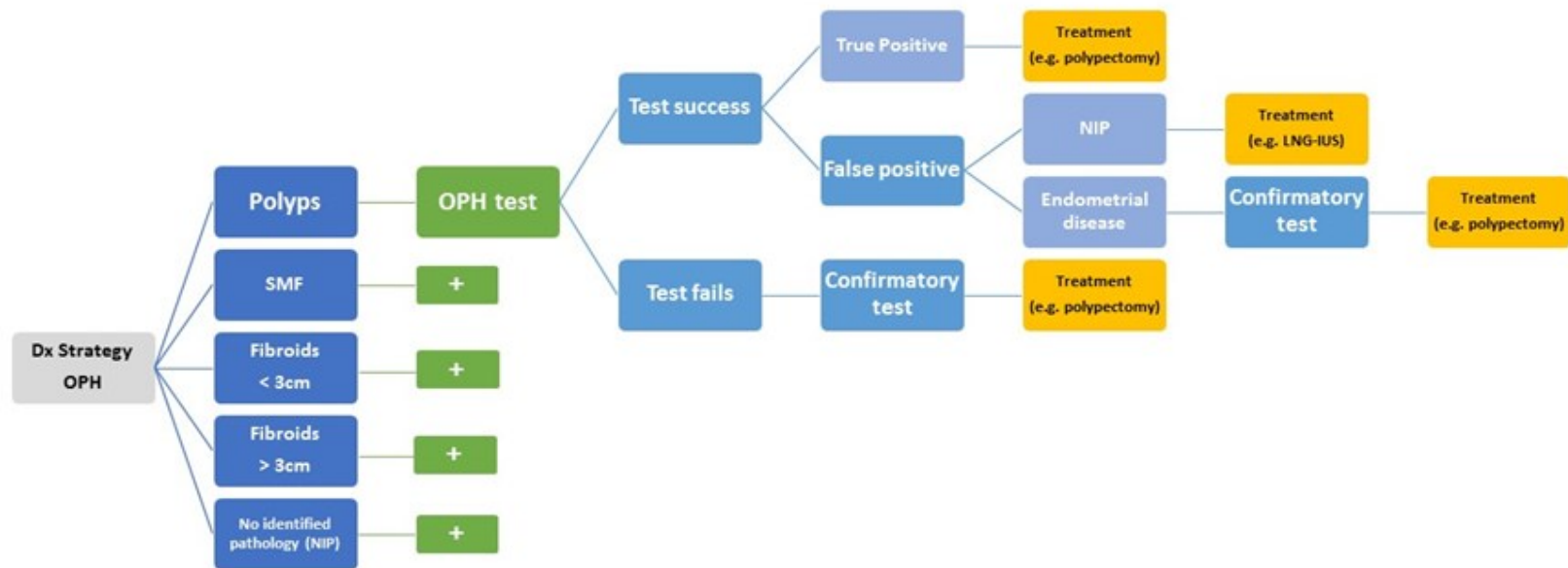


Dx: diagnosis; HMB: heavy menstrual bleeding; LNG-IUS: levonorgestrel-releasing intrauterine system; NIP: no identified pathology; OPH: outpatient hysteroscopy; SMF: submucosal fibroids

The outcome of the diagnostic tests was used to direct treatment according to the woman's underlying pathology. In the model, diagnostic test accuracy was used to estimate the proportion of women who would be correctly identified and receive the appropriate first line treatment. False positive rates were estimated to determine the proportion of women who would receive 'incorrect' treatment based on a diagnosis that differed from their true underlying pathology. The model comprised 5 underlying pathologies (polyps, submucosal fibroids, fibroids less than 3 cm in diameter, fibroids 3 cm or more in diameter and no identifiable pathology) and a simplifying assumption was made that the woman could only have a single underlying pathology.

The following surgical and pharmacological interventions were included as possible treatment alternatives in the model:

- LNG-IUS
- tranexamic acid
- combined oral contraceptives
- hysterectomy
- first generation endometrial ablation techniques
- second generation endometrial ablation techniques
- transcervical resection of fibroids
- nonsteroidal anti-inflammatory drugs
- medroxyprogesterone acetate
- polypectomy.

One important limitation of the model relates to how treatment gain was ascertained. Diagnosis of the underlying pathology is considered important to direct the woman to the most appropriate treatment. However, there are treatments which can be considered appropriate across a range of pathologies which is why empiric treatment with LNG-IUS, for example, can be considered as a plausible clinical option and is commonly used in UK current practice. This means that a woman incorrectly diagnosed can potentially still receive appropriate treatment. Furthermore, the network meta-analysis (NMA) EuroQol five dimensions questionnaire (EQ-5D) data allows a QALY gain to be estimated according to the treatment received but not according to the appropriateness of that treatment for the underlying pathology. To address this the committee were asked to dichotomise treatments according to whether they thought they were effective or not for a given pathology. Again this was a simplifying assumption as the committee acknowleged that a treatment may still provide some benefit for a given pathology even if it was considered sub-optimal. To reflect the uncertainty about the effectiveness of treatments the committee classified the treatments by pathology as always effective, partially effective and never effective. In the base case scenario it was assumed that both effective and partially effective treatments for a particular pathology would give the QALY gain derived from the NMA when used for a woman with that pathology. However, as a sensitivity analysis, a more conservative assumption was made where QALY gain was limited to only those treatments deemed effective for a given pathology. No QALY gain would result if the woman received a treatment assessed as only partially effective for her underlying uterine pathology in this sensitivity anaysis.

The analysis used probabilistic sensitivity analysis (PSA) to generate results. This involves Monte Carlo simulation where, instead of using a deterministic model input value, those values subject to uncertainty around their point estimate are sampled from a probability distribution over multiple iterations. The mean costs and QALYs are then calculated over these simulations and used to generate a mean net monetary benefit (NMB) which is calculated as follows:

NMB = QALY x cost-effectiveness threshold – cost

In line with NICE social value judgements (https://www.nice.org.uk/media/default/about/what-we-do/research-and-development/social-value-judgements-principles-for-the-development-of-nice-guidance.pdf) described in the methods chapter, a cost-effectiveness threshold of £20,000 per QALY was used. The strategy with the highest mean NMB was the most cost-effective strategy although to help assess any uncertainty an estimate was also made of the probability that a particular strategy was the most cost-effective. This was based on the proportion of simulations that the strategy is assessed as the most cost-effective.

The model results suggested that empiric LNG-IUS was a cost-effective strategy under the base case assumptions about treatment gain with a NMB of £30,131 and a 96.8% probability of being cost-effective. Under conservative assumption where LNG-IUS was deemed to be an appropriate treatment for a smaller subset of underlying pathology then that was no longer the case with the NMB falling to £19,039.

When treatment alternatives were held constant the model did not find large differences in the mean NMB of the 3 diagnostic tests compared. However, endometrial biopsy was dominated (the most expensive test strategy and the strategy generating the least QALY gain) by both TVUS and outpatient hysteroscopy. The comparison of the relative cost-effectiveness of outpatient hysteroscopy and TVUS is more complicated. The analyses suggested that TVUS was a more costly strategy than outpatient hysteroscopy despite being the cheaper diagnostic test. This is because outpatient hysteroscopy facilitates a "see and treat" approach, lowering the combined cost of diagnosis and treatment. In the context of initial presentation of the woman with HMB in primary care, TVUS was generally more cost-effective than outpatient hysteroscopy. This is because the overall diagnostic hysteroscopy may be limited where the prevalence of intramural or subserosal fibroids is sufficiently high as these would not be detected. However, empiric pharmacological treatment is considered to be effective for intramural and subserosal fibroids less than 3cm in diameter whereas women with a different underlying pathology, where outpatient hysteroscopy has superior diagnostic accuracy, are more likely to be refractory to such pharmacological treatment. Therefore, the prevalence of intramural and subserosal fibroids less than 3cm in diameter is likely to be much reduced when considering investigation in a population of women refractory to pharmacological treatment and referred to secondary care. Consequently, as indicated by sensitivity analysis, outpatient hysteroscopy becomes more cost-effective relative to TVUS as the prevalence of intramural and subserosal fibroids of less than 3 cm in diameter as the underlying pathology in women presenting with HMB falls. As reflected in the recommendations, it is likely that outpatient hysteroscopy would be the most cost-effective diagnostic test strategy for women with a history suggesting polyps or SMFs, and that TVUS would be the most cost-effective test where intramural and subserosal fibroids were suspected.

Pharmacological treatments generated relatively high mean NMB values when using base case assumptions about treatment gain across the underlying uterine pathologies.This may support their use in primary care, especially in women who are not refractory to treatment. Whilst hysterectomy is the most expensive intervention, analyses showed scenarios where it would be more cost-effective than other surgical intervention, such as second generation endometrial ablation.

This model is described in more detail in the Health economics chapter.

## Resource impact

The guideline recommendations are likely to lead to a change in current practice with outpatient hysteroscopy being the recommended investigation in preference to pelvic ultrasound, for women with HMB when polyps, submucous fibroids or endometrial pathology

are suspected. This change in practice will have a resource impact on service organisation and training.

Ultrasound is widely available through direct booking in primary care, whereas hysteroscopy is not. Changes to services will be needed to allow direct access booking into one-stop hysteroscopy services and to increase delivery in community-based clinics. GPs or nurses may need training to perform hysteroscopy in primary care. However, the commitee anticipate that there should be ongoing savings as the number of unnecessary investigations is reduced and women are offered effective treatment as a result of more accurate diagnosis.

Although diagnostic hysteroscopy is more expensive than transvaginal ultrasound the economic analysis undertaken for this guideline suggested that it may be a cheaper strategy overall. This is largely because diagnostic hysteroscopy can facilitate a 'see and treat' approach for women with polyps or submucosal fibroids which obviates the need for treatment at a later date.

Women who decline hysteroscopy can receive the investigation under anaesthesia. This was not formally considered in the analysis as the numbers of women was considered to be a relatively small sub-group of the population having diagnostic hysteroscopy, approximately 10% in the oinion of the committee. These women in turn are a sub-group of those with HMB, many of whom will commence empiric treatment without diagnostic investigation. Therfore, the recommendation with respect to hysterectomy under anaesthesia is not expected to have an important resource impact on the NHS.

The committee also believe that the recommendation to not offer 'blind' endometrial biopsy will lead to a reduction in unnecessary investigations with resulting savings to the NHS.

## Evidence statements

### Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting polyps

Very low quality evidence from 9 studies (n=955) found 2D-TVUS to have low sensitivity and high specificity in detecting polyps. LR+ indicated that 2D-TVUS is moderately useful in 'ruling in' polyps but LR- indicated that 2D-TVUS is not useful in 'ruling out' polyps. The studies came from India, Iran, Italy, Pakistan and Turkey and were published between 1995 and 2012.

This meta-analysis showed high heterogeneity especially for sensitivity, therefore, possible reasons for heterogeneity were explored and subgroup analysis was conducted when possible according to pre-specified groups in the protocol. Studies published before 2007 were excluded because the committee considered that technology has developed rapidly over the last years and older studies might not be comparable to newer studies. The subgroup analysis with 7 studies (n=853) including studies published in 2007 or later showed no considerable change in the results or heterogeneity of sensitivity. The quality of the evidence was very low.

### Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting fibroids

Very low quality evidence from 8 studies (n=870) found 2D-TVUS to have moderate sensitivity and high specificity in detecting fibroids. LR+ indicated that 2D-TVUS is very useful in 'ruling in' fibroids whereas LR- indicated that 2D-TVUS is not useful in 'ruling out' fibroids. The studies came from India, Iran, Italy, Pakistan and Turkey and were published between 1995 and 2012.

This meta-analysis showed moderate heterogeneity, therefore, possible reasons for heterogeneity were explored and subgroup analysis was conducted when possible according to pre-specified groups in the protocol. Studies published before 2007 were excluded. The

subgroup analysis with 6 studies (n=768) including studies published in 2007 or later showed no considerable change in the results or heterogeneity. The quality of the evidence was very low.

Additionally, because hysteroscopy-guided biopsy or D&C are considered inadequate to histologically confirm fibroids, evidence on the diagnostic accuracy of 2D-TVUS compared to histopathology from hysterectomy alone was considered separately. Very low quality evidence from 2 studies showed mixed findings. One study (n=52) from Italy from 1995 showed 2D-TVUS to have high sensitivity in detecting fibroids whereas the other study (n=50) from India from 2002 showed 2D-TVUS to have low sensitivity in detecting fibroids. LR+ evidence from both studies indicated that 2D-TVUS is a very useful test in 'ruling in' fibroids. LR- evidence from one study indicated 2D-TVUS to be very useful in 'ruling out' fibroids whereas LR- evidence from the other study indicated 2D-TVUS to not be useful in 'ruling out' fibroids.

### Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting polyps or fibroids

Very low quality evidence from 1 study (n=189) from Denmark from 2001 showed 2D-TVUS to have high sensitivity but low specificity in detecting either polyps or fibroids. On the contrary, very low quality evidence from 1 study (n=88) from Norway from 2001 showed 2D-TVUS to have low sensitivity and high specificity in detecting polyps or fibroids. LR+ evidence from both studies indicated that 2D-TVUS is not useful in 'ruling in' polyps or fibroids. LR- evidence from the first study indicated that 2D-TVUS is moderately useful in 'ruling out' polyps or fibroids whereas LR- evidence from the second study indicated that it is not useful.

### Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting endometrial hyperplasia

Very low quality evidence from 3 studies (n=122; n=85; n=89) showed 2D-TVUS to have low to borderline moderate sensitivity and moderate to high specificity in detecting endometrial hyperplasia. LR+ indicated the test to be moderately to very useful in 'ruling in' hyperplasia whereas LR- indicated that the test is not useful in 'ruling out' endometrial hyperplasia. The studies were published in 2007 and 2012 and two came from Turkey and one from India.

### Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting endometrial carcinoma

Very low quality evidence from 1 study (n=89) from Turkey from 2012 showed 2D-TVUS to have low sensitivity and high specificity in detecting endometrial carcinoma. LR+ indicated the test to be moderately useful in 'ruling in' carcinoma and LR- indicated the test to be not useful in 'ruling out' carcinoma.

### Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting abnormal endometrial thickness (double-layer endometrium 12 mm or thicker and single-layer endometrium 6 mm or thicker)

Very low quality evidence from 1 study (n=88) from Norway from 2001 showed 2D-TVUS to have low sensitivity and moderate specificity in detecting abnormal endometrial thickness (double-layer endometrium 12 mm or thicker and single-layer endometrium 6 mm or thicker). LR+ and LR- indicated that the test is not useful in 'ruling in' or 'ruling out' abnormal endometrial thickness.

### Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting any abnormal finding

Very low to low quality evidence from 4 studies (n=213; n=83; n=89; n=39) showed mixed findings relating to any abnormal finding (for example abnormal thickness, hyperplasia,

carcinoma, polyp or fibroid). Two studies showed 2D-TVUS to have moderate to high sensitivity whereas two studies showed low sensitivity. Two studies showed 2D-TVUS to have moderate to high specificity, whereas two studies showed low specificity. LR+ in the studies indicated 2D-TVUS to be either moderately useful or not useful in 'ruling in' any abnormal finding. LR- in the studies varied. In one study LR- indicated that 2D-TVUS is very useful in 'ruling out' any abnormal finding, in another study LR- indicated that 2D-TVUS is moderately useful, whereas in the two other studies LR- indicated that 2D-TVUS is not useful in 'ruling out' any abnormal finding.

### Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) in detecting polyps

Very low quality evidence from 2 studies (n=89; n=85) from Turkey and India from 2012 and 2007 show mixed results. The evidence from both studies showed hysteroscopy under general anaesthetic to have high specificity in detecting polyps, however, sensitivity was high in one study and low in the other study. LR+ in both studies indicated that hysteroscopy under general anaesthetic is very useful in 'ruling in' polyps. However, LR- in one study indicated that hysteroscopy under general anaesthetic is very useful in 'ruling out' polyps but LR- in the other study indicated that hysteroscopy under general anaesthetic is not useful in 'ruling out' polyps.

### Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting polyps

Very low quality evidence from 2 studies (n=52; n=269) from Italy and Pakistan from 1995 and 2010 showed outpatient hysteroscopy to have moderate to high sensitivity and high specificity in detecting polyps. LR+ and LR- indicated that outpatient hysteroscopy is very useful in 'ruling in' and 'ruling out' polyps.

### Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) in detecting fibroids

Very low quality evidence from 1 study (n=89) from Turkey from 2012 showed hysteroscopy under general anaesthetic to have high sensitivity and specificity in detecting fibroids. LR+ and LR- indicated that hysteroscopy under general anaesthetic is very useful in 'ruling in' and 'ruling out' fibroids.

### Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting fibroids

Very low quality evidence from 1 study (n=51) from Italy from 1995 showed outpatient hysteroscopy to have high sensitivity and specificity in detecting fibroids. LR+ and LR- indicted outpatient hysteroscopy to be very useful in 'ruling in' and 'ruling out' fibroids.

### Diagnostic accuracy of hysteroscopy under spinal or general anaesthetic (versus histopathology) in detecting polyps or fibroids

Very low quality evidence from 1 study (n=88) from Norway from 2001 showed day case hysteroscopy to have high sensitivity and moderate specificity in detecting either polyps or fibroids. LR+ indicated day case hysteroscopy to be moderately useful in 'ruling in' polyps or fibroids and LR- indicated that day case hysteroscopy to be very useful in 'ruling out' polyps or fibroids.

### Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) following a 2D-TVUS in detecting polyps or fibroids

Very low quality evidence from 1 study (n=50) from Egypt from 2016 showed hysteroscopy under general anaesthetic following a 2D-TVUS to have moderate sensitivity and high specificity in detecting either polyps or fibroids. LR+ indicated hysteroscopy under general

anaesthetic following 2D-TVUS to be very useful in 'ruling in' polyps and fibroids and LR-indicated hysteroscopy under general anaesthetic following 2D-TVUS to be moderately useful in 'ruling out' polyps or fibroids.

### Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) in detecting endometrial hyperplasia

Very low quality evidence from 2 studies (n=89; n=85) from Turkey and India from 2012 and 2007 showed mixed findings. Both studies showed hysteroscopy under general anaesthetic to have high specificity in detecting endometrial hyperplasia, however, one study showed low sensitivity and the other study moderate sensitivity. LR+ from both studies indicated that hysteroscopy under general anaesthetic is very useful in 'ruling in' hyperplasia, whereas LR- in one study indicated hysteroscopy under general anaesthetic is moderately useful in 'ruling out' hyperplasia and LR- in the other study indicated hysteroscopy under general anaesthetic not to be useful in 'ruling out' hyperplasia.

### Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting endometrial hyperplasia

Very low quality evidence from 1 study (n=269) from Pakistan from 2010 showed outpatient hysteroscopy to have low sensitivity and high specificity in detecting endometrial hyperplasia. LR+ indicated that outpatient hysteroscopy is moderately useful in 'ruling in' endometrial hyperplasia whereas LR- indicated the test to not be useful in 'ruling out' endometrial hyperplasia.

### Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) in detecting endometrial carcinoma

Very low quality evidence from 1 study (n=89) from Turkey from 2012 showed hysteroscopy under general anaesthetic to have high sensitivity and specificity in detecting endometrial carcinoma. LR+ and LR- indicated that hysteroscopy under general anaesthetic is very useful in 'ruling in' and 'ruling out' endometrial carcinoma.

### Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting endometrial carcinoma

Very low quality evidence from 1 study (n=269) from Pakistan from 2010 showed outpatient hysteroscopy to have high sensitivity and specificity in detecting endometrial carcinoma. LR+ and LR- indicated that outpatient hysteroscopy is very useful in 'ruling in' and 'ruling out' endometrial carcinoma.

### Diagnostic accuracy of hysteroscopy under spinal or general anaesthetic (versus histopathology) in detecting abnormal endometrial thickness (double-layer endometrium 12 mm or thicker and single-layer endometrium 6 mm or thicker)

Very low quality evidence from 1 study (n=88) from Norway from 2001 showed day case hysteroscopy to have low sensitivity and moderately high specificity in detecting abnormal endometrial thickness (double-layer endometrium 12 mm or thicker and single-layer endometrium 6 mm or thicker). LR+ and LR- indicates that day case hysteroscopy is not useful in 'ruling in' or 'ruling out' abnormal endometrial thickness.

### Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting endometritis

Very low quality evidence from 1 study (n=269) from Pakistan from 2010 showed outpatient hysteroscopy to have low sensitivity but high specificity in detecting endometritis. LR+ indicated that outpatient hysteroscopy is very useful in 'ruling in' endometritis whereas LR- indicated that outpatient hysteroscopy is not useful in 'ruling out' endometritis.

**Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting retained products of conception**

Very low quality evidence from 1 study (n=269) from Pakistan from 2010 showed outpatient hysteroscopy to have high sensitivity and specificity in detecting retained products of conception. LR+ and LR- indicated that outpatient hysteroscopy is very useful in 'ruling in' and 'ruling out' retained products of conception.

**Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) in detecting any abnormal finding**

Very low quality evidence from 1 study (n=89) from Turkey from 2012 showed hysteroscopy under general anaesthetic to have high sensitivity and specificity in detecting any abnormal finding (defined as polyp, fibroid, hyperplasia or carcinoma). LR+ and LR- indicated that hysteroscopy under general anaesthetic is very useful in 'ruling in' and ruling out' any abnormal finding.

**Diagnostic accuracy of hysteroscopy with or without general or local anaesthetic (versus histopathology) in detecting any abnormal finding**

Very low quality evidence from 1 study (n=86) from Turkey from 2009 showed hysteroscopy (with general anaesthesia, with spinal anaesthesia or without any anaesthesia) to have high sensitivity and specificity in detecting any abnormal finding (defined as presence of adhesion, polyp, submucosal fibroid, pressure effect or any other abnormality in the uterine cavity). LR+ and LR- indicated that hysteroscopy is very useful in 'ruling in' or 'ruling out' abnormal endometrial finding.

**Diagnostic accuracy of 2D-TVUS (versus hysteroscopy) in detecting polyps**

Very low quality evidence from 1 study (n=196) from the UK from 2001 showed that 2D-TVUS and hysteroscopy compare poorly in terms of sensitivity but compare well in terms of specificity in detecting polyps.

**Diagnostic accuracy of 2D-TVUS (versus hysteroscopy) in detecting suspicious focal thickening**

Very low quality evidence from 1 study (n=196) from the UK from 2001 showed that 2D-TVUS and hysteroscopy compare poorly in terms of sensitivity but compare well in terms of specificity in detecting suspicious focal thickening.

**Diagnostic accuracy of 2D-TVUS (versus hysteroscopy) in detecting any abnormal finding**

Moderate quality evidence from 1 study (n=770) from Italy from 1997 showed that 2D-TVUS and hysteroscopy compare well in terms of sensitivity and moderately well in terms of specificity in detecting abnormal endometrial finding (defined as a lesion inside the cavity or when the maximum endometrial thickness measured in the sagittal plane was more than 14 mm).

**Patient acceptability and satisfaction**

Very low quality evidence was obtained from 1 study (n=326) from the UK from 2004 among premenopausal women either aged 40 years or more, or aged less than 40 years but with specific risk factors for endometrial cancer, who were undergoing investigations for abnormal uterine bleeding (68% had heavy menstrual bleeding). This study showed that more women who underwent hysteroscopy (with biopsy) and blind endometrial biopsy alone reported the investigation to be 'markedly unpleasant' than women who underwent ultrasound investigation. No difference were observed in the reporting of abdominal discomfort at home one day after investigation between women who underwent hysteroscopy and women who

did not undergo hysteroscopy or between women who underwent ultrasound and women who did not undergo ultrasound.

The study also reported on feelings about the investigation one day after the clinic visit and the results did not show marked differences between women who underwent hysteroscopy, who did not undergo hysteroscopy, who underwent ultrasound, and who did not undergo ultrasound. Similarly, no marked differences were observed in how worthwhile the women in these different groups considered the clinic visit.

At 10 months post-investigation, only minimal differences were observed across intervention groups on self-report for persistence of symptoms and failure to cure the problem. The differences in responses for being satisfied with care, being reassured by clinic attendance, being glad to have attended the clinic, and feeling it was worthwhile attending the clinic were small, however, they seemed to favour either hysteroscopy or ultrasound rather than blind endometrial biopsy alone. Similar patterns were observed at 24 months post-investigation.

## Health economic evidence statements

One cost-utility analysis (Cooper 2014) undertaken in the UK included 13 different strategies: transvaginal ultrasound scan, saline infusion sonography, global endometrial biopsy and outpatient hysteroscopy used alone, or in combination. LNG-IUS alone and hysterectomy alone were also included as empiric treatment strategies. Using a 1-year time horizon, they found outpatient hysteroscopy alone and outpatient hysteroscopy plus endometrial biopsy to remain non-dominated by alternative empirical treatment or diagnostic testing strategies. The most effective strategy is outpatient hysteroscopy plus endometrial biopsy, generating an ICER of £21,500 (cost to gain an extra woman satisfied following treatment for HMB) compared with outpatient hysteroscopy alone and an ICER of £21,859 when compared with LNG-IUS alone. Outpatient hysteroscopy alone is less effective than outpatient hysteroscopy plus endometrial biopsy, but is less costly with an ICER of £360. If HMB is associated with a reduction of 0.125 QALYs in any year, they estimate that an ICER of £21,000 per case satisfied is approximately equivalent to an ICER of £26,500 per QALY. This analysis is directly applicable with potentially serious limitations.

An economic model developed for the guideline found that empiric treatment with LNG-IUS was cost-effective when compared to strategies where diagnosis was used to determine treatment under the assumption that LNG-IUS was effective for all underlying pathology (see Health Economics Chapter, Analyses 1, 3, and 10).

An economic model developed for the guideline found that TVUS was cost-effective when compared to empiric LNG-IUS, EBx and OPH under conservative assumptions about the treatment effectiveness of LNG-IUS ((see Health Economics Chapter, Analyses 2 and 11).

An economic model developed for the guideline found that TVUS was cost-effective compared to EBx and OPH when empiric treatment was not alternative for given set of commonly used first and second line treatments (Analyses 5 and 6).

An economic model developed for the guideline found that TVUS and OPH were of equivalent cost-effectiveness and dominated EBx when the prevalence of fibroids less than 3 cm in diameter was assumed to be 5% (see Health Economics Chapter, Analysis 7).

An economic model developed for the guideline found that EBx was dominated by TVUS and OPH when for commonly used first and second line treatments (see Health Economics Chapter, Analyses 5, 6 and 7).

# Review question 2. What is the most clinically effective imaging strategy for diagnosing adenomyosis in women with heavy menstrual bleeding?

## Introduction

Adenomyosis is a benign gynaecological disorder in which the inner lining of the uterus breaks through into the muscle wall of the uterus. The most common symptoms are pelvic pain and heavy menstrual bleeding. Traditionally, adenomyosis has been diagnosed from histopathology following a hysterectomy. While improvements in diagnostic imaging in recent years have shown that adenomyosis could be diagnosed through diagnostic radiology, there are currently no standard diagnostic imaging criteria for adenomyosis.

The aim of this review was to determine the most clinically effective imaging strategy for detecting adenomyosis in women presenting with heavy menstrual bleeding.

## Summary of the protocol

Please see Table 5 for a summary of the characteristics of this review including population, index tests, reference standard and outcomes.

**Table 5: Summary of the protocol**

| Population | Premenopausal women with heavy menstrual bleeding (HMB)<br>At least 66% of the population should be women with HMB. |
|---|---|
| Index test(s) | • Magnetic resonance imaging (MRI)<br>• Transvaginal ultrasound scan (TVUS)<br>  ○ Two-dimensional (2D)<br>  ○ Three-dimensional (3D)<br>• Transabdominal ultrasound scan (TAUS)<br>  ○ 2D<br>  ○ 3D<br>• Combination of two or more of the above |
| Reference standard | Histopathology |
| Outcomes | • sensitivity<br>• specificity<br>• positive likelihood ratio (LR+)<br>• negative likelihood ratio (LR-)<br>• area under the curve (AUC) if meta-analysis can be conducted |
| Target condition | Adenomyosis |

*2D: two-dimensional; 3D: three-dimensional; AUC: area under the curve; HMB: heavy menstrual bleeding; LR+: positive likelihood ratio; LR-: negative likelihood ratio; MRI: magnetic resonance imaging; sens: sensitivity; spec: specificity; TAUS: transabdominal ultrasound scan; TVUS: transvaginal ultrasound scan*

For full details see Appendix A – Review protocols.

## Clinical evidence

Histopathology was considered as the reference standard to which diagnostic accuracy of MRI, ultrasound were compared. Histopathology was derived from surgery specimen from hysterectomy or deep hysteroscopy-guided biopsy.

A combined literature search was undertaken for this review question and the review question on the diagnostic accuracy of ultrasound and hysteroscopy in the investigation of women presenting with heavy menstrual bleeding.

Due to the limited evidence available when the population was restricted only to women presenting with heavy menstrual bleeding, the committee agreed that one third of the population could be women without heavy menstrual bleeding and these results could be extrapolated to women presenting with heavy menstrual bleeding as long as the indirectness of the population was accounted for when assessing the quality of the evidence.

Meta-analysis was conducted when appropriate with a minimum of 5 studies. In the presence of heterogeneity, potential reasons for heterogeneity were explored and subgroup analyses were conducted when possible according to pre-specified groups in the protocol.

Test sensitivity or specificity was considered high when sensitivity or specificity was 90% or higher, and moderate when sensitivity or specificity was between 75% and 89%. A positive likelihood ratio (LR+) of 10 or higher was considered to indicate that the test was very useful in 'ruling in' the condition, and a LR+ between 5 and 9.9 was considered moderately useful in 'ruling in' the condition. A negative likelihood ratio (LR-) of 0.1 or lower was considered to indicate that the test was very useful in 'ruling out' the condition, and a LR- between 0.1 and 0.2 was considered to indicate that the test was moderate useful in 'ruling out' the condition.

**Included studies**

Eight studies (n=1028) were included in the review (Abdel Hak 2010; Alborzi 2007; Bazot 2002; Botsis 1998; Dakhly 2016; Duelholm 2001; Exacoustos 2011; Vercellini 1998).

All included studies included two-dimensional transvaginal ultrasound scan (2D-TVUS) as the index test (Abdel Hak 2010; Alborzi 2007; Bazot 2002; Botsis 1998; Dakhly 2016; Duelholm 2001; Exacoustos 2011; Vercellini 1998).  One of these studies also looked at three-dimensional (3D) TVUS (Exacoustos 2011). One study also looked at magnetic resonance imaging (MRI) and a combination of 2D-TVUS and MRI as the index tests (Dueholm 2001b). One study also included 2D transabdominal ultrasound scan (2D-TAUS) as the index test (Bazot 2002).

All studied included histopathology as the reference standard. Seven studies used surgical specimen from hysterectomy as the reference standard (Abdel Hak 2010; Bazot 2002; Botsis 1998; Dakhly 2016; Duelholm 2001; Exacoustos 2011; Vercellini 1998) and one study used a deep biopsy from hysteroscopy as the reference standard (Alborzi 2007).

The included studies were from Egypt (Abdel Hak 2010; Dakhly 2016); Italy (Exacoustos 2011; Vercellini 1998); Denmark (Dueholm 2001b); France (Bazot 2002); Greece (Botsis 1998); and Iran (Alborzi 2007).

Evidence from these are presented in Appendix G – GRADE tables.

See also Appendix D – Clinical evidence study selection, Appendix H – Forest plots and hierarchical summary receiver operating characteristic (HSROC) plots, and Appendix F – Clinical evidence tables.

**Excluded studies**

Studies not included in this review with reasons for their exclusions are provided in Appendix I – Excluded studies.

**Summary of clinical studies included in the evidence review**

Table 6 provides a brief summary of the included studies

## Table 6: Summary of included studies

| Study | Population | Index test | Reference standard | Diagnositc criteria of adenomyosis in index test |
|---|---|---|---|---|
| Abdel Hak 2010 (Egypt) | N=50 perimenopausal women undergoing hysterectomy due to HMB. | 2D-TVUS<br><br>The paper did not report who performed or interpreted the TVUS or the level of experience of the person(s). | Histopathology (hysterectomy) | A poorly defined area of abnormal echo texture within the myometrium. Abnormal myometrial echo texture was defined if the myometrium demonstrated heterogeneity, decreased or increased echogenicity, and/or the presence of cysts, presence of linear striation, globular configuration of the uterus. |
| Alborzi 2007 (Iran) | N=81 women with abnormal uterine bleeding. Proportion of women with HMB not reported. | 2D-TVUS<br><br>The paper did not report who performed or interpreted the TVUS or the level of experience of the person(s). | Histopathology (hysteroscopic biopsy)<br>The paper reports that "in all patients a relatively deep specimen from the anterior and posterior wall of the uterus was resected and sent to a pathologist". | Diffuse uterine enlargement with no alteration in echotexture and contour. Focal adenomyosis was diagnosed when a poorly defined area of abnormal echotexture is present in the myometrium with increased or decreased echogenecity. |
| Bazot 2002 (France) | N=129 women undergoing hysterectomy due to various reasons divided into two groups:<br>Group 1 (n=23) women with recurrent menometrorrhagia but no evidence of leiomyomata and endometrial diseases on transabdominal examination. 100% had menometrorrhagia.<br>Group 2 (n=106) all other women. 67.9% had menometrorrhagia. | 2D-TAUS; 2D-TVUS<br><br>The TVUS were performed by two investigators with 8 and 3 years of experience in female pelvic ultrasound scan. | Histopathology (hysterectomy) | TAUS<br>Enlarged regular uterus with no evidence of leiomyoma and/or presence of myometrial cysts.<br><br>TVUS<br>A globular and/or asymmetric uterus, a poorly defined focus of abnormal myometrial echotexture, distorted and heterogeneous myometrial echotexture, myometrial linear striations, and myometrial cysts. With the exception of diffuse heterogeneous myometrium that appeared non-specific for adenomyosis, the diagnosis was made |

| Study | Population | Index test | Reference standard | Diagnositc criteria of adenomyosis in index test |
|---|---|---|---|---|
| | | | | when at least one of the above criteria was met. |
| Botsis 1998 (Greece) | N=206 women undergoing hysterectomy for various reasons. 83% had HMB and/or dysmenorrhea. | 2D-TVUS The paper did not report who performed or interpreted the TVUS or the level of experience of the person(s). | Histopathology (hysterectomy) | Heterogeneous myometrial areas that were not encapsulated and that contained anechoic lacunae measuring 1–3 mm in diameter and an area characterized by irregular cystic spaces measuring 1–7 mm in diameter (honeycomb pattern) and disrupting the normal fine speckled echo pattern of the uterus. The sonographic examination was considered diagnostic of adenomyosis when at least 3 parameters were positive. |
| Dakhly 2016 (Eqypt) | N=404 original sample N=292 included in analysis premenopausal women with clinical signs and symptoms of adenomyosis. 64% had HMB and 36% had menometrorrhagia. | 2D-TVUS The paper did not report who performed or interpreted TVUS or the level of experience of the person(s). | Histopathology (hysterectomy) | Presence of 2 or more of the following 5 criteria: heterogeneous myometrial echo-texture; myometrial cysts; subendometrial echogenic linear striations; asymmetry of the anterior and posterior myometrium; and a poorly defined endometrial–myometrial junction. |
| Dueholm 2001b (Denmark) | N=106 premenopausal women undergoing hysterectomy for various reasons. 77% had abnormal uterine bleeding. Proportion of women with HMB not reported. | 2D-TVUS; MRI The TVUS was performed by one experienced gynaecologists. The MRI was evaluated by one MRI specialist. | Histopathology (hysterectomy) | Presence of heterogeneity, increased or decreased areas of echogenicity, or presence of myometrial cysts. |
| Exacoustos 2011 (Italy) | N=72 premenopausal women undergoing hysterectomy due to benign pelvic pathology. | 2D-TVUS; 3D-TVUS The TVUS were performed by one of three expert sonographers. | Histopathology (hysterectomy) | 2D-TVUS Presence of 2 or more of the following individual ultrasonographic features: myometrial cysts; asymmetrical myometrial cysts; hypoechoic striations; |

| Study | Population | Index test | Reference standard | Diagnositc criteria of adenomyosis in index test |
|---|---|---|---|---|
| | 76% had HMB. | | | heterogenous myometrial cysts.<br><br>3D-TVUS<br>Presence of 2 or more of the following ultrasonographic features: JZmax 8 mm or more; JZmax − JZmin 4 mm or more; JZ ratio 50% or more; JZ alteration; myometrial cysts; asymmetrical myometrial cysts; heterogeneous myometrial cysts. |
| Vercellini 1998 (Italy) | N=102 premenopausal women undergoing hysterectomy for HMB and/or worsening dysmenorrhea.<br><br>Proportion of women with HMB not reported. | 2D-TVUS<br><br>All the TVUS were performed by one expert sonographer. | Histopathology (hysterectomy) | Indistinctly demarcated heterogeneous myometrial areas with distorted echotexture. Myometrial echotexture was defined as distorted by the presence of abnormally decreased or increased echogenicity and/or round anechoic areas. |

*2D: two-dimensiona; 3D: three-dimensional; HMB: heavy menstrual bleeding; MRI: magnetic resonance imaging; TAUS: transabdominal ultrasound scan; TVUS: transvaginal ultrasound scan*

See Appendix F – Clinical evidence tables for full evidence tables.

## Quality assessment of clinical studies included in the evidence review

The included studies were individually assessed using QUADAS-2 checklist. QUADAS-2 assesses the risk of bias in the study and the applicability of the study for the review question.

The quality of each piece of evidence, whether from meta-analysis or from individual studies was then assessed using adapted GRADE methodology.

See Appendix G – GRADE tables for full GRADE tables.

For more details on the quality assessment of clinical studies in the evidence review, please see Methods chapter.

## Economic evidence

### Included studies

No economic evaluations of imaging technologies for the diagnosis of adenomyosis were identified in the literature search conducted for this guideline.

## Excluded studies

There were no excluded economic studies relating to the diagnosis of adenomyosis.

## Summary of studies included in the economic evidence review

There were no included economics studies relating to the diagnosis of adenomyosis.

## Economic model

No economic modelling was done for the evaluation of imaging technologies for the diagnosis of adenomyosis.

## Resource impact

Heavy menstrual bleeding is not the main presenting symptom of women with adenomyosis and therefore women with possible adenomyosis represent a small subset of the population covered by this guideline. TVUS is the recommended diagnostic test for women with possible adenomyosis which costs £147 (NHS Reference Costs, 2015-16) when provided in an outpatient setting. Whilst adenomyosis was not considered in previous NICE guidance the committee did not think that this would represent a change in practice. Transabdominal ultrasound or MRI are less accurate and do not offer any significant saving when compared to TVUS although both can be considered if TVUS is not acceptable to the woman.

## Evidence statements

### Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting adenomyosis in women with heavy menstrual bleeding

Very low quality evidence from 7 studies (n=1078) found 2D-TVUS to have moderately high sensitivity (76%, 95% CI 69 to 82%) and moderately high specificity (83%, 95% CI 73 to 90%) in diagnosing adenomyosis. 2D-TVUS was not found to be very useful in 'ruling in' or 'ruling out' adenomyosis (LR+ 4.6, 95% CI 2.8 to 7.4; LR- 0.29, 95% CI 0.22 to 0.37). The area under the curve (AUC) was 0.83 (95% CI 0.80-0.86). Histopathology on surgical specimens from hysterectomy was the reference standard for all studies except in one study where deep biopsy specimens from hysteroscopy examination were used for the reference standard. The studies included in this meta-analysis were published between 1998 and 2016 and came from five different countries (Denmark, Egypt, Greece, Iran, and Italy). The populations in these studies varied to an extent, however, at least around two thirds of the women included in these studies had heavy menstrual bleeding as a symptom.

Low quality evidence from 1 study (n=23) from France from 2002 among women with recurrent menometrorrhagia but no evidence of fibroids or endometrial diseases on transabdominal examination showed 2D-TVUS to have moderately high sensitivity (81%, 95% CI 58 to 95%) and high specificity (100%, 95% CI 16 to 100%) in diagnosing adenomyosis in this population. 2D-TVUS was found to be a useful test in 'ruling in' (LR+ infinite, not calculable) and moderately useful test in 'ruling out' (LR- 0.19, 95% CI 0.08 to 0.46) adenomyosis in this population. Moderate quality evidence from the same study among all other women (n=106, presumably women with evidence of fibroids or endometrial diseases on transabdominal examination) showed 2D-TVUS to have low sensitivity (39%, 95% CI 20 to 59%) but high specificity (98%, 95% CI 91 to 100%) in diagnosing adenomyosis in this population. 2D-TVUS was found to be a useful test in 'ruling in' adenomyosis (LR+ 15.4, 95% CI 3.6 to 65.7) but not a useful test in 'ruling out' adenomyosis (LR- 0.63, 95% CI 0.46 to 0.86) in this population.

### Diagnostic accuracy of 3D-TVUS (versus histopathology) in detecting adenomyosis in women with heavy menstrual bleeding

Very low quality evidence from 1 study (n=72) from Italy from 2011 found 3D-TVUS to have high sensitivity (91%, 95% CI 74 to 97%) and moderately high specificity (88%, 95% CI 72 to 95%) in diagnosing adenomyosis (surgical specimen from hysterectomy as the reference standard). Likelihood ratios showed that 3D-TVUS is a moderately useful test in 'ruling in' and 'ruling out' adenomyosis (LR+ 7.3, 95% CI 3.2 to 16.6; LR- 0.11, 95% CI 0.03 to 0.31).

**Diagnostic accuracy of 2D-TAUS (versus histopathology) in detecting adenomyosis in women with heavy menstrual bleeding**

Moderate quality evidence from 1 study (n=23) from France from 2002 among women with recurrent menometrorrhagia but no evidence of fibroids or endometrial diseases on transabdominal examination showed 2D-TAUS to have low sensitivity (54%, 95% CI 34 to 78%) and specificity (50%, 95% CI 27 to 99%) in diagnosing adenomyosis and not to be useful in 'ruling in' or 'ruling out' adenomyosis (LR+ 1.1, 95% CI 0.3 to 4.8; LR- 0.9, 95% CI 0.2 to 3.7). Moderate quality evidence from the same study among all other women (n=106) who we assume, based on the group explicitly defined, have evidence of fibroids or endometrial diseases on transabdominal examination) showed 2D-TAUS to have very low sensitivity (8%, 95% CI 1 to 25%) but high specificity (96%, 95% CI 89 to 99%) and not to be useful in 'ruling in' or 'ruling out' adenomyosis (LR+ 2.1, 95% CI 0.4 to 11.6; LR- 0.96, 95% CI 0.85 to 1.08). Surgical specimen from hysterectomy was the reference standard.

**Diagnostic accuracy of MRI (versus histopathology) in detecting adenomyosis in women with heavy menstrual bleeding**

Low quality evidence from 1 study (n=106) from Denmark from 2001 found MRI to have low sensitivity (64%, 95% CI 41 to 83%) and moderately high specificity (88%, 95% CI 79 to 94%) in diagnosing adenomyosis (surgical specimen from hysterectomy as the reference standard). MRI was found to be moderately useful test in 'ruling in' adenomyosis (LR+ 5.4, 95% CI 2.8 to 10.4) but not useful in 'ruling out' adenomyosis (LR- 0.4, 95% CI 0.2 to 0.7). The study reported 'indefinite' results from the index test for 13 cases which have been included as negative test results in the results above.

**Diagnostic accuracy of 2D-TVUS combined with MRI (versus histopathology) in detecting adenomyosis in women with heavy menstrual bleeding**

Low quality evidence from 1 study (n=106) from Denmark from 2001 found the combination of 2D-TVUS and MRI to have a relatively low sensitivity (73%, 95% CI 50 to 89%) and moderately high specificity (77%, 67 to 86%) in diagnosing adenomyosis (surgical specimen from hysterectomy as the reference standard). 2D-TVUS combined with MRI was not found to be a useful test in 'ruling in' or 'ruling out' adenomyosis (LR+ 3.2, 95% CI 2.0 to 5.2; LR- 0.35, 95% CI 0.18 to 0.70) in this one study. The study reported 'indefinite' results from the index test for 41 cases which have been included as negative test results in the results above.

# The committee's discussion of the evidence

## Interpreting the evidence

### The outcomes that matter most

The committee agreed that the correct identification of the cause of HMB is important as this can impact the treatment options offered to women. The committee considered sensitivity, LR+ and LR- to be critical outcomes and specificity and AUC to be important outcomes. If a test is sensitive, it may help the clinicians to choose the right initial treatment to be offered to women. The committee recognised that it was important to avoid false positives because unnecessary treatment, especially surgical treatment, can cause harm. In relation to adenomyosis, the committee identified that it was important to avoid false negatives as adenomyosis might not respond well to conventional pharmacological treatments or endometrial ablation. Likelihood ratios were considered to be clinically helpful indicators of a useful test.

Owing to concerns about the acceptability of hysteroscopy to some women, patient satisfaction and acceptability was considered as a critical outcome for the review on the diagnostic accuracy of hysteroscopy and ultrasound for investigation of women with HMB. The committee considered that the experience and preference of women undergoing investigations is crucial in assessing which diagnostic test is most suitable.

### The quality of the evidence

The evidence on diagnostic accuracy was assessed using adapted GRADE methodology. The evidence on patient satisfaction or acceptability was assessed using Cochrane Collaboration's tool for assessing risk of bias.

The quality of evidence in these reviews ranged from very low to moderate with most evidence being of very low quality. The committee recognised that the evidence was fragmented and with several limitations. The committee agreed that the quality of evidence was most often downgraded because of unclear sampling, unclear inclusion and exclusion criteria, unclear diagnostic criteria, and at times, considerable number of drop-outs.

The committee discussed that the populations in the included studies were not always identical to the population of interest in this guideline (premenopausal women with heavy menstrual). The committee had agreed in the review protocol that one third of the women included in the studies could be other than women with HMB, for example, women with pelvic pain without HMB. Therefore, most studies in these reviews included a proportion of women that were not directly the population of interest. This was accounted for in the quality assessment of the evidence although the committee also noted that the diagnostic accuracy of the test would not be expected differ in a population that was not directly of interest.

The committee also agreed that the population of women in the review on the most effective investigation to detect adenomyosis in women with HMB do not represent the general HMB population since most of the women in the studies underwent hysterectomy. Milder forms of adenomyosis that do not require hysterectomy are much more common. The prevalence of adenomyosis in the included studies varied

from 11% to 55%. The committee discussed that since the populations in the studies included women undergoing hysterectomy, i.e. women with severe symptoms, the prevalence rates are likely underestimated. HMB is not the only, nor necessarily the most common presenting symptom for adenomyosis. Pelvic pain is another common symptom reported. In addition, an estimated 30% of women with adenomyosis are asymptomatic. Therefore, the prevalence of adenomyosis in the premenopausal population could be even higher.

The level of experience of the clinician performing and interpreting the diagnostic test was considered an important determinant of the diagnostic accuracy of the investigation, particularly for the diagnosis of adenomyosis for which there are no established diagnostic criteria. The committee recognised that the level of experience of the investigator was often not reported in the studies included in the reviews.

The reference standard for detecting the target conditions to which the index tests of interest are compared to is histopathology. The comparison of the index tests (mainly hysteroscopy and 2D-TVUS) are therefore indirect and relies in part on cross-study comparisons. Therefore, there is some uncertainty with respect to the extent that hysteroscopy is superior to 2D-TVUS in detecting submucosal fibroids and endometrial polyps. However, the results from the studies that examined the accuracy of both hysteroscopy and 2D-TVUS among the same women (histopathology as reference standard) were more or less in agreement with the overall conclusion regarding the superiority of hysteroscopy over TVUS in detecting submucosal fibroids and endometrial polyps. This was also supported by other studies known to the committee which were excluded from the review due to indirect population.

Considerable heterogeneity was observed in the meta-analyses conducted in the reviews, especially in the sensitivity of 2D-TVUS in detecting polyps and specificity of 2D-TVUS in detecting adenomyosis. Pre-specified subgroup analyses were conducted to investigate whether or not the year of publication could influence heterogeneity since diagnostic techniques have evolved over time, however, this was not found to impact the level of heterogeneity. The committee also considered other factors that might cause heterogeneity, including varying populations across studies, variation in the diagnostic criteria of adenomyosis on ultrasound, varying or unreported level of experience of the investigators, and varying reference standards used (hysterectomy, hysteroscopic biopsy, D&C). Despite the high heterogeneity of the analysis, the results of the meta-analysis on the accuracy of 2D-TVUS in diagnosing adenomyosis corresponded well with the results of two previous systematic reviews and meta-analysis, even though the inclusion criteria in these reviews were not the same as in this review (Champaneria 2010; Meredith 2009).

Limited or no evidence was found on the accuracy of 3D-TVUS and 2D- or 3D-TAUS to detect different pathologies and of MRI to detect adenomyosis in women with HMB. Furthermore, no evidence was found on vaginoscopic hysteroscopy. However, the committee agreed that the diagnostic accuracy of vaginoscopic hysteroscopy is expected to be similar to other outpatient hysteroscopy approaches, however, patient acceptability is expected to be higher.

Evidence on patient acceptability and satisfaction comparing hysteroscopy and ultrasound was scarce. The evidence came from one study published over a decade ago with limited and unclear reporting in relation to patient acceptability and satisfaction. The committee considered the techniques used in the study to be outdated, therefore, not reflecting the current standards of best practice. As with diagnostic accuracy, evidence on patient acceptability and satisfaction of diagnostic tests was limited to women presenting with heavy menstrual bleeding (at least 2/3 of

the participants presenting with heavy menstrual bleeding). The committee acknowledged that there might have been more evidence available on patient acceptability and satisfaction of the diagnostic tests of interest in wider population groups. Whereas the committee considered that evidence on postmenopausal women could not be extrapolated to premenopausal women with heavy menstrual bleeding, evidence on the acceptability and diagnostic accuracy of the tests in premenopausal women presenting with other symptoms might have been relevant. However, this was taken into account by allowing some deviation in the study population (i.e. one third of the study population could be other than women with heavy menstrual bleeding).

## Benefits and harms

The committee agreed that many women presenting to primary care with symptoms of HMB can be offered treatment without the need for further examination or investigation. However, investigation via a diagnostic technique might be warranted for women for whom history or examination suggests a structural or endometrial pathology or for whom the initial treatment has failed.

Traditionally, 2D-TVUS has been the first-line investigation for women presenting with heavy menstrual bleeding. The clinical evidence still supports the use of 2D-TVUS in the detection of fibroids outside the uterine cavity and adenomyosis. However, the evidence showed hysteroscopy to have superior sensitivity, specificity, LR+, and LR- over 2D-TVUS in detecting submucosal fibroids, polyps and endometrial pathology. This was also evident from a number of studies which were excluded from the review due to indirect population (less than two thirds of the population had HMB). In addition, a recent systematic review and meta-analysis among a mixed population of women (and therefore not included in our review) showed very high accuracy of hysteroscopy on submucosal fibroids (sensitivity 97% and specificity 99%, pooled from 7 studies) and on endometrial polyps (sensitivity 95% and specificity 96%, pooled from 9 studies) (Gkrozou 2015).

The committee considered outpatient hysteroscopy to be an efficient and safe technique with a low risk of complications, and acceptable to most women if done according to best practice guidance. It would also allow for services to be developed to offer women the option of see-and-treat by having submucosal fibroids or polyps identified and removed in one process when appropriate. The women should be explained what the procedure involves and what alternatives there are.

Because hysteroscopy is not able to detect abnormalities outside the uterine cavity, the committee agreed that pelvic ultrasound (TVUS and/or TAUS) should be offered to women whose history and examination suggest larger fibroids.

TVUS showed better accuracy in detecting adenomyosis compared to TAUS or MRI, therefore, the committee recommended the first-line investigation for suspected adenomyosis to be TVUS.

Diagnostic accuracy was not, however, the only factor considered in making the recommendations. Women's preferences and acceptability was also very important to the committee. The evidence on patient acceptability and satisfaction in the evidence review came from a study that used techniques that were considered outdated and not according to the current best practice, and therefore, possibly painful for the women (larger hysteroscopes, blind biopsies taken, and use of non-vaginoscopic methods). The experience of the committee was that if performed according to current best practice standards, outpatient hysteroscopy is acceptable to most women. One of the committee members had collected patient-reported

outcomes from over 1500 women that confirms acceptability using the best practice guidelines with mean pain scores from the procedure less than that experienced by the women at menstruation (not published). The other committee members agreed that this concurs with their own experience and is in line with the literature review presented in the Royal College of Obstetricians and Gynaecologists (RCOG) and British Society for Gynaecological Endoscopy (BSGE) Green-top Guideline No. 59 Best Practice in Outpatient Hysteroscopy (RCOG and BSGE 2011).

However, the committee did have concerns that patient groups report poor experiences, and that some women do experience significant distress. The committee discussed the variability in hysteroscopic techniques in the UK, with previous surveys among BSGE members suggesting poor provision of best practice. In order to minimise women's discomfort and dissatisfaction, implementing hysteroscopy as the first-line investigation for women with suspected uterine cavity abnormalities or endometrial pathology requires the use of appropriate equipment, training of clinicians, and information provision in line with RCOG best current practice (RCOG and BSGE 2011). The committee felt that it was essential that all best practice elements needed to be delivered by services offering hysteroscopy, but that there was potential for these services to be offered more widely in community settings. The committee identified the following as essential elements for an integrated outpatient hysteroscopy service:

- vaginoscopy as the standard technique, using miniature hysteroscopes (3.5 mm or smaller) for diagnosis

- service organisation to enable 'see-and-treat' in a single setting where feasible

- system to advise women to take oral analgesia prior to their procedure.

In addition, the committee considered it is important that the staff has necessary training, skills and expertise to perform outpatient hysteroscopy; facilities are appropriately sized, equipped and staffed with a toilet and private changing facilities; a nurse is available to act as the woman's advocate; and regular audit of outcomes that include patient-reported outcomes is performed and benchmarked against local and national standards.

The committee recognised that not every woman would agree to undergo an outpatient hysteroscopy and emphasised that women's choice was important in deciding the diagnostic pathway. In women who declined an outpatient hysteroscopy the risks and benefits of anaesthesia (either general or regional) should be discussed and a hysteroscopy under anaesthesia should be offered.

The committee discussed that currently many women undergo endometrial biopsy unnecessarily and that the risk of endometrial cancer in premenopausal women with HMB as the only symptom is very low (Pennant 2017). Endometrial biopsy is painful and 'blind' biopsy may miss treatable pathology. Thus, 'blind' biopsy should not be offered to women presenting with HMB. An endometrial biopsy was only deemed necessary in women at high risk of endometrial hyperplasia or malignancy. According to the committee's knowledge and expertise, these include women with persistent intermenstrual bleeding, persistent irregular bleeding, infrequent bleeding in women who are obese or who have polycystic ovary syndrome (due to prolonged unopposed aestrogen effect on the endometrium), women taking tamoxifen, and women in whom treatment has failed or was ineffective. Reflecting the low risk of endometrial cancer, the committee considered that investigations should be instigated on the basis of symptoms rather than an arbitrary age cut-off as this would result in too many unnecessary biopsies.  When indicated a biopsy should be taken in the context of hysteroscopy in line with RCOG best practice guidelines (RCOG and BSGE 2011). If not obtained during hysteroscopy, the endometrial biopsy could be obtained

immediately after the endometrium has been visualised via a hysteroscope using a global sampler if appropriate.

In cases where women decline hysteroscopy or for women for whom it is not appropriate, pelvic ultrasound should be considered. If pelvic ultrasound scan is considered as an alternative to hysteroscopy or is requested by the woman, it should be recognised and explained to the woman that an ultrasound scan might not reliably detect or exclude treatable pathology within the uterine cavity. The committee discussed that a trial of a pharmacological agent might sometimes be a better option than undergoing an ultrasound scan unless there are specific indications such as suspected pelvic mass or adenomyosis.

The place of pelvic ultrasound scan in the diagnosis of structural causes of heavy menstrual bleeding was discussed by the committee. Given ultrasound scan's superiority over hysteroscopy in detecting non-cavity structural abnormalities but inferiority in detecting abnormality or pathology within the uterine cavity, pelvic ultrasound scan would be appropriate for women where the uterus is palpable abdominally, or where the history or a vaginal examination suggests a pelvic mass. Furthermore, in women where examination is inconclusive or difficult, for example, in women who are obese, pelvic ultrasound scan is indicated to detect or rule out fibroids that would normally be identified on examination. Even though the evidence was on TVUS, the committee considered TAUS to be clinically as appropriate in detecting fibroids that are large enough to be palpable. In practice these two ultrasound modalities are sometimes used in conjunction and are therefore not mutually exclusive. Therefore, pelvic ultrasound, meaning either TVUS or TAUS, was recommended as an investigation for these women.

The committee recognised that in obese women an ultrasound scan can be difficult to perform and interpret, however, when a physical examination is difficult or inconclusive, ultrasound scan is still recommended to complement the inconclusive examination. In practice and when appropriate, clinicians will likely offer transvaginal ultrasound scan for obese women for better resolution.

In general, the committee emphasised that the accuracy of an ultrasound scan is dependent on the experience and skills of the person performing the scan. It should be recognised that in practice not all GPs or gynaecologists are adequately skilled to perform or interpret a pelvic ultrasound.

The evidence on the most effective imaging strategy for suspected adenomyosis showed TVUS to have better accuracy in terms of sensitivity and specificity compared to MRI and TAUS. The committee agreed that, despite the relatively small amount of evidence, the evidence reflected their expectations from a clinical perspective. In practice, 2D-TVUS is widely available and even though it is intrusive as the transducer is inserted in the vagina, it is known to be a widely accepted method among women and has greater diagnostic accuracy than transabdominal scanning of pelvic organs. 3D-TVUS, which showed better accuracy albeit with limited evidence, is rarely available outside of tertiary care or research centres. MRI is less accurate, less widely available and more expensive. It can also be an unpleasant or claustrophobic experience for women. 2D-TAUS on the other hand is widely available but has low accuracy. It can also cause discomfort in women since it requires a full bladder. The committee, therefore, agreed that MRI and 2D-TAUS should not be recommended as the first-line diagnostic investigation for women with suspected adenomyosis.

However, the committee recognised that TVUS is not appropriate for all women and some women may decline it, for example adolescents, women who have not been

sexually active, women who have had a traumatic sexual experience, or women with history of female genital mutilation. Therefore, the committee agreed that TAUS or MRI could be offered as an alternative as long as the lower accuracy of these tests was taken into consideration.

In addition to HMB, pelvic pain is a common symptom of adenomyosis. The committee agreed that these symptoms could also be signs of endometriosis and NICE guideline on Endometriosis: diagnosis and management (NG73) should be referred to.

The committee noted that while diagnostic accuracy parameters give useful information about the test's ability to detect a condition or an absence of a condition, no matter how accurate a test is, it does not automatically indicate a better overall outcome for the woman. The overall outcome for the woman depends on a myriad of factors, including the treatment decisions after the diagnosis is made. According to the committee, a correct diagnosis of the cause of heavy menstrual bleeding is key in optimising treatment outcomes. The committee discussed the benefits and harms of false positives and false negatives. False positives can lead to over treatment, especially unnecessary surgical treatments, including hysterectomy which could carry risk and ideally should be avoided when unnecessary. However, it was thought by the committee that despite being a more aggressive trearment some women (who did not wish to preserve fertility or uterus) would still find hysterectomy acceptable because it would take away the symptoms (HMB and other symptoms such as pain or pressure symptoms) and improve quality of life. On the other hand, false negatives can prevent women from receiving a treatment that would improve their quality of life or ease the symptoms.

The committee also discussed that it can be important for a woman to obtain a diagnosis in order to explain the cause for her symptoms, even if the treatment strategy would be similar regardless of the diagnosis. The committee recognised that many women have to endure symptoms without an identified pathology, but felt that some women may be reassured from knowing that there is no significant or treatable pathology.

## Cost-effectiveness and resource use

A high quality economic evaluation from the UK (Cooper 2014) compared a number of diagnostic strategies for HMB. This analysis took an NHS perspective and the setting was a 'one-stop' secondary care clinical setting. The study concluded that either outpatient hysteroscopy or outpatient hysteroscopy in combination with endometrial biopsy represented cost-effective strategies for HMB. Treatment effectiveness was estimated through patient satisfaction although the authors also derived a cost per QALY estimate based on this.

An original economic model developed for the guideline compared combined diagnostic and treatment strategies for HMB. The diagnostic aspect was modelled using the approach used in the above study (Cooper 2014). However, treatment effectiveness was derived from 2 NMAs on short and long term quality of life based on EQ-5D data. This analysis suggested that endometrial biopsy was not cost-effective relative to TVUS and outpatient hysteroscopy. However, the findings with respect to the relative cost-effectiveness of TVUS and outpatient hysteroscopy were less clear cut. Outpatient hysteroscopy was generally the cheapest strategy but TVUS generated a higher QALY gain, which was due to the ability of TVUS to detect intramural and subserosal fibroids. In many of the analyses the model suggested that this additional QALY gain warranted the additional cost of TVUS relative to outpatient

hysteroscopy at a cost-effectiveness threshold of £20,000 per QALY. However, that finding was sensitive to the prevalence of intramural and subserosal fibroids as an underlying cause of HMB.

Diagnostic accuracy is important as it can lead to better targeted treatment, however this depends in the context of HMB, on the extent to which less appropriate treatments for a given underlying benefit may, nevertheless, confer some treatment benefit. Outpatient hysteroscopy was the most expensive diagnostic test but the least expensive diagnostic strategy. An important contributing factor to this is that hysteroscopy can facilitate a one stop 'see-and-treat' approach which reduces treatment cost. The superior diagnostic accuracy of outpatient hysteroscopy for polyps, submucosal fibroids and no identified pathology means that this is likely to be the most cost-effective test in women where history is suggestive of those pathologies. Conversely, TVUS would be cost-effective where the woman's uterus is palpable abdominally or where history or examination suggests a pelvic mass.

It is anticipated that the guideline recommendation on investigations using hysteroscopy may increase the burden on secondary care at least in the short run. Furthermore, some units may have to adapt facilities and equipment in order to deliver hysteroscopy in lines with RCOG best practice guidelines (RCOG and BSGE 2011).  However, it should be noted that the guideline recommends empiric LNG-IUS as a first-line treatment for many women presenting with HMB and therefore the population of women who would be offered hysteroscopy is only a subset of all women with HMB. The committee also believed that hysteroscopy could lead to a reduction in unnecessary scans and biopsies by better targeting treatment at the underlying pathology.

The committee have also recommended that 'blind' biopsy should not be offered and the committee expect that to generate savings to the NHS by also reducing the number of unnecessary biopsies.

Whilst there are recommendations in the guideline that will have a resource impact on the NHS, especially in the short term, it is not anticipated that any will have a significant resource impact (£1 million). Outpatient hysteroscopy is a more expensive investigation than pelvic ultrasound but there are potential off-setting savings to treatment costs as the technique can allow a 'see and treat' approach. It is expected that the recommendation to not perform 'blind' biopsy will lead to savings to the NHS but in the absence of data outlining baseline current practice it is not possible to quantify the potential size of any saving.

## Other factors the committee took into account

The committee agreed that no special consideration regarding diagnosis is needed for women who wish to preserve their fertility since hysteroscopy, TVUS, TAUS and MRI do not affect fertility.

During the scoping phase the following groups were identified as needing special consideration:

- women who have difficulties communicating in English
- women with learning difficulties
- women from some minority ethnic groups (because women from some minority ethnic group might find it difficult to talk about HMB with health care professionals)
- women from disadvantaged socio-economic groups.

The committee noted that these groups might need special consideration in terms of information provision and communication, however, the committee agreed that this is not specific to HMB and is covered by the NICE guideline on Patient experience in adult NHS services: improving the experience of care for people using adult NHS services (CG138). The committee also recognised that some women might prefer a female practitioner when discussing HMB and undergoing diagnostic procedures.

Updated recommendations have taken into account new guidelines on the identification and management of high risk groups for endometrial hyperplasia (RCOG and BSGE 2016) and cancer (NICE guideline on suspected cancer: recognition and referral (NG12)), as these groups may also present with heavy menstrual bleeding. The committee agreed that in the case of suspected cancer, the clinicians should refer to NICE guideline on suspected cancer: recognition and referral (NG12).

The committee noted that some studies used hysteroscopy as the reference standard when comparing the ability of hysteroscopy and ultrasound to detect causes of HMB. Even though in general histopathology was considered as the gold standard for detecting focal abnormalities and pathology, the committee discussed that when blind biopsy was used as a reference standard, it can easily miss focal pathology (fibroids and polyps distorting to the cavity) and therefore, hysteroscopy with a direct visualisation of the uterine cavity (rather than histopathology) can be considered as the reference standard for these pathologies.

No evidence from test and treat RCTs was identified in this review. The committee agreed that a research recommendation is needed because a test-plus-treatment study design would offer better evidence of the clinical and cost-effectiveness benefits of choosing one test over another. The committee agreed it would be important to include empiric treatment as one of the treatment arms to reflect current clinical practice, as many women presenting with HMB in primary care are often offered pharmacological treatment without prior investigations. This research is needed because although diagnostic accuracy parameters provide useful information about a test's ability to detect the presence or absence of a condition, no matter how accurate a test is, it does not automatically translate to better clinical outcomes for the woman. The value of a diagnostic test lies in whether it actually guides treatment decisions (see Appendix C – Research recommendations).

See Appendix J – Diagnostic care path for illustration of the diagnostic recommendations.

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**Vercellini 1998**

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# Appendices

## Appendix A – Review protocols

**Protocol for review question 1. Diagnostic accuracy of ultrasound and hysteroscopy for investigation of women presenting with heavy menstrual bleeding**

| Component | Description |
|---|---|
| Review question | What is the diagnostic accuracy of ultrasound and hysteroscopy for investigation of women presenting with heavy menstrual bleeding? |
| Objective | The CG44 surveillance report identified 1 UK based study evaluating the cost-effectiveness of different diagnostic strategies for HMB (including transvaginal scanning, endometrial biopsy, saline infusion sonography and outpatient hysteroscopy). |
| | The study concluded that outpatient hysteroscopy was the most cost-effective option for women referred to secondary care for investigation of HMB. |
| | Endometrial biopsy, in addition to hysteroscopy, had an incremental cost-effectiveness ratio of £21,000 per additional satisfied patient. |
| | Current guidance recommends the use of ultrasound as the first-line diagnostic tool, with hysteroscopy only used when ultrasound results are inconclusive. Therefore, the GC44 surveillance report concluded that this new evidence could have a potential impact on current recommendations. |
| | It is important to note, however, that cost-effectiveness was not assessed in terms of cost per quality adjusted life year, as is the usual NICE approach. |
| | The CG44 surveillance report did not identify other evidence that could affect current recommendations. |
| | Based on this, the guideline committee agreed it is necessary to look at the evidence comparing the effectiveness and cost-effectiveness of hysteroscopy compared with ultrasound. |
| | The objective of this review is to determine the diagnostic accuracy of hysteroscopy compared to ultrasound in diagnosing structural causes for heavy menstrual bleeding in women presenting with heavy menstrual bleeding. |
| Population | Women of reproductive age (post-pubertal and premenopausal) who present with heavy menstrual bleeding. |
| | We will include women with abnormal uterine bleeding, and studies where more than 66% of the population have heavy menstrual bleeding. |
| Subgroups and sensitivity analyses | The following sub-groups will be assessed separately in the presence of heterogeneity: |
| | • women with suspected fibroids |
| | • women who have inter-menstrual bleeding in addition to heavy menstrual bleeding |

| | |
|---|---|
| | • women who had a previous index test (hysteroscopy or ultrasound scan)<br>• time of publication (pre 2007, post 2007) |
| Index test: | • Transvaginal ultrasound scan (TVUS)<br>  ○ two-dimensional (2D)<br>  ○ three-dimensional (3D)<br>• Transabdominal ultrasound scan (TAUS)<br>  ○ 2D<br>  ○ 3D<br>• Hysteroscopy<br>  ○ inpatient/day case (under general anaesthesia/sedation or spinal/epidural anaesthesia)<br>  ○ outpatient vaginoscopy (alternative method for performing hysteroscopy that does not require inserting a vaginal speculum or other cervical instruments)<br>  ○ outpatient all other cases<br>• Transvaginal ultrasound scan followed by hysteroscopy if needed<br><br>Note: saline infusion sonography was not included as an index test because the committee agreed with the old guideline recommendation that it should not be used as a first-line diagnostic investigation. |
| Reference standard | • Histopathologic diagnosis (biopsy or surgery specimen)<br>• Ultrasound scan (when compared with hysteroscopy)<br>• Inpatient hysteroscopy (when compared to different outpatient types) |
| Outcomes | • Sensitivity<br>• Specificity<br>• Positive likelihood ratio (LR+)<br>• Negative likelihood ratio (LR-)<br>• Area under the curve (AUC) if meta-analysis can be conducted<br>• Patient satisfaction and acceptability of the test, including pain score<br><br>Results will be presented per pathology, for example submucosal fibroids, polyps, hyperplasia, cancer, abnormal uterine thickness, synechiae, endometritis, retained products of conception (RPOC), fibroids smaller than 3 cm in diameter, fibroids larger than 3cm in diameter, congenital abnormalities. |
| Importance of outcomes | Critical outcomes:<br>• sensitivity<br>• LR+<br>• LR-<br>• patient satisfaction |
| Study design | Studies in which the index test and the reference<br>standard would be compared in the same individuals and 2x2 tables will be constructed:<br>• test and treat randomised controlled trials (RCTs) or systematic reviews of test and treat RCTs<br>• cross-sectional studies |

| | |
|---|---|
| | • prospective cohort studies (where cross-sectional data were reported therefore 2 x 2 table could be tabulated)<br><br>Exclude: case-control studies |
| Setting | Any healthcare setting where NHS care is delivered (primary, secondary, tertiary or community) |
| Search strategy | Sources searched: Embase, Medline, PreMedline, CENTRAL, CDSR, DARE<br><br>Limits: The search undertaken for Clinical guideline CG44 met all quality criteria and was updated for articles published between 2007 (the end of the search period for CG44) to 13 October 2016. As a diagnostic review, the search strategy included all study types.<br><br>Supplementary search techniques: Checking reference lists of included and potentially relevant studies. |
| Review strategy | Appraisal of methodological quality<br>• The methodological quality of each study will be assessed using the QUADAS-2 checklist<br>• The quality of the evidence for an outcome (i.e. across studies) will be assessed using adapted GRADE.<br>• Studies with 80-99% women with HMB will be downgraded once for indirectness. Studies with 66-80% women with HMB, or where the proportion of women with HMB is not specified, will be downgraded twice for indirectness.<br><br>Synthesis of data<br>• Meta-analysis will be conducted when appropriate<br><br>The cut-offs for diagnostic accuracy measures:<br>• sensitivity and specificity:<br>  o high: higher than 90%<br>  o moderate: 75-90%<br>  o low: lower than 75%<br>• positive likelihood ratio:<br>  o very useful test: higher than 10<br>  o moderately useful test: 5-10<br>  o not a useful test: lower than 5<br>• negative likelihood ratio:<br>  o very useful test: lower than 0.1<br>  o moderately useful test: 0.1 to 0.2<br>  o not a useful test: higher than 0.2 |
| Equalities | Potential equality issues were considered. The following groups were identified in the scoping phase:<br>• women who have difficulties communicating in English<br>• women with learning difficulties<br>• women from minority ethnic groups<br>• women from disadvantaged socio-economic groups |

| | |
|---|---|
| Notes/additional information | The level of experience of the investigators should be considered. |
| | Clinician's judgement should be independent of index test/reference standard results and be blinded from the index test/reference standard results. |If blinding is not done, the evidence will be downgraded according to QUADAS-2. |
| Key papers | • Surveillance review of CG44: Heavy menstrual bleeding. |
| | • Critchley, H. O., Warner, P., Lee, A. J., Brechin, S., Guise, J., Graham, B., Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status, Health Technology Assessment, 8, 1-139, 2004 |
| | • Cooper, N. A., Barton, P. M., Breijer, M. et al., Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): a decision analysis, Health Technology Assessment, 18, 1-201, 2014 |

*2D: two-dimenstional; 3D: three-dimensional; AUC: area under the curve; LR-: negative likelihood ratio; LR+: positive likelihood ratio; RCT: randomised controlled trial; TAUS: transabdominal ultrasound scan; TVUS: transvaginal ultrasound scan*

## Protocol for review question 2. Clinically effective imaging strategy for detecting adenomyosis in women presenting with heavy menstrual bleeding

| Component | Description |
|---|---|
| Review question | What is the most clinically effective imaging strategy for diagnosing adenomyosis in women with heavy menstrual bleeding? |
| Objective | Adenomyosis is a benign gynaecological disorder in which the inner lining of the uterus breaks through the muscle wall of the uterus. The most common symptoms are pelvic pain and heavy menstrual bleeding. The diagnosis of adenomyosis is challenging because the symptoms are similar to other uterine pathology and might coexist with other uterine abnormalities. Traditionally adenomyosis was only diagnosed through histopathology after hysterectomy. Improvements in diagnostic imaging in recent years have shown that adenomyosis can be diagnosed with non-invasive methods as well. However, currently there are no standard diagnostic imaging criteria for adenomyosis. |
| | The objective of this review is to assess the accuracy of imaging techniques in diagnosing adenomyosis in women presenting with heavy menstrual bleeding. |
| Population | Women of reproductive age (post-pubertal and premenopausal) who present with heavy menstrual bleeding. |
| | Studies with indirect population (women with pelvic pain or dysmenorrhea) will be considered but at least two thirds of the population in the study should be women with heavy menstrual bleeding. |
| Subgroups and sensitivity analyses | The following sub-groups will be assessed separately in the presence of heterogeneity: |
| | • women who have coexisting uterine abnormalities such as fibroids |
| | • women who have inter-menstrual bleeding in addition to heavy menstrual bleeding |
| Index test: Severity assessment | • Magnetic resonance imaging (MRI) |
| | • Transvaginal ultrasound scan (TVUS) |
| | ○ two-dimensional (2D) |

| Component | Description |
|---|---|
| tools/clinical markers |    o three-dimensional (3D)<br>• Transabdominal ultrasound scan (TAUS)<br>   o 2D<br>   o 3D<br>• Combination of two or more of the above |
| Reference standard or target condition/patient outcomes | • Histopathologic diagnosis (biopsy or surgery specimen)<br>• Ultrasound (when compared with MRI) |
| Outcomes | • Sensitivity<br>• Specificity<br>• Positive likelihood ratio (LR+)<br>• Negative likelihood ratio (LR-)<br>• Area under the curve (AUC) if meta-analysis can be conducted |
| Importance of outcomes | Critical outcomes:<br>• sensitivity<br>• LR+<br>• LR- |
| Study design | Studies in which the index test and the reference<br>standard would be compared in the same individuals and 2x2 tables will be constructed:<br>• test and treat randomised controlled trials (RCTs) or systematic reviews of test and treat RCTs<br>• cross-sectional studies<br>• prospective cohort studies where cross-sectional data were reported therefore 2 x 2 table could be tabulated<br><br>Exclude: case-control studies |
| Setting | Any healthcare setting where NHS care is delivered (primary, secondary, tertiary or community) |
| Search strategy | Sources searched: Embase, Medline, PreMedline, CENTRAL, CDSR, DARE<br><br>Limits: The search undertaken for Clinical guideline CG44 met all quality criteria and was updated for articles published between 1996 and 13 October 2016. As a diagnostic review, the search strategy included all study types.<br><br>Supplementary search techniques: Checking reference lists of included and potentially relevant studies. |
| Review strategy | Appraisal of methodological quality<br>• The methodological quality of each study will be assessed using the QUADAS-2 checklist<br>• The quality of the evidence for an outcome (i.e. across studies) will be assessed using adapted GRADE. |

| Component | Description |
|---|---|
| | • Studies with 80-99% women with HMB will be downgraded once for indirectness. Studies with 66-80% women with HMB, or where the proportion of women with HMB is not specified, will be downgraded twice for indirectness.<br><br>Synthesis of data<br>• Meta-analysis will be conducted when appropriate<br><br>The cut-offs for diagnostic accuracy measures:<br>• sensitivity and specificity:<br>  ○ high: higher than 90%<br>  ○ moderate: 75-90%<br>  ○ low: lower than 75%<br>• positive likelihood ratio:<br>  ○ very useful test: higher than 10<br>  ○ moderately useful test: 5-10<br>  ○ not a useful test: lower than 5<br>• negative likelihood ratio:<br>  ○ very useful test: lower than 0.1<br>  ○ moderately useful test: 0.1 to 0.2<br>  ○ not a useful test: higher than 0.2 |
| Equalities | Potential equality issues were considered. The following groups were identified in the scoping phase:<br>women who have difficulties communicating in English<br>women with learning difficulties<br>women from minority ethnic groups<br>women from disadvantaged socio-economic groups |
| Notes/additional information | The level of experience of the investigators should be considered.<br>Clinician's judgement should be independent of index test/reference standard results and be blinded from the index test/reference standard results. \|If blinding is not done, the evidence will be downgraded according to QUADAS-2. |
| Key papers | • Champaneria, R., Abedin, P., Daniels, J., Balogun, M., Khan, K.,S. Ultrasound scan and magnetic resonance imaging for the diagnosis of adenomyosis: systematic review comparing test accuracy, Acta Obstet Gynecol Scand, 89, 1374-84, 2010<br>• Cooper, N. A., Barton, P. M., Breijer, M., Caffrey, O., Opmeer, B. C., Timmermans, A., Mol, B. W., Khan, K. S., Clark, T. J., Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): a decision analysis, Health Technology Assessment, 18, 1-201, 2014<br>• Herman, M. C., Mol, B. W., Bongers, M. Y., Diagnosis of heavy menstrual bleeding, Women's Health, 12, 15-20, 2016<br>• Meredith, S. M., Sanchez-Ramos, L., Kaunitz, A. M., Diagnostic accuracy of transvaginal sonography for the diagnosis of adenomyosis: systematic review and metaanalysis, American Journal of Obstetrics and Gynecology, 201, 107.e1-107.e6, 2009 |

| Component | Description |
|---|---|
| | • Senturk, L. M., Imamoglu, M., Adenomyosis: what is new?, Womens Health, 11, 717–724, 2015 <br> • Struble, J., Reid, S., Bedaiwy, M. A., Adenomyosis: A Clinical Review of a Challenging Gynecologic Condition, Journal of Minimally Invasive Gynecology, 23, 164-185, 2016 |

*2D: two-dimenstional; 3D: three-dimensional; AUC: area under the curve; LR-: negative likelihood ratio; LR+: positive likelihood ratio; MRI: magnetic resonance imaging; RCT: randomised controlled trial; TAUS: transabdominal ultrasound scan; TVUS: transvaginal ultrasound scan*

## Appendix B – Health economic quality assessment

| Study identification |
|---|
| **Cooper, N. A., Barton, P. M., Breijer, M., Caffrey, O., Opmeer, B. C., Timmermans, A., Mol, B. W., Khan, K. S., Clark, T. J., Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): a decision analysis, Health Techonology Assessment, 18, 2014** |

| Guidance topic: HMB | | Question no: 1 |
|---|---|---|
| Section 1: Applicability (relevance to specific review questions and the NICE reference case as described in section 7.5) | Yes/partly/no/unclear/NA | Comments |
| 1.1 Is the study population appropriate for the review question? | Yes | Women referred to secondary care by their GP presenting with HMB |
| 1.2 Are the interventions appropriate for the review question? | Yes | 13 different investigation scenarios. <br> TVUS, SIS, global EBx and OPH used in alone, or in combination. <br> No investigation was also considered where treatment was initiated with LNG-IUS or hysterectomy. |
| 1.3 Is the system in which the study was conducted sufficiently similar to the current UK context? | Yes | UK |
| 1.4 Are the perspectives clearly stated and are they appropriate for the review question? | Yes | NHS |
| 1.5 Are all direct effects on individuals included, and are all other effects included where they are material? | Yes | |
| 1.6 Are all future costs and outcomes discounted appropriately? | N/A | Time horizon 1 year |
| 1.7 Is QALY used as an outcome, and was it derived using NICE's preferred methods? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.4 above). | No | Satisfaction used as the measure of effectiveness. Assumptions to translate |

| Study identification |
|---|
| **Cooper, N. A., Barton, P. M., Breijer, M., Caffrey, O., Opmeer, B. C., Timmermans, A., Mol, B. W., Khan, K. S., Clark, T. J., Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): a decision analysis, Health Techonology Assessment, 18, 2014** |

| | | |
|---|---|---|
| | | satisfaction to QALYs was reported in places. |
| 1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued? | Yes | |
| 1.9 Overall judgement: Directly applicable | | |
| **Other comments:** This study does not use the preferred measure of effects (QALYs), but is still thought to be useful for decision making given that all other criteria are applicable and the alternative outcome measure reported is unlikely to change the conclusions about cost-effectiveness | | |

| Section 2: Study limitations (the level of methodological quality) | Yes/partly/ no/unclear /NA | Comments |
|---|---|---|
| 2.1 Does the model structure adequately reflect the nature of the topic under evaluation? | Yes | Decision tree informed by clinical expertise |
| 2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes? | Partly | Time horizon 1 year. Chosen primarily as satisfaction data was not reported beyond this |
| 2.3 Are all important and relevant outcomes included? | Unclear | Satisfaction is treatment specific rather than health state specific and may not be able to incorporate all changes in health-related quality of life that can occur along the pathway |
| 2.4 Are the estimates of baseline outcomes from the best available source? | Yes | Parameter inputs were derived from systematic reviews, individual patient data and focused searches and in the absence of estimates, the consensus view of an expert clinical panel was obtained. |
| 2.5 Are the estimates of relative intervention effects from the best available source? | Yes | See 2.4 |
| 2.6 Are all important and relevant costs included? | Yes | See 2.4 |
| 2.7 Are the estimates of resource use from the best available source? | Yes | See 2.4 |
| 2.8 Are the unit costs of resources from the best available source? | Yes | NHS Reference Costs, PSSRU, BNF |
| 2.9 Is an appropriate incremental analysis presented or can it be calculated from the data? | Yes | |
| 2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis? | Yes | Extensive SA and PSA (1,000 iterations) |
| 2.11 Is there any potential conflict of interest? | No | |

| Study identification |
|---|
| **Cooper, N. A., Barton, P. M., Breijer, M., Caffrey, O., Opmeer, B. C., Timmermans, A., Mol, B. W., Khan, K. S., Clark, T. J., Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): a decision analysis, Health Techonology Assessment, 18, 2014** |
| 2.12 Overall assessment: Potentially serious limitations |

# Appendix C – Research recommendations

**Research recommendation 1. Hysteroscopy compared with ultrasound or empiric pharmacological treatment in the diagnosis and management of heavy menstrual bleeding**

Is initial testing using hysteroscopy more effective than testing with pelvic ultrasound or empiric pharmacological treatment in the diagnosis and management of heavy menstrual bleeding?

**Why is this important?**

There is no consensus about the best test-and-treat strategy for women with HMB and empiric pharmacological treatment is often initiated as a first treatment without investigation. Parameters of diagnostic accuracy give useful information about a test's ability to detect a condition (or the absence of a condition). But accurate diagnosis does not automatically result in a better overall outcome for the woman, because this also depends on treatment decisions after the diagnosis is made. However, it is thought that optimal treatment depends on accurate diagnosis of the underlying pathology causing HMB. In the absence of clinical trials, decision analytical economic models evaluating all possible outpatient testing algorithms have indicated that using ultrasound or hysteroscopy for initial diagnostic testing for women with HMB are the most effective diagnostic strategies. Pelvic ultrasound has been most commonly used because it has been more widely available and is considered less intrusive than hysteroscopy. However, advances in technology mean that the hysteroscopy is well tolerated in the outpatient setting, and it can potentially be performed outside the traditional hospital environment in a community setting. Moreover, in contrast with ultrasound, hysteroscopy allows concomitant treatment of intrauterine pathologies such as endometrial polyps and submucosal fibroids. It also facilitates the fitting of levonorgesterol-releasing intrauterine systems (LNG-IUS). A test-and-treat randomised controlled trial with cost-effectiveness analysis could help to answer the crucial question of whether hysteroscopy improves outcomes for women and results in more effective use of NHS resources.

**Table 7: Reseach recommendation rationale**

| Research question | Is initial testing with hysteroscopy more effective than with pelvic ultrasound or empiric pharmacological treatment in the diagnosis and management of women with heavy menstrual bleeding? |
|---|---|
| **Why this is needed** | |
| Importance to 'patients' or the population | Heavy menstrual bleeding (HMB) is common and associated with significant morbidity including adverse impacts upon all domains of health related quality of life, restriction of daily activities including absenteeism from work and other responsibilities including impairment of family roles. |
| Relevance to NICE guidance | Evidence from economic decision analytical modelling has shown that an initial outpatient diagnostic strategies of women with HMB based upon hysteroscopy or transvaginal ultrasound are the most cost-effective strategies. In practice, many women presenting with HMB in primary care are offered empiric pharmacological treatment without investations. However, there is substantial uncertainty regarding which approach is the more cost-effective. |
| Relevance to the NHS | HMB is common and adversely affects women's quality of life and utilises significant health service resources. HMB is caused by several different pathologies. Correct diagnosis allows the most appropriate medical or surgical treatments to be selected, thereby optimising clinical outcomes and saving health care resources by avoiding the need for further diagnostic testing and additional treatment. |
| National priorities | Women's health. |
| Current evidence base | The 2017 partial guideline update did not identify evidence from diagnostic randomised controlled trials. The available diagnostic cohort studies inform us about the diagnostic accuracy of ultrasound and hysteroscopy compared to a reference standard, however it is not possible to assess whether the differences in accuracy are clinically important or the impact on patient outcomes.<br><br>One RCT conducted in Scotland between 1999 and 2001 compared three outpatient diagnostic tests (outpatient endometrial biopsy, pelvic ultrasound and hysteroscopy) (Critchley 2004). The utility of the findings from this RCT are limited because a mixed population of women with abnormal uterine bleeding were evaluated (women with HMB and post-menopausal women with unexpected vaginal bleeding). This is because the aim of investigation of women with postmenopausal bleeding is to exclude the possibility of endometrial cancer, whereas in pre-menopausal women it is to optimise management of benign uterine pathologies associated with HMB (i.e. selection of appropriate treatment modalities). The trial did not evaluate clinical outcomes, rather feasibility and acceptability. Furthermore, technological advancement in the 20 years since this study was conceived has restricted the relevance of the findings especially because imaging has improved, instruments are miniaturised and less traumatic, hysteroscopy is more widely available and now conducted in an outpatient setting and failure rates are much lower than reported here.<br><br>Several decision analytical economic models (Cooper 2014; De Vries 2000; NICE 2007) have been conducted to evaluate the optimal testing strategies for HMB from a cost-effectiveness standpoint. No consistent findings have been found because of limitations in the constructed models, namely differing assumptions and simplifications being made; not accounting for clinical examination findings, not accounting for the range of possible underlying diagnoses, limited accuracy and effectiveness data from sequential testing such that a heavy reliance has been necessary from 'expert opinion' and the |

| Research question | Is initial testing with hysteroscopy more effective than with pelvic ultrasound or empiric pharmacological treatment in the diagnosis and management of women with heavy menstrual bleeding? |
|---|---|
| | use of outmoded or restricted therapeutic options as well as eclectic outcome measures. Not surprisingly the findings of these analysis were sensitive to changes in the key assumptions limiting the robustness of clinical inferences. Overall, the findings from the RCT and economic models has shown that an initial outpatient diagnostic strategies of women with HMB based upon hysteroscopy or transvaginal ultrasound are potentially the most effective and cost-effective strategies. However, there are no published trials including empiric pharmacological treatment without prior investigation as a comparator.<br>Therefore, there remains considerable uncertainty surrounding clinical effectiveness and patient acceptability / preferences. Only an RCT can resolve this uncertainty. |
| Equality | HMB affects women of all reproductive ages and races. Thus the optimising clinical outcomes through better diagnosis will benefit all women with this condition. |
| Feasibility | HMB is common. Pelvic ultrasound and outpatient hysteroscopy are now widely available tests in gynaecological practice. However, whilst there is general consensus regarding treatment options for HMB, according to the suspected underlying causes, there is variation in current practice for diagnostic work in HMB across the NHS. Thus, given the high prevalence of HMB, the widespread availability of tests and uncertainty amongst clinicians regarding optimal diagnostic work up, an RCT to evaluate the effectiveness and cost-effectiveness of initial testing strategies based upon pelvic ultrasound and outpatient hysteroscopy is highly feasible. |
| Other comments | References:<br>• Cooper, N. A. M., Barton, P. M., Breijer, M., Caffrey, O., Opmeer, B. C., Timmermans, A., et al, Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): a decision analysis, Health Technology Assessment, 18, 2014<br>• Critchley, H. O. D., Warner, P., Lee, A. J., Brechin, S., Guise, J., Graham, B., Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status, Health Technology Assessment, 8, 2004<br>• De Vries, L. D., Dijkhuizen, F. P. H. L., Mol, B. W. J., Brolmann, H. A. M., Moret, E., Heintz, A. P. M., Comparison of transvaginal sonography, saline infusion sonography, and hysteroscopy in premenopausal women with abnormal uterine bleeding, Journal of Clinical Ultrasound, 28, 217-23, 2000<br>• National Institute for Health and Care Excellence (NICE), NICE guideline on Heavy menstrual bleeding: assessment and management (CG44), London: NICE, 2007 |

**Table 8: Characteristics of the study design**

| Criterion | Explanation |
|---|---|
| Population | Women with heavy menstrual bleeding |
| Intervention | • Outpatient hysteroscopy followed by treatment<br>• Pelvic ultrasound followed by treatment |

| Criterion | Explanation |
|---|---|
| | • Empiric pharmacological treatment only (no test) |
| Comparators | Any of the above |
| Outcomes | • Primary outcome at 12 months: Quality of life (condition specific); longer term effects measured at two years and 5 years<br><br>• Secondary outcomes: Other clinical (e.g. satisfaction, generic quality of life, complications and feasibility of testing); qualitative (e.g. patient acceptability and preferences); economic (cost-utility (cost/QALY)) |
| Study design | Test-and-treat randomised controlled trial |
| Timeframe | 5 years |

## Appendix D – Clinical evidence study selection

**Figure 2: Flow diagram of clinical article selection for reviews on diagnostic test accuracy for investigations of women presenting with heavy menstrual bleeding**
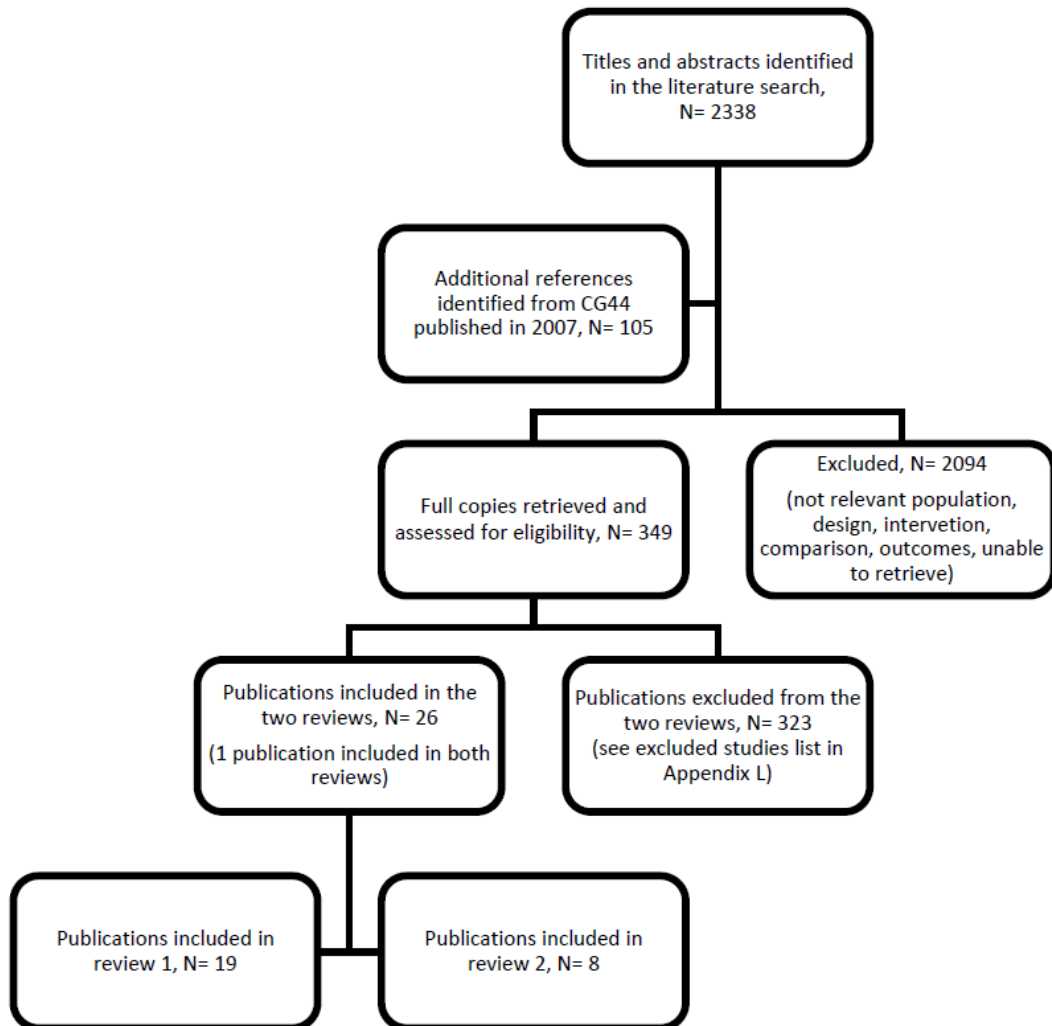
# Appendix E – Literature search strategies

**Cochrane Library (CDSR, DARE, CENTRAL) – Wiley (last searched 13.10.2016)**

| ID | Search |
|---|---|
| #1 | mesh descriptor: [menorrhagia] this term only |
| #2 | (menorrhag* or hypermenorrh* or menometrorrhag* or metromenorrhag* or (menstru* near/3 (bleed* or blood loss)) or (heavy near/1 (period* or menses or menstruation)) or ((abnormal* or dysfunction*) near/3 (uterine or uterus) near/3 (bleed* or blood*))):ti |
| #3 | (menorrhag* or hypermenorrh* or menometrorrhag* or metromenorrhag* or (menstru* near/3 (bleed* or blood loss)) or (heavy near/1 (period* or menses or menstruation)) or ((abnormal* or dysfunction*) near/3 (uterine or uterus) near/3 (bleed* or blood*))):ab |
| #4 | #1 or #2 or #3 |
| #5 | mesh descriptor: [adenomyosis] this term only |
| #6 | (adenomyo* or adenomyi*):ti |
| #7 | (adenomyo* or adenomyi*):ab |
| #8 | #5 or #6 or #7 |
| #9 | mesh descriptor: [area under curve] explode all trees |
| #10 | mesh descriptor: [predictive value of tests] this term only |
| #11 | mesh descriptor: [reproducibility of results] this term only |
| #12 | mesh descriptor: [roc curve] this term only |
| #13 | mesh descriptor: [sensitivity and specificity] this term only |
| #14 | mesh descriptor: [validation studies] this term only |
| #15 | (accurac* or accurat* or 'area under curve' or 'auc value*' or 'clinical utilit*' or (likelihood near/3 ratio*) or (diagnostic near/2 odds ratio*) or ((pretest or 'pre test' or posttest or 'post test') near/2 probabilit*) or (predict* near/3 value*) or 'receiver operating characteristic' or (roc near/2 curv*) or reliabil* or sensitiv* or ecificit* or valid*):ti |
| #16 | (accurac* or accurat* or 'area under curve' or 'auc value*' or 'clinical utilit*' or (likelihood near/3 ratio*) or (diagnostic near/2 odds ratio*) or ((pretest or 'pre test' or posttest or 'post test') near/2 probabilit*) or (predict* near/3 value*) or 'receiver operating characteristic' or (roc near/2 curv*) or reliabil* or sensitiv* or specificit* or valid*):ab |

| ID | Search |
|---|---|
| #17 | (satisf* or acceptab*):ti |
| #18 | (satisf* or acceptab*):ab |
| #19 | satisf*:kw |
| #20 | #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 |
| #21 | #17 or #18 or #19 or #20 |
| #22 | mesh descriptor: [diagnostic imaging] this term only |
| #23 | mesh descriptor: [imaging, three-dimensional] this term only |
| #24 | mesh descriptor: [ultrasonography] explode all trees |
| #25 | mesh descriptor: [ultrasonography] explode all trees |
| #26 | mesh descriptor: [tomography] this term only |
| #27 | mesh descriptor: [tomography, x-ray] explode all trees |
| #28 | mesh descriptor: [magnetic resonance imaging] explode all trees |
| #29 | mesh descriptor: [hysterosalpingography] this term only |
| #30 | mesh descriptor: [hysteroscopy] this term only |
| #31 | (ultrasonograph* or sonograph* or ultrasound* or ultrasonic* or echograph* or echotomograph* or endosonograph* or ((uterine or uterus or medical) near/3 imaging) or hysterosalpongograph* or hysterograph* or hysterosonograph* or sonohysterograph* or (magnetic near/3 (resonance or imaging)) or (mri or mr imaging or nmr) or hysteroscop* or taus or tvus):ti |
| #32 | (ultrasonograph* or sonograph* or ultrasound* or ultrasonic* or echograph* or echotomograph* or endosonograph* or ((uterine or uterus or medical) near/3 imaging) or hysterosalpongograph* or hysterograph* or hysterosonograph* or sonohysterograph* or (magnetic near/3 (resonance or imaging)) or (mri or mr imaging or nmr) or hysteroscop* or taus or tvus):ab |
| #33 | #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 |
| #34 | #4 and #33 publication year from 2007 to 2016, in cochrane reviews (reviews and protocols) and other reviews |
| #35 | #4 and #21 and #33 publication year from 2007 to 2016, in trials, technology assessments and economic evaluations |
| #36 | #8 and #33 publication year from 1996 to 2016, in cochrane reviews (reviews and protocols) and other reviews |
| #37 | #8 and #20 and #33 publication year from 1996 to 2016, in trials, technology assessments and economic evaluations |

| ID | Search |
|---|---|
| #38 | #34 or #35 or #36 or #37 |

**OVID MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R);**
**Embase** 1980 to 2016  (last searched 13.10.2016)

| # | Searches |
|---|---|
| 1 | menorrhagia/ or 'menorrhagia and metrorrhagia'/ (12537) |
| 2 | 1 use emez (8425) |
| 3 | menorrhagia/ (12470) |
| 4 | 3 use mesz, prem (4113) |
| 5 | (menorrhag* or hypermenorrh* or menometrorrhag* or metromenorrhag* or (menstru* adj3 (bleed* or blood loss)) or (heavy adj1 (period* or menses or menstruation)) or ((abnormal* or dysfunction*) adj3 (uterine or uterus) adj3 (bleed* or blood*))).ti,ab. (18679) |
| 6 | or/2,4-5 (22025) |
| 7 | adenomyosis/ (3927) |
| 8 | 7 use emez (3549) |
| 9 | adenomyosis/ (3927) |
| 10 | 9 use mesz, prem (378) |
| 11 | (adenomyo* or adenomyi*).ti,ab. (7190) |
| 12 | or/8,10-11 (8216) |
| 13 | '*area under the curve'/ or *predictive validity/ or *receiver operating characteristic/ or *reliability/ or '*sensitivity and specificity'/ or *test retest reliability/ or *validity/ (35178) |
| 14 | 13 use emez (31257) |
| 15 | 'area under curve'/ or 'predictive value of tests'/ or 'reproducibility of results'/ or roc curve/ or 'sensitivity and specificity'/ or validation studies/ (1358993) |
| 16 | 15 use mesz, prem (806587) |

| # | Searches |
|---|---|
| 17 | (accurac* or accurat* or area under curve or auc value* or clinical utilit* or (likelihood adj3 ratio*) or (diagnostic adj2 odds ratio*) or ((pretest or pre test or posttest or post test) adj2 probabilit*) or (predict* adj3 value*) or receiver operating characteristic or (roc adj2 curv*) or reliabil* or sensititiv* or specificit* or valid*).tw. (3326518) |
| 18 | or/14,16-17 (3747277) |
| 19 | imaging/ (357914) |
| 20 | diagnostic imaging/ (174189) |
| 21 | exp echography/ or hysteroscopy/ (916865) |
| 22 | gynecological radiography/ (116) |
| 23 | hysterosalpingography/ (8923) |
| 24 | tomography/ (38627) |
| 25 | computer assisted tomography/ (637444) |
| 26 | exp nuclear magnetic resonance/ (1259850) |
| 27 | three dimensional imaging/ (134632) |
| 28 | or/19-27 (2894095) |
| 29 | 28 use emez (2282821) |
| 30 | diagnostic imaging/ (174189) |
| 31 | exp imaging, three-dimensional/ (148746) |
| 32 | exp ultrasonography/ (905916) |
| 33 | tomography/ or exp tomography, x-ray/ (1272329) |
| 34 | exp magnetic resonance imaging/ (1121066) |
| 35 | hysterosalpingography/ (8923) |
| 36 | hysteroscopy/ (14119) |
| 37 | uterus/us (2297) |
| 38 | leiomyoma/us (961) |
| 39 | or/30-38 (2989587) |

| # | Searches |
|---|---|
| 40 | 39 use mesz, prem (1028816) |
| 41 | (ultrasonograph* or sonograph* or ultrasound* or ultrasonic* or echograph* or echotomograph* or endosonograph* or ((uterine or uterus or medical) adj3 imaging) or hysterosalpongograph* or hysterograph* or hysterosonograph* or sonohysterograph* or (magnetic adj3 (resonance or imaging)) or (mri or mr imaging or nmr) or hysteroscop* or tvus or taus).ti,ab. (1853552) |
| 42 | or/29,40-41 (3881741) |
| 43 | meta analysis/ or 'meta analysis (topic)'/ or systematic review/ (332848) |
| 44 | 43 use emez (252004) |
| 45 | meta analysis.sh,pt. or 'meta-analysis as topic'/ or 'review literature as topic'/ (310231) |
| 46 | 45 use mesz, prem (102226) |
| 47 | (exp bibliographic database/ or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,sh,pt. or systematic$.ti,ab.) (253845) |
| 48 | (exp databases, bibliographic/ or (((electronic or computer$ or online) adj database$) or bids or cochrane or embase or index medicus or isi citation or medline or psyclit or psychlit or scisearch or science citation or (web adj2 science)).ti,ab.) and (review$.ti,ab,sh,pt. or systematic$.ti,ab.) (253845) |
| 49 | ((analy$ or assessment$ or evidence$ or methodol$ or quantativ$ or systematic$) adj2 (overview$ or review$)).tw. or ((analy$ or assessment$ or evidence$ or methodol$ or quantativ$ or systematic$).ti. and review$.ti,pt.) or (systematic$ adj2 search$).ti,ab. (486134) |
| 50 | (metaanal$ or meta anal$).ti,ab. (228536) |
| 51 | (research adj (review$ or integration)).ti,ab. (2657) |
| 52 | reference list$.ab. (28511) |
| 53 | bibliograph$.ab. (30896) |
| 54 | published studies.ab. (40368) |
| 55 | relevant journals.ab. (2105) |
| 56 | selection criteria.ab. (53262) |
| 57 | (data adj (extraction or synthesis)).ab. (36561) |
| 58 | (handsearch$ or ((hand or manual) adj search$)).ti,ab. (22026) |
| 59 | (mantel haenszel or peto or dersimonian or der simonian).ti,ab. (11716) |

| # | Searches | # |
|---|----------|---|
| 60 | (fixed effect$ or random effect$).ti,ab. (73352) | |
| 61 | ((pool$ or combined or combining) adj2 (data or trials or studies or results)).ti,ab. (113198) | |
| 62 | 47 use emez (153761) | |
| 63 | 48 use mesz, prem (100084) | |
| 64 | or/44,46,49-63 (961624) | |
| 65 | 64 or review$.ti,ab,pt. (6564182) | |
| 66 | (12 and 18 and 42) or (12 and 42 and 65) (1321) | |
| 67 | limit 66 to yr='1996 -current' (1178) | |
| 68 | (satisf* or acceptab*).ti,ab. or 18 (4447557) | |
| 69 | (6 and 68 and 42) or (6 and 42 and 65) (2548) | |
| 70 | limit 69 to yr='2007 -current' (1405) | |
| 71 | or/67,70 (2436) | |

# Appendix F – Clinical evidence tables

The clinical evidence tables are presented in a separate document.

# Appendix G – GRADE tables

**Review question 1. Adapted GRADE tables for diagnostic accuracy of ultrasound and hysteroscopy for investigations of women presenting with heavy menstrual bleeding review**

**Table 9:   Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting polyps**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Polyps - All eligible studies** | | | | | | | | | | | | |
| 9 | 955 | very serious risk of bias[1] | very serious inconsistency[2] | very serious indirectness[3] | serious imprecision[4] | none | 57.4 (30.0-81.0) | 94.1 (91.6-95.9) | 9.73 (5.32-17.79) | 0.45 (0.23-0.87) | 0.93 (0.91-0.95) | VERY LOW |
| **Polyps - Studies published in 2007 or later** | | | | | | | | | | | | |
| 7 | 853 | very serious risk of bias[5] | very serious inconsistency[2] | very serious indirectness[6] | serious imprecision[4] | none | 60.2 (29.0-84.9) | 93.1 (90.8-94.8) | 8.7 (4.8-15.9) | 0.43 (0.19-0.94) | 0.94 (0.92-0.96) | VERY LOW |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; sens: sensitivity; spec: specificity*
*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*
*a Risk of bias was assessed using the QUADAS-2 checklist.*
*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*
*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*
*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*
*1 The evidence was downgraded by 2 because 8 studies did not report if a consecutive or random sample of women were enrolled; 4 studies failed to report exclusion criteria or reported them unclearly; 3 studies did not reported diagnostic criteria or reported unclearly; 3 studies had drop-puts, however, the reasons were described; 2 studies did not report clearly if reference standard was interpreted without knowledge of the index test; 1 study had an interval of 1 month between the investigations; 1 study used varying methods of obtaining histological sample including D&C, hysteroscopy-guided biopsy and hysterectomy.*
*2 The evidence was downgraded by 2 because of high heterogeneity.*
*3 The evidence was downgraded by 2 because of high concern about applicability of population since 8 studies did not report the exact proportion of women with HMB and 1 study had less than 80% women with HMB; unclear concern about the interpretation of the index test since the level of experience of the investigators were not reported in most studies.*
*4 The evidence was downgraded by 1 because 95% CI for sensitivity crosses 75%.*

*5 The evidence was downgraded by 2 because 6 studies did not report if a consecutive or random sample of women were enrolled; 2 studies did not report diagnostic criteria or reported it unclearly; 2 studies did not report clearly if reference standard was interpreted without knowledge of the index test; 1 study made unclear exclusions; 1 study reported inclusion and exclusion criteria unclearly; 1 study had an interval of 1 month between the investigations; 1 study used varying methods of obtaining histological sample including D&C, hysteroscopy-guided biopsy and hysterectomy; 3 studies had drop-puts, however, the reasons were described.*
*6 The evidence was downgraded by 2 because of high concern about applicability of population since 7 studies did not report the exact proportion of women with HMB, unclear concern about the interpretation of the index test since the level of experience of the investigators were not reported in most studies.*

### Table 10: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting fibroids

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Fibroids - All eligible studies** | | | | | | | | | | | | |
| 8 | 870 | very serious risk of bias[1] | serious inconsistency[2] | very serious indirectness[3] | serious indirectness[4] | none | 77.0 (65.8-85.4) | 96.5 (92.7-98.4) | 22.3 (10.5-47.5) | 0.23 (0.16-0.36) | 0.92 (0.89-0.94) | VERY LOW |
| **Fibroids - Studies published in 2007 or later** | | | | | | | | | | | | |
| 6 | 768 | serious risk of bias5 | very serious inconsistency6 | very serious indirectness[7] | very serious imprecision[8] | none | 81.6 (65.3-91.2) | 96.8 (91.4-98.9) | 25.9 (9.1-73.8) | 0.19 (0.09-0.38) | 0.96 (0.94-0.97) | VERY LOW |
| **Fibroids – Studies using hysterectomy as reference standard** | | | | | | | | | | | | |
| 1 | 52 | no serious risk of bias | no serious inconsistency | very serious indirectness[9] | very serious imprecision[8] | none | 90 (55.5-99.8) | 97.6 (87.4-99.9) | 37.80 (3.59-265.0) | 0.10 (0.02-0.66) | N/A | VERY LOW |
| 1 | 50 | serious risk of bias10 | no serious inconsistency | very serious indirectness[11] | very serious imprecision[8] | none | 70 (48.8-90.9) | 96.7 (83.3-99.9) | 21.2 (3.25-160.0) | 0.30 (0.13-0.58) | N/A | VERY LOW |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*
*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*
*a Risk of bias was assessed using the QUADAS-2 checklist.*
*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted..*
*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*
*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*
*1 The evidence was downgraded by 2 because 7 studies did not report if a consecutive or random sample of women were enrolled; 3 studies failed to report exclusion criteria or reported them unclearly; 2 studies did not reported diagnostic criteria or reported unclearly; 3 studies had drop-puts, however, the reasons were described; 1 study did not report clearly if reference standard was interpreted without knowledge of the index test; 1 study had an interval of 1 month between the investigations; 1 study used varying methods of*

*obtaining histological sample including D&C, hysteroscopy-guided biopsy and hysterectomy.*

2 The evidence was downgraded by 1 because of moderately high heterogeneity.

3 The evidence was downgraded by 2 because of high concern about applicability of population since 7 studies did not report the exact proportion of women with HMB and 1 study had less than 80% women with HMB; unclear concern about the interpretation of the index test since the level of experience of the investigators were not reported in most studies.

4 The evidence was downgraded by 1 because 95% CI for sensitivity crosses 75%.

5 The evidence was downgraded by 1 because 5 studies did not report if a consecutive or random sample of women were enrolled; 1 study reported diagnostic criteria unclearly; 1 study did not report clearly if reference standard was interpreted without knowledge of the index test; 1 study reported inclusion and exclusion criteria unclearly; 1 study had an interval of 1 month between the investigations; 1 study used varying methods of obtaining histological sample including D&C, hysteroscopy-guided biopsy and hysterectomy; 3 studies had drop-puts, however, the reasons were described.

6 The evidence was downgraded by 2 because of high heterogeneity.

7 The evidence was downgraded by 2 because of high concern about applicability of population since 6 studies did not report the exact proportion of women with HMB; unclear concern about the interpretation of the index test since the level of experience of the investigators were not reported in most studies.

8 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.

9 The evidence was downgraded by 2 because of high concern about applicability since the study had less than 80% women with HMB; unclear concern about the interpretation of the index test since the level of experience of the investigator was not reported.

10 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; the study did not report any exclusion criteria; the study did not define the diagnostic criteria.

11 The evidence was downgraded by 2 because of high concern about applicability since the study did not report the proportion of women with HMB; unclear concern about the interpretation of the index test since the level of experience of the investigator was not reported.

## Table 11: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting polyps or fibroids

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Polyps or fibroids** | | | | | | | | | | | | |
| 1 | 189 | very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | serious imprecision[3] | none | 92 (85-96) | 62 (50-73) | 2.41 (1.78-3.26) | 0.14 (0.07-0.25) | N/A | VERY LOW |
| 1 | 88 | serious risk of bias[4] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | 23.5 (6.8-49.9) | 93.0 (78.0-97.7) | 3.19 (1.02-9.96) | 0.82 (0.64-1.06) | N/A | VERY LOW |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*

*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*

*a Risk of bias was assessed using the QUADAS-2 checklist.*

*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*

*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*

*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*

*1 The evidence was downgraded by 2 because the study did not report if a consecutive or random sample of women were enrolled; study made unclear or inappropriate exclusions; unclear if reference standard was interpreted without knowledge of the index test; interval between investigations was 4 months; reference standard differed between women (hysteroscopy or hysterectomy).*

*2 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; unclear who interpreted the index test and what was his/her level of experience.*

*3 The evidence was downgraded by 1 because 95% CI for sensitivity crosses 90%.*

*4 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; unclear if reference standard was interpreted without knowledge of the index test; 12% of enrolled women not included in analysis, however, reasons for dropping out were described.*

### Table 12: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting endometrial hyperplasia

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Endometrial hyperplasia** | | | | | | | | | | | | |
| 1 | 122 | very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | very serious imprecision[3] | none | 75.0 (19.4-99.4) | 92.4 (86.0-96.5) | 9.83 (4.22-22.90) | 0.27 (0.05-1.48) | N/A | VERY LOW |
| 1 | 85 | very serious risk of bias[4] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | 43.8 (19.8-70.1) | 95.7 (87.8-99.1) | 10 (2.92-34.72) | 0.59 (0.38-0.91) | N/A | VERY LOW |
| 1 | 89 | no serious risk of bias | no serious inconsistency | very serious indirectness[2] | very serious imprecision3 | none | 71.4 (29.0-96.3) | 85.4 (75.8-92.2) | 4.9 (3.0-7.9) | 0.3 (0.09-1.2) | N/A | VERY LOW |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*

*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*

*a Risk of bias was assessed using the QUADAS-2 checklist.*

*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*

*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*

*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*

*1 The evidence was downgraded by  2 because the study did not report if a consecutive or random sample of women were enrolled; unclear if reference standard was interpreted*

*without knowledge of the index test; interval between investigations was 1 month; study used varying methods of obtaining histological sample including D&C, hysteroscopy-guided biopsy and hysterectomy; 11/133 of enrolled women were not included in analysis and the reasons for dropping out were not described.*

*2 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; unclear who interpreted the index test and what was his/her level of experience.*

*3 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.*

*4 The evidence was downgraded by 2 because the study did not report if a consecutive or random sample of women were enrolled; study made unclear exclusions; study did not report diagnostic criteria; unclear if reference standard was interpreted without knowledge of the index test.*

### Table 13: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting endometrial carcinoma

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Endometrial carcinoma | | | | | | | | | | | | |
| 1 | 89 | no serious risk of bias | no serious inconsistency | very serious indirectness[1] | very serious imprecision[2] | none | 50 (1.3-98.7) | 93.1 (85.6-97.4) | 7.25 (1.8-29) | 0.54 (0.1-2.6) | N/A | VERY LOW |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*

*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*

*a Risk of bias was assessed using the QUADAS-2 checklist.*

*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*

*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*

*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*

*1 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; unclear who interpreted the index test and what was his/her level of experience.*

*2 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.*

### Table 14: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting abnormal endometrium (double-layer endometrium 12 mm or thicker and single-layer endometrium 6 mm or thicker)

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abnormal endometriume (abnormal thickness) | | | | | | | | | | | | |

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 88 | serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | 33.3 (7.5-70.1) | 88.6 (79.5-94.7) | 2.93 (0.96-8.88) | 0.75 (0.47-1.20) | N/A | VERY LOW |

2D-TVUS: two-dimensional transvaginal ultrasound scan; AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

e In premenopausal women, double-layer endometrium thickness of less than 12mm and single-layer endometrium thickness of less than 6mm were arbitrarily considered to be normal, and thicker endometrium was classified as abnormal. In postmenopausal women 4mm was used as a cut-off level to define normality. Irregularly thickened hyperechogenic endometrium was considered to be suggestive of endometrial carcinoma.

1 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; unclear if reference standard was interpreted without knowledge of the index test; 12% of enrolled women were not included in analysis, however, the reasons for dropouts were described.

2 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; unclear who interpreted the index test and what was his/her level of experience.

## Table 15: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting any abnormal finding

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Any abnormal finding[e] | | | | | | | | | | | | |
| 1 | 213 | no serious risk of bias | N/A | very serious indirectness[1] | no serious imprecision | none | 94.6 (91-98) | 77.2 (67-87) | 4.16 (2.66-6.50) | 0.07 (0.04-0.14) | N/A | LOW |
| 1 | 83 | serious risk of bias2 | N/A | very serious indirectness[1] | serious imprecision[3] | none | 74 (61-84) | 55 (37-71) | 1.65 (1.07-2.55) | 0.47 (0.27-0.82) | N/A | VERY LOW |
| 1 | 89 | no serious risk of bias | N/A | very serious indirectness[1] | serious imprecision[4] | none | 89.4 (76.9-96.5) | 71.4 (55.4-84.3) | 3.13 (2.5-3.9) | 0.15 (0.06-0.40) | N/A | VERY LOW |

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 39 | very serious risk of bias5 | N/A | very serious indirectness[1] | very serious imprecision[6] | none | 67 (35-90) | 93 (76-99) | 9.0 (2.24-36.22) | 0.36 (0.16-0.81 | N/A | VERY LOW |

2D-TVUS: two-dimensional transvaginal ultrasound scan; AUC: area under the curve; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

e Defined slightly differently across studies but in general either abnormal endometrial thickness, hyperplasia, carcinoma, or focal abnormalities such as fibroids or polyps.

1 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; unclear who interpreted the index test and what was his/her level of experience.

2 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; 22/274 were not included in analysis, however, reasons for dropping out were described.

3 The evidence was downgraded by1 because 95% CI for sensitivity crosses 75%.

4 The evidence was downgraded by1 because 95% CI for sensitivity crosses 90%.

5 The evidence was downgraded by 2 because the study did not report if a consecutive or random sample of women were enrolled; diagnostic criteria not reported; unclear if reference standard was interpreted without knowledge of the index test; 8/47 women not included in analysis, however, reasons for dropping out were described; the study used varying methods of obtaining histological sample.

6 The evidence was downgraded by2 because 95% CI for sensitivity crosses 75% and 90%.

### Table 16: Clinical evidence profile: Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) in detecting polyps

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Polyps | | | | | | | | | | | | |
| 1 | 89 | no serious risk of bias | no serious inconsistency | very serious indirectness[1] | serious imprecision[2] | none | 91.1 (76.3-98.1) | 98.2 (90.3-100) | 50.2 (44.9-56) | 0.09 (0.01-0.8) | N/A | VERY LOW |

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 85 | very serious risk of bias3 | no serious inconsistency | very serious indirectness[1] | very serious imprecision4 | none | 71.4 (41.9-91.6) | 100 (94.9-100) | Inf | 0.29 (0.12-0.65) | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity
The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.
a Risk of bias was assessed using the QUADAS-2 checklist.
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.
1 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; the level of experience of the index test investigator not reported.
2 The evidence was downgraded by 1 because 95% CI for sensitivity crosses 90%.
3 The evidence was downgraded by 2 because the study did not report if a consecutive or random sample of women were enrolled; unclear exclusions made; diagnostic criteria not reports; unclear if reference standard was interpreted without knowledge of the index test.
4 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.

## Table 17: Clinical evidence profile: Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting polyps

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Polyps | | | | | | | | | | | | |
| 1 | 52 | no serious risk of bias | no serious inconsistency | very serious indirectness[1] | very serious imprecision[2] | none | 100 (2.5-100) | 100 (93.02-100) | Inf | 0.00 | N/A | VERY LOW |
| 1 | 223 | serious risk of bias3 | no serious inconsistency | very serious indirectness[1] | very serious imprecision[2] | none | 88 (67.64-97.34) | 93 (88.48-96.10) | 12.44 (7.34-21.07) | 0.13 (0.05-0.39) | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; Inf: infinite; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity
The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.
a Risk of bias was assessed using the QUADAS-2 checklist.
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*

*1 The evidence was downgraded by 2 because the proportion of women with HMB was less than 80%; the level of experience of the index test investigator not reported.*

*2 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.*

*3 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; diagnostic criteria unclear; 67/290 were not included in analysis, however, the reasons for dropping out were described.*

### Table 18: Clinical evidence profile: Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) in detecting fibroids

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Fibroids** | | | | | | | | | | | | |
| 1 | 89 | no serious risk of bias | no serious inconsistency | very serious indirectness[1] | very serious imprecision[2] | none | 100 (39.8-100) | 100 (95.8-100) | Inf | 0.00 | N/A | VERY LOW |

*AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*

*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*

*a Risk of bias was assessed using the QUADAS-2 checklist.*

*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*

*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*

*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*

*1 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; the level of experience of the index test investigator not reported.*

*2 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.*

### Table 19: Clinical evidence profile: Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting fibroids

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Fibroids** | | | | | | | | | | | | |
| 1 | 51 | no serious risk of bias | no serious inconsistency | very serious indirectness[1] | very serious imprecision[2] | none | 100 (69.15-100) | 100 (91.59-100) | Inf | 0.00 | N/A | VERY LOW |

*AUC: area under the curve; CI: confidence interval; Inf: infinite; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*
*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*
*a Risk of bias was assessed using the QUADAS-2 checklist.*
*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*
*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*
*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*
*1 The evidence was downgraded by 2 because the proportion of women with HMB was less than 80%; level of experience of investigator not reported.*
*2 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.*

**Table 20: Clinical evidence profile: Diagnostic accuracy of hysteroscopy under spinal or general anaesthetic (versus histopathology) in detecting polyps or fibroids**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Polyps or fibroids** | | | | | | | | | | | | |
| 1 | 88 | serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | serious imprecision[3] | Not clearly reported how hysteroscopy was performed but likely as a day case according to reporting. | 100 (80.5-100) | 87.3 (77.3-94.0) | 7.44 (4.05-13.67) | Inf | N/A | VERY LOW |

*AUC: area under the curve; CI: confidence interval; Inf: infinite; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*
*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*
*a Risk of bias was assessed using the QUADAS-2 checklist.*
*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*
*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*
*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*
*1 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; unclear if reference standard was interpreted without knowledge of the index test; 12% of enrolled women were not included in analysis, however, the reasons for dropouts were described.*

2 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; level of experience of investigator not reported.

3 The evidence was downgraded by 1 because 95% CI for sensitivity crosses 90%.

**Table 21: Clinical evidence profile: Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) following a 2D transvaginal ultrasound in detecting polyps or fibroids**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Polyps or fibroids | | | | | | | | | | | | |
| 1 | 50 | serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | very serious imprecision[3] | none | 87.5 (71.01-96.49) | 100 (81.47-100) | Inf | 0.12 (0.05-0.31) | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; Inf: infinite; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

1 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; diagnostic criteria not reported; unclear if reference standard was interpreted without knowledge of the index test.

2 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; level of experience of investigator not reported.

3 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.

**Table 22: Clinical evidence profile: Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) in detecting endometrial hyperplasia**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Endometrial hyperplasia | | | | | | | | | | | | |
| 1 | 89 | no serious risk of bias | no serious inconsistency | very serious indirectness[1] | very serious imprecision[2] | none | 85.7 (42.1-99.6) | 97.6 (91.5-99.7) | 35.1 (25.9-47.6) | 0.15 (0.02-1.4) | N/A | VERY LOW |

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other conside rations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 85 | very serious risk of bias[3] | no serious inconsistency | very serious indirectness[1] | serious imprecision[4] | none | 50 (23.0-77.0) | 95.8 (88.1-99.1) | 11.8 (3.48-40.29) | 0.52 (0.31-0.88) | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

1 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; level of experience of the investigator not reported.

2 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.

3 The evidence was downgraded by 2 because the study did not report if a consecutive or random sample of women were enrolled; unclear exclusions made; diagnostic criteria not reports; unclear if reference standard was interpreted without knowledge of the index test.

4 The evidence was downgraded by 1 because 95% CI for sensitivity crosses 75%.

**Table 23: Clinical evidence profile: Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting endometrial hyperplasia**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Endometrial hyperplasi[a] | | | | | | | | | | | | |
| 1 | 223 | serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | serious imprecision[3] | none | 63 (43.7-78.9) | 92 (86.8-95.1) | 7.46 (4.35-12.81) | 0.41 (0.26-0.64) | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the

test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

1 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; diagnostic criteria unclear; 67/290 were not included in analysis, however, the reasons for dropping out were described.

2 The evidence was downgraded by 2 because the proportion of women with HMB was less than 80%; level of experience of investigator not reported.

3 The evidence was downgraded by 1 because 95% CI for sensitivity crosses 75%.

**Table 24: Clinical evidence profile: Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) in detecting endometrial carcinoma**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Endometrial carcinoma** | | | | | | | | | | | | |
| 1 | 89 | no serious risk of bias | no serious inconsistency | very serious indirectness[1] | very serious imprecision[2] | none | 100 (15.8-100) | 96.4 (90.3-99.3) | 29.0 (27.9-30.2) | 0.00 | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

1 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; the level of experience of the investigator not reported.

2 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.

**Table 25: Clinical evidence profile: Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting endometrial carcinoma**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Endometrial carcinoma** | | | | | | | | | | | | |
| 1 | 223 | serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | very serious imprecision[3] | none | 100 (15.8-100) | 98 (95.4-99.5) | 55.2 (20.9-145.9) | 0.00 | N/A | VERY LOW |

*AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*
*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*
*a Risk of bias was assessed using the QUADAS-2 checklist.*
*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*
*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*
*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*
*1 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; diagnostic criteria unclear; 67/290 were not included in analysis, however, the reasons for dropping out were described.*
*2 The evidence was downgraded by 2 because the proportion of women with HMB was less than 80%; level of experience of investigator not reported.*
*3 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.*

**Table 26: Clinical evidence profile: Diagnostic accuracy of hysteroscopy under spinal or general anaesthetic (versus histopathology) in detecting abnormal endometrium (double-layer endometrium 12 mm or thicker and single-layer endometrium 6 mm or thicker)**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abnormal endometrium[e] (abnormal thickness) | | | | | | | | | | | | |
| 1 | 88 | serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | Not clearly reported how hysteroscopy was performed but likely as a day case according to reporting. | 22.2 (2.8-60.6) | 87.3 (78.0-93.8) | 1.76 (0.45-6.79) | 0.89 (0.062-1.28) | N/A | VERY LOW |

*AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*
*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*
*a Risk of bias was assessed using the QUADAS-2 checklist.*
*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*
*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*
*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*

e In premenopausal women, double-layer endometrium thickness of less than 12mm and single-layer endometrium thickness of less than 6mm were arbitrarily considered to be normal, and thicker endometrium was classified as abnormal. In postmenopausal women 4mm was used as a cut-off level to define normality. Irregularly thickened hyperechogenic endometrium was considered to be suggestive of endometrial carcinoma.

1 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; unclear if reference standard was interpreted without knowledge of the index test; 12% of enrolled women were not included in analysis, however, the reasons for dropouts were described.

2 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; level of experience of investigator not reported.

**Table 27: Clinical evidence profile: Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting endometritis**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Endometritis** | | | | | | | | | | | | |
| 1 | 223 | serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | 41 (27.00-56.77) | 99 (95.98-99.86) | 36.55 (8.83-1451.30) | 0.59 (0.47-0.76) | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity
The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.
a Risk of bias was assessed using the QUADAS-2 checklist.
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.
1 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; diagnostic criteria unclear; 67/290 were not included in analysis, however, the reasons for dropping out were described.
2 The evidence was downgraded by 2 because the proportion of women with HMB was less than 80%; level of experience of investigator not reported.

**Table 28: Clinical evidence profile: Diagnostic accuracy of outpatient hysteroscopy (versus histopathology) in detecting retained products of conception**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Retained products of conception** | | | | | | | | | | | | |

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 223 | serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | very serious imprecision[3] | none | 100 (47.8-100) | 100 (97.5-100) | 218 (30.85-1540) | 0.00 | N/A | VERY LOW |

*AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*
*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*
*a Risk of bias was assessed using the QUADAS-2 checklist.*
*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*
*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*
*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*
*1 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; diagnostic criteria unclear; 67/290 were not included in analysis, however, the reasons for dropping out were described.*
*2 The evidence was downgraded by 2 because the proportion of women with HMB was less than 80%; level of experience of investigator not reported.*
*3 The evidence was downgraded by 2 because 95% CI for sensitivity crosses 75% and 90%.*

## Table 29: Clinical evidence profile: Diagnostic accuracy of hysteroscopy under general anaesthetic (versus histopathology) in detecting any abnormal finding

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Any abnormal finding[e]** | | | | | | | | | | | | |
| 1 | 89 | no serious risk of bias | no serious inconsistency | very serious indirectness[1] | serious imprecision[2] | none | 97.9 (88.7-99.9) | 92.9 (80.5-98.5) | 13.7 (12.5-15.1) | 0.02 (0.002-0.2) | N/A | VERY LOW |

*AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*
*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*
*a Risk of bias was assessed using the QUADAS-2 checklist.*
*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*
*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*
*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the*

test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

e Defined as polyp, fibroid, hyperplasia, or carcinoma.

1 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB; the level of experience of the investigator not reported.

2 The evidence was downgraded by 1 because 95% CI for sensitivity crosses 90%.

### Table 30: Clinical evidence profile: Diagnostic accuracy of hysteroscopy with or without general or local anasthesia (versus histopathology) in detecting any abnormal finding

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Any abnormal finding[e] | | | | | | | | | | | | |
| 1 | 86 | very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | serious imprecision[3] | none | 94 (86.01-98.42) | 100 (79.41-100) | Inf | 0.06 (0.02-0.15) | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; Inf: infinite; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

e Defined as presence of adhesion, polyp, submucosal fibroid, pressure effect or any other abnormality in the uterine cavity.

1 The evidence was downgraded by 2 because the study did not report if a consecutive or random sample of women were enrolled; diagnostic criteria not defined; unclear if reference standard was interpreted without knowledge of the index test.

2 The evidence was downgraded by 2 because the proportion of women with HMB was less than 80%; level of experience of investigator not reported.

3 The evidence was downgraded by 1 because 95% CI for sensitivity crosses 90%.

### Table 31: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus hysteroscopy) in detecting polyps

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Polyps | | | | | | | | | | | | |

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 196 | very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | 32.35 (17.39-50.53) | 95.06 (90.50-97.84) | 6.55 (2.85-15.06) | 0.71 (0.56-0.90) | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity
The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.
a Risk of bias was assessed using the QUADAS-2 checklist.
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.
1 The evidence was downgraded by 2 because the study did not report if a consecutive or random sample of women were enrolled; exclusion criteria not reported; diagnostic criteria not defined; unclear if reference standard was interpreted without knowledge of the index test; 23/219 women were not included in analysis, however, the reasons for dropping out were described.
2 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB.

## Table 32: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus hysteroscopy) in detecting suspicious focal thickening

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Suspicious focal thickening | | | | | | | | | | | | |
| 1 | 196 | very serious risk of bias[1] | no serious inconsistency | very serious indirectness[2] | no serious imprecision | none | 0 (0-45.93) | 93.68 (89.23-96.69) | 0.00 | 1.07 (1.03-1.11) | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity
The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.
a Risk of bias was assessed using the QUADAS-2 checklist.
b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.
c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.
d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

1 The evidence was downgraded by 2 because the study did not report if a consecutive or random sample of women were enrolled; exclusion criteria not reported; diagnostic criteria not defined; unclear if reference standard was interpreted without knowledge of the index test; 23/219 women were not included in analysis, however, the reasons for dropping out were described.

2 The evidence was downgraded by 2 because the study did not report the proportion of women with HMB.

**Table 33: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus hysteroscopy) in detecting any abnormal finding**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other consideration s | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Any abnormal finding[e]** | | | | | | | | | | | | |
| 1 | 770 | serious risk of bias[1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 96 (93.41-97.41) | 86 (82.25-89.99) | 7.07 (5.37-9.31) | 0.05 (0.03-0.08) | N/A | MODERATE |

AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

e Defined as a lesion inside the cavity or when the maximum endometrial thickness measured in the sagittal plane was more than 14 mm.

1 The evidence was downgraded by 1 because the study did not report if a consecutive or random sample of women were enrolled; exclusion criteria not reported; inappropriate/unclear exclusions; unclear if reference standard was interpreted without knowledge of the index test.

**Review question 2. Adapted GRADE tables for the most clinically effective imaging strategy for diagnosing adenomyosis in women presenting with heavy menstrual bleeding review**

**Table 34: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting adenomyosis**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 7 | 1078 | serious risk of bias[2] | very serious inconsistency[3] | very serious indirectness[4] | serious imprecision[5] | none | 76 (69-82) | 83 (73-90) | 4.59 (2.84-7.42) | 0.29 (0.22-0.37) | 0.83 (0.80-0.86) | VERY LOW |
| 1 | 23 | no serious risk of bias | no serious inconsistency | no serious indirectness | very serious imprecision[6] | Population: women with recurrent menometrorrhagia but no evidence of leiomyomata and endometrial diseases on transabdominal examination | 81.0 (58.1-94.6) | 100.0 (15.8-100.0) | Infinite | 0.19 (0.08-0.46) | N/A | LOW |
| 1 | 106 | no serious risk of bias | no serious inconsistency | very serious indirectness[7] | no serious imprecision | Population: women with recurrent menometrorrhagia and evidence of leiomyomata and endometrial diseases on transabdominal examination | 38.5 (20.2-59.4) | 97.5 (91.3-99.7) | 15.4 (3.6-65.7) | 0.63 (0.46-0.86) | N/A | LOW |

2D-TVUS: two-dimensional transvaginal ultrasound scan; AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*

*1 The study reported 'indefinite' results from the index test for 36 cases which have been included as negative test results in the results.*

*2 The evidence was downgraded by 1 because three studies did not report if consecutive or random sample of women were enrolled; three studied did not report inclusion and exclusion criteria clearly; in one study it was unclear if the index test results were interpreted without the knowledge of the results of the reference standard; in one study 28% of the original sample were not included in the analysis*

*3 The evidence was downgraded by 2 because of high heterogeneity.*

*4 The evidence was downgraded by 2 because the population in 6 studies also included a varying proportion of women that did not have heavy menstrual or the exact proportion was unclearly reported; four papers do not report who performed or interpreted the index test or what was the level of experience of the person(s)*

*5 The evidence was downgraded by 1 because the 95% CI of test sensitivity crosses 75%.*

*6 The evidence was downgraded by 2 because the 95% CI of test sensitivity crosses 75% and 90%.*

*7 The evidence was downgraded by 2 because less than 80% of included women did not had HMB; the paper does not report who interpreted the index test or what was the level experience of the person(s).*

### Table 35: Clinical evidence profile: Diagnostic accuracy of 3D-TVUS (versus histopathology) in detecting adenomyosis

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 72 | no serious risk of bias | no serious inconsistency | very serious indirectness[1] | very serious imprecision[2] | none | 91 (74-97) | 88 (72-95) | 7.3 (3.2-16.6) | 0.11 (0.03-0.31) | N/A | VERY LOW |

*3D-TVUS: three-dimensional transvaginal ultrasound scan; AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*

*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*

*a Risk of bias was assessed using the QUADAS-2 checklist.*

*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*

*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*

*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*

*1 The evidence was downgraded by 2 because less than 80% of included women had HMB.*

*2 The evidence was downgraded by 2 because the 95% CI of test sensitivity crosses 75% and 90%.*

**Table 36: Clinical evidence profile: Diagnostic accuracy of 2D-TAUS (versus histopathology) in detecting adenomyosis**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 23 | no serious risk of bias | no serious inconsistency | no serious indirectness | serious imprecision[1] | Population: women with recurrent menometrorrhagia but no evidence of leiomyomata and endometrial diseases on transabdominal examination | 54.1 (34.0-78.2) | 50.0 (27.0-98.7) | 1.1 (0.3-4.8) | 0.9 (0.2-3.7) | N/A | MODERATE |
| 1 | 106 | no serious risk of bias | no serious inconsistency | very serious indirectness[2] | no serious imprecision | Population: women with recurrent menometrorrhagia and evidence of leiomyomata and endometrial diseases on transabdominal examination | 7.7 (1.0-25.1) | 96.3 (89.4-99.2) | 2.1 (0.4-11.6) | 0.96 (0.85-1.08) | N/A | LOW |

*2D-TAUS: two-dimensional transabdominal ultrasound scan; AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; N/A: not applicable; sens: sensitivity; spec: specificity*

*The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.*

*a Risk of bias was assessed using the QUADAS-2 checklist.*

*b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.*

*c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.*

*d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.*

*1 The evidence was downgraded by 1 because the 95% CI of test sensitivity crosses 75%.*

*2 The evidence was downgraded by 2 because less than 80% of included women had HMB.*

**Table 37: Clinical evidence profile: Diagnostic accuracy of MRI (versus histopathology) in detecting adenomyosis**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[1] | 106 | no serious risk of bias | no serious inconsistency | very serious indirectness[2] | serious imprecision[3] | none | 63.6 (40.7-82.8) | 88.1 (79.2-94.1) | 5.4 (2.8-10.4) | 0.4 (0.2-0.7) | N/A | VERY LOW |

AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; MRI: magnetic resonance imaging; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

1 The study reported 'indefinite' results from the index test for 13 cases which have been included as negative test results in the results.

2 The evidence was downgraded by 2 because less than 80% of included women had HMB.

3 The evidence was downgraded by 1 because the 95% CI of test sensitivity crosses 75%.

**Table 38: Clinical evidence profile: Diagnostic accuracy of 2D-TVUS combined with MRI (versus histopathology) in detecting adenomyosis**

| No of studies | n | Risk of bias[a] | Inconsistency[b] | Indirectness[c] | Imprecision[d] | Other considerations | Sens % (95% CI) | Spec % (95% CI) | LR+ (95% CI) | LR- (95% CI) | AUC (95% CI) | Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1[1] | 106 | no serious risk of bias | no serious inconsistency | very serious indirectness[2] | serious imprecision[3] | none | 72.7 (49.8-89.3) | 77.4 (67.0-85.8) | 3.2 (2.0-5.2) | 0.35 (0.18-0.70) | N/A | VERY LOW |

2D-TVUS: two-dimensional transvaginal ultrasound scan; AUC: area under the curve; CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio; MRI: magnetic resonance imaging; N/A: not applicable; sens: sensitivity; spec: specificity

The assessment of the evidence quality was conducted with emphasis on test sensitivity as this was the primary measure discussed in decision-making.

a Risk of bias was assessed using the QUADAS-2 checklist.

b Inconsistency was assessed by inspection of the 95% prediction region in a HSROC plot if a diagnostic meta-analysis was conducted.

c Indirectness was assessed using the QUADAS-2 checklist items referring to applicability.

d The judgement of precision was based on the confidence interval of test sensitivity as this was considered to be the primary measure of interest. If the 95% CI crosses either 75% or 90%, the result was judged to be seriously imprecise (90% was considered to be the cut-off for the test to be highly sensitive and if the sensitivity was less than 75% the test was considered to be of low sensitivity). If the 95% CI crosses both 75% and 90%, the results was judged to be very seriously imprecise.

1 The study reported 'indefinite' results from the index test for 41 cases which have been included as negative test results in the results.

2 The evidence was downgraded by 2 because less than 80% of included women had HMB.

3 The evidence was downgraded by 1 because the 95% CI of test sensitivity crosses 75%.

# Appendix H – Forest plots and hierarchical summary receiver operating characteristic (HSROC) plots

**Review question 1. Forest plots and HSROC plots for diagnostic accuracy of ultrasound and hysteroscopy for investigations of women presenting with heavy menstrual bleeding review**

**Figure 3: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting polyps (meta-analysis with all eligible studies)**
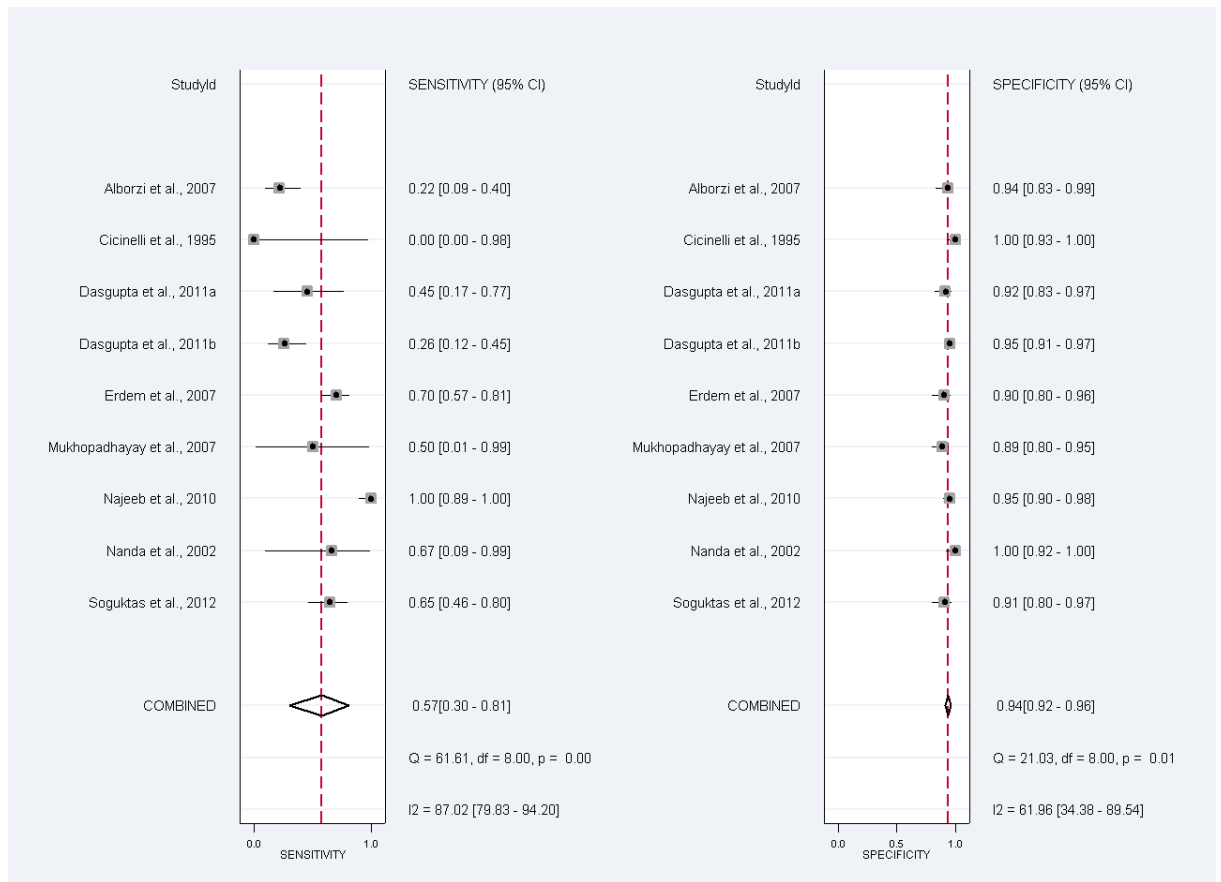


*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval*

**Figure 4: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting polyps (all eligible studies without meta-analysis)**

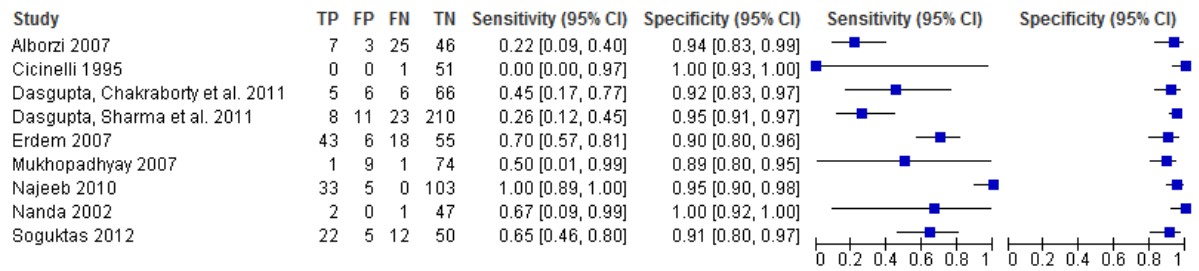| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Alborzi 2007 | 7 | 3 | 25 | 46 | 0.22 [0.09, 0.40] | 0.94 [0.83, 0.99] |
| Cicinelli 1995 | 0 | 0 | 1 | 51 | 0.00 [0.00, 0.97] | 1.00 [0.93, 1.00] |
| Dasgupta, Chakraborty et al. 2011 | 5 | 6 | 6 | 66 | 0.45 [0.17, 0.77] | 0.92 [0.83, 0.97] |
| Dasgupta, Sharma et al. 2011 | 8 | 11 | 23 | 210 | 0.26 [0.12, 0.45] | 0.95 [0.91, 0.97] |
| Erdem 2007 | 43 | 6 | 18 | 55 | 0.70 [0.57, 0.81] | 0.90 [0.80, 0.96] |
| Mukhopadhyay 2007 | 1 | 9 | 1 | 74 | 0.50 [0.01, 0.99] | 0.89 [0.80, 0.95] |
| Najeeb 2010 | 33 | 5 | 0 | 103 | 1.00 [0.89, 1.00] | 0.95 [0.90, 0.98] |
| Nanda 2002 | 2 | 0 | 1 | 47 | 0.67 [0.09, 0.99] | 1.00 [0.92, 1.00] |
| Soguktas 2012 | 22 | 5 | 12 | 50 | 0.65 [0.46, 0.80] | 0.91 [0.80, 0.97] |



2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive

**Figure 5: HSROC plot for diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting polyps (meta-analysis with all eligible studies)**



*2D-TVUS: two-dimensional transvaginal ultrasound scan; HSROC: hierarchical summary receiver operating characteristic*

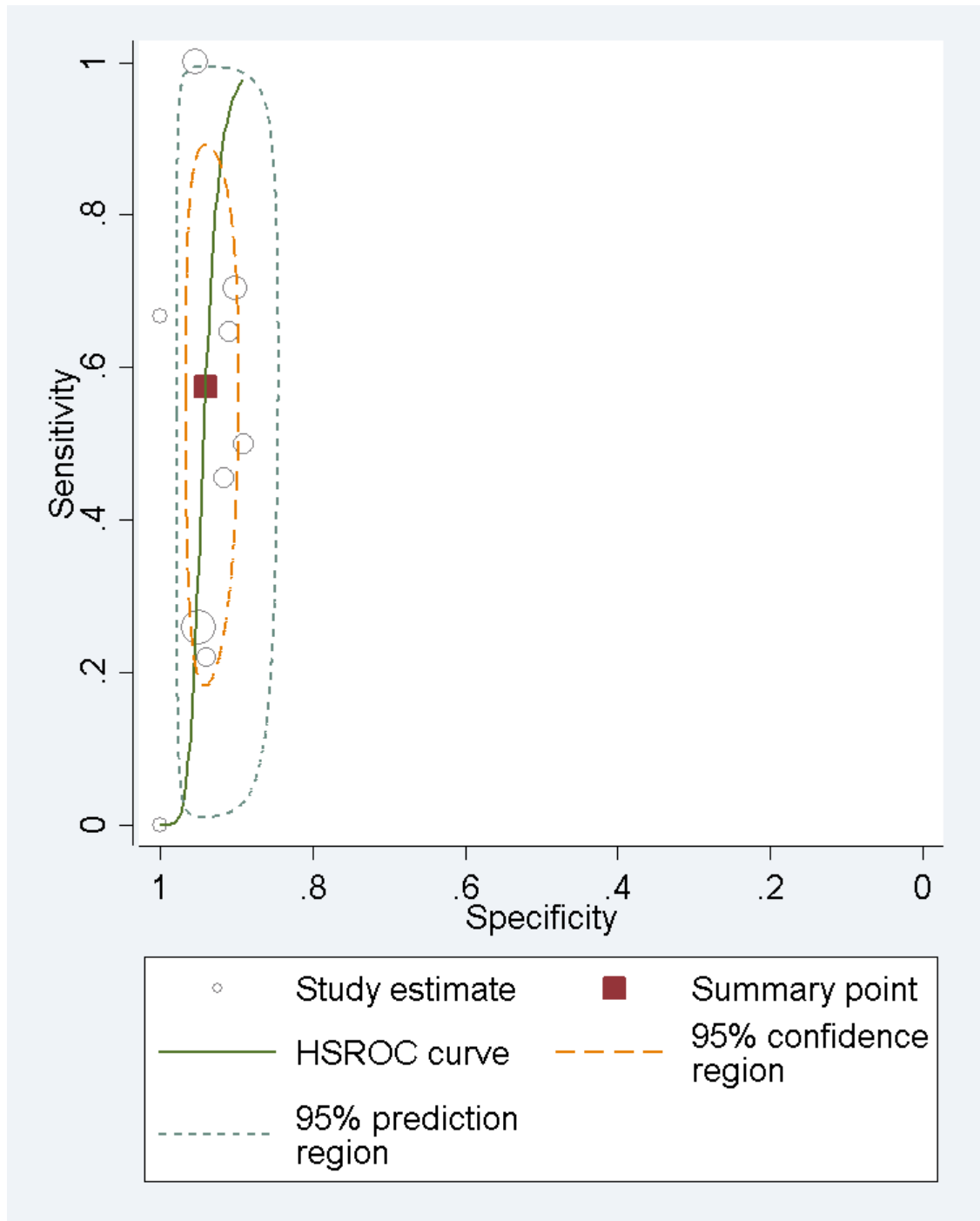**Figure 6: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting polyps (meta-analysis with studies published in 2007 or later)**



*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval*

**Figure 7: HSROC plot for diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting polyps (meta-analysis of studies published in 2007 or later)**



2D-TVUS: two-dimensional transvaginal ultrasound scan; HSROC: hierarchical summary receiver operating characteristic

**Figure 8: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting fibroids (meta-analysis with all eligible studies)**



2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval

**Figure 9: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting fibroids (all eligible studies without meta-analysis)**
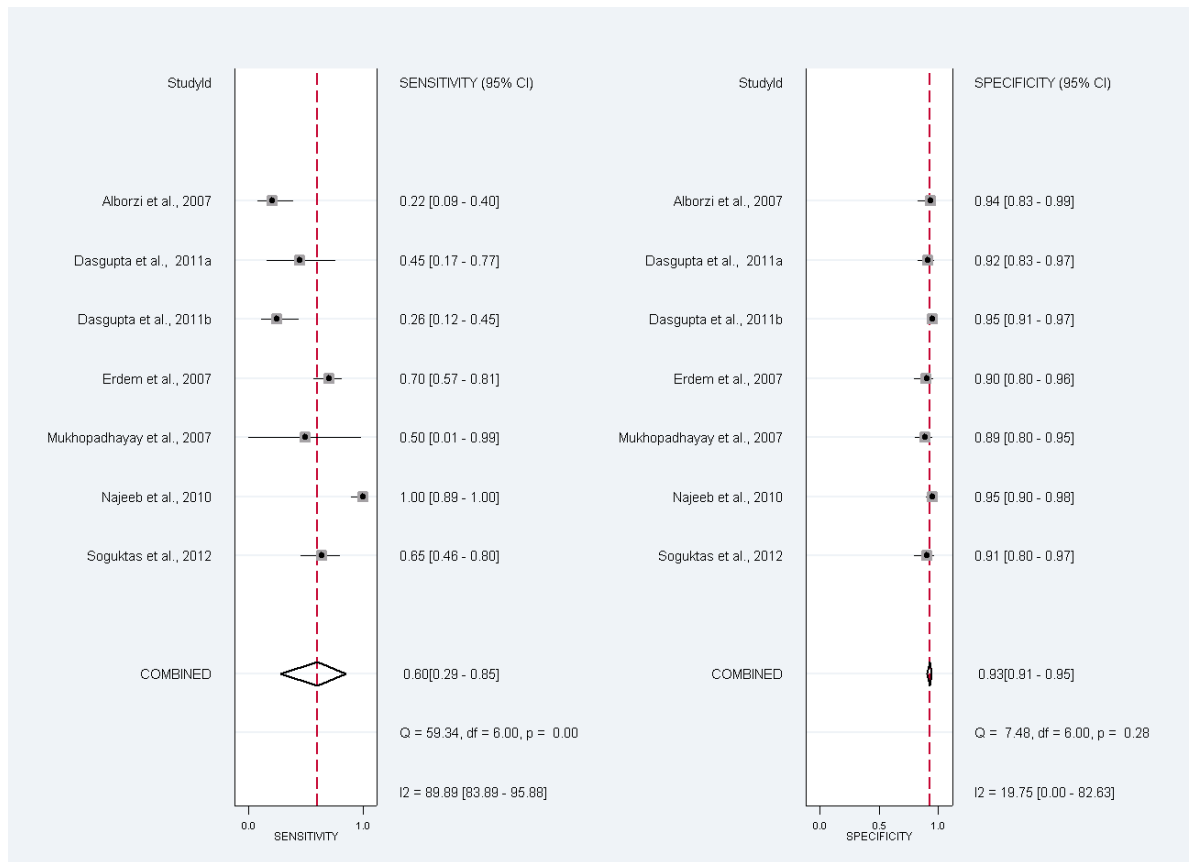


2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive

**Figure 10: HSROC plot for diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting fibroids (meta-analysis with all eligible studies)**
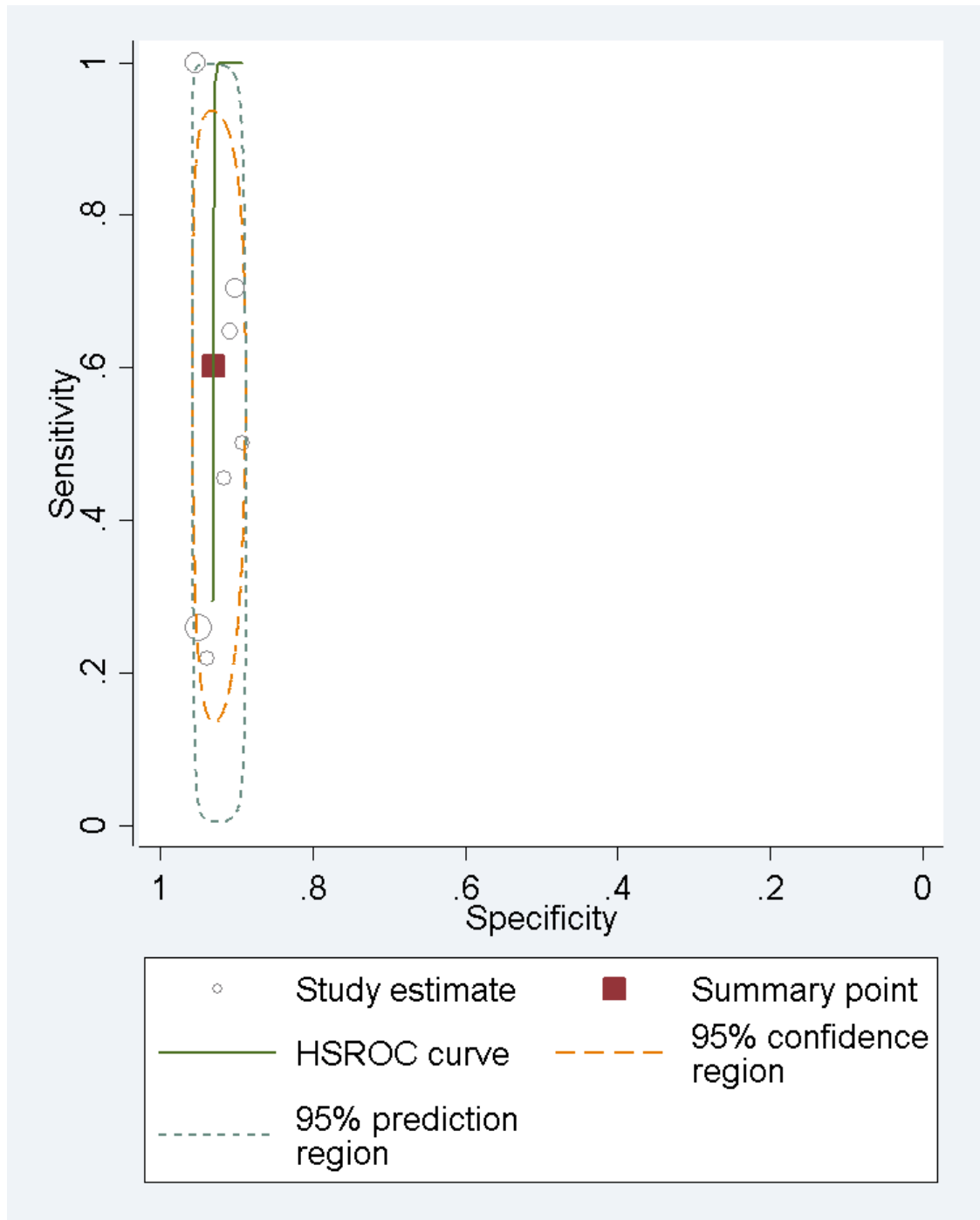


*2D-TVUS: two-dimensional transvaginal ultrasound scan; HSROC: hierarchical summary receiver operating characteristic*

**Figure 11: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting fibroids (meta-analysis with studies published in 2007 or later)**
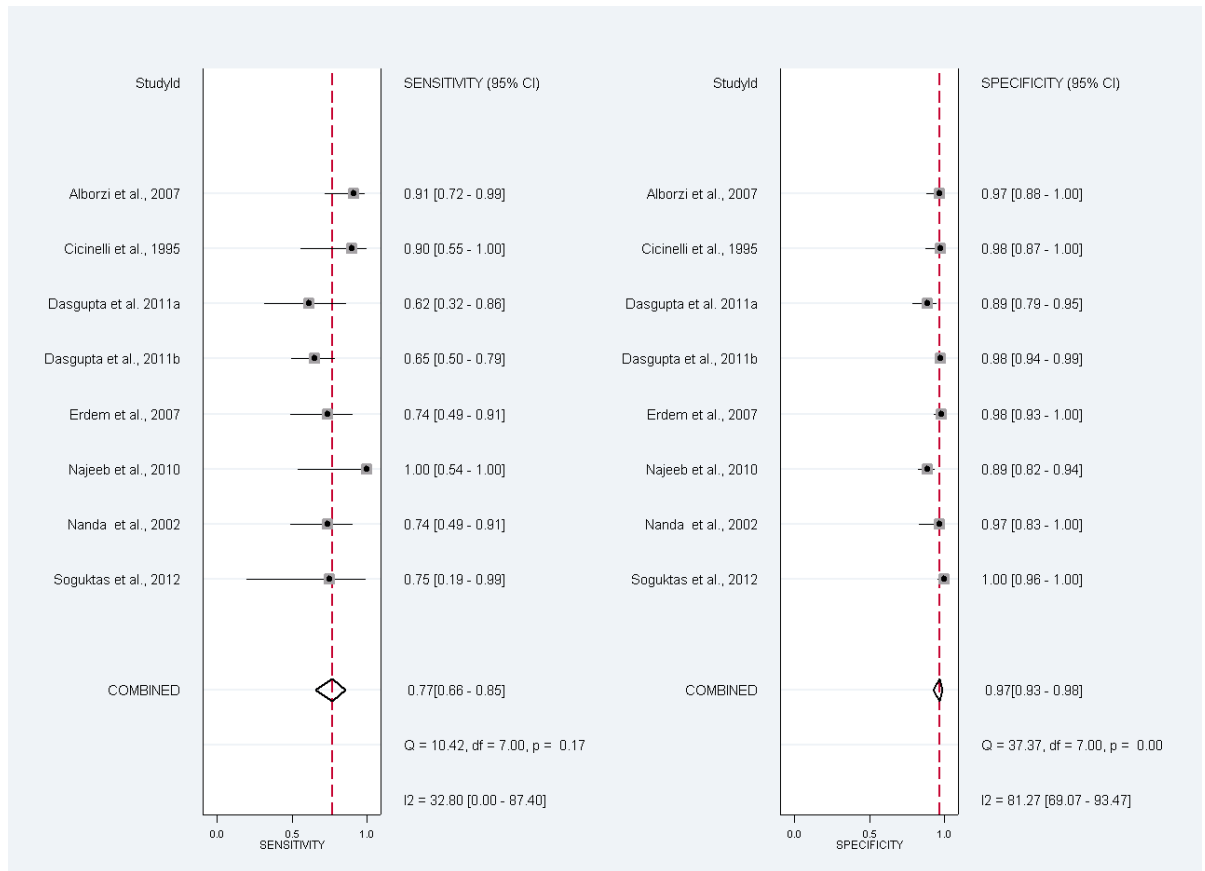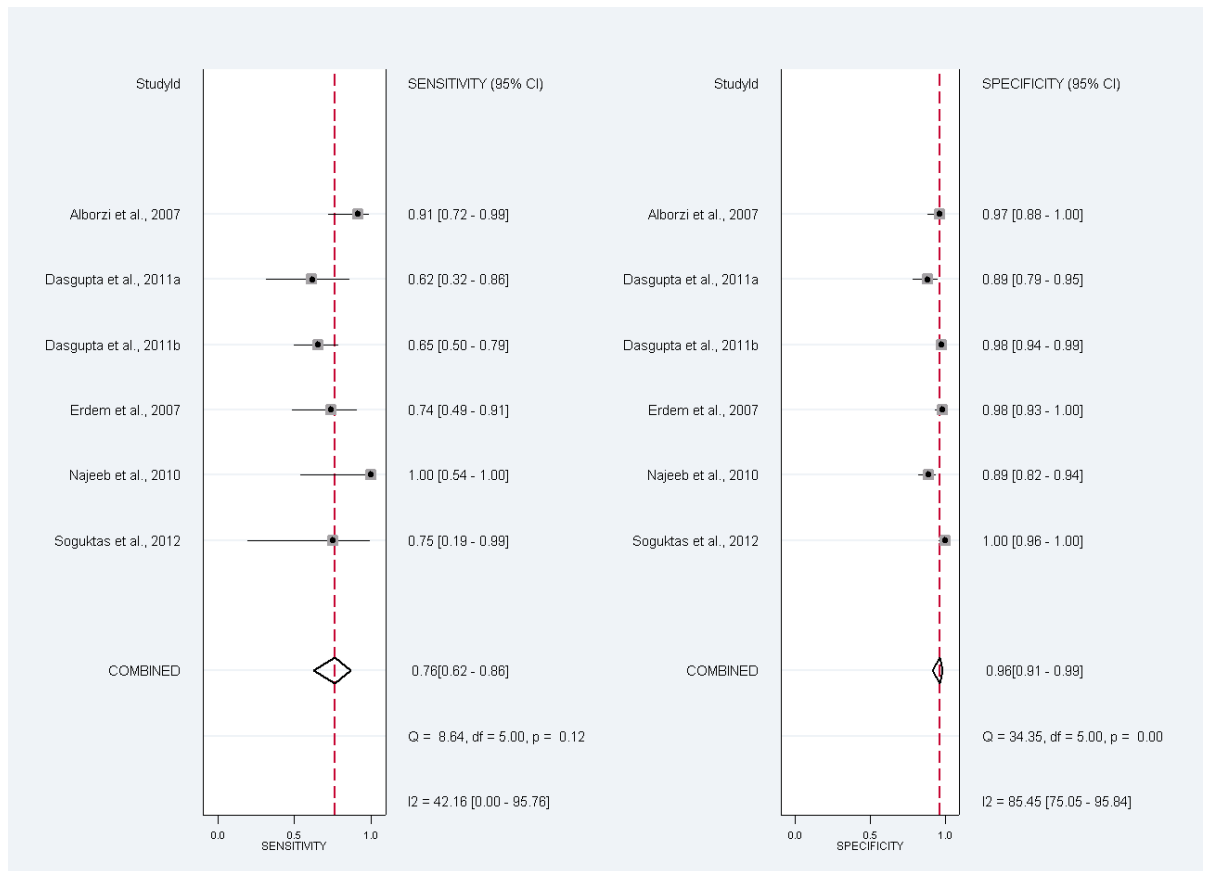


2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval

**Figure 12: HSROC plot for diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting fibroids (meta-analysis with studies published in 2007 or later)**
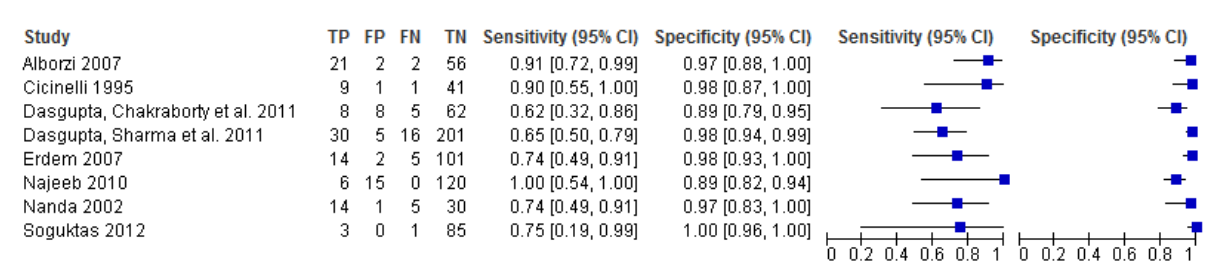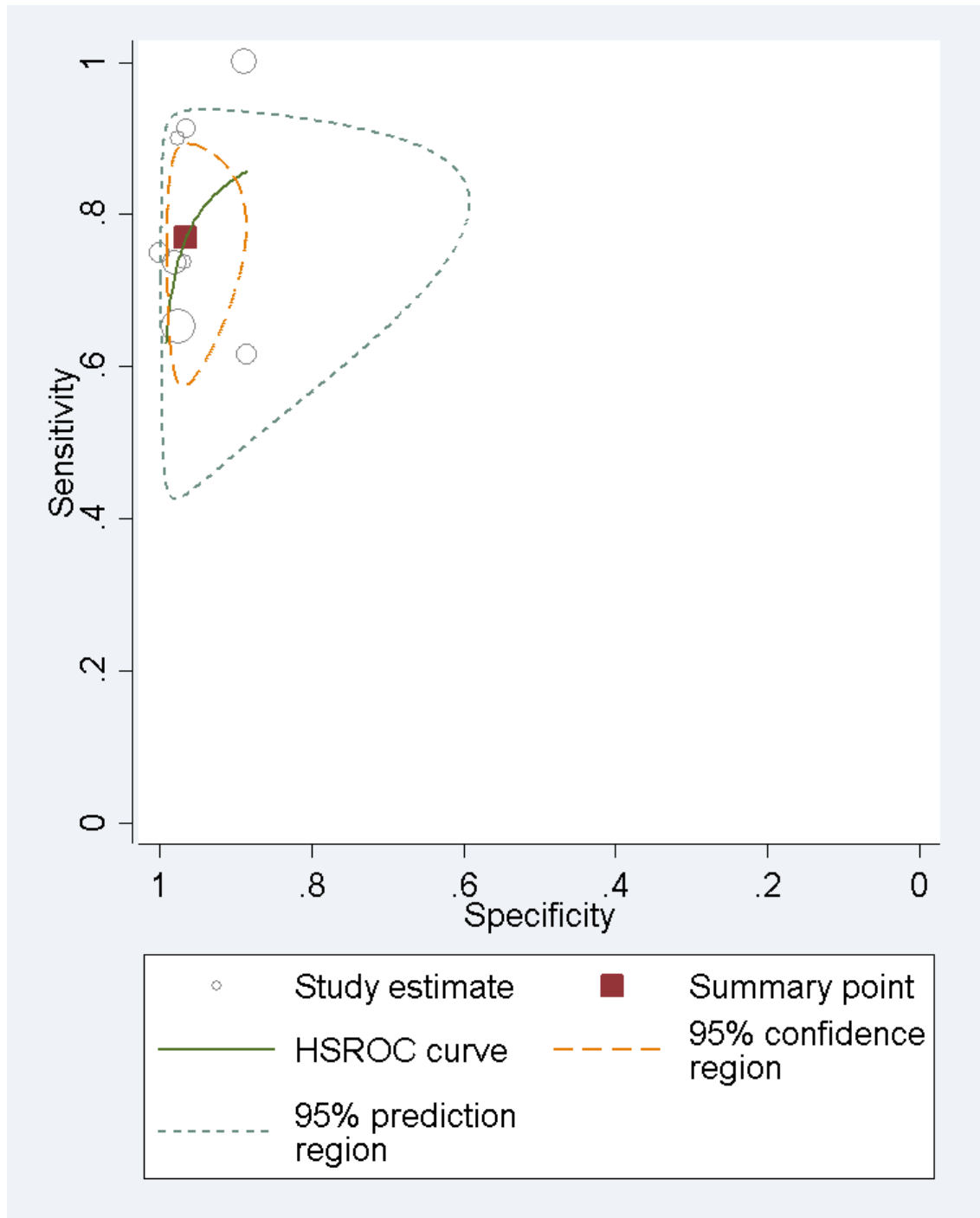


*2D-TVUS: two-dimensional transvaginal ultrasound scan; HSROC: hierarchical summary receiver operating characteristic*

**Figure 13: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting fibroids (studies using hysterectomy as reference standard)**

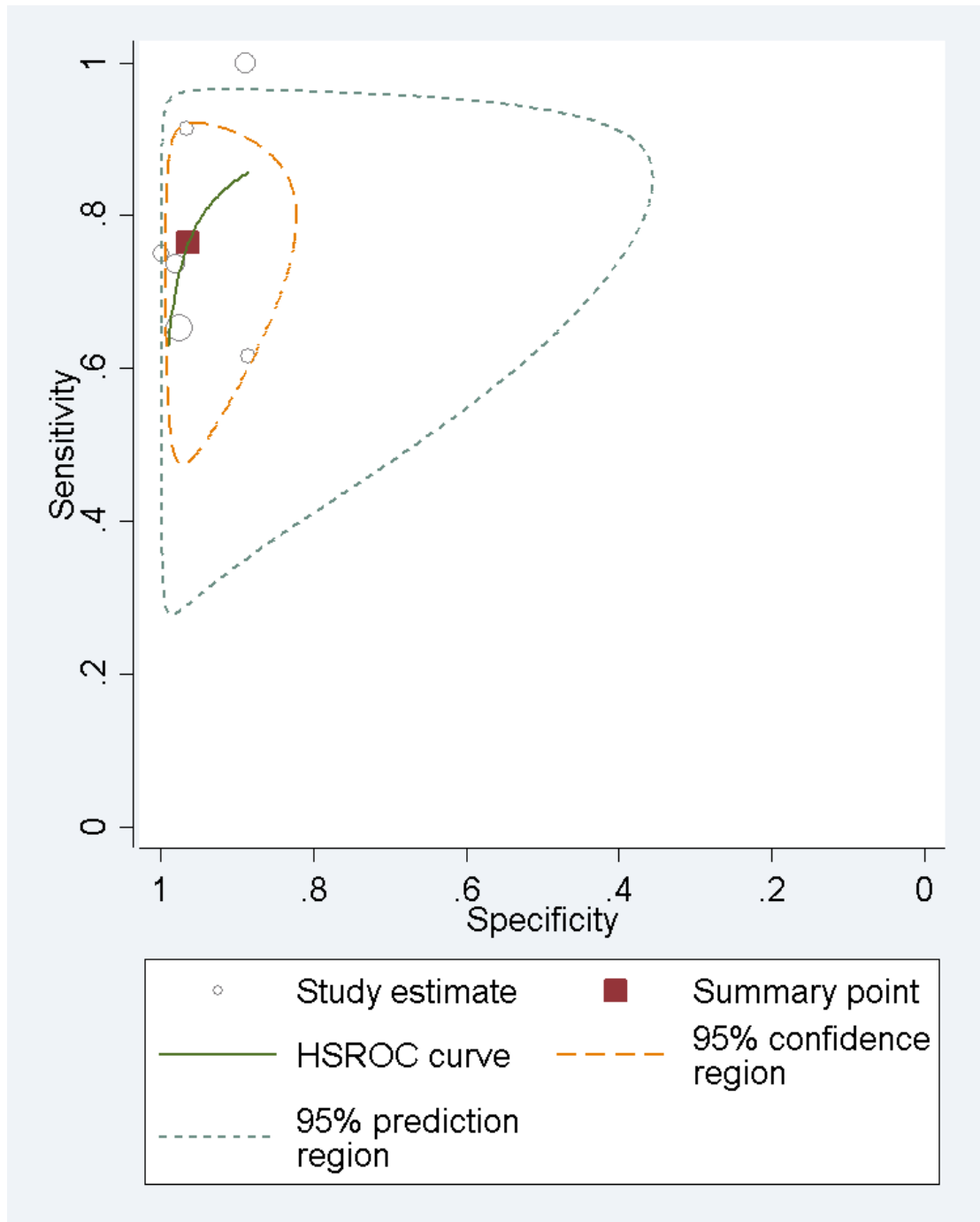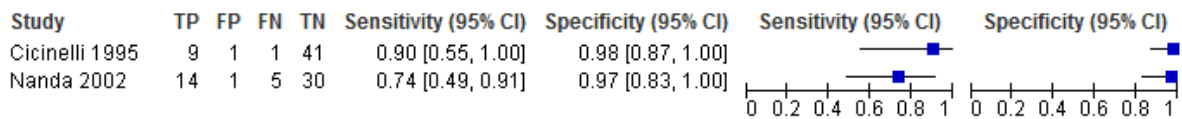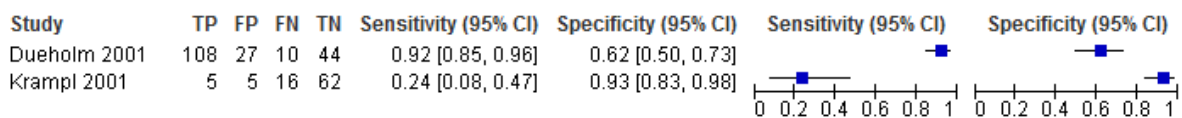| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Cicinelli 1995 | 9 | 1 | 1 | 41 | 0.90 [0.55, 1.00] | 0.98 [0.87, 1.00] | | |
| Nanda 2002 | 14 | 1 | 5 | 30 | 0.74 [0.49, 0.91] | 0.97 [0.83, 1.00] | | |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 14: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting polyps or fibroids**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Dueholm 2001 | 108 | 27 | 10 | 44 | 0.92 [0.85, 0.96] | 0.62 [0.50, 0.73] | | |
| Krampl 2001 | 5 | 5 | 16 | 62 | 0.24 [0.08, 0.47] | 0.93 [0.83, 0.98] | | |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 15: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting endometrial hyperplasia**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Erdem 2007 | 3 | 9 | 1 | 109 | 0.75 [0.19, 0.99] | 0.92 [0.86, 0.96] | | |
| Mukhopadhyay 2007 | 7 | 3 | 9 | 66 | 0.44 [0.20, 0.70] | 0.96 [0.88, 0.99] | | |
| Soguktas 2012 | 5 | 12 | 2 | 70 | 0.71 [0.29, 0.96] | 0.85 [0.76, 0.92] | | |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 16: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting endometrial carcinoma**

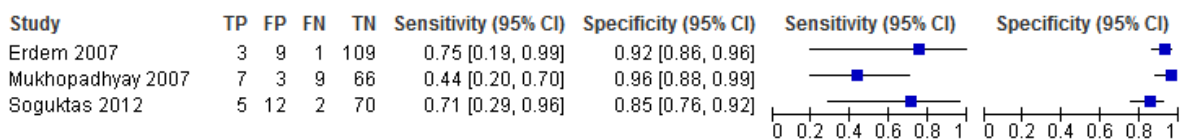| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Soguktas 2012 | 1 | 6 | 1 | 81 | 0.50 [0.01, 0.99] | 0.93 [0.86, 0.97] | | |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 17: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting abnormal endometrium (double-layer endometrium 12 mm or thicker and single-layer endometrium 6 mm or thicker)**

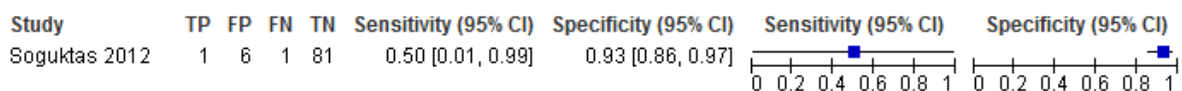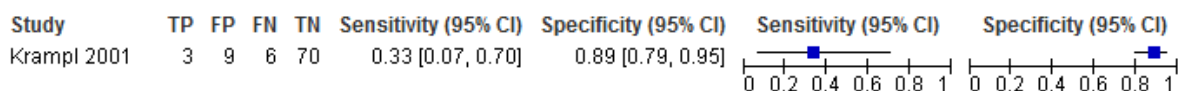| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Krampl 2001 | 3 | 9 | 6 | 70 | 0.33 [0.07, 0.70] | 0.89 [0.79, 0.95] | | |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

### Figure 18: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting any abnormal finding

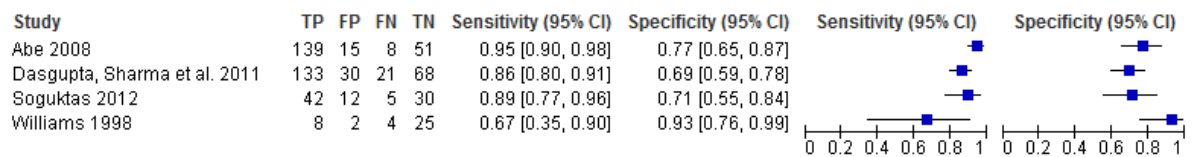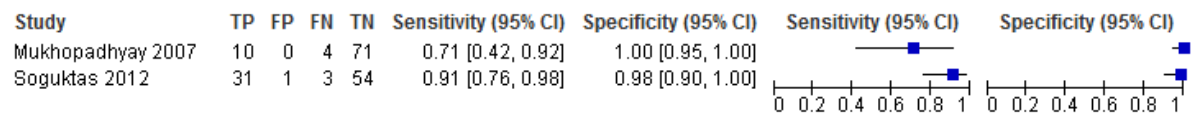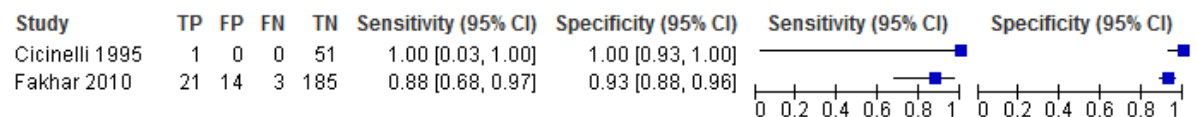| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Abe 2008 | 139 | 15 | 8 | 51 | 0.95 [0.90, 0.98] | 0.77 [0.65, 0.87] | | |
| Dasgupta, Sharma et al. 2011 | 133 | 30 | 21 | 68 | 0.86 [0.80, 0.91] | 0.69 [0.59, 0.78] | | |
| Soguktas 2012 | 42 | 12 | 5 | 30 | 0.89 [0.77, 0.96] | 0.71 [0.55, 0.84] | | |
| Williams 1998 | 8 | 2 | 4 | 25 | 0.67 [0.35, 0.90] | 0.93 [0.76, 0.99] | | |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

### Figure 19: Forest plot for sensitivity and specificity of hysteroscopy under general anaesthetic (versus histopathology) in detecting polyps

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Mukhopadhyay 2007 | 10 | 0 | 4 | 71 | 0.71 [0.42, 0.92] | 1.00 [0.95, 1.00] | | |
| Soguktas 2012 | 31 | 1 | 3 | 54 | 0.91 [0.76, 0.98] | 0.98 [0.90, 1.00] | | |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

### Figure 20: Forest plot for sensitivity and specificity of outpatient hysteroscopy (versus histopathology) in detecting polyps

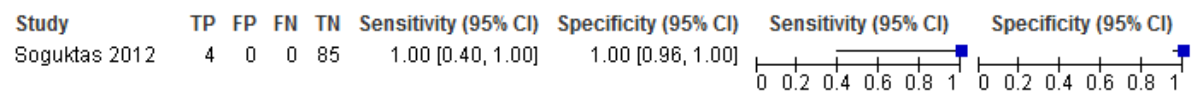| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Cicinelli 1995 | 1 | 0 | 0 | 51 | 1.00 [0.03, 1.00] | 1.00 [0.93, 1.00] | | |
| Fakhar 2010 | 21 | 14 | 3 | 185 | 0.88 [0.68, 0.97] | 0.93 [0.88, 0.96] | | |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

### Figure 21: Forest plot for sensitivity and specificity of hysteroscopy under general anaesthetic (versus histopathology) in detecting fibroids

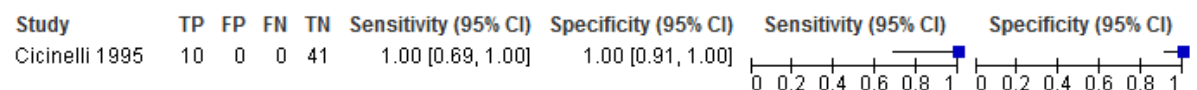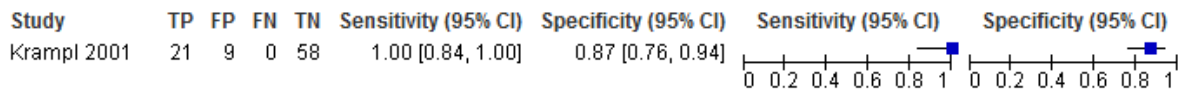| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Soguktas 2012 | 4 | 0 | 0 | 85 | 1.00 [0.40, 1.00] | 1.00 [0.96, 1.00] | | |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

### Figure 22: Forest plot for sensitivity and specificity of outpatient hysteroscopy (versus histopathology) in detecting fibroids

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Cicinelli 1995 | 10 | 0 | 0 | 41 | 1.00 [0.69, 1.00] | 1.00 [0.91, 1.00] | | |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 23: Forest plot for sensitivity and specificity of hysteroscopy under spinal or general anaesthetic (versus histopathology) in detecting polyps or fibroids**

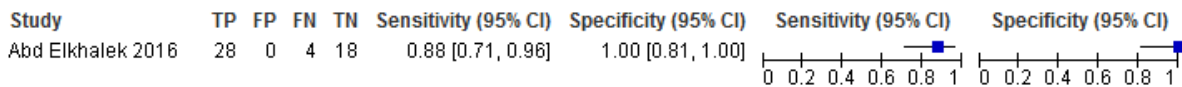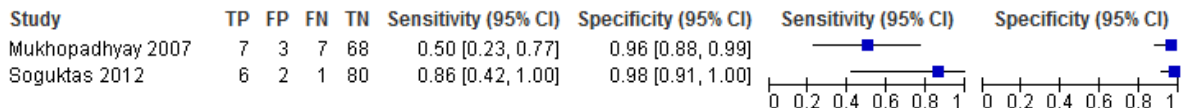| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|
| Krampl 2001 | 21 | 9 | 0 | 58 | 1.00 [0.84, 1.00] | 0.87 [0.76, 0.94] |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 24: Forest plot for sensitivity and specificity of hysteroscopy under general anaesthetic following 2D-TVUS (versus histopathology) in detecting polyps or fibroids**
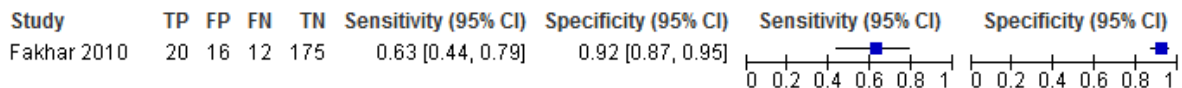
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|
| Abd Elkhalek 2016 | 28 | 0 | 4 | 18 | 0.88 [0.71, 0.96] | 1.00 [0.81, 1.00] |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 25: Forest plot for sensitivity and specificity of hysteroscopy under general anaesthetic (versus histopathology) in detecting endometrial hyperplasia**
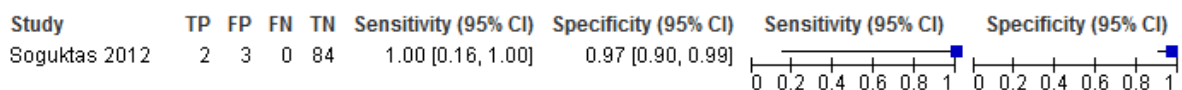
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|
| Mukhopadhyay 2007 | 7 | 3 | 7 | 68 | 0.50 [0.23, 0.77] | 0.96 [0.88, 0.99] |
| Soguktas 2012 | 6 | 2 | 1 | 80 | 0.86 [0.42, 1.00] | 0.98 [0.91, 1.00] |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 26: Forest plot for sensitivity and specificity of outpatient hysteroscopy (versus histopathology) in detecting endometrial hyperplasia**

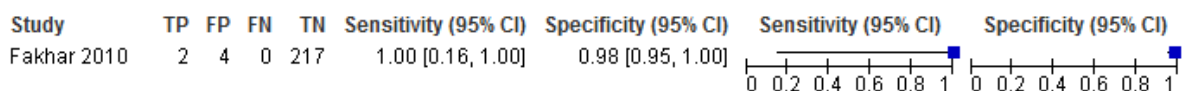| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|
| Fakhar 2010 | 20 | 16 | 12 | 175 | 0.63 [0.44, 0.79] | 0.92 [0.87, 0.95] |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 27: Forest plot for sensitivity and specificity of hysteroscopy under general anaesthetic (versus histopathology) in detecting endometrial carcinoma**
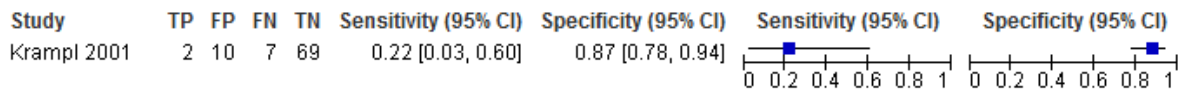
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|
| Soguktas 2012 | 2 | 3 | 0 | 84 | 1.00 [0.16, 1.00] | 0.97 [0.90, 0.99] |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 28: Forest plot for sensitivity and specificity of outpatient hysteroscopy (versus histopathology) in detecting endometrial carcinoma**

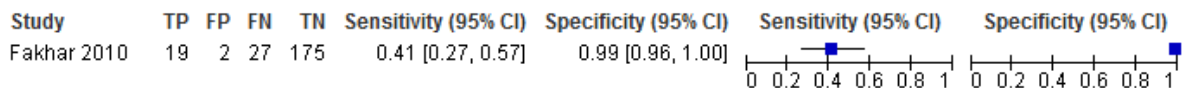| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|
| Fakhar 2010 | 2 | 4 | 0 | 217 | 1.00 [0.16, 1.00] | 0.98 [0.95, 1.00] |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 29: Forest plot for sensitivity and specificity of hysteroscopy under spinal or general anaesthetic (versus histopathology) in detecting abnormal endometrium (double-layer endometrium 12 mm or thicker and single-layer endometrium 6 mm or thicker)**
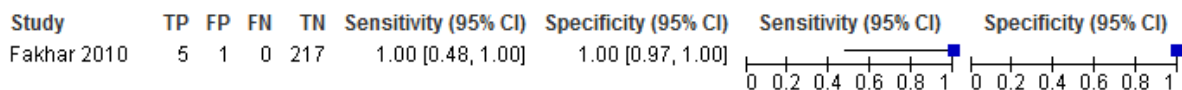
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Krampl 2001 | 2 | 10 | 7 | 69 | 0.22 [0.03, 0.60] | 0.87 [0.78, 0.94] | | |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 30: Forest plot for sensitivity and specificity of outpatient hysteroscopy (versus histopathology) in detecting endometritis**

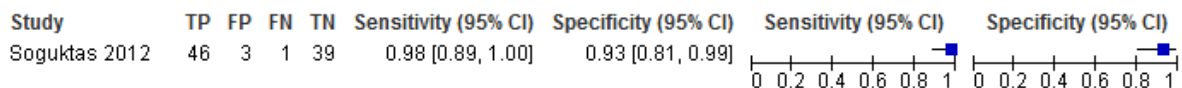| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Fakhar 2010 | 19 | 2 | 27 | 175 | 0.41 [0.27, 0.57] | 0.99 [0.96, 1.00] | | |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 31: Forest plot for sensitivity and specificity of outpatient hysteroscopy (versus histopathology) in detecting retained products of conception**
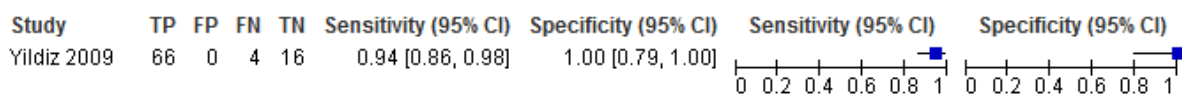
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Fakhar 2010 | 5 | 1 | 0 | 217 | 1.00 [0.48, 1.00] | 1.00 [0.97, 1.00] | | |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 32: Forest plot for sensitivity and specificity of hysteroscopy under general anaesthetic (versus histopathology) in detecting any abnormal finding**
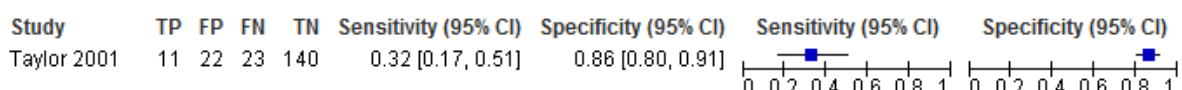
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Soguktas 2012 | 46 | 3 | 1 | 39 | 0.98 [0.89, 1.00] | 0.93 [0.81, 0.99] | | |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 33: Forest plot for sensitivity and specificity of hysteroscopy with or without general or local anaesthesia (versus histopathology) in detecting any abnormal finding**
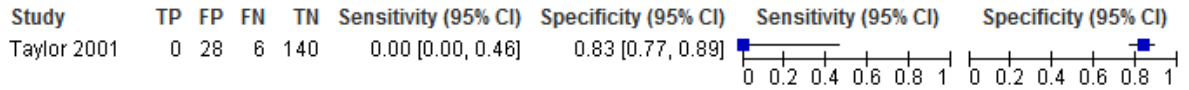
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Yildiz 2009 | 66 | 0 | 4 | 16 | 0.94 [0.86, 0.98] | 1.00 [0.79, 1.00] | | |

*CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 34: Forest plot for sensitivity and specificity of 2D-TVUS (versus hysteroscopy) in detecting polyps**

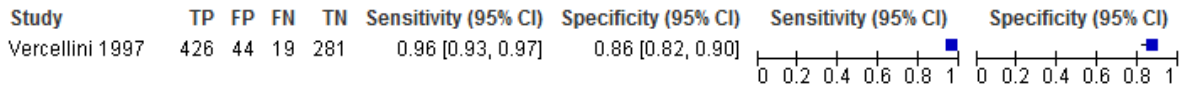| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|-------|----|----|----|----|----------------------|----------------------|----------------------|----------------------|
| Taylor 2001 | 11 | 22 | 23 | 140 | 0.32 [0.17, 0.51] | 0.86 [0.80, 0.91] | | |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*
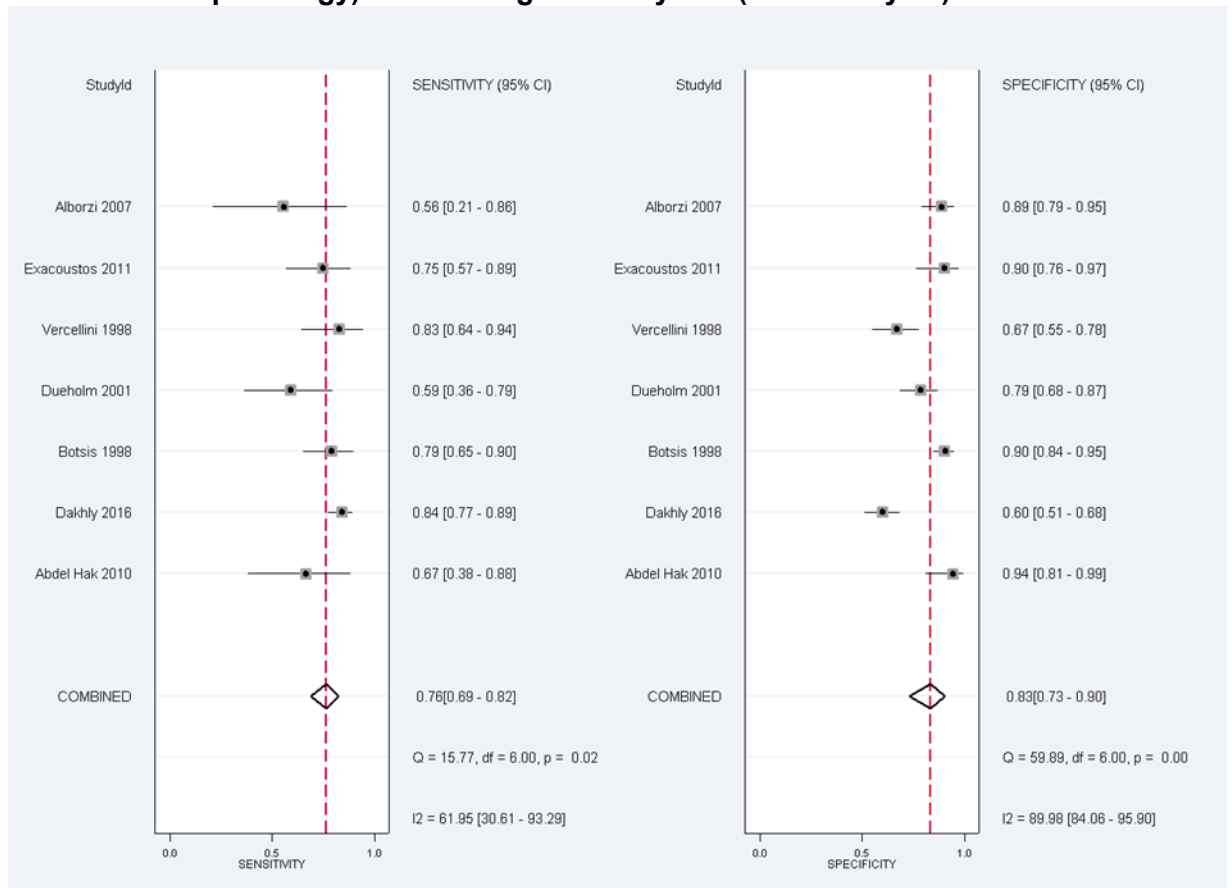
**Figure 35: Forest plot for sensitivity and specificity of 2D-TVUS (versus hysteroscopy) in detecting suspicious focal thickening**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Taylor 2001 | 0 | 28 | 6 | 140 | 0.00 [0.00, 0.46] | 0.83 [0.77, 0.89] |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 36: Forest plot for sensitivity and specificity of 2D-TVUS (versus hysteroscopy) in detecting any abnormal finding**

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Vercellini 1997 | 426 | 44 | 19 | 281 | 0.96 [0.93, 0.97] | 0.86 [0.82, 0.90] |

*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Review question 2. Forest plots and HSROC plots for the most clinically effective imaging strategy for diagnosing adenomyosis in women presenting with heavy menstrual bleeding review**

**Figure 37:** Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting adenomyosis (meta-analysis)
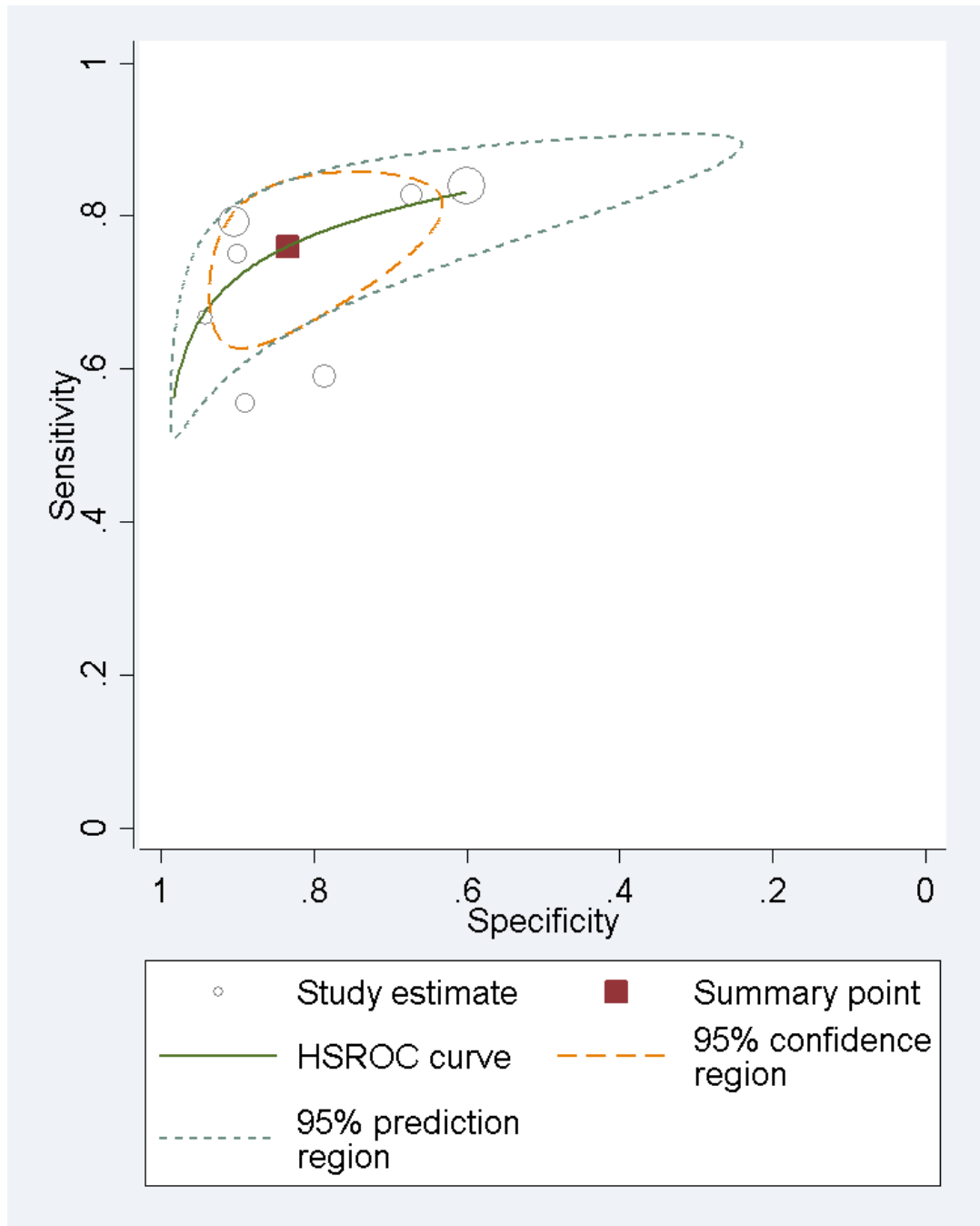


*2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval*

**Figure 38:** Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting adenomyosis (studies included in the meta-analysis)
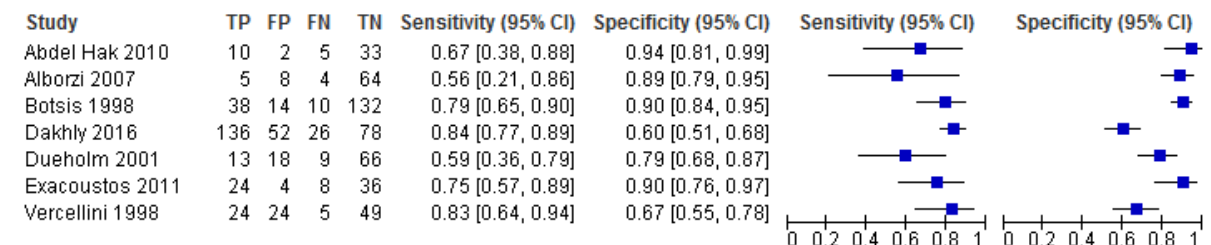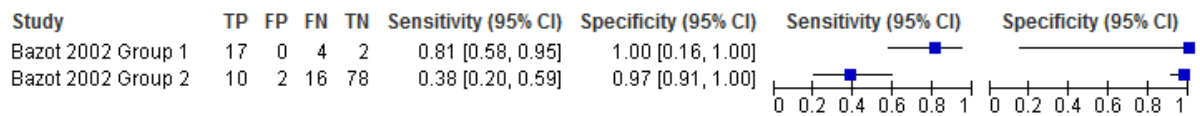


*Dueholm 2001 reported 'indefinite' results from the index test for 36 cases which have been included as negative test results in the results. 2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

**Figure 39:     HSROC plot for diagnostic accuracy of 2D-TVUS (versus histopathology) in detecting adenomyosis (meta-analysis)**
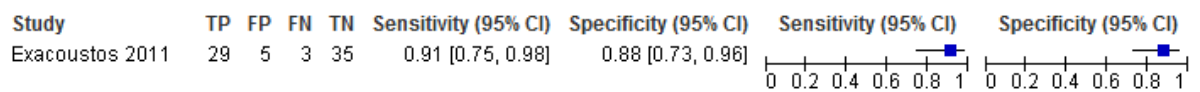


2D-TVUS: two-dimensional transvaginal ultrasound scan; HSROC: hierarchical summary receiver operating characteristic

### Figure 40: Forest plot for sensitivity and specificity of 2D-TVUS (versus histopathology) in detecting adenomyosis in Bazot 2002
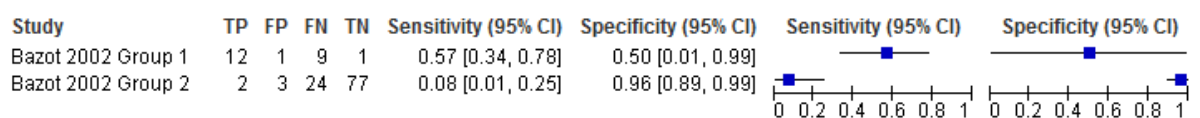
| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Bazot 2002 Group 1 | 17 | 0 | 4 | 2 | 0.81 [0.58, 0.95] | 1.00 [0.16, 1.00] | | |
| Bazot 2002 Group 2 | 10 | 2 | 16 | 78 | 0.38 [0.20, 0.59] | 0.97 [0.91, 1.00] | | |

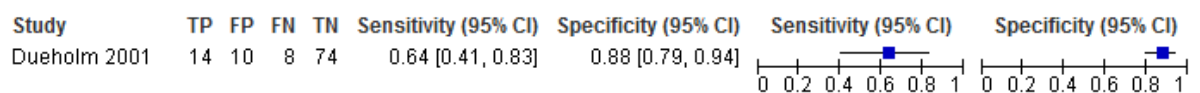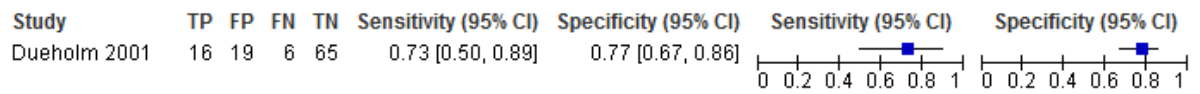*Group 1, women with recurrent menometrorrhagia but no evidence of leiomyomata and endometrial diseases on transabdominal examination; Group 2, all other women. 2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

### Figure 41: Forest plot for sensitivity and specificity of 3D-TVUS (versus histopathology) in detecting adenomyosis

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Exacoustos 2011 | 29 | 5 | 3 | 35 | 0.91 [0.75, 0.98] | 0.88 [0.73, 0.96] | | |

*3D-TVUS: three-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

### Figure 42: Forest plot for sensitivity and specificity of 2D-TAUS (versus histopathology) in detecting adenomyosis

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Bazot 2002 Group 1 | 12 | 1 | 9 | 1 | 0.57 [0.34, 0.78] | 0.50 [0.01, 0.99] | | |
| Bazot 2002 Group 2 | 2 | 3 | 24 | 77 | 0.08 [0.01, 0.25] | 0.96 [0.89, 0.99] | | |

*Group 1, women with recurrent menometrorrhagia but no evidence of leiomyomata and endometrial diseases on transabdominal examination; Group 2, all other women. 2D-TAUS: two-dimensional transabdominal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; TN: true negative; TP: true positive*

### Figure 43: Forest plot for sensitivity and specificity of MRI (versus histopathology) in detecting adenomyosis

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Dueholm 2001 | 14 | 10 | 8 | 74 | 0.64 [0.41, 0.83] | 0.88 [0.79, 0.94] | | |

*The study reported 'indefinite' results from the index test for 13 cases which have been included as negative test results in the results. CI: confidence interval; FN: false negative; FP: false positive; MRI: magnetic resonance imaging; TN: true negative; TP: true positive*

**Figure 44:** Forest plot for sensitivity and specificity of 2D-TVUS combined with MRI (versus histopathology) in detecting adenomyosis

| Study | TP | FP | FN | TN | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|
| Dueholm 2001 | 16 | 19 | 6 | 65 | 0.73 [0.50, 0.89] | 0.77 [0.67, 0.86] |

*The study reported 'indefinite' results from the index test for 41 cases which have been included as negative test results in the results. 2D-TVUS: two-dimensional transvaginal ultrasound scan; CI: confidence interval; FN: false negative; FP: false positive; MRI: magnetic resonance imaging; TN: true negative; TP: true positive*

# Appendix I – Excluded studies

## Clinical studies

**Table 39: Studies excluded from the clinical evidence reviews for diagnostic test accuracy for investigations of women presenting with heavy menstrual bleeding**

| Reference | Reason for exclusion |
| --- | --- |
| Abd El Aal, D. E., Ali, M., Shaaban, O., Sabra, A., Color doppler ultrasound to improve the diagnostic accuracy of the transvaginal ultrasound in diagnosis of adenomyosis: A cross sectional study, International Journal of Gynecology and Obstetrics, 131, E203, 2015 | Conference abstract. |
| Abou-Salem, N., Elmazny, A., El-Sherbiny, W., Value of 3-Dimensional Sonohysterography for Detection of Intrauterine Lesions in Women with Abnormal Uterine Bleeding, Journal of Minimally Invasive Gynecology, 17, 2010 | Wrong population: 57% of participants with heavy menstrual bleeding. |
| Acog Committee on Gynecologic Practice, Committee Opinion: number 263, December 20001. von Willebrand's disease in gynecologic practice, Obstetrics & GynecologyObstet Gynecol, 98, 1185-6, 2001 | No relevant data. |
| Adishesh, M., Subramanian, M., Patient satisfaction survey of outpatient hysteroscopy service, BJOG: An International Journal of Obstetrics and Gynaecology, Conference, 2013 | Conference abstract. |
| Agarwal, A., Lee, L., The feasibility and yield of outpatient hysteroscopy, International Journal of Gynecology and Obstetrics, Conference, 2012 | Conference abstract. |
| Aggarwal, A., Lilley, A., Sproston, T., Outpatient hysteroscopy audit, BJOG: An International Journal of Obstetrics and Gynaecology, Conference, 2013 | Conference abstract. |
| Aghajanyan, H., The improvement of the outpatient diagnostics of intrauterine pathology, Gynecological Surgery, Conference, 2013 | Conference abstract. |
| Aghajanyan, H., Outpatient diagnostics of endometrial polyps, Gynecological Surgery, Conference, 2013 | Conference abstract. |

| Reference | Reason for exclusion |
|---|---|
| Ahmadi,F., Zafarani,F., Niknejadi,M., Vosough,A., Uterine leiomyoma: Hysterosalpingographic appearances, International Journal of Fertility and Sterility, 1, 137-144, 2008 | Pictorial review, references checked for relevant studies. |
| Ajao, M. O., Laughlin-Tommaso, S. K., Hopkins, M. R., Breitkopf, D. M., Famuyide, A. O., Years of hysteroscopic experience in correctly predicting pathologic diagnosis, Journal of Minimally Invasive Gynecology, Conference, 41st Global Congress of Minimally Invasive Gynecology, AAGL 2012. Las Vegas, NV United States. Conference Start: 20121105. Conference End: 20121109. Conference Publication: (var.pagings). 19 (6 SUPPL. 1) (pp S111), 2012 | Conference abstract. |
| Akhavan Tafti, M., Davar, R., Nafisi Moghadam, R., Lotfi, M. H., Panahande Ali, M., Comparing findings of transvaginal ultrasonography and endometrial histopathology in patients with abnormal uterine bleeding, Iranian Journal of Obstetrics, Gynecology and Infertility, 15, 7-13, 2012 | Wrong population: 48% of women with HMB. |
| Alcazar, J. L., Auba, M., Olartecoechea, B., Three-dimensional ultrasound in gynecological clinical practice, Reports in Medical Imaging, 5, 2012 | Expert review. Relevant references checked. |
| Alcazar, J. L., Galvan, R., Garcia-Manero, M., Ajossa, S., Guerriero, S., Melis, G. B., Transvaginal ultrasound in the diagnosis of uterine pathology, Expert Review of Obstetrics and Gynecology, 3, 753-760, 2008 | Expert review. Relevant references checked. |
| Anastasiadis, P. G., Koutlaki, N. G., Skaphida, P. G., Galazios, G. Ch, Tsikouras, P. N., Liberis, V. A., Endometrial polyps: Prevalence, detection, and malignant potential in women with abnormal uterine bleeding, European Journal of Gynaecological Oncology, 21, 180-183, 2000 | Unclear/wrong population. HMB status or premenopausal status of the women are not reported for the whole sample. For the 126 women with polyps and who were studied more, more than half were postmenopausal. |
| Andrade, A. T. L., Souza, J. P., Shaw Jr, S. T., Belsey, E. M., Rowe, P. J., Menstrual blood loss and body iron stores in Brazilian women, Contraception, 43, 241-249, 1991 | No relevant data. |
| Andreotti, R. F., Fleischer, A. C., The sonographic diagnosis of adenomyosis, Ultrasound Quarterly, 21, 167-70, 2005 | Narrative review, references checked. |
| Anonymous,, AAGL Practice Report: Practice Guidelines for the Diagnosis and Management of Submucous Leiomyomas, Journal of Minimally Invasive Gynecology, 19, 152-171, 2012 | Practice guideline. Relevant references checked. |
| Antunes, A., The efficacy of hysteroscopy in diagnosis and treatment of endometrial pathology: See and treat, Gynecological Surgery, Conference, 2009 | Conference abstract. |

| Reference | Reason for exclusion |
|---|---|
| Arslan, M., Erdem, A., Erdem, M., Yazici, G., Himmetoglu, O., Gursoy, R., Transvaginal color Doppler ultrasonography for prediction of pre-cancerous endometrial lesions, International Journal of Gynecology and Obstetrics, 80, 299-306, 2003 | Wrong population, majority of the women are postmenopausal. |
| Ascher, S. M., Jha, R. C., Reinhold, C., Benign Myometrial Conditions: Leiomyomas and Adenomyosis, Topics in Magnetic Resonance Imaging, 14, 281-304, 2003 | A narrative/pictorial review, references checked. |
| Ash, S. J., Farrell, S. A., Flowerdew, G., Endometrial biopsy in DUB, Journal of Reproductive Medicine for the Obstetrician and Gynecologist, 41, 892-896, 1996 | Index test not of interest. |
| Atri, M., Reinhold, C., Mehio, A. R., Chapman, W. B., Bret, P. M., Adenomyosis: US features with histologic correlation in an in vitro study, Radiology, 215, 783-790, 2000 | Wrong population. |
| Atzori, E., Tronci, C., Sionis, L., Transvaginal ultrasound in the diagnosis of diffuse adenomyosis, Gynecologic and Obstetric Investigation, 42, 39-41, 1996 | Wrong/unclear population. |
| Babacan, A., Gun, I., Kizilaslan, C., Ozden, O., Muhcu, M., Mungen, E., Atay, V., Comparison of transvaginal ultrasonography and hysteroscopy in the diagnosis of uterine pathologies, International Journal of Clinical and Experimental Medicine, 7, 764-769, 2014 | Population not well defined: % of women with HMB unclear, age of patients not reported. |
| Badawy, A., Ash, A., Nagele, F., Mohamed, H., O'Connor, H., Magos, A., Ultrasonography, hysteroscopy or both?, Journal of Obstetrics and Gynaecology, 16, 551-555, 1996 | No sufficient data to form 2x2 tables and calculate diagnostic accuracy. |
| Bain, C., Parkin, D. E., Cooper, K. G., Is outpatient diagnostic hysteroscopy more useful than endometrial biopsy alone for the investigation of abnormal uterine bleeding in unselected premenopausal women? A randomised comparison, BJOG: An International Journal of Obstetrics and Gynaecology, 109, 805-811, 2002 | No data on diagnostic accuracy but some data on patient acceptability/satisfaction, however, wrong test comparisons (hysteroscopy compared to endometrial biopsy alone). |
| Balogun, M., Imaging diagnosis of adenomyosis, Reviews in Gynaecological and Perinatal Practice, 6, 63-69, 2006 | A narrative review, references checked. |
| Banerjee, R., Ofuasia, E., Study to assess correlation between diagnostic imaging and histology of adenomyosis at hysterectomy, Gynecological Surgery, 1), S61, 2012 | Conference abstract. |
| Banu, L. F., Hysteroscopy a diagnostic and therapeutic tool-500 case series, BJOG: An International Journal of Obstetrics and Gynaecology, Conference, 2014 | Conference abstract. |

| Reference | Reason for exclusion |
|---|---|
| Basu, A., Lewis, P., Transvaginal scan, saline infusion sonography and hysteroscopy in abnormal uterine bleeding, International Journal of Gynecology and Obstetrics, Conference, 2009 | Conference abstract. |
| Batistatou, A., Ntoulia, A., Gkrozou, F., Paschopoulos, M., Malamou-Mitsi, V., Correlation of hyperspectral hysteroscopy with histopathological features in endometrial pathology, Virchows Archiv, Conference, 2013 | Conference abstract. |
| Baxter, A. J., Beck, B., Phillips, K., A randomized prospective trial of rigid and flexible hysteroscopy in an outpatient setting, Gynaecological Endoscopy, 11, 357-364, 2002 | Wrong population, less than two thirds with HMB. |
| Bazot, M., Cortez, A., Darai, E., Rouger, J., Chopier, J., Antoine, J. M., Uzan, S., Ultrasonography compared with magnetic resonance imaging for the diagnosis of adenomyosis: Correlation with histopathology, Human Reproduction, 16, 2427 | Wrong population. |
| Bazot, M., Darai, E., De Givry, S. C., Boudghene, F., Uzan, S., Le Blanche, A. F., Fast breath-hold T2-weighted MR imaging reduces interobserver variability in the diagnosis of adenomyosis, American Journal of Roentgenology, 180, 1291 | Wrong population, less than two thirds with HMB. |
| Bazot, M., Robert, Y., Diagnostic imaging of menometrorrhagia, Journal de Gynecologie Obstetrique et Biologie de la Reproduction, 37, 2008 | Full article in French language. |
| Bazot, M., Salem, C., Frey, I., Darai, E., Imaging of myomas: Is MRI useful before operating?, Gynecologie Obstetrique Fertilite, 30, 2002 | Full article in French language. |
| Becker Jr, E., Lev-Toaff, A. S., Kaufman, E. P., Halpern, E. J., Edelweiss, M. I., Kurtz, A. B., The added value of transvaginal sonohysterography over transvaginal sonography alone in women with known or suspected leiomyoma, Journal of Ultrasound in Medicine, 21, 237-247, 2002 | Population not defined. |
| Belli, P., De Gaetano, A. M., Mirk, P., Speca, S., Valentini, A. L., Uterine adenomyosis and tubal endometriosis: diagnostic imaging, Rays, 23, 693-701, 1998 | Not a study, not relevant. |
| Benagiano, G., Habiba, M., Brosens, I., The pathophysiology of uterine adenomyosis: an update, Fertility & Sterility, 98, 572-9, 2012 | Narrative review. Possibly relevant references checked. |
| Ben-Baruch, G., Seidman, D. S., Schiff, E., Moran, O., Menczer, J., Outpatient endometrial sampling with the pipelle curette, Gynecologic and Obstetric Investigation, 37, 260-262, 1994 | Index test not of interest. |

| Reference | Reason for exclusion |
|---|---|
| Ben-Yehuda, O. M., Kim, Y. B., Leuchter, R. S., Does hysteroscopy improve upon the sensitivity of dilatation and curettage in the diagnosis of endometrial hyperplasia or carcinoma?, Gynecologic Oncology, 68, 4-7, 1998 | Wrong population: 46% of women postmenopausal. |
| Bernard, J. P., Lecuru, F., Darles, C., Robin, F., De Bievre, P., Taurelle, R., Saline contrast sonohysterography as first-line investigation for women with uterine bleeding, Ultrasound in Obstetrics and Gynecology, 10, 121-125, 1997 | Wrong population: 67.3% premenopausal women with abnormal uterine bleeding (rest postmenopausal), proportion with HMB not reported. |
| Bettocchi, S., Ceci, O., Vicino, M., Marello, F., Impedovo, L., Selvaggi, L., Diagnostic inadequacy of dilatation and curettage, Fertility and Sterility, 75, 803-805, 2001 | Index test not of interest. |
| Bignardi, T., Van den Bosch, T., Condous, G., Abnormal uterine and post-menopausal bleeding in the acute gynaecology unit, Best Practice and Research: Clinical Obstetrics and Gynaecology, 23, 595-607, 2009 | Expert review. Possible relevant references checked. |
| Bingol,B., Gunenc,Z., Gedikbasi,A., Guner,H., Tasdemir,S., Tiras,B., Comparison of diagnostic accuracy of saline infusion sonohysterography, transvaginal sonography and hysteroscopy, Journal of Obstetrics and Gynaecology, 31, 54-58, 2011 | Wrong population: women with infertility, 43.4% women without abnormal bleeding or hypomenorrhea. |
| Bocca, S. M., Oehninger, S., Stadtmauer, L., Agard, J., Duran, E. H., Sarhan, A., Horton, S., Abuhamad, A. Z., A study of the cost, accuracy, and benefits of 3-dimensional sonography compared with hysterosalpingography in women with uterine abnormalities, Journal of Ultrasound in Medicine, 31, 81-5, 2012 | Wrong/unclear population: % of women with HMB unclear. |
| Bodur, S., Dundar, O., Pektas, M. K., Babayigit, M. A., Ozden, O., Kucukodaci, Z., The clinical significance of classical and new emerging determinants of adenomyosis, International Journal of Clinical and Experimental Medicine, 8, 7958-7964, 7958 | Wrong index test. |
| Bougie, O., Wang, V., Lortie, K., Shenassa, H., Singh, S. S., High patient satisfaction with outpatient hysteroscopy with use of tailored analgesia protocols, Journal of Minimally Invasive Gynecology, Conference, 2013 | Conference abstract. |
| Bourdel, N., Modaffari, P., Tognazza, E., Pertile, R., Chauvet, P., Botchorishivili, R., Savary, D., Pouly, J. L., Rabischong, B., Canis, M., Does experience in hysteroscopy improve accuracy and inter-observer agreement in the management of abnormal uterine bleeding?, Surgical Endoscopy and Other Interventional Techniques., 2016 | Wrong population: 48.9% of women post-menopausal. |

| Reference | Reason for exclusion |
|---|---|
| Bouzid, A., Ayachi, A., Ben Khedija, M., Menjli, S., Mkaouar, L., Mourali, M., Journal de Gynecologie Obstetrique et Biologie de la Reproduction. (no pagination), 2016, Date of Publication, February 08, 2016 | Full text in French language. |
| Bradley, L. D., Falcone, T., Magen, A. B., Radiographic imaging techniques for the diagnosis of abnormal uterine bleeding, Obstetrics and Gynecology Clinics of North America, 27, 245-276, 2000 | Narrative review, not relevant. |
| Bradley,L.D., Diagnosis of abnormal uterine bleeding with biopsy or hysteroscopy, Menopause, 18, 425-433, 2011 | Expert review. Relevant references checked. |
| Brasic, N., Feldstein, V. A., Dysfunctional uterine bleeding: Diagnostic approach and therapeutic options, Ultrasound Clinics, 5, 2010 | Expert review. Relevant references checked. |
| Breitkopf, D. M., Frederickson, R. A., Snyder, R. R., Detection of benign endometrial masses by endometrial stripe measurement in premenopausal women, Obstetrics and Gynecology, 104, 120-125, 2004 | Index test not of interest. |
| Bromley, B., Shipp, T. D., Benacerraf, B., Adenomyosis: Sonographic findings and diagnostic accuracy, Journal of Ultrasound in Medicine, 19, 529-534, 2000 | Wrong population. |
| Bronz, L., Suter, T., Rusca, T., The value of transvaginal sonography with and without saline instillation in the diagnosis of uterine pathology in pre- and postmenopausal women with abnormal bleeding or suspect sonographic findings, Ultrasound in Obstetrics and Gynecology, 9, 53-58, 1997 | Wrong population: only a small proportion of the women had HMB. |
| Brown, M. A., MR Imaging of Benign Uterine Disease, Magnetic Resonance Imaging Clinics of North America, 14, 2006 | Expert review on MRI on benign uterine disease. Relevant references checked. |
| Byun, J. Y., Kim, S. E., Choi, B. G., Ko, G. Y., Jung, S. E., Choi, K. H., Diffuse and focal adenomyosis: MR imaging findings, Radiographics : a review publication of the Radiological Society of North America, Inc, 19 Spec No, S161-170, 1999 | Wrong population. |
| Cepni, I., Ocal, P., Erkan, S., Saricali, F. S., Akbas, H., Demirkiran, F., Idil, M., Bese, T., Comparison of transvaginal sonography, saline infusion sonography and hysteroscopy in the evaluation of uterine cavity pathologies, Australian and New Zealand Journal of Obstetrics and Gynaecology, 45, 30-35, 2005 | Wrong population: only 33% had abnormal uterine bleeding (% of HMB not reported). |

| Reference | Reason for exclusion |
|---|---|
| Champaneria, R., Abedin, P., Daniels, J., Balogun, M., Khan, K. S., Ultrasound scan and magnetic resonance imaging for the diagnosis of adenomyosis: Systematic review comparing test accuracy, Acta Obstetricia et Gynecologica Scandinavica, 89, 1374 | A systematic review with wrong population. Included studies assessed individually. |
| Chandra, C., Shekhar, S., Vyas, J., The role of transvaginal ultrasonography in initial evaluation of abnormal uterine bleeding (AUB) in premenopausal women, BJOG: An International Journal of Obstetrics and Gynaecology, Conference, 2014 | Conference abstract. |
| Chauhan, M., Dahiya, P., Nanda, S., Role of hysteroscopy in evaluation of abnormal uterine bleeding in perimenopausal women, Maturitas, Conference, 2009 | Conference abstract. |
| Chawla, I., Tripathi, S., Vohra, P., Singh, P., To evaluate the accuracy of saline infusion sonohysterography (SIS) for evaluation of uterine cavity abnormalities in patients with abnormal uterine bleeding, Journal of Obstetrics and Gynecology of India, 64, 2014 | Wrong population: 51.7% of women postmenopausal. |
| Chittacharoen, A., Theppisai, U., Linasmita, V., Manonai, J., Sonohysterography in the diagnosis of abnormal uterine bleeding, Journal of Obstetrics and Gynaecology Research, 26, 277-281, 2000 | Wrong index test. |
| Chopra, S., Lev-Toaff, A. S., Ors, F., Bergin, D., Adenomyosis: Common and uncommon manifestations on sonography and magnetic resonance imaging, Journal of Ultrasound in Medicine, 25, 617-627, 2006 | Wrong/unclear population. |
| Chu, L. C., Coquia, S. F., Hamper, U. M., Ultrasonography evaluation of pelvic masses, Radiologic Clinics of North America, 52, 1237 | Expert review. Possible relevant references checked. |
| Claessens, E. A., Cowell, C. A., Acute adolescent menorrhagia, American Journal of Obstetrics and Gynecology, 139, 277-280, 1981 | No relevant data. |
| Clark, T. J., Voit, D., Gupta, J. K., Hyde, C., Song, F., Khan, K. S., Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review, JAMAJama, 288, 1610-21, 2002 | Systematic review with different inclusion criteria. Included studies checked individually. |
| Cockerham, A. Z., Adenomyosis: a challenge in clinical gynecology, Journal of Midwifery & Women's Health, 57, 212-20, 2012 | A narrative review. References checked. |
| Cogendez, E., Eken, M. K., Bakal, N., Gun, I., Kaygusuz, E. I., Karateke, A., The role of transvaginal power Doppler ultrasound in the differential diagnosis of benign intrauterine focal lesions, Journal of Medical Ultrasonics, 42, 2015 | Wrong index test (power Doppler). |

| Reference | Reason for exclusion |
|---|---|
| Cooper, N. A. M., Barton, P. M., Breijer, M. C., Opmeer, B. C., Mol, B. W. J., Khan, K. S., Clark, T. J., Cost-effectiveness of diagnostic strategies for the management of heavy menstrual bleeding, BJOG: An International Journal of Obstetrics and Gynaecology, Conference, 2013 | Conference abstract. |
| Cooper, N., Barton, P., Breijer, M., Khan, K., Mol, B., Clark, J., Outpatient hysteroscopy is the most costeffective investigation for heavy menstrual bleeding, Gynecological Surgery, Conference, 2012 | Conference abstract. |
| Cooper,N.A.M., Barton,P.M., Breijer,M., Caffrey,O., Opmeer,B.C., Timmermans,A., Mol,B.W.J., Khan,K.S., Clark,T.J., Cost-effectiveness of diagnostic strategies for the management of abnormal uterine bleeding (heavy menstrual bleeding and post-menopausal bleeding): A decision analysis, Health Technology Assessment, 18, 1-201, 2014 | Clinical and cots-effectiveness review, wrong inclusion criteria, relevant references checked individually. |
| Cowan, F., Shirol, V., Burnham, A., Patient feedback on outpatient hysteroscopy in a busy UK district general hospital-the importance of improving patient care in ambulatory gynaecology, Gynecological Surgery, Conference, 2015 | Conference abstract. |
| Crispi Jr, C. P., Soares, L. C., Adenomyosis, Revista Brasileira de Medicina, 70, 409-414, 2013 | Full text in Portuguese. |
| Daniele,A., Ferrero,A., Maggiorotto,F., Perrini,G., Volpi,E., Sismondi,P., Suspecting malignancy in endometrial polyps: Value of hysteroscopy, Tumori, 99, 204-209, 2013 | Wrong population: 61.5% postmenopausal women. |
| Daniilidis, A., Pantelis, A., Dinas, K., Tantanasis, T., Loufopoulos, P. D., Angioni, S., Carcea, F., Indications of diagnostic hysteroscopy, a brief review of the literature, Gynecological Surgery., 2011 | Narrative review, references checked for relevant studies. |
| Dartmouth, K., A systematic review with meta-analysis: the common sonographic characteristics of adenomyosis, Ultrasound, 22, 148-57, 2014 | Systematic review and meta-analysis on the ultrasound characteristics of adenomyosis. |
| Darwish, A. M. M., Sayed, E. H., Reliability of out-patient hysteroscopy in one-stop clinic for abnormal uterine bleeding atef M. Darwish MD PHD, Ezzat H. Sayed MD, Safwat A. Mohammad MD, Ibraheem I. Mohammad MSC, Hoida I Hassan , PHD, Gynecological Surgery, Conference, 2011 | Conference abstract. |
| De Crespigny, L., Kuhn, R., McGinnes, D., Saline infusion sonohysterosalpingography, an underutilized technique, Australian and New Zealand Journal of Obstetrics and Gynaecology, 37, 206-209, 1997 | Wrong comparison of tests, no relevant data. |

| Reference | Reason for exclusion |
|---|---|
| De Kroon, C. D., De Bock, G. H., Dieben, S. W. M., Jansen, F. W., Saline contrast hysterosonography in abnormal uterine bleeding: A systematic review and meta-analysis, BJOG: An International Journal of Obstetrics and Gynaecology, 110, 938-947, 2003 | Systematic review, wrong index test. |
| De Sousa Filogonio, I. D., De Avila, I., Gouvea, P. S., Carneiro, M. M., Accuracy of hysteroscopic view in the diagnosis of intrauterine pathology: A Brazilian experience, Journal of Gynecologic Surgery, 26, 23-30, 2010 | Wrong population: 29% of women with abnormal uterine bleeding. |
| De Vries, L. D., Dijkhuizen, F. P. H. L. J., Mol, B. W. J., Brolmann, H. A. M., Moret, E., Heintz, A. P. M., Comparison of transvaginal sonography, saline infusion sonography, and hysteroscopy in premenopausal women with abnormal uterine bleeding, Journal of Clinical Ultrasound, 28, 217-223, 2000 | Wrong population: only 53% with HMB. |
| Decloedt, J. F., Fenton, D. W., Outpatient hysteroscopy: Indications and hysteroscopic findings in pre- and postmenopausal patients, Gynaecological Endoscopy, 8, 137-141, 1999 | No relevant data. |
| Deffieux, X., Fernandez, H., Adenomyosis: New concepts on pathophysiology, diagnosis and treatment, Journal de Gynecologie Obstetrique et Biologie de la Reproduction, 33, 703-712, 2004 | Full text in French language. |
| Dijkhuizen, F. P. H. L. J., Brolmann, H. A. M., Potters, A. E., Bongers, M. Y., Heintz, A. P. M., The accuracy of transvaginal ultrasonography in the diagnosis of endometrial abnormalities, Obstetrics and Gynecology, 87, 345-349, 1996 | Wrong population: women with metrorrhagia or postmenopausal bleeding included. |
| Dijkhuizen, F. P. H. L. J., De Vries, L. D., Mol, B. W. J., Brolmann, H. A. M., Peters, H. M., Moret, E., Heintz, A. P. M., Comparison of transvaginal ultrasonography and saline infusion sonography for the detection of intracavitary abnormalities in premenopausal women, Ultrasound in Obstetrics and Gynecology, 15, 372-376, 2000 | Wrong population: only around half of the population with HMB. |
| Dijkhuizen, F. P., Mol, B. W., Brolmann, H. A., Heintz, A. P., The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis, Cancer, 89, 1765-72, 2000 | Index test not of interest. |
| Dinic, S. P. T., Kopitovic, V., Antic, V., Stamenovic, S., Mitic, D., Milosevic, J., Role of hysteroscopy in evaluation of patients with abnormal uterine bleeding, Acta Facultatis Medicae Naissensis, 28, 2011 | Number of post-menopausal women not reported. |

| Reference | Reason for exclusion |
|---|---|
| Dipi, R. M., Amin, M. S., Islam, M. N., Khan, N. A., Chaiti, M. M., Hossain, M. M., Comparison of transabdominal and transvaginal sonography in the evaluation of uterine mass with histopathological correlation, Mymensingh medical journal : MMJ, 22, 69-74, 2013 | Only 60% of the women present with HMB. |
| Donnez, J., Menometrorrhagia during the premenopause: An overview, Gynecological Endocrinology, 27, 1114 | Expert review. Relevant references checked. |
| Doubilet,P.M., Diagnosis of abnormal uterine bleeding with imaging, Menopause, 18, 421-424, 2011 | Wrong population: post-menopausal women. |
| Dueholm, M., Transvaginal ultrasound for diagnosis of adenomyosis: a review, Best Practice and Research: Clinical Obstetrics and Gynaecology, 20, 569-582, 2006 | A review, different inclusion criteria. Included studies assessed individually. |
| Dueholm, M., Jensen, M. L., Laursen, H., Kracht, P., Can the endometrial thickness as measured by trans-vaginal sonography be used to exclude polyps or hyperplasia in pre-menopausal patients with abnormal uterine bleeding?, Acta Obstetricia et Gynecologica Scandinavica, 80, 645-651, 2001 | No relevant diagnostic accuracy data. Another publication with the same cohort already included in the review. |
| Dueholm, M., Lundorf, E., Transvaginal ultrasound or MRI for diagnosis of adenomyosis, Current Opinion in Obstetrics & Gynecology, 19, 505-12, 2007 | A review, different inclusion criteria. Included studies assessed individually. |
| Dueholm, M., Lundorf, E., Olesen, F., Imaging techniques for evaluation of the uterine cavity and endometrium in premenopausal patients before minimally invasive surgery, Obstetrical and Gynecological Survey, 57, 388-403, 2002 | Literature review, included studies checked individually. |
| Eldred, J. M., Thomas, E. J., Pituitary and ovarian hormone levels in unexplained menorrhagia, Obstetrics and Gynecology, 84, 775-778, 1994 | No relevant data. |
| Elgantri, R., Khalifa, N., Rhoma, N., Almsalati, S., Hysteroscopy in abnormal uterine bleeding in Libyan women. Is it helpful?, International Journal of Gynecology and Obstetrics, Conference, 2009 | Conference abstract. |
| ElKattan, E. A., Omran, E. F., Al Inany, H. G., The accuracy of transvaginal ultrasound and uterine artery Doppler in the prediction of adenomyosis, Middle East Fertility Society Journal, 15, 73-78, 2010 | Wrong population. |
| El-Khayat,W., Sleet,M.E., Mahdi,E.Y., Comparative study of transvaginal sonography and ysteroscopy for the detection of pathological endometrial esions in women with perimenopausal bleeding, Middle East Fertility Society Journal, 16, 77-82, 2011 | The paper does not report confidence intervals or enough data to calculate them. |

| Reference | Reason for exclusion |
|---|---|
| El-Sharkawy, M., El-Mazny, A., Ramadan, W., Hatem, D., Abdel-Hafiz, A., Hammam, M., Nada, A., Three-dimensional ultrasonography and power Doppler for discrimination between benign and malignant endometrium in premenopausal women with abnormal uterine bleeding, BMC Women's Health. 16 (1) (no pagination), 2016, Article Number, 2016 | Wrong population: women with polyps, fibroids, adenomyosis etc. excluded. A cut-off of endometrial thickness used in the study (19mm) is not used normally, thus, is not useful. |
| El-Sherbiny, W., El-Mazny, A., Abou-Salem, N., Mostafa, W. S., The diagnostic accuracy of two- vs three-dimensional sonohysterography for evaluation of the uterine cavity in the reproductive age, Journal of Minimally Invasive Gynecology, 22, 2015 | Wrong population: only 35% women with abnormal uterine bleeding. |
| Emanuel, M. H., Is dilatation and curettage obsolete for diagnosing intrauterine disorders in premenopausal patients with persistent abnormal uterine bleeding?, Acta Obstetricia et Gynecologica Scandinavica, 76, 65-68, 1997 | Index test not of interest. |
| Emanuel, M. H., Verdel, M. J., Wamsteker, K., Lammes, B., A prospective comparison of transvaginal ultrasonography and diagnostic hysteroscopy in the evaluation of patients with abnormal uterine bleeding: Clinical implications, American Journal of Obstetrics and Gynecology, 172, 547-552, 1995 | Wrong population: less than half of the population with HMB. |
| Evans, P., Brunsell, S., Uterine fibroid tumors: Diagnosis and treatment, American Family Physician, 75, 1503 | Expert review. Possible relevant references checked. |
| Farquhar, C., Ekeroma, A., Furness, S., Arroll, B., A systematic review of transvaginal ultrasonography, sonohysterography and hysteroscopy for the investigation of abnormal uterine bleeding in premenopausal women, Acta Obstetricia et Gynecologica Scandinavica, 82, 493-504, 2003 | A systematic review, not the same inclusion criteria. Included studies checked individually. |
| Fascilla, F. D., Cramarossa, P., Cannone, R., Olivieri, C., Vimercati, A., Exacoustos, C., Ultrasound diagnosis of uterine myomas, Minerva Ginecologica, 68, 297-312, 2016 | Expert review. Relevant references checked. |
| Fedele, L., Bianchi, S., Dorta, M., Arcaini, L., Zanotti, F., Carinelli, S., Transvaginal ultrasonography in the diagnosis of diffuse adenomyosis, Fertility and Sterility, 58, 94-97, 1992 | Wrong/unclear population, old study published in 1992. |
| Fedele, L., Bianchi, S., Dorta, M., Brioschi, D., Zanotti, F., Vercellini, P., Transvaginal ultrasonography versus hysteroscopy in the diagnosis of uterine submucous myomas, Obstetrics and Gynecology, 77, 745-748, 1991 | Wrong/unclear population: women with menometrorrhagia and/or pelvic pain included, proportions not reported. |

| Reference | Reason for exclusion |
|---|---|
| Ferry, J., Farnsworth, A., Webster, M., Wren, B., The efficacy of the Pipelle endometrial biopsy in detecting endometrial carcinoma, Australian and New Zealand Journal of Obstetrics and Gynaecology, 33, 76-78, 1993 | Index test not of interest. |
| Filiz, T., Doger, E., Corakci, A., Ozeren, S., Caliskan, E., The efficacy, cost and patient satisfaction of classic versus office hysteroscopy in cases with suspected intrauterine space occupying lesions with 3-dimension ultrasound and abnormal uterine bleeding, Journal of the Turkish German Gynecology Association, 10, 2009 | Wrong population: only 45% of women with menorrhagia or menometrorrhagia. |
| Fothergill, D. J., Brown, V. A., Hill, A. S., Histological sampling of the endometrium - A comparison between formal curettage and the Pipelle sampler, British Journal of Obstetrics and Gynaecology, 99, 779-780, 1992 | Index test not of interest. |
| Fukuda, M., Shimizu, T., Fukuda, K., Yomura, W., Shimizu, S., Transvaginal hysterosonography for differential diagnosis between submucous and intramural myoma, Gynecologic and Obstetric Investigation, 35, 236-239, 1993 | Unclear population: a total of 36 patients with hypermenorrhea, dysmenorrhea or anemia, with patients with distinct intramural myomas in TVUS were excluded. Proportion with HMB not reported. |
| Gao, J., Zeng, S., Sun, B. L., Fan, H. M., Han, L. H., Menstrual blood loss and hematologic indices in healthy Chinese women, Journal of Reproductive MedicineJ Reprod Med, 32, 822-6, 1987 | No relevant data. |
| Garcia, L. E., Morris, S., Isaacson, K., Adenomyosis: Risk factors and diagnosis, Journal of Minimally Invasive Gynecology, 1), S17-S18, 2011 | Conference abstract. |
| Garcia,L., Isaacson,K., Adenomyosis: Review of the Literature, Journal of Minimally Invasive Gynecology, 18, 428-437, 2011 | Narrative review on adenomyosis, references checked. |
| Garuti, G., Sambruni, I., Colonnelli, M., Luerti, M., Accuracy of hysteroscopy in predicting histopathology of endometrium in 1500 women, Journal of the American Association of Gynecologic Laparoscopists, 8, 207-213, 2001 | Wrong population: only 310 out of 1500 with HMB. |
| Georgantopoulou, C., Simm, A., Roberts, M., Transvaginal saline hysterosonography: A comparison with local anaesthetic hysteroscopy for the diagnosis of benign lesions associated with menorrhagia, Gynecological Surgery, 5, 2008 | Wrong index test: saline hysterosonography. |

| Reference | Reason for exclusion |
|---|---|
| Gimpelson, R. J., Rappold, H. O., A comparative study between panoramic hysteroscopy with directed biopsies and dilatation and curettage: A review of 276 cases, American Journal of Obstetrics and Gynecology, 158, 489-492, 1988 | Wrong comparison: compares biopsy and curettage; unclear population: only 76% have abnormal uterine bleeding of which proportion of HMB not reported. |
| Gkrozou, F., Dimakopoulos, G., Vrekoussis, T., Lavasidis, L., Koutlas, A., Navrozoglou, I., Stefos, T., Paschopoulos, M., Hysteroscopy in women with abnormal uterine bleeding: a meta-analysis on four major endometrial pathologies, Archives of Gynecology and Obstetrics., 19, 2014 | Systematic review; no additional relevant studies. |
| Goldschmit, R., Katz, Z., Blickstein, I., Caspi, B., Dgani, R., The accuracy of endometrial pipelle sampling with and without sonographic measurement of endometrial thickness, Obstetrics and Gynecology, 82, 727-730, 1993 | Wrong index test; unclear population. |
| Goldstein,S.R., Zeltser,I., Horan,C.K., Snyder,J.R., Schwartz,L.B., Ultrasonography-based triage for perimenopausal patients with abnormal uterine bleeding, American Journal of Obstetrics and Gynecology, 177, 102-108, 1997 | No sufficient data to calculate diagnostic accuracy of TVUS. Not all who underwent TVUS had a reference standard test. |
| Gordts, S., Brosens, J. J., Fusi, L., Benagiano, G., Brosens, I., Uterine adenomyosis: a need for uniform terminology and consensus classification, Reproductive Biomedicine Online, 17, 244-8, 2008 | A narrative review. References checked. |
| Goyal, B. K., Gaur, C. I., Sharma, G. C. S., Saha, M. A., Das, N. K., Transvaginal sonography versus hysteroscopy in evaluation of abnormal uterine bleeding, Medical Journal Armed Forces India, 71, 2015 | Wrong comparison; wrong population: less than two thirds of the population with HMB. |
| Graziano, A., Lo Monte, G., Piva, I., Caserta, D., Karner, M., Engl, B., Marci, R., Diagnostic findings in adenomyosis: A pictorial review on the major concerns, European Review for Medical and Pharmacological Sciences, 19, 1146 | Pictorial review on adenomyosis. References checked. |
| Griffin, Y., Sudigali, V., Jacques, A., Radiology of benign disorders of menstruation, Seminars in Ultrasound, CT & MR, 31, 414-32, 2010 | Expert review. Relevant references checked. |
| Grimbizis, G. F., Tsolakidis, D., Mikos, T., Anagnostou, E., Asimakopoulos, E., Stamatopoulos, P., Tarlatzis, B. C., A prospective comparison of transvaginal ultrasound, saline infusion sonohysterography, and diagnostic hysteroscopy in the evaluation of endometrial pathology, Fertility and Sterility, 94, 2720 | Wrong population: 52% pre-menopausal women with abnormal uterine bleeding. |

| Reference | Reason for exclusion |
|---|---|
| Guido, R. S., Ultrasound and magnetic resonance imaging (MRI) screening of patients with heavy menstrual bleeding and suspected uterine fibroids, Journal of Minimally Invasive Gynecology, Conference, 2013 | Conference abstract. |
| Gungoren, A., Dolapcioglu, K., Hakverdi, A. U., Ciftci, S. C., Yetim, C., How effective TV-USG, SIS and hysteroscopy are in evaluating uterine cavity?, Turkiye Klinikleri Jinekoloji Obstetrik, 21, 2011 | Full text in Turkish. |
| Guven, M. A., Bese, T., Demirkiran, F., Comparison of hydrosonography and transvaginal ultrasonography in the detection of intracavitary pathologies in women with abnormal uterine bleeding, International Journal of Gynecological Cancer, 14, 57-63, 2004 | Wrong population: only 66% premenopausal with abnormal uterine bleeding, proportion of these with HMB not reported. |
| Guyatt, G. H., Oxman, A. D., Ali, M., Willan, A., McIlroy, W., Patterson, C., Laboratory diagnosis of iron-deficiency anemia: An overview, Journal of General Internal Medicine, 7, 145-153, 1992 | No relevant data. |
| Hallberg, L., Hogdahl, A. M., Nilsson, L., Rybo, G., Menstrual blood loss--a population study. Variation at different ages and attempts to define normality, Acta Obstetricia et Gynecologica Scandinavica, 45, 320-351, 1966 | No relevant data. |
| Hanafi, M., Ultrasound diagnosis of adenomyosis, leiomyoma or combined with histopathological correlation, Gynecological Surgery, Conference, 2012 | Unclear population. |
| Harmanli, O. H., Bevilacqua, S. A., Dandolu, V., Chatwani, A. J., Hernandez, E., Adenomyosis interferes with accurate ultrasonographic detection of uterine leiomyomas, Archives of Gynecology and Obstetrics, 273, 146-149, 2005 | Unclear population. |
| Haynes, P J; Anderson ABM., Patterns of menstrual blood loss in menorrhagia., Research and Clinical Forums, 1, 73-8, 1979 | No relevant data. |
| Herman, M. C., Mol, B. W., Bongers, M. Y., Diagnosis of heavy menstrual bleeding, Women's Health, 12, 2016 | Expert review. Relevant references checked. |
| Herman, P., Gaspard, U., Meno-metrorrhagia, Revue Medicale de Liege, 54, 1999 | Full text in French. |
| Hong, S. C., Khoo, C. K., An update on adenomyosis uteri, Gynecology and Minimally Invasive Therapy, 5, 132-133, 2016 | Review on adenomyosis. References checked. |
| Hunter, D. C., McClure, N., Abnormal uterine bleeding: an evaluation endometrial biopsy, vaginal ultrasound and outpatient hysteroscopy, The Ulster medical journal, 70, 25-30, 2001 | Wrong population: 42% postmenopausal women. |

| Reference | Reason for exclusion |
|---|---|
| Hurskainen, R., Grenman, S., Komi, I., Kujansuu, E., Luoto, R., Orrainen, M., Patja, K., Penttinen, J., Silventoinen, S., Tapanainen, J., Toivonen, J., Diagnosis and treatment of menorrhagia, Acta Obstetricia et Gynecologica Scandinavica, 86, 2007 | An article about Finnish guideline on diagnosis and treatment of heavy menstrual bleeding from 2007. Relevant references checked. |
| Indman, P. D., Abnormal uterine bleeding: Accuracy of vaginal probe ultrasound in predicting abnormal hysteroscopic findings, Journal of Reproductive Medicine for the Obstetrician and Gynecologist, 40, 545-548, 1995 | Wrong/unclear population: 40% of women 50 years, menopausal status or proportion with HMB not reported. |
| Issat, T., Beta, J., Nowicka, M. A., Jakimiuk, A. J., Accuracy and diagnostic value of outpatient hysteroscopy for malign and benign disease, European Journal of Gynaecological Oncology, 35, 52-55, 2014 | Wrong population: 27% abnormal uterine bleeding, 56% postmenopausal. |
| Jain, N., Verma, R., Imaging diagnosis of accessory and cavitated uterine mass, a rare mullerian anomaly, Indian Journal of Radiology and Imaging, 24, 2014 | A case report. |
| Jakimiuk, A. J., Grzybowski, W., Beta, J., Dysfunctional uterine bleeding--diagnostics and treatment, Ginekologia Polska, 79, 2008 | Full text in Polish. |
| James, A., Matchar, D. B., Myers, E. R., Testing for von Willebrand disease in women with menorrhagia: A systematic review, Obstetrics and Gynecology, 104, 381-388, 2004 | No relevant data. |
| Janssen, C. A. H., Scholten, P. C., Heintz, A. P. M., Reconsidering menorrhagia in gynecological practice. Is a 30-year-old definition still valid?, European Journal of Obstetrics Gynecology and Reproductive Biology, 78, 69-72, 1998 | No relevant data. |
| Jason, M., Dechenne, V., Chantraine, F., Nisolle, M., Adenomyosis, Revue Medicale de Liege, 68, 160-162, 2013 | Full text in French. |
| Jeng, C. J., Huang, S. H., Shen, J., Chou, C. S., Tzeng, C. R., Laparoscopy-guided myometrial biopsy in the definite diagnosis of diffuse adenomyosis, Human Reproduction, 22, 2016 | Wrong/unclear population. |
| Kadir, R. A., Economides, D. L., Sabin, C. A., Owens, D., Lee, C. A., Frequency of inherited bleeding disorders in women with menorrhagia, Lancet, 351, 485-489, 1998 | No relevant data. |
| Katsetos, C., Radhakrishnan, S., Koumousidis, A., Kontoyannis, M., Boutas, I., Kalampokas, E., Kalampokas, T., Sofoudis, C., Comparison of transvaginal 3D sonohysterography with outpatient hysteroscopy in the evaluation of abnormal uterine bleeding, International Journal of Gynecological Cancer, Conference, 2013 | Conference abstract. |

| Reference | Reason for exclusion |
|---|---|
| Kavak, Z., Ceyhan, N., Pekin, S., Combination of vaginal ultrasonography and Pipelle sampling in the diagnosis of endometrial disease, Australian and New Zealand Journal of Obstetrics and Gynaecology, 36, 63-66, 1996 | Wrong population: more than half postmenopausal women. |
| Keckstein, J., Hysteroscopy and adenomyosis, Contributions to Gynecology & Obstetrics, 20, 41-50, 2000 | Not a study. Hysteroscopy is not of interest for the diagnosis of adenomyosis in the review. |
| Keeling, A. N., Reidy, J. F., Imaging and treatment of uterine fibroids, including the role of uterine artery embolization, Imaging, 19, 374-384, 2007 | Expert review. Possible relevant references checked. |
| Kelekci, S., Kaya, E., Alan, M., Alan, Y., Bilge, U., Mollamahmutoglu, L., Comparison of transvaginal sonography, saline infusion sonography, and office hysteroscopy in reproductive-aged women with or without abnormal uterine bleeding, Fertility and Sterility, 84, 682-686, 2005 | Wrong population: less than two thirds with HMB. |
| Kent, A. S. H., Haines, P., Manners, B. T. B., Coats, P. M., Blind endometrial biopsies: Insufficient for diagnosis in women with intrauterine pathology, Gynaecological Endoscopy, 7, 273-278, 1998 | Index test not of interest. |
| Kepkep, K., Tuncay, Y. A., Goynumer, G., Tutal, E., Transvaginal sonography in the diagnosis of adenomyosis: Which findings are most accurate?, Ultrasound in Obstetrics and Gynecology, 30, 341-345, 2007 | Wrong population. |
| Khan, F., Jamaat, S., Al-Jaroudi, D., Saline infusion sonohysterography versus hysteroscopy for uterine cavity evaluation, Annals of Saudi Medicine, 31, 2011 | Wrong population: only 43% with HMB. |
| Khan, Z., Famuyide, A. O., Hopkins, M. R., Breitkopf, D. M., Laughlin-Tommaso, S. K., Sensitivity of flexible hysteroscopy for endometrial polyps and the role of endometrial biopsies, Journal of Minimally Invasive Gynecology, Conference, 2012 | Conference abstract. |
| Khan,A.T., Shehmar,M., Gupta,J.K., Uterine fibroids: Current perspectives, International Journal of Women's Health, 6, 95-114, 2014 | Expert review. Relevant references checked. |
| Khanna, A., Gupta, M., Shukla, R. C., Saline perfusion sonography and transvaginal sonography in abnormal uterine bleeding, Ultrasound International, 7, 31-36, 2001 | Wrong population: 9/70 women had HMB. |
| Kinkel, K., Vincent, B., Balleyguier, C., Helenon, O., Moreau, J., Value of MR imaging in the diagnosis of benign uterine conditions, Journal de Radiologie, 81, 2000 | Full text in French language. |

| Reference | Reason for exclusion |
|---|---|
| Knol, H. M., Bogchelman, D. H., Meijer, K., Van Der Zee, A. G. J., Van Der Meer, J., Unexplained menorrhagia and hemostatic evaluation in gynaecological practice, a retrospective study, Journal of Thrombosis and Haemostasis, Conference, 2009 | Conference abstract. |
| Koc, H., Noyan, V., Yucel, A., Sagsoz, N., Comparison of uterine artery Doppler sonography, saline infusion sonography and endometrial biopsy in premenopausal patients with abnormal uterine bleeding who were found to have endometrial polyps, Turkiye Klinikleri Jinekoloji Obstetrik, 20, 2010 | Full text in Turkish. |
| Kolhe, S., Prospective study of one-stop diagnostic and see-and-treat outpatient hysteroscopy service at royal derby hospital, BJOG: An International Journal of Obstetrics and Gynaecology, Conference, 2014 | Wrong population: 42% of women with postmenopausal bleeding. |
| Koonings, P. P., Moyer, D. L., Grimes, D. A., A randomized clinical trial comparing Pipelle and Tis-u-trap for endometrial biopsy, Obstetrics and Gynecology, 75, 293-295, 1990 | Index test not of interest. |
| Korczynski, J., Sobkiewicz, S., Adenomyosis. Diagnostic technique and treatment, Ginekologia Polska, 72, 317-321, 2001 | Full text in Polish language. |
| Koss, L. G., Schreiber, K., Oberlander, S. G., Moussouris, H. F., Lesser, M., Detection of endometrial carcinoma and hyperplasia in asymptomatic women, Obstetrics and Gynecology, 64, 1-11, 1984 | Index test not of interest. |
| Krampl, E., Soby, B., Istre, O., How representative are Pipelle endometrial biopsies? A retrospective analysis of 324 biopsies followed by transcervical resection of the endometrium or hysterectomy, Gynaecological Endoscopy, 6, 277-281, 1997 | Index test not of interest. |
| Krassas, G. E., Pontikides, N., Kaltsas, Th, Papadopoulu, Ph, Batrinos, M., Menstrual disturbances in thyrotoxicosis, Clinical Endocrinology, 40, 641-644, 1994 | No relevant data. |
| Kroencke, T. J., MRI for diagnosis of adenomyosis: Unsung and underutilized, Gynecologic and Obstetric Investigation, 60, 2005 | A letter to editor. |
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| Nicholson, Y., Chan, J., Patient satisfaction in outpatient hysteroscopy, BJOG: An International Journal of Obstetrics and Gynaecology, Conference, 2015 | Conference abstract. |
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| Ogutcuoglu, B., Karadag, C., Inan, C., Dolgun, Z. N., Yoldemir, A. T., Aslanova, L., Diagnostic utility of saline infusion doppler sonohysterography in endometrial mass lesions, Pakistan Journal of Medical Sciences, 32, 2016 | Unclear population: 85% premenopausal, proportion with HMB not reported; inclusion criteria was women with suspected masses in TVUS, index test of interest in this study was SIS. |
| Ossola, M. W., Bertulessi, C., Iasi, L., Bianchini, B., Hanozet, F., Grassini, E., Capetta, P., Comparison of saline infusion sonography to transvaginal echography and hysteroscopy in the diagnostic evaluation of abnormal uterine bleeding, Italian Journal of Gynaecology and Obstetrics, 11, 145-150, 1999 | Wrong population: less than two thirds premenopausal women. |
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| Ozer, A., Ozer, S., Kanat-Pektas, M., Correlation between transvaginal ultrasound measured endometrial thickness and histopathological findings in Turkish women with abnormal uterine bleeding, Journal of Obstetrics and Gynaecology Research, 42, 2016 | Unclear population; unclear exclusions. |
| Pallavi, P., Krishna, L., Havaldar, N. A., Shailaja, N., Saravana, A., Pradeep, S., A comparative diagnostic evaluation of abnormal uterine bleeding by hysteroscopy and transvaginal sonography, Biomedicine, 33, 2013 | Wrong/unclear population: number of women postmenopausal versus premenopausal not reported. |
| Parveen, S., Azad, S. A., Mohammad, J., Haque, S., Shanta, R. S., Rahman, S. M., Role of sonohysterography in evaluation of abnormally thickened endometrium causing abnormal uterine bleeding with histopathological correlation, Bangladesh Medical Research Council Bulletin, 40, 2014 | Unclear population: 85% pre/perimenopausal but proportion of women with HMB not reported; reporting of results of index test and reference standard unclear, the text contradicts itself and figure explaining the results is also unclear/missing some observations. Therefore, difficult to form a definite 2x2 table. |
| Paschopoulos, M., Lolis, E. D., Alamanos, Y., Koliopoulos, G., Paraskevaidis, E., Vaginoscopic hysteroscopy and transvaginal sonography in the evaluation of patients with abnormal uterine bleeding, Journal of the American Association of Gynecologic Laparoscopists, 8, 506-510, 2001 | Wrong population: less than half with HMB. |
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| Pasqualotto,E.B., Margossian,H., Price,L.L., Bradley,L.D., Accuracy of preoperative diagnostic tools and outcome of hysteroscopic management of menstrual dysfunction, Journal of the American Association of Gynecologic Laparoscopists, 7, 201-209, 2000 | Wrong population: 44% postmenopausal women. |
| Pasrija, S., Trivedi, S. S., Narula, M. K., Prospective study of saline infusion sonohysterography in evaluation of perimenopausal and postmenopausal women with abnormal uterine bleeding, Journal of Obstetrics and Gynaecology Research, 30, 27-33, 2004 | Wrong population: less than two thirds with HMB. |
| Patil, S. G., Bhute, S. B., Inamdar, S. A., Acharya, N. S., Shrivastava, D. S., Role of diagnostic hysteroscopy in abnormal uterine bleeding and its histopathologic correlation, Journal of Gynecological Endoscopy and Surgery, 1, 2009 | Wrong population: 25% with HMB. |
| Pehlivan, H., Keskin, U., Yenen, M. C., Guler, A. E., Dede, M., Ergun, A., The comparison of the effectiveness of biopsy combined with hysteroscopy and dilatation and curettage for the | Conference abstract. |

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| detection of endometrial pathologies, International Journal of Gynecological Cancer, Conference, 2012 | |
| Perrot, N., Mergui, J. L., Frey, I., Uzan, M., Ultrasound exams in the diagnosis of menorrhagia, Gynecologie Obstetrique Fertilite, 30, 2002 | Full text in French. |
| Philipp, C. S., Dilley, A., Miller, C. H., Evatt, B., Baranwal, A., Schwartz, R., Bachmann, G., Saidi, P., Platelet functional defects in women with unexplained menorrhagia, Journal of thrombosis and haemostasis : JTH, 1, 477-484, 2003 | No relevant data. |
| Philipp, C. S., Miller, C. H., Faiz, A., Dilley, A., Michaels, L. A., Ayers, C., Bachmann, G., Dowling, N., Saidi, P., Screening women with menorrhagia for underlying bleeding disorders: The utility of the platelet function analyser and bleeding time, Haemophilia, 11, 497-503, 2005 | No relevant data. |
| Phillips, D. R., Nathanson, H. G., Milim, S. J., Haselkorn, J. S., Magnetic resonance imaging for diagnosing adenomyomata, Journal of the American Association of Gynecologic Laparoscopists, 3, 245-250, 1996 | Wrong/unclear population. |
| Pinheiro, W., Pereira, A. K. C., Ejzenberg, D., Ricci, M. D., Motta, E. V., Baracat, M. C. P., Simoes, R. S., Anzai, M., Soares Jr, J. M., Baracat, E. C., How is the accucary of ultrasound diagnosis of polyp after hysteroscopy?, International Journal of Gynecology and Obstetrics, Conference, 2015 | Conference abstract. |
| Rajan, D. K., Margau, R., Kroll, R., Simons, M. E., Tan, K., Beecroft, R., Kachura, J., Sniderman, K. W., Comparison of ultrasound versus MRI prior to uterine artery embolization in symptomatic patients with presumed uterine fibroids, CardioVascular and Interventional Radiology, Conference, 2009 | Conference abstract. |
| Rashid, S. Q., Chou, Y. H., Tiu, C. M., Ultrasonography of Uterine Leiomyomas, Journal of Medical Ultrasound, 24, 3-12, 2016 | Expert review. Relevant references checked. |
| Reinhold, C., McCarthy, S., Bret, P. M., Mehio, A., Atri, M., Zakarian, R., Glaude, Y., Liang, L., Seymour, R. J., Diffuse adenomyosis: Comparison of endovaginal US and MR imaging with histopathologic correlation, Radiology, 199, 151-158, 1996 | Wrong population. |
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| Reinhold, C., Tafazoli, F., Wang, L., Imaging features of adenomyosis, Human Reproduction Update, 4, 337-49, 1998 | A review. References checked. |
| Riaz, S., Ibrar, F., Dawood, N. S., Jabeen, A., Endometrial pathology by endometrial curettage in menorrhagia in premenopausal age group, Journal of Ayub Medical College, Abbottabad : JAMC, 22, 2010 | No comparison of diagnostic tests. |
| Robert, Y., Bazot, M., Meno-metrorrhagia imaging, Journal de Radiologie, 89, 2008 | Full article in French. |
| Rodeghiero, F., Castaman, G., Dini, E., Epidemiological investigation of the prevalence of von Willebrand's disease, BloodBlood, 69, 454-9, 1987 | No relevant data. |
| Rodriguez, M. A., Gualtieri, B. M., Mouhayar, Y., Mejia, A., Brookfield, K. F., Cruz-Pachano, F., Comparison of 3D/4D ultrasound to 3D saline infused sonohysterographyfor evaluation of endometrial polyps in pre and postmenopausal women, Fertility and Sterility, Conference, 2012 | Conference abstract. |
| Rodriquez, M., Gualtieri, M., Mouhayar, Y., Mejia, A., Cruz, F., Brookfield, K., 3D/4D ultrasoundtransvaginal ultrasound can beuseful alternative to saline infusion sonohysterography for evaluation of polyps, Fertility and Sterility, Conference, 60th Annual Meeting of The Pacific Coast Reproductive Society, PCRS 2012. Rancho Mirage, CA United States. Conference Start: 20120418. Conference End: 20120422. Conference Publication: (var.pagings). 97 (3 SUPPL. 1) (pp S21-S22), 2012 | Conference abstract. |
| Rokita, W., Stanislawska, M., Nowak-Markwitz, E., Kedzia, W., Spaczynski, M., Karowicz-Bilinska, A., Bednarek, W., Diagnostic hysteroscopy in women with endometrial hyperplasia and endometrial cancer - 9 years of experience, analysis of 142 cases, International Journal of Gynecology and Obstetrics, Conference, 2009 | Conference abstract. |
| Ryu, J. A., Kim, B., Lee, J., Kim, S., Lee, S. H., Comparison of transvaginal ultrasonography with hysterosonography as a screening method in patients with abnormal uterine bleeding, Korean Journal of Radiology, 5, 39-46, 2004 | Wrong population: only 55% premenopausal women. |
| Saadati, N., Mohammad Jafary, R., Shojaie, K., Comparison of sensitivity and specificity of transvaginal ultra sonography, saline infusion sonohysterography and hysteroscopy in evaluation of the women with abnormal uterine bleeding in Ahvaz Imam Khomeini and Razi Hospitals during 2008, Iranian Journal of Reproductive Medicine, Conference, 2013 | Conference abstract. |

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| Sadecky, A. M., Guido, R., Lee, T., Mansuria, S., Rindos, N., Donnellan, N. M., Clinical diagnosis of adenomyosis: Use of predictive uterine characteristics to improve accuracy and reliability, American Journal of Obstetrics and Gynecology, 1), S485, 2016 | Conference abstract. |
| Saidi, M. H., Sadler, R. K., Theis, V. D., Akright, B. D., Farhart, S. A., Villanueva, G. R., Comparison of sonography, sonohysterography, and hysteroscopy for evaluation of abnormal uterine bleeding, Journal of Ultrasound in Medicine, 16, 587-91, 1997 | Unclear population: proportion of women with HMB or who are premenopausal not reported. Age range 40-89 years, mean age around 50. |
| Sakhel, K., Abuhamad, A., Sonography of adenomyosis, Journal of Ultrasound in Medicine, 31, 805-8, 2012 | A narrative review. References checked. |
| Saleh, S. S., Fram, K., Histopathology diagnosis in women who underwent a hysterectomy for a benign condition, Archives of Gynecology and Obstetrics, 285, 1339 | Wrong population: 39% with HMB. |
| Salim, S., Won, H., Nesbitt-Hawes, E., Campbell, N., Abbott, J., Diagnosis and Management of Endometrial Polyps: A Critical Review of the Literature, Journal of Minimally Invasive Gynecology, 18, 2011 | Expert review. Possible relevant references checked. |
| Salim,R., Lee,C., Davies,A., Jolaoso,B., Ofuasia,E., Jurkovic,D., A comparative study of three-dimensional saline infusion sonohysterography and diagnostic hysteroscopy for the classification of submucous fibroids, Human Reproduction, 20, 253-257, 2005 | Wrong index test. |
| Sanna, S., Stochino Loi, E., Pirarba, S., Arena, I., Maricosu, G., Melis, G. B., Angioni, S., Office operative hysteroscopy. Results on pain, diagnosis and treatment of uterine pathologies, Gynecological Surgery, Conference, 2010 | Conference abstract. |
| Scarpellini, F., Curto, C., Caracussi, U., Letta, C., Scarpellini, L., Transvaginal ultrasound versus histology in endometrial hyperplasia, Clinical and Experimental Obstetrics and Gynecology, 21, 266-269, 1994 | Wrong population: most women postmenopausal. |
| Schneider, S. L., Craig, M., Branning, P., Improved sonographic accuracy in the presurgical diagnosis of diffuse adenomyosis: A case series and review, Journal of Diagnostic Medical Sonography, 18, 2002 | A case series and review. No relevant data or references. |
| Schwarzler, P., Concin, H., Bosch, H., Berlinger, A., Wohlgenannt, K., Collins, W. P., Bourne, T. H., An evaluation of sonohysterography and diagnostic hysteroscopy for the assessment of intrauterine pathology, Ultrasound in Obstetrics and Gynecology, 11, 337-342, 1998 | Wrong population: 70.4% of women were premenopausal with abnormal uterine bleeding including HMB, or irregular bleeding or postcoital bleeding. Proportion of HMB not |

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|---|---|
| | reported but presumably lower than two thirds of the whole population since only 70% were premenopausal. |
| Sconfienza, L. M., Lacelli, F., Caldiera, V., Perrone, N., Piscopo, F., Gandolfo, N., Serafini, G., Three-dimensional sonohysterography for examination of the uterine cavity in women with abnormal uterine bleeding: Preliminary findings, Journal of Ultrasound, 13, 2010 | Unclear population: menstrual/menopausal status not reported. |
| Senturk, L.M., Adenomyosis: What is new?, Journal of Endometriosis, 4, 142-143, 2012 | Narrative review. Possibly relevant references checked. |
| Seto, M. T. Y., Ip, P. P. C., Ngu, S. F., Cheung, A. N. Y., Pun, T. C., Positive predictive value of endometrial polyps in Pipelle aspiration sampling: A histopathological study of 195 cases, European Journal of Obstetrics Gynecology and Reproductive Biology, 203, 2016 | Unclear population; wrong index test. |
| Shankar, M., Lee, C. A., Sabin, C. A., Economides, D. L., Kadir, R. A., Von Willebrand disease in women with menorrhagia: A systematic review, BJOG: An International Journal of Obstetrics and Gynaecology, 111, 734-740, 2004 | No relevant data. |
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| Shwayder, J., Sakhel, K., Imaging for Uterine Myomas and Adenomyosis, Journal of Minimally Invasive Gynecology, 21, 362-376, 2014 | Expert review. No relevant data. |
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| Smith, A., O'Brien, K., Ficquet, J., Can the number of hysteroscopies for the investigation of abnormal uterine bleeding be reduced?, International Journal of Gynecology and Obstetrics, Conference, 20th FIGO World Congress of Gynecology and Obstetrics. Rome Italy. Conference Start: 20121007. Conference End: 20121012. Conference Publication: (var.pagings). 119 (pp S743), 2012 | Wrong population: 64% of women postmenopausal. |
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| Song, Y., Shen, L. C., Huang, W., Lei, H. K., Wang, Q. S., Zhu, H. L., Diagnostic value of endometrial thickness determined by transvaginal sonography in infertile women with endometrial polyps, Chinese Medical Journal, 125, 2279 | Wrong population: infertile women. |
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| Struble, J., Reid, S., Bedaiwy, M. A., Adenomyosis: A Clinical Review of a Challenging Gynecologic Condition, Journal of Minimally Invasive Gynecology, 23, 164-85, 2016 | A review. Possibly relevant references assessed individually. |
| Sudderuddin, S., Helbren, E., Telesca, M., Williamson, R., Rockall, A., MRI appearances of benign uterine disease, Clinical Radiology, 69, 1095 | Expert review on uterine MRI. Relevant references checked. |

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| Tafazoli, F., Reinhold, C., Uterine adenomyosis: current concepts in imaging, Seminars in Ultrasound, CT & MR, 20, 267-77, 1999 | Narrative review on adenomyosis. References checked. |
| Tahir, M. M., Bigrigg, M. A., Browning, J. J., Brookes, S. T., Smith, P. A., A randomised controlled trial comparing transvaginal ultrasound, outpatient hysteroscopy and endometrial biopsy with inpatient hysteroscopy and curettage, British Journal of Obstetrics and Gynaecology, 106, 1259-1264, 1999 | Wrong population: less than half of women had HMB. |
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| Teale, G. R., Dunster, G. D., The Pipelle endometrial suction curette: How useful is it in clinical practice?, Journal of Obstetrics and Gynaecology, 18, 53-55, 1998 | Index test not of interest. |
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| To, J. K., Levie, M., Chudnoff, S., Endometrial pipelle biopsy identifying a polyp versus office hysteroscopy, Journal of Minimally Invasive Gynecology, Conference, 2015 | Conference abstract. |
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| Tsai, M. C., Goldstein, S. R., Office diagnosis and management of abnormal uterine bleeding, Clinical Obstetrics and Gynecology, 55, 635-650, 2012 | Expert review. Relevant references checked. |
| Turkgeldi, E., Urman, B., Ata, B., Role of Three-Dimensional Ultrasound in Gynecology, Journal of Obstetrics and Gynecology of India, 65, 146-154, 2015 | Expert review. Relevant references checked. |
| Valentini, A. L., Speca, S., Gui, B., Soglia, G., Micco, M., Bonomo, L., Adenomyosis: from the sign to the diagnosis. Imaging, diagnostic pitfalls and differential diagnosis: a pictorial review, La Radiologia medica, 116, 1267-1287, 1267 | A pictorial review. References checked. |
| Valle, R. F., Hysteroscopic evaluation of patients with abnormal uterine bleeding, Surgery Gynecology and Obstetrics, 153, 521-526, 1981 | No sufficient data to form 2x2 table and calculate diagnostic accuracy. |
| Van den Bosch, T., Valentin, L., Van Schoubroeck, D., Luts, J., Bignardi, T., Condous, G., Epstein, E., Leone, F. P., Testa, A. C., Van Huffel, S., Bourne, T., Timmerman, D., Detection of intracavitary uterine pathology using offline analysis of three-dimensional ultrasound volumes: interobserver agreement and diagnostic accuracy, Ultrasound in Obstetrics & Gynecology, 40, 459-63, 2012 | Wrong/unclear population: 30% postmenopausal women, rest premenopausal but with AUB, % with HMB not reported. |
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| Van Dongen, H., De Kroon, C. D., Jacobi, C. E., Trimbos, J. B., Jansen, F. W., Diagnostic hysteroscopy in abnormal uterine bleeding: A systematic review and meta-analysis, BJOG: An International Journal of Obstetrics and Gynaecology, 114, 2007 | Systematic review with different inclusion criteria; included studies checked individually. |
| Veena, B. T., Shivalingaiah, N., Role of transvaginal sonography and diagnostic hysteroscopy in abnormal uterine bleeding, Journal of Clinical and Diagnostic Research, 8, OC06-OC08, 2014 | Wrong population: less than two thirds with HMB. |

| Reference | Reason for exclusion |
|---|---|
| Venugopalan, S. K., Pandian, N. S., Pavani, M., Srinivasa Rao, T., Rajini, Y., Khadeer, S. K., Ravichandiran, V., Abnormal uterine bleeding in reproductive women: Diagnosis, management and treatment, Asian Journal of Pharmaceutical and Clinical Research, 8, 42-45, 2015 | No relevant data. |
| Vitner, D., Filmer, S., Goldstein, I., Khatib, N., Weiner, Z., A comparison between ultrasonography and hysteroscopy in the diagnosis of uterine pathology, European Journal of Obstetrics Gynecology and Reproductive Biology, 171, 2013 | Unclear population: referring symptoms and menopausal status not reported. |
| Walker, K., Jayaprakasan, K., Raine-Fenning, N. J., Ultrasound in benign gynaecology, Obstetrics, Gynaecology and Reproductive Medicine, 17, 2007 | Expert review. Possible relevant references checked. |
| Walker, W. J., Jones, K., Transvaginal ultrasound guided biopsies in the diagnosis of pelvic lesions, Minimally Invasive Therapy and Allied Technologies, 12, 2003 | Unclear/wrong population. |
| Wery, O., Thille, A., Gaspard, U., Van Den Brule, F., Adenomyosis: Update on a frequent but difficult diagnosis, Journal de Gynecologie Obstetrique et Biologie de la Reproduction, 34, 633-648, 2005 | Full text in French. |
| Whitaker, L., Critchley, H. O. D., Abnormal uterine bleeding, Best Practice and Research: Clinical Obstetrics and Gynaecology., 2016 | Expert review. Relevant references checked. |
| Widrich, T., Bradley, L. D., Mitchinson, A. R., Collins, R. L., Comparison of saline infusion sonography with office hysteroscopy for the evaluation of the endometrium, American Journal of Obstetrics and Gynecology, 174, 1327-1334, 1996 | Wrong population: 73% premenopausal, 68% had abnormal uterine bleeding, proportion with HMB not reported. |
| Wolfman, D. J., Allison, S. J., Ascher, S. M., Imaging of benign uterine conditions, Applied Radiology, 40, 2011 | Narrative review, possible relevant references checked. |
| Wong, I. K. C., Visvanathan, D., Do women having an outpatient hysteroscopy have a higher anxiety level compared to a day case hysteroscopy? A prospective questionnaire research study, BJOG: An International Journal of Obstetrics and Gynaecology, Conference, 2016 | Conference abstract. |
| Wood, C., Hurley, V. A., Leoni, M., The value of vaginal ultrasound in the management of menorrhagia, Australian and New Zealand Journal of Obstetrics and Gynaecology, 33, 198-200, 1993 | Not data to calculate diagnostic accuracy measures. |
| Wu, K. K., Wang, Y. Y., Qian, B., Pan, Y., Chang, C., The classification of uterine myoma and uterine adenomyosis based on ultrasound image features, Chinese Journal of Biomedical Engineering, 26, 2007 | Full text in Chinese. |

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| Xyda, A., Moyle, P., Addley, H., Freeman, S., Imaging of the female pelvis, Obstetrics, Gynaecology and Reproductive Medicine, 25, 283-294, 2015 | Narrative expert review. Possibly relevant references checked. | |
| Yang, P. Y., Wu, J. L., Wu, P. W., Wu, C. H., Lin, C. J., Fan, L. R., Yang, Y. H., Yeh, G. P., Accuracy of transvaginal ultrasonography for detecting intrauterine lesions at a Taiwan medical center: A correlation with ultrasound and hysteroscopic histopathology, Journal of Medical Ultrasound, 22, 37-42, 2014 | Wrong/unclear population: 66.8% with abnormal uterine bleeding, % of HMB not reported and presumably less than 66.6%. | |
| Yildizhan, B., Yildizhan, R., Ozkesici, B., Suer, N., Transvaginal ultrasonography and saline infusion sonohysterography for the detection of intra-uterine lesions in pre- and post-menopausal women with abnormal uterine bleeding, Journal of International Medical Research, 36, 1205 | Wrong population: less than two thirds with HMB. | |
| Yumru, A. E., Bozkurt, M., Coskun, E. I., Erkilincoglu, M., Ayanoglu, Y. T., Evaluation of diagnostic methods in abnormal uterine bleeding and endometrial carcinoma: Sectional prospective study, Nobel Medicus, 5, 2009 | Wrong population: less than two thirds with HMB. | |
| Zegura, B., Office operative hysteroscopy, Gynecological Surgery, Conference, 2015 | Wrong population: 45% women post-menopausal. | |
| Zhao, F., Zhang, H., Ren, Y., Kong, F., Transvaginal sonographic characteristics of paraovarian borderline tumor, International Journal of Clinical and Experimental Medicine, 8, 2684 | Wrong population: women with diagnosis of parovarian tumour; small sample (n=4). | |
| Zhu, H. L., Liang, X. D., Wang, J. L., Cui, H., Wei, L. H., Hysteroscopy and directed biopsy in the diagnosis of endometrial carcinoma, Chinese Medical Journal, 123, 3524 | Wrong population: women with diagnosed endometrial carcinoma. | |

## Economic studies

There were no excluded economic studies.

## Appendix J – Diagnostic care pathway
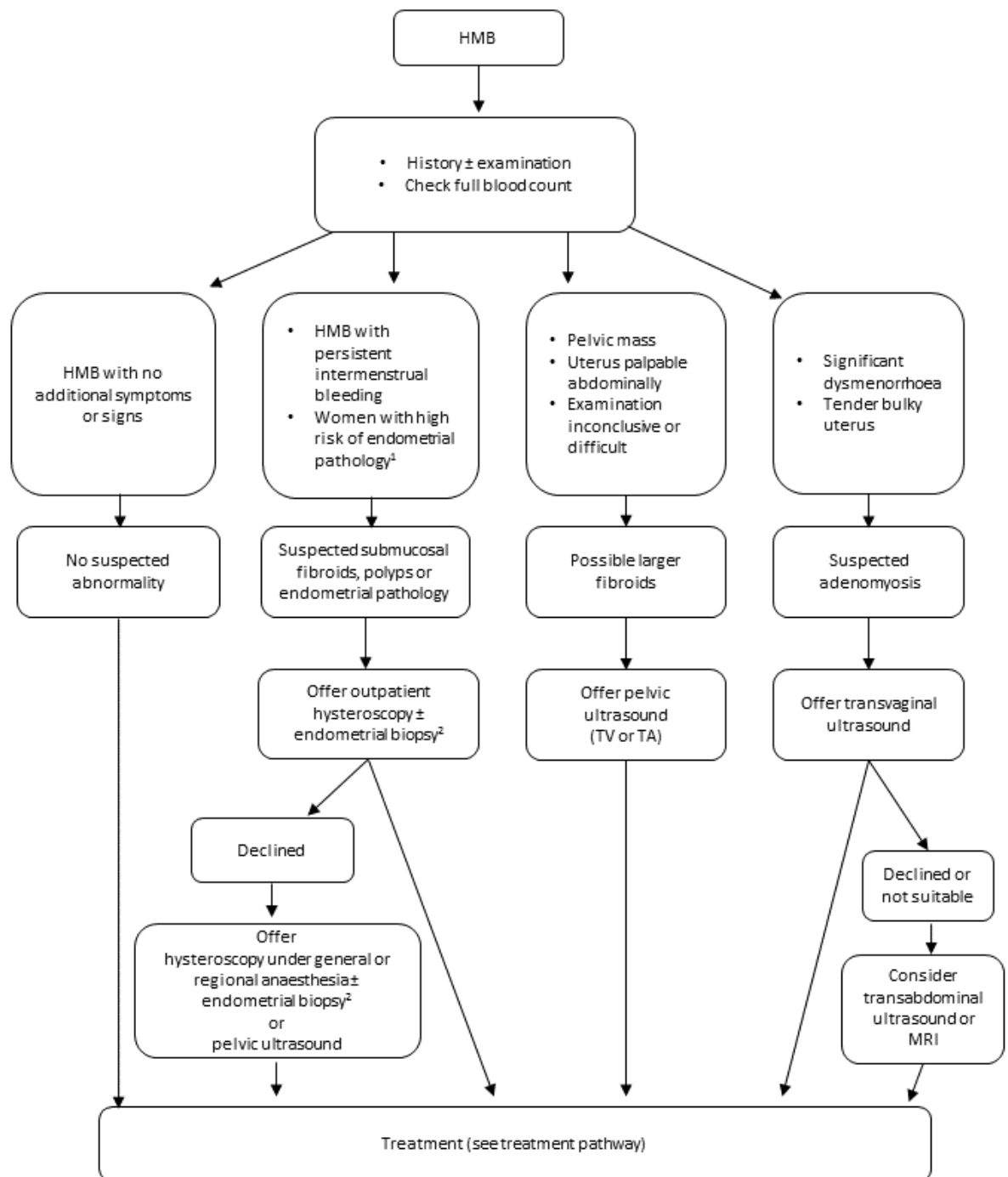


HMB: heavy menstrual bleeding; LNG-IUS: levonorgestrel-releasing intrauterine system; MRI: magnetic resonance imaging; NSAIDs: nonsteroidal anti-inflammatory drugs; TA: transabdominal; TV: transvaginal; TXA: tranexamic acid
[1] For example, women with persistent intermenstrual or persistent irregular bleeding and women with infrequent bleeding who are obese or have polycystic ovary syndrome, women taking tamoxifen, women for whom treatment for HMB has been unsuccessful
[2] If high risk for endometrial pathology (see footnote 1)

Heavy Menstrual Bleeding (update): evidence reviews for diagnostic test accuracy FINAL
March 2018