ASERNIP-S

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical

Rapid Review

Hysteroscopy for Abnormal Uterine Bleeding: Review of Clinical Evidence and Guidelines

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Australian Safety & Efficacy Register of New Interventional Procedures – Surgical

The Royal Australasian College of Surgeons

This report has been produced for the Victorian Government Department of Health

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Please note that this brief report, while broad in some aspects of systematic review methodology, should not be considered a comprehensive systematic review. Rather, this is a rapid review in which the methodology has been limited in one or more of the following areas to shorten the timeline for its completion: search strategy, inclusion criteria, assessment of study quality and data analysis. This report also contains non-systematic elements, such as qualitative information gathered from local surgeons. However, it is considered that these amendments would not significantly alter the overall findings of the rapid review when compared to a full systematic review.

The methodology used for the rapid review is described in detail, including the limits for this particular topic. These limits were applied following the requirements of the specific review topic, in consultation with the requester.

For a more comprehensive understanding of this topic, a broader analysis of the literature may be required. As such, all readers of this document should be aware of the limitations of this review.

This brief was prepared by Ms Lynda McGahan and Dr Ann Scott from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S).

Declaration of competing interest:

The authors of this publication claim no competing interests.

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Scope of the Report

The objective of this rapid systematic review is to facilitate the appropriate use of hysteroscopy for the diagnosis of abnormal uterine bleeding by providing a synthesis of the evidence on the following research questions.

1. Is hysteroscopy (with or without dilation and curettage) an effective diagnostic procedure for abnormal uterine bleeding?
2. Are there alternative diagnostic procedures for abnormal uterine bleeding that are superior to hysteroscopy (with or without dilation and curettage) with respect to effectiveness, safety and quality?
3. For the alternative diagnostic procedures that are superior to hysteroscopy (with or without dilation and curettage), if any, are there any limitations in their application with respect to patient characteristics or conditions?

Executive Summary

Context and policy issues

Abnormal uterine bleeding (AUB), defined as any variation from the normal menstrual cycle, includes changes in the regularity and frequency of menses, duration of flow or amount of blood lost. AUB most commonly presents as heavy menstrual bleeding (HMB) when excessive menstrual blood loss interferes with a woman's physical, emotional, social and material quality of life. Occurring more than a year after the last menstrual period, postmenopausal bleeding (PMB) is commonly associated with structural uterine pathology and malignancy.

History and physical examination are used to distinguish ovulatory from anovulatory bleeding, to identify cervical pathology or endometrial polyps and to direct further investigation and management. Imaging, endometrial biopsy (EB) or both may be used to further investigate AUB when structural causes are suspected, there is a risk of malignancy or conservative management has failed to improve symptoms.

Imaging techniques include transvaginal ultrasound (TVUS), sonohysterography (SHG) and hysteroscopy. Hysteroscopy is considered the gold standard for evaluating the uterine cavity and is often used without endometrial sampling as a reference standard. However, risks associated with hysteroscopy include perforation, infection, cervical laceration and fluid overload. Studies have shown that TVUS can reliably exclude cancer without the need for biopsy in some postmenopausal women, guide the selection of a biopsy technique and detect endometrial cancer with the same sensitivity as EB.

The objective of this rapid systematic review (SR) is to facilitate the appropriate use of diagnostic hysteroscopy in women AUB by providing a synthesis of the evidence on the following research questions.

1. Is hysteroscopy (with or without dilation and curettage [D&C]) an effective diagnostic procedure for AUB?
2. Are there alternative diagnostic procedures for AUB that are superior to hysteroscopy (with or without D&C) with respect to effectiveness, safety and quality?
3. For the alternative diagnostic procedures that are superior to hysteroscopy (with or without D&C), if any, are there any limitations in their application with respect to patient characteristics or conditions?

Methods

A systematic search of MEDLINE, EMBASE, *The Cochrane Library*, the NHS Centre for Reviews and Dissemination databases and the websites of various international health technology assessment agencies and clinical practice guideline (CPG) clearinghouses was conducted to identify relevant SRs, HTAs, CPGs and diagnostic accuracy studies

published in English from January 2005 (January 2009 for guidelines) to July 2015. A focused internet search was also conducted to identify grey literature. Study selection, data extraction and quality appraisal were undertaken by one reviewer. Two surgeons from Melbourne, Victoria, who specialise in obstetrics and gynaecology, were asked to provide their expert opinion on the use of diagnostic hysteroscopy for AUB in Victoria.

Key results

Evidence was derived from five CPGs, an overview of SRs and CPGs and a randomised, crossover diagnostic cohort study on the effectiveness of diagnostic hysteroscopy for investigating AUB and the effectiveness, safety, quality and limitations of alternative diagnostic procedures. Most of the evidence regarding the diagnostic accuracy of alternative diagnostic procedures was based on level II evidence. While values for diagnostic accuracy were reported for hysteroscopy, TVUS, SHG and EB, adverse events and complications were seldom reported. The quality of alternative diagnostics tests in terms of patient-related factors was reported in one randomised, crossover diagnostic cohort study.

Effectiveness of diagnostic hysteroscopy for AUB

Hysteroscopy is an effective diagnostic procedure for investigating AUB and for diagnosing endometrial cancer. Hysteroscopy had a sensitivity of 86 per cent and a specificity of 99 per cent for detecting endometrial cancer or hyperplasia. Hysteroscopy also detected uterine cavity abnormalities in postmenopausal women with a sensitivity of 96 per cent and a specificity of 90 per cent.

Effectiveness, safety, and quality of alternative diagnostic procedures for AUB

Alternative diagnostic procedures for investigating AUB include TVUS, EB and SHG. TVUS, recommended as first-line imaging for AUB, had a sensitivity of 19 to 96 per cent and a specificity of 53 to 100 per cent for detecting endometrial polyps, compared with hysteroscopically guided biopsy. EB was highly sensitive for diagnosing endometrial carcinoma and hyperplasia (sensitivity of 91.9% and specificity of 99.7%). Office-based EB was recommended as the first-line assessment for women over 40 years of age who are unresponsive to medical therapy and for women at risk of endometrial cancer. EB was also recommended for women who have undergone TVUS and have endometrial thickening. The sensitivity of SHG was 72% for diagnosing polyps, 93% for detecting fibroids and 100% for diagnosing an abnormal endometrium, compared with hysteroscopy. Despite the mean pain scores being comparable in both procedures, there was a marked patient preference for SHG over hysteroscopy (68% versus 15%).

Limitations associated with alternative diagnostic procedures for AUB

Alternative diagnostic procedures for evaluating AUB were associated with some limitations. Postmenopausal women who have undergone TVUS and have an EEC >4 mm, localised thickening or an indistinct EEC should undergo EB. Women experiencing

AUB while receiving adjuvant tamoxifen therapy are advised to undergo EB because TVUS is neither sensitive nor specific for neoplasia. SHG was not recommended as a first-line diagnostic procedure. Clinical experts reported that while SHG does not allow the collection of a pathology sample, it can indicate the likelihood of pathology, which is particularly useful in elderly patients with poor operative risk. Office-based EB should replace D&C as the first-line assessment for AUB in premenopausal women. Blind D&C or biopsy should not be used to diagnose polyps because it has a low sensitivity compared with hysteroscopically guided biopsy.

Conclusions and policy implications

There is a role for hysteroscopy in women with AUB; however, it should be used as the final step in the diagnostic pathway. Two procedures should precede diagnostic hysteroscopy with D&C in the triage of AUB:

- TVUS performed by an appropriately trained operator for measuring endometrial thickness and detecting polyps;
- Outpatient EB with a Pipelle® endometrial sampler or similar device for diagnosing endometrial carcinoma and hyperplasia.

Office-based EB should replace D&C as the first-line assessment for AUB in premenopausal women. SHG was sensitive for detecting polyps, fibroids and an abnormal endometrium, and was preferred by patients over hysteroscopy. However, the use of SHG is limited to tertiary-level hospitals.

Little information was found regarding the safety and limitations of alternative diagnostic procedures in terms of adverse events and patient-related factors. No relevant Australian CPGs were identified. The included CPGs were developed in the United States and Canada, and there may be inherent differences between the populations and healthcare contexts that the limit transferability of the recommendations.

Decision makers should consider that tests are commonly combined in diagnostic sequences in clinical practice. There may be opportunities to review current practice in the Victorian public system given the large volume of procedures being performed.

Important note:

The information contained in this report is a synthesis of the best available evidence located at the time the searches were completed.

Abbreviations

3D	three-dimensional
AAGL	American Association of Gynecologic Laparoscopists
ACOG	American College of Obstetricians and Gynecologists
AGREE	Appraisal of Guidelines for Research and Evaluation
AMSTAR	Assessment of Multiple Systematic Reviews
AUB	abnormal uterine bleeding
CI	confidence interval
CPG	clinical practice guideline
D&C	dilation and curettage
EB	endometrial biopsy
EEC	endometrial echo complex
GDG	guideline development group
HMB	heavy menstrual bleeding
HTA	health technology assessment
KPSC	Kaiser Permanente Southern California
LR	likelihood ratios
NICE	National Institute for Health and Care Excellence
NPV	negative predictive value
PMB	postmenopausal bleeding
PPV	positive predictive value
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomised controlled trial
SD	standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
SHG	sonohysterography
SOGC	Society of Obstetricians and Gynaecologists of Canada
SR	systematic review
TVUS	transvaginal ultrasound

1. Context and Policy Issues

Abnormal uterine bleeding (AUB), defined as any variation from the normal menstrual cycle, includes changes in the regularity and frequency of menses, the duration of flow or the amount of blood loss. AUB is differentiated as heavy menstrual bleeding (HMB), heavy and prolonged menstrual bleeding, intermenstrual bleeding and postmenopausal bleeding (PMB) based on the volume, regularity, frequency, duration, chronicity and timing of menses in relation to reproductive status (Fraser et al. 2011). During a normal menstrual period, up to 80 mL of blood and mucosal tissue is shed from the inner lining (the endometrium) of the uterus through the vagina over three to six days. AUB most commonly presents as HMB where the excessive menstrual blood loss interferes with a woman's physical, emotional, social and material quality of life. Heavy and prolonged menstrual bleeding is less common than HMB and occurs when menstrual blood loss continues for longer than eight days. Intermenstrual bleeding involves short, light episodes of bleeding between normal menstrual periods. PMB occurs more than a year after the last natural menstrual period and is commonly associated with structural uterine pathology or malignancy (Fraser et al. 2011). Approximately 10 per cent of PMB cases are associated with endometrial cancer, and 20 to 40 per cent are associated with benign endometrial polyps (Van Hanegem et al. 2011).

The objective prevalence of AUB ranges from 11 to 13 per cent in the general population and increases with age, reaching 24 per cent in women aged 36 to 40 years (Marret et al. 2010). Objective measures only capture one of the symptoms experienced by women with AUB, whereas self-reported measures consider the overall impact of AUB on quality of life, resulting in higher prevalence rates (Fraser et al. 2009). While rarely life-threatening, AUB may require surgical intervention and can have a significant impact on a woman's quality of life, productivity and use of healthcare resources (Singh et al. 2013). It has been estimated that women with HMB work 3.6 fewer weeks per year and lose an estimated $1,692 annually in wages, compared with other women in the general workforce (Association of Reproductive Health Professionals 2008).

History and physical examination are used to distinguish anovulatory from ovulatory bleeding, to identify anatomic causes such as cervical pathology or endometrial polyps and to direct further investigation and management (Singh et al. 2013). Ovulatory AUB is usually regular and is often associated with premenstrual symptoms and dysmenorrhoea. Anovulatory bleeding, which is more common, frequently occurs near menarche and perimenopause, is often irregular, heavy and prolonged and is more commonly associated with endometrial hyperplasia and cancer. The aetiology of AUB is classified into nine categories within the PALM-COEIN (Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia-Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic, Not yet specified) classification system (Munro 2013; Singh et al. 2013). The PALM side of the classification refers to structural causes that may be evaluated and diagnosed using

imaging, biopsy or both; the COEIN side accounts for underlying medical conditions that may result in AUB (Singh et al. 2013).

Imaging, endometrial biopsy (EB) or both may be used to further investigate AUB when structural causes are suspected, when there is a risk of malignancy, or when conservative management has failed to improve symptoms (Singh et al. 2013). Imaging techniques include transvaginal ultrasound (TVUS), using transvaginal sonography or saline infusion sonography, and hysteroscopy. Transvaginal sonography, in which the ultrasound probe is placed in the vagina, allows detailed assessment of the uterus and endometrium to assist in diagnosing endometrial polyps, adenomyosis, leiomyomas, uterine anomalies and endometrial thickening associated with hyperplasia and malignancy (Singh et al. 2013). In saline infusion sonography, also known as sonohysterography (SHG), saline is infused into the uterine cavity during abdominal sonography to improve the visualisation of uterine polyps and fibroids (Singh et al. 2013). SHG performed with three-dimensional (3D) ultrasound may provide more information about the location of abnormalities than two-dimensional scanning (Katsetos et al. 2013). During hysteroscopy an endoscope is introduced through the cervix into the uterine cavity, which is insufflated with an electrolyte solution to provide visualisation of the uterine cavity (Singh et al. 2013).

EB can be performed with (directed biopsy) or without (blind biopsy) a hysteroscope using dilation and curettage (D&C) or a Pipelle® Endometrial Suction Curette (CooperSurgical, Inc., Trumbull, CT, USA). In D&C, the cervix is dilated and a curette is used to remove tissue from the uterus for histological assessment. The Pipelle® biopsy uses a syringe-like device to create a vacuum that removes tissue from the endometrial wall. Office-based EB can be performed with various other sampling devices including the Vabra® aspirator (Berkeley Medevices, Inc., Richmond, CA, USA) and the Tao Brush™ (Cook Medical, Bloomington, IN, USA) (Van Hanegem et al. 2011).

Hysteroscopy is superior to EB, D&C and TVUS for identifying structural lesions such as polyps and leiomyomas, but is inadequate for diagnosing hyperplasia and carcinoma (Munro 2014). Hysteroscopy with directed sampling is recommended for obtaining a biopsy of focal lesions found on ultrasound (Singh et al. 2013). Diagnostic hysteroscopy can be performed in an office or clinic with or without minor anaesthesia, or in the operating room with regional or general anaesthesia (Singh et al. 2013). If abnormalities are found, the use of an operative hysteroscope with a channel allows the introduction of specialised instruments into the uterine cavity to ablate the endometrium and remove polyps or fibroids. The risks associated with hysteroscopy include perforation of the uterus, infection, cervical lacerations, creation of false passages and fluid overload (Singh et al. 2013).

In Australia, the self-reported prevalence of AUB is 21 per cent (Fraser et al. 2009). Between 2012 and 2013, approximately 31,110 women were diagnosed with excessive, frequent or irregular menstruation and 11,687 women had abnormal uterine or vaginal bleeding (Australian Government Department of Human Servcies 2015). Over the same

time period, diagnostic hysteroscopy or D&C accounted for over 38,000 same-day hospital separations; approximately 18,061 (46%) were in public hospitals and 20,883 (54%) were in private hospitals (AIHW 2015). Of the 16,756 hysteroscopic procedures performed in Victoria and Tasmania between 2013 and 2014, approximately 47 hysteroscopies with biopsy were performed in a specialist practice and 11,489 hysteroscopies with dilation of the cervix or EB were performed in the operating theatre of a hospital; the remainder were conducted for therapeutic purposes (Australian Government Department of Human Servcies 2015).

Hysteroscopy is considered the gold standard for evaluating the uterine cavity and is often used without endometrial sampling as a reference standard. However, studies have shown that TVUS can reliably exclude cancer without the need for biopsy in some women with PMB, guide the selection of a biopsy technique and detect endometrial cancer with the same sensitivity as EB (Munro 2014).

The objective of this rapid systematic review (SR) is to facilitate the appropriate use of hysteroscopy for the diagnosis of AUB by providing a synthesis of the evidence on the following research questions.

Research questions

1. Is hysteroscopy (with or without D&C) an effective diagnostic procedure for AUB?
2. Are there alternative diagnostic procedures for AUB that are superior to hysteroscopy (with or without D&C) with respect to effectiveness, safety and quality?
3. For the alternative diagnostic procedures that are superior to hysteroscopy, if any, are there any limitations in their application with respect to patient characteristics or conditions?

2. Methodology

Literature review

Literature search strategy

A limited systematic search of MEDLINE, EMBASE, *The Cochrane Library*, the NHS Centre for Reviews and Dissemination databases and the websites of international health technology assessment (HTA) agencies and clinical practice guideline (CPG) clearinghouses was conducted to identify relevant research published in English from January 2005 (January 2009 for guidelines) to January 2015. A focused internet search was also conducted to identify grey literature. Filters were applied to limit the retrieval to SRs, HTAs, meta-analyses, guidelines and randomised controlled trials (RCTs). Details of the search strategies are provided in Appendix A.

Study selection criteria and methods

One reviewer screened all citations and selected studies. On initial screening, titles and abstracts were reviewed for relevance. Full-text publications were retrieved and assessed for inclusion based on the criteria in Table 1. Only studies conducted in Australia, Canada, Japan, New Zealand, the United States and European countries (except for those with transitional economies) were included for review. These countries, which have developed economies as defined by the United Nations, are likely to have populations whose health status, cultural norms, access to health care and disease burden are comparable to those in Australia (United Nations 2009).

Table 1: Study selection criteria

Population	Women of any age with abnormal uterine bleeding
Intervention	Hysteroscopy with or without dilation and curettage
Comparator	Any alternative diagnostic procedure including, but not limited to, endometrial biopsy, transvaginal ultrasound and sonohysterography
Outcomes	Sensitivity, specificity, change in patient management or outcomes, safety, patient experience
Study design	HTA, SR, meta-analysis and test accuracy studies with a reference standard Evidence-based CPGs that provide criteria for or recommendations on hysteroscopy for diagnosing an abnormal uterine bleeding

CPG: clinical practice guideline; HTA: health technology assessment; SR: systematic review

Exclusion criteria

Studies were excluded if they: were included in a selected overview of reviews or SR; did not meet the selection criteria; were based on a CPG published prior to 2009; had incomplete or inappropriate methods; or were an ineligible study design. RCTs and non-randomised comparative studies published prior to the literature search end date reported in the most recent, eligible SR were also excluded.

Data extraction and analysis

One reviewer extracted data on patient characteristics, sensitivity, specificity, clinical benefits and harms and guideline recommendations on hysteroscopy and alternative diagnostic procedures for AUB.

Critical appraisal of included studies

One reviewer evaluated the methodological quality of the included studies. SRs were evaluated using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) checklist (Shea et al. 2007), while the Appraisal of Guidelines for Research and Evaluation II (AGREE II) instrument was used to appraise CPGs (Brouwers et al. 2010). The domains assessed by AMSTAR include design, study selection and data extraction, literature searching, study characteristics, quality assessment, methods used to combine findings, publication bias and conflict of interest. The domains assessed by AGREE II include scope and purpose, stakeholder involvement, rigour of development, clarity and presentation, applicability and editorial independence. RCTs and non-randomised comparative studies were evaluated using an instrument by Downs and Black (1998) that was modified to include the source of funding. Primary study evidence was assessed with regard to method of randomisation, concealment of randomisation, degree of blinding, use of intention-to-treat analysis and description of dropouts and withdrawals. Instead of calculating numeric scores, the strengths and weaknesses were described narratively for each study. The evidence presented in the selected studies was classified, where possible, using the levels of evidence defined by the National Health and Medical Research Council (Merlin et al. 2009) (Appendix B).

Data analysis

Study design, quantity of evidence, heterogeneity of interventions and populations and timelines prevented formal meta-analysis. Study characteristics, quality assessment and results were summarised narratively in relation to the research questions.

Expert opinion

Two surgeons from Melbourne, Victoria who specialise in obstetrics and gynaecology were identified by the Victorian Government Department of Health. The following set of three questions, developed in consultation with the Victorian Government Department of Health, was emailed to each surgeon.

1. Is hysteroscopy (with or without D&C) an effective diagnostic procedure for AUB?
2. Are there alternative diagnostic procedures for AUB that are superior to hysteroscopy (with or without D&C) with respect to effectiveness, safety, and quality?

3. For the alternative diagnostic procedures that are superior to hysteroscopy, if any, are there any limitations in their application with respect to patient characteristics or conditions?

Responses were de-identified, grouped into themes and reported narratively.

3. Studies Included in the Review

Literature search results

The literature search yielded 169 citations. Upon screening titles and abstracts, 13 potentially relevant articles were retrieved for full-text review. Reviewing references of studies and searching of grey literature identified seven additional potentially relevant reports. Of the 20 potentially relevant reports, two were included in an overview of SRs, three did not meet the study selection criteria, one was based on an outdated guideline and seven were an ineligible study design. Seven studies were included in this review (AAGL 2012; Katsetos et al. 2013; Munro 2013; Munro 2014; Singh et al. 2013; University of Texas 2012; Van Hanegem et al. 2011). The study selection process is outlined in Appendix A (Figure A.1) and the excluded studies are listed in Appendix C.

Description of studies

Evidence regarding the effectiveness of hysteroscopy as a diagnostic procedure for AUB was derived from four CPGs (Munro 2013; Munro 2014; Singh et al. 2013; University of Texas 2012) and an overview of SRs and CPGs (Van Hanegem et al. 2011). The effectiveness, safety and quality of alternative diagnostic procedures for investigating AUB were reported in four CPGs (AAGL 2012; Munro 2014; Singh et al. 2013; University of Texas 2012), an overview of SRs and CPGs (Van Hanegem et al. 2011) and a randomised, crossover diagnostic cohort study (Katsetos et al. 2013). The limitations associated with alternative diagnostic procedures for investigating AUB were identified from five CPGs (AAGL 2012; Munro 2013; Munro 2014; Singh et al. 2013; University of Texas 2012), an overview of SRs (Van Hanegem et al. 2011) and a randomised, crossover diagnostic cohort study (Katsetos et al. 2013).

Clinical practice guidelines

The recommendation and evidence grading categories used in the CPGs are summarised in Appendix D (Table D.1).

Kaiser Permanente's Southern California AUB Working Group provided an update of recommendations published in 2005 on the investigation and management of women with PMB (Munro 2014). The recommendations were formulated based on the results of a SR of evidence published since January 2005, which was graded for quality based on criteria by the United States Preventive Services Task Force.

The Kaiser Permanente AUB Working Group also updated evidence-based guidelines to assist healthcare professionals in investigating and managing non-pregnant women with acute uterine bleeding who require immediate intervention. The guideline was based on a rigorous SR of evidence published since January 2005 (Munro 2013).

The Society of Obstetricians and Gynaecologists of Canada (SOGC) provided evidence-based recommendations for the diagnosis and management of AUB among

premenopausal women. The guideline development group (GDG) formulated recommendations based on a SR of evidence published up to 2013, which was graded for quality as described in the Report of the Canadian Task Force on Preventive Health Care (Singh et al. 2013).

The American Association of Gynecologic Laparoscopists (AAGL) developed evidence-based recommendations to assist clinicians in diagnosing and managing endometrial polyps. Recommendations were based on a SR of evidence published up to 2010, with quality ratings based on the criteria outlined by the United States Preventive Services Task Force (AAGL 2012).

The University of Texas in the United States published a national guideline on the evaluation and management of HMB in primary care that included evaluation, diagnosis, medical and pharmacological management, referral indications and patient educational interventions. The recommendations were formulated based on a SR of the evidence, which was graded for quality using the United States Preventive Services Task Force criteria (University of Texas 2012).

Overview of systematic reviews and CPGs

An overview of SRs and CPGs (level I evidence), containing nine SRs involving 15,454 participants and five CPGs compared the diagnostic accuracy of TVUS, EB, SHG and hysteroscopy in evaluating the endometrium in women with PMB (Van Hanegem et al. 2011) (Appendix D, Table D.4). Of the included SRs, four reported on TVUS, two on EB, one on SHG and two on hysteroscopy. Two of the CPGs were from the United States and three were from Europe. The outcomes reported included the accuracy with which endometrial cancer and hyperplasia were diagnosed, sensitivity, specificity, likelihood ratios and the pre-test probability of endometrial cancer or hyperplasia.

Randomised, crossover diagnostic cohort study

Katsetos et al. (2012) (level II diagnostic evidence) compared 3D SHG with outpatient hysteroscopy with respect to diagnostic accuracy, procedure time and patient discomfort in a prospective, randomised, crossover diagnostic cohort study conducted at a teaching hospital in London (Katsetos et al. 2013) (Appendix D, Table D.4). The study population included 44 women, ranging in age from 26 to 63 years, who had symptoms of AUB for an average of 14.8 months. Patients were randomly assigned to either hysteroscopy followed by SHG or SHG followed by hysteroscopy.

Appraisal of study quality

Summaries of the appraisals of the CPGs, overview of SRs and CPGs and the randomised, crossover diagnostic study are provided in Appendix D (Tables D.2 and D.5).

Clinical practice guidelines

Kaiser Permanente's guidelines on the investigation of AUB in postmenopausal women and acute uterine bleeding in non-pregnant women both provided updates of recommendations published in 2005 (Munro 2013; Munro 2014). Relevant literature, published between 2005 and 2012, was identified by searching MEDLINE and the Cochrane Database of Systematic Reviews. The websites of the American College of Obstetricians and Gynecologists (ACOG), the SOGC, the New Zealand Guidelines Group, the National Institute for Health and Care Excellence and the Geneva Foundation for Medical Education and Research were also searched (Munro 2013; Munro 2014). While the GDG met to review the methods of guideline development, the method by which the evidence was selected for inclusion was not reported. Recommendations were formulated through expert and formal consensus and key action items were easily identified, with explicit links between the evidence and the recommendations. The final recommendations were reviewed by all GDG members and approved by regional chiefs. However, the CPGs did not report seeking preferences from the target population, review criteria for monitoring or audit, the guideline update procedure, implementation strategies or sources of funding (Munro 2013; Munro 2014).

The SOGC developed evidence-based guidelines for the diagnosis and management of AUB among premenopausal women by systematically searching MEDLINE and *The Cochrane Library* for evidence published from 1999 to 2013 (Singh et al. 2013). Grey literature was also identified by searching the websites of HTA agencies, CPG collections, relevant professional societies and clinical trial registries. However, the methods by which evidence was selected and recommendations were formulated were not reported. The recommendations were explicitly linked to supporting evidence, but the guideline did not report: seeking the preferences of the target population; criteria for monitoring and audit; the guideline update procedure; barriers or facilitators to implementation; the cost of implementing the guidelines; funding sources; or conflicts of interest.

The objective of the AAGL guideline was to provide clinicians with evidence-based information about the management of endometrial polyps (AAGL 2012). A GDG comprising members of the AAGL with expertise in minimally invasive gynaecology and laparoscopy developed the guideline. Literature published from 1951 to 2010 was identified by systematically searching electronic databases. The methods used to select studies and formulate recommendations were not reported, but key recommendations were easily identifiable and were explicitly linked to supporting evidence. The guideline failed to report seeking the preferences of the target population, barriers to implementation, resource implications or criteria for monitoring and audit. Several members of the GDG reported some financial interest or affiliation with corporations, but funding sources and conflicts of interest were not reported.

The University of Texas published a national guideline on the evaluation and management of HMB in primary care based on evidence identified by systematically

reviewing literature published between 2007 and 2012 (University of Texas 2012). Recommendations were formulated through expert and informal consensus, were easily identifiable and linked to supporting evidence and took into consideration health benefits and risks. The guideline was validated through internal and external review prior to publication and included a clinical algorithm to facilitate implementation. These guidelines did not report the methods used to select evidence for inclusion, the views and preferences of the target population, barriers to implementation, resource implications, criteria for monitoring and audit, financial disclosures or conflicts of interest.

Overview of SRs and CPGs

An overview of SRs and CPGs compared the diagnostic accuracy of TVUS, EB, SHG and hysteroscopy for evaluating the endometrium in women with PMB (Van Hanegem et al. 2011). Evidence was identified by systematically searching the literature for studies published between 1965 and 2010. A search was also conducted for national and international guidelines, but evidence may have been missed as only two electronic sources were searched. Two reviewers independently selected studies based on predefined inclusion criteria, and a list of excluded studies was available from the author. Study quality was considered in formulating the results and conclusions. It was unclear whether data extraction and quality assessment of the SRs were performed in duplicate, or whether the guidelines were assessed for quality. The authors reported no conflicts of interest, but the funding source was not stated.

Randomised, crossover diagnostic cohort study

The objectives, patient characteristics, interventions, outcomes and findings were clearly described in the study by Katsetos et al. (2012). Limited patient characteristics were provided, although the study design minimised the likelihood of statistically significant differences in baseline characteristics between groups. The internal validity of the study was sound as all women with AUB requiring investigation were included for study. Patients were randomly assigned to hysteroscopy or SHG first, followed by sonography for group 1 or hysteroscopy for group 2. Patients were allocated to the two groups based on assignments provided in sealed, opaque envelopes that were opened upon recruitment. Investigators were blinded to the study results, and patient drop-outs were reported. Adverse events, funding source and conflicts of interest were not reported.

4. Literature Review Results

Effectiveness of diagnostic hysteroscopy for AUB

Evidence was derived from four CPGs (Munro 2013; Munro 2014; Singh et al. 2013; University of Texas 2012) and an overview of SRs and CPGs (Van Hanegem et al. 2011) (Table 2).

Clinical practice guidelines

Kaiser Permanente's guideline recommended that women with persistent, spontaneous PMB undergo office-based contrast sonography or hysteroscopy, or both, to evaluate the endometrial cavity for focal lesions (Munro 2014) (Appendix D, Table D.3). This approach is necessary even when EB is satisfactory and there is no evidence of hyperplasia, regardless of the thickness of the endometrial echo complex (EEC) (a measure of endometrial wall thickness). Hysteroscopy can be used to investigate PMB in women suspected of having cancer (Munro 2014).

Another CPG by Kaiser Permanente recommended that hysteroscopy accompany D&C in the evaluation or treatment of AUB in non-pregnant women (Munro 2013). D&C should be reserved for patients who are inappropriate for, unresponsive to or contraindicated from using medical therapy.

The SOGC guideline recommended that SHG and diagnostic hysteroscopy be used to diagnose and characterise discrete intrauterine abnormalities such as submucosal fibroids (Singh et al. 2013). Focal lesions of the endometrium that require biopsy should be managed through hysteroscopically guided evaluation in premenopausal women with AUB.

A guideline by the University of Texas recommended that women with HMB be referred for diagnostic hysteroscopy to determine the location of a fibroid or the nature of an abnormality only when ultrasound results are inconclusive (University of Texas 2012).

Overview of SRs and CPGs

An overview of SRs and CPGs (level I evidence) by Van Hanegem et al. (2011) found that hysteroscopy was highly accurate and useful in diagnosing rather than excluding cancer according to two SRs involving 2,254 women with PMB (Clark et al. 2002; Van Dongen et al. 2007) (Table 2) (Appendix D, Table D.6). The SR by Clark et al. (2002), hysteroscopy was reported to have a sensitivity of 87 per cent, a specificity of 99 per cent, a pre-test probability of 4 per cent and a post-test probability of 72 per cent (95% confidence interval [CI] 67.0% to 76.6%). Van Dongen at al. (2007) reported a sensitivity of 96 per cent, a specificity of 90 per cent, a pre-test probability of 61 per cent and a post-test probability of 93 per cent (95% CI 88.0% to 95.0%) for detecting abnormalities in the uterine cavity.

Table 2: Summary of evidence on the effectiveness of diagnostic hysteroscopy

Intervention	Evidence Statement/Recommendation
Effectiveness of hysteroscopy	PMB • Women with persistent PMB should undergo office-based contrast sonography or hysteroscopy, or both, to evaluate the endometrial cavity for focal lesions. [1 CPG] • Hysteroscopy is not contraindicated in PMB cases suggestive of cancer. [1 CPG] AUB • Hysteroscopy should accompany D&C in the evaluation of AUB in non-pregnant women who are inappropriate for, unresponsive to or contraindicated from using medical therapy. [1 CPG] • SHG and diagnostic hysteroscopy should be used to diagnose and characterise discrete intrauterine abnormalities such as fibroids in premenopausal women with AUB. [1 CPG] • Focal lesions that require biopsy should be managed through hysteroscopically guided evaluation in premenopausal women with AUB. [1 CPG] HMB • Diagnostic hysteroscopy should only be used when ultrasound results are inconclusive in order to determine the location of a fibroid or the nature of an abnormality in women with HMB. [1 CPG]
Limitations in the effectiveness of hysteroscopy	• Hysteroscopy is accurate and useful in diagnosing rather than excluding cancer in PMB. [1 Overview of SRs] • Sensitivity of 86% and specificity of 99% for detecting endometrial cancer or hyperplasia. [1 Overview of SRs] • Sensitivity of 96% and specificity of 90% for detecting uterine cavity abnormalities in postmenopausal women. [1 Overview of SRs]

AUB: abnormal uterine bleeding; CPG: clinical practice guideline; D&C: dilation and curettage; HMB: heavy menstrual bleeding; PMB: postmenstrual bleeding; SHG: sonohysterography; SR: systematic review

Effectiveness, safety and quality of alternative diagnostic procedures for AUB

The effectiveness, safety and quality of alternative diagnostic procedures for investigating AUB were reported in four CPGs (AAGL 2012; Munro 2014; Singh et al. 2013; University of Texas 2012), an overview of SRs and CPGs (Van Hanegem et al. 2011) and a randomised, crossover diagnostic cohort study (Katsetos et al. 2013) (Table 3).

Clinical practice guidelines

Kaiser Permanente's guideline recommended that women with spontaneous PMB be primarily evaluated with either EB or TVUS to measure the thickness of the EEC (Munro 2014) (Appendix D, Table D.3). Women who undergo TVUS and have an EEC of more than 4 mm, localised thickening or an indistinct or nonvisible EEC should undergo EB as a next step (Munro 2014).

Guidelines by the SOGC and the University of Texas also recommended that TVUS be used as the first-line imaging modality for AUB in premenopausal women and women with HMB, respectively (Singh et al. 2013; University of Texas 2012). EB should be considered for women with AUB who are older than 40 years and have not responded

to medical therapy, as well as younger women with risk factors for endometrial cancer (Singh et al. 2013).

The AAGL suggested that TVUS provides reliable information for detecting endometrial polyps and should be the investigation of choice, where available. TVUS provides the most reliable results during the proliferative phase of the menstrual cycle. Compared with hysteroscopically guided biopsy, TVUS has a sensitivity of 19 to 96 per cent, a specificity of 53 to 100 per cent, a positive predictive value of 75 to 100 per cent and a negative predictive value of 87 to 97 per cent for diagnosing endometrial polyps. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of TVUS are 86 per cent, 94 per cent, 91 per cent and 90 per cent, respectively. Power Doppler increases the sensitivity of TVUS to 95 per cent in patients with symptoms. The specificity and NPV may be increased to 95 per cent and 94 per cent, respectively, when colour-flow Doppler is added to grey-scale TVUS.

According to guidelines by the AAGL, SHG has a sensitivity ranging from 58 to 100 per cent, a specificity ranging from 35 to 100 per cent, a PPV range of 70 to 100 per cent and a NPV range of 83 to 100 per cent, compared with hysteroscopically guided biopsy. Adding intrauterine contrast to sonography (with or without 3D imaging) improves its capacity for detecting endometrial polyps. Several studies reported no detectable difference between SHG and hysteroscopy in diagnosing endometrial polyps. The advantages of SHG include assessment of both the uterine cavity and other pelvic structures and the potential to assess tubal patency. The disadvantages include an inability to determine final endometrial disease, a longer learning curve than for TVUS and greater patient discomfort. Studies with non-contrast 3D TVUS showed limited improvement in diagnostic ability compared with two-dimensional TVUS (sensitivity of 100%, specificity of 71% to 99%, PPV of 89% to 99% and NPV of 100%). Adding saline contrast solution to 3D sonography increased the specificity to 88 to 99 per cent and the PPV to 97 to 100 per cent for endometrial polyps, compared with 3D ultrasonography (sensitivity of 92% to 95% and NPV of 97%) (AAGL 2012).

Overview of systematic reviews and CPGs

An overview of SRs and CPGs (level I evidence) compared the diagnostic accuracy of TVUS, EB, SHG and hysteroscopy for evaluating the endometrium in women with PMB (Van Hanegem et al. 2011) (Table 3) (Appendix D, Table D.6). TVUS was accurate in excluding endometrial cancer at a cut-off value of 3 mm for endometrial thickness, based on four SRs involving 11,952 women with PMB and two CPGs. TVUS had a sensitivity of 95 per cent and specificity of 47 per cent at 4 mm of endometrial thickness; post-test probability for a negative test was one per cent. TVUS had a sensitivity of 98 per cent and a specificity of 36 per cent at 3 mm or less of endometrial thickness: the likelihood ratio for a negative test result was 0.06. A cut-off value of 3 mm or less for endometrial thickness reduced a pre-test probability of 10 per cent to 0.7 per cent post-test probability; therefore a cut-off of 3 mm or less for endometrial thickness was justified. TVUS was recommended as a first-line diagnostic evaluation for AUB in

postmenopausal women based on its high sensitivity and non-invasive character, although cut-off values ranged from 3 mm to 5 mm for endometrial thickness. Either TVUS or outpatient EB was recommended as the first step in assessing women with PMB, based on their similar sensitivities and cost-effectiveness for detecting endometrial carcinoma (Van Hanegem et al. 2011).

Table 3: Summary of evidence on the effectiveness, safety and quality of alternative diagnostic tests

Intervention	Evidence Statement/Recommendation
SHG	• SHG has a sensitivity of 58% to 100% and a specificity of 35% to 100%, compared with hysteroscopically guided biopsy. There was no statistically significant difference between SHG and diagnostic hysteroscopy in ability to detect endometrial polyps. [1 CPG] • Adding saline contrast to 3D sonography increases specificity from 88% to 99% for endometrial polyps, compared with 3D ultrasonography (sensitivity 92.0% to 95.0%). [1 CPG] • SHG may be used to distinguish between a diffusely thickened endometrium, for which dilation and curettage could be the next step, and a focal lesion, for which hysteroscopy would be performed. [1 Overview of SRs] • Sensitivity of SHG was 72% for diagnosing polyps, 93% for detecting fibroids and 100% for diagnosing an abnormal endometrium, compared with hysteroscopy. [1 randomised, crossover diagnostic cohort study] • Patient discomfort caused by fluid leakage or pain during examination. [1 CPG, 1 randomised, crossover diagnostic cohort study]
TVUS	• Premenopausal and postmenopausal women should undergo TVUS as a first-line imaging procedure for AUB. [1 CPG, 1 Overview of SRs] • Diagnostic test of choice for detecting endometrial polyps. [1CPG] • Sensitivity of 19% to 96% and specificity of 53% to 94%; for diagnosing endometrial polyps, compared with hysteroscopy with guided biopsy. [1 CPG] • Sensitivity of 98% and specificity of 35% at ≤3 mm endometrial thickness, with a likelihood ratio for a negative test result of 0.06; a cut off of ≤3 mm in endometrial thickness is justified. [1 Overview of SRs]
TVUS or EB	• Women with spontaneous PMB should be primarily evaluated with either EB or TVUS to measure the thickness of the EEC. [1 CPG, 1 Overview of SRs]
EB	• Women who undergo TVUS and have an EEC >4 mm, localised thickening or an indistinct EEC should undergo EB. [1 CPG] • Office EB should be the first-line assessment for women older than 40 years who have not responded to medical therapy and women with risk factors for endometrial cancer. [1 CPG, 1 Overview of SRs] • Sensitivity of 91.9% and specificity of 99.7% with different diagnostic devices. [1 Overview of SRs]

3D: three-dimensional; AUB: abnormal uterine bleeding; CPG: clinical practice guideline; EB: endometrial biopsy; EEC: endometrial echo complex; PMB: postmenstrual bleeding; SHG: sonohysterography; SR: systematic review; TVUS: transvaginal ultrasound

EB was moderately accurate for diagnosing pre-malignant endometrial pathology and highly sensitive for diagnosing endometrial carcinoma, based on two SRs involving 980 women with PMB (Van Hanegem et al. 2011). According to Clark et al. (2001), EB had a sensitivity of 91.9 per cent and a specificity of 99.7 per cent with various diagnostic devices. The pre-test probability of 14 per cent was increased to a post-test probability for a positive result of 67 per cent (95% CI 42.3% to 83.9%).

SHG was reported to have a sensitivity of 95 per cent and a specificity of 88 per cent for detecting abnormalities of the uterus in premenopausal and postmenopausal women. It was suggested that SHG be used to distinguish between a diffusely thickened endometrium, for which D&C could be the next step, and a focal lesion, for which a hysteroscopy is the next step (Van Hanegem et al. 2011).

Randomised, crossover diagnostic cohort study

Hysteroscopy and SHG were comparable in their ability to diagnose intracavity lesions, pain rating and procedure time in women with AUB (level II diagnostic evidence) (Katsetos et al. 2013) (Appendix D, Table D.6). Intracavity lesions were noted in 26 of 44 (59%) women presenting with AUB. Three-dimensional SHG missed three uterine polyps that were detected by hysteroscopy. In all cases, the uterus was enlarged with intramural and subserous fibroids. In comparison with hysteroscopy, the sensitivity of SHG was 72 per cent for diagnosing polyps, 93 per cent for detecting fibroids and 100 per cent for diagnosing an abnormal endometrium. The specificity for each was 100 per cent (Katsetos et al. 2013). The mean pain score for patients undergoing hysteroscopy was 2.8 (standard deviation [SD] 2.65, 95% CI 2.0 to 3.6), while the score for patients having SHG ranged from 0 to 9.2 (SD 2.63, 95% CI 1.8 to 3.4; P=0.55). Despite the pain being comparable in both procedures, there was a marked patient preference for SHG over hysteroscopy (68% versus 15%) (Katsetos et al. 2013).

Limitations associated with alternative diagnostic procedures for AUB

The limitations associated with alternative diagnostic procedures for investigating AUB were identified from five CPGs (AAGL 2012; Munro 2013; Munro 2014; Singh et al. 2013; University of Texas 2012), an overview of SRs (Van Hanegem et al. 2011) and a randomised, crossover diagnostic cohort study (Katsetos et al. 2013) (Table 4) (Appendix D, Tables D.3 and D.6).

Clinical practice guidelines

Kaiser Permanente's guidelines recommended that women with spontaneous PMB who undergo TVUS and have an EEC of more than 4 mm, localised thickening or an indistinct or nonvisible EEC undergo EB as a next step (Munro 2014). Operating room-based D&C of women with PMB should only be performed when office-based EB is indicated but cannot be performed because of patient discomfort or technical reasons, or when EB is inconclusive and the results of TVUS or SHG are not reassuring (Munro 2014). Women experiencing AUB while receiving adjuvant tamoxifen therapy for breast cancer should undergo EB because TVUS is neither sensitive nor specific for neoplasia (Munro 2014). While EB is not considered mandatory for all instances of acute uterine bleeding, it should be considered when risk factors are present, such as chronic anovulation, prolonged exposure to unopposed oestrogens or tamoxifen, obesity or a family history of increased risk of endometrial neoplasia (Munro 2013). The SOGC

recommended that office-based EB replace D&C as the initial assessment of the endometrium for premenopausal women with AUB (Singh et al. 2013).

The AAGL recommended that blind D&C or biopsy not be used for diagnosing endometrial polyps. While blind D&C has a specificity and PPV of 100 per cent, it has a low sensitivity (8% to 46%) and a NPV of 7 to 58 per cent, compared with hysteroscopically guided biopsy (AAGL 2012).

The University of Texas guideline recommended that a biopsy be taken to exclude endometrial cancer or atypical hyperplasia when: there is persistent PMB or no definite cause of HMB; the woman is 35 years of age or older; or treatment was ineffective. Imaging should be undertaken when the uterus is palpable abdominally, the vaginal examination reveals a pelvic mass of uncertain origin or pharmaceutical treatment has failed. SHG is not recommended as a first-line diagnostic tool (University of Texas 2012).

Table 4: Summary of evidence on the limitations associated with alternative diagnostic tests

Intervention	Evidence Statement/Recommendation
TVUS	• Women with spontaneous PMB who undergo TVUS and have an EEC >4 mm, localised thickening or an indistinct or nonvisible EEC should undergo EB as a next step. [1 CPG] • Women experiencing AUB while receiving adjuvant tamoxifen therapy for breast cancer should undergo EB because TVUS is neither sensitive nor specific for neoplasia. [1 CPG] • Imaging should be undertaken when the uterus is palpable abdominally, the vaginal examination reveals a pelvic mass of uncertain origin or pharmaceutical treatment has failed. [1 CPG] • TVUS is recommended when EB is deemed insufficient. [1 Overview of SRs]
SHG	• SHG should not be used as a first-line diagnostic tool. [1 CPG]
EB	• EB should be used only when the endometrial thickness is >5 mm, possibly together with SHG, to distinguish between diffuse and focal pathology. [1 Overview of SRs] • EB should be considered in cases of chronic anovulation, prolonged exposure to unopposed oestrogen or tamoxifen, obesity or a family history of increased risk of endometrial neoplasia. [1 CPG] • EB should be undertaken to exclude endometrial cancer or atypical hyperplasia when: there is persistent PMB or no definite cause of HMB; the woman is 35 years of age or older; or treatment has failed or is ineffective. [1 CPG]
D&C	• Operating room based D&C of women with PMB should only be performed when office-based EB is indicated but cannot be performed because of patient discomfort or technical reasons, or when EB is inconclusive and the results of TVUS or SHG are not reassuring. [1 CPG] • Office-based EB should replace D&C as the first-line endometrial assessment for premenopausal women with AUB. [1 CPG] • Blind D&C or biopsy should not be used to diagnose endometrial polyps as it has a low sensitivity compared with hysteroscopically guided biopsy. [1 CPG]

AUB: abnormal uterine bleeding; CPG: clinical practice guideline; D&C: dilation and curettage; EB: endometrial biopsy; EEC: endometrial echo complex; HMB: heavy menstrual bleeding; PMB: postmenstrual bleeding; SHG: sonohysterography; SR: systematic review; TVUS: transvaginal ultrasound

Overview of systematic reviews and CPGs

The overview of SRs and CPGs (level I evidence) recommended EB, with a cut-off value for endometrial thickness of 5 mm, for evaluating the endometrium in women with PMB (Van Hanegem et al. 2011) (Table 4) (Appendix D, Table D.6). TVUS was recommended when EB was deemed insufficient (Van Hanegem et al. 2011).

Randomised, crossover diagnostic cohort study

Three-dimensional SHG missed three uterine polyps that were detected by hysteroscopy. In all cases, the uterus was enlarged with intramural and subserous fibroids (Katsetos et al. 2013) (Appendix D, Table D.6).

5. Expert Opinion

Responses were received from two surgeons specialising in obstetrics and gynaecology, each from Melbourne, Victoria, who were asked to provide their expert opinion on the three questions below.

Question 1: Is hysteroscopy (with or without D&C) an effective diagnostic procedure for AUB?

Hysteroscopy with endometrial sampling (by sharp curettage or directed biopsy) is the standard diagnostic procedure that forms part of the diagnostic assessment of AUB. There are two main types:

- Outpatient ambulatory hysteroscopy performed under cervical block in the clinic setting (no anaesthetic, fasting or analgesia required): this is a purely diagnostic procedure—endometrial sampling is not always possible.
- Diagnostic hysteroscopy performed under general anaesthesia with D&C and possible conversion to an operative procedure for removal of, for example, endometrial polyps or submucous fibroids.

Diagnostic hysteroscopy with D&C is a better procedure because it can provide tissue for histology and can be converted to an operative procedure when necessary. It is an effective procedure for AUB, particularly in older women when pathology is more likely to be present.

Question 2: Are there alternative diagnostic procedures for AUB that are superior to hysteroscopy (with or without D&C) with respect to effectiveness, safety and quality?

Two procedures should precede diagnostic hysteroscopy with D&C in the triage assessment of AUB:

- TVUS performed by an appropriately trained operator;
- Outpatient EB with a Pipelle® endometrial sampler or similar device.

Alternative procedures would be a tertiary-level SHG magnetic resonance imaging. Currently in Australia there is more experience with the former. While ultrasound does not give a histological result, it can indicate the likelihood of pathology, especially in an elderly patient who is a poor operative risk. In such a patient, if the endometrium is thin and there is no polyp present, the likelihood of endometrial cancer is low. The one drawback of ultrasound is the need to insert a catheter to instil the saline, which may be difficult in an elderly patient with a stenosed cervix. However, if the procedure is performed at a tertiary level hospital, it will be performed by a gynaecologically trained ultrasonologist.

Question 3: For the alternative diagnostic procedures that are superior to hysteroscopy, if any, are there any limitations in their application with respect to patient characteristics or conditions?

The gold standard remains diagnostic hysteroscopy with D&C. If ultrasound replaced hysteroscopy, it would have to be performed at a tertiary level hospital with an appropriately trained ultrasonologist.

The establishment of outpatient hysteroscopy may be limited by the availability of resources such as equipment and office space, appropriately skilled clinicians and nursing support staff.

6. Discussion

Findings

This rapid review summarised evidence regarding the effectiveness of diagnostic hysteroscopy for investigating AUB and the effectiveness, safety, quality and limitations of alternative diagnostic procedures.

Effectiveness of diagnostic hysteroscopy for AUB

Evidence regarding the effectiveness of hysteroscopy as a diagnostic procedure for AUB was derived from four CPGs (Munro 2013; Munro 2014; Singh et al. 2013; University of Texas 2012) and an overview of SRs and CPGs (Van Hanegem et al. 2011). Hysteroscopy was highly accurate and useful in diagnosing rather than excluding endometrial cancer according to two SRs involving 2,254 women with PMB (Clark et al. 2002; Van Dongen et al. 2007). Hysteroscopy has a sensitivity of 86 per cent and a specificity of 99 per cent for detecting endometrial cancer or hyperplasia (Clark et al. 2002). Hysteroscopy can also detect uterine cavity abnormalities in postmenopausal women with a sensitivity of 96 per cent and a specificity of 90 per cent (Van Dongen et al. 2007; Van Hanegem et al. 2011). In women with HMB, diagnostic hysteroscopy should only be used to determine the location of a fibroid or the nature of an abnormality when ultrasound results are inconclusive (Singh et al. 2013). Focal lesions that require biopsy should be managed through hysteroscopically guided evaluation (Singh et al. 2013). Hysteroscopy should accompany D&C in evaluating AUB in non-pregnant women who are inappropriate for, unresponsive to or contraindicated from using medical therapy (Munro 2013). Women with persistent PMB should undergo office-based contrast sonography and/or hysteroscopy to evaluate the endometrial cavity for focal lesions, even in cases suggestive of cancer (Munro 2014).

Expert opinion suggested that hysteroscopy with D&C is the standard diagnostic procedure for assessing AUB in Australia. Outpatient diagnostic hysteroscopy can be performed in a clinic setting under cervical block without the need for fasting or analgesia. Diagnostic hysteroscopy may also be performed in a hospital setting in combination with D&C under general anaesthesia for possible removal of endometrial polyps and submucous fibroids. This procedure is particularly effective in older women when pathology is likely to be present.

Effectiveness, safety and quality of alternative diagnostics

The effectiveness, safety and quality of alternative diagnostic procedures for investigating AUB were reported in four CPGs (AAGL 2012; Munro 2014; Singh et al. 2013; University of Texas 2012), an overview of SRs and CPGs (Van Hanegem et al. 2011) and a randomised, crossover diagnostic cohort study (Katsetos et al. 2013).

TVUS was recommended as the first-line imaging procedure for AUB in premenopausal and postmenopausal women (Singh et al. 2013; Van Hanegem et al. 2011) for measuring

endometrial thickness, and was the test of choice for detecting endometrial polyps (AAGL 2012). While TVUS had a reported sensitivity of 19 to 96 per cent and a specificity of 53 to 100 per cent for diagnosing endometrial polyps, compared with hysteroscopically guided biopsy, power Doppler increased its diagnostic capacity (AAGL 2012).

EB was moderately accurate for diagnosing pre-malignant endometrial pathology and was highly sensitive for diagnosing endometrial carcinoma in postmenopausal women (Van Hanegem et al. 2011). Office EB was recommended as the first-line assessment for women over 40 years of age who have not responded to medical therapy and for women who are at risk of endometrial cancer (Singh et al. 2013). EB was also recommended for women who have undergone TVUS and have an EEC of more than 4 mm, a localised thickening or an indistinct EEC (Munro 2014). EB had a sensitivity of 91.9 per cent and specificity of 99.7 per cent using various sampling devices (Clark et al. 2001).

SHG had a sensitivity of 58 to 100 per cent and a specificity of 35 to 100 per cent, compared with hysteroscopically guided biopsy (AAGL 2012). There was no significant difference between SHG and hysteroscopy in diagnosing endometrial polyps. Its advantages of SHG included the ability to assess the uterine cavity and other pelvic structures and to distinguish between a diffusely thickened endometrium and a focal lesion. The disadvantages included the inability to definitively determine the type of endometrial disease present and patient discomfort during the procedure (AAGL 2012; Katsetos et al. 2013). The sensitivity of SHG was 72 per cent for diagnosing polyps, 93 per cent for detecting fibroids and 100 per cent for diagnosing an abnormal endometrium, compared with hysteroscopy (Katsetos et al. 2013). The addition of saline contrast to 3D ultrasonography increased its specificity for detecting endometrial polyps (AAGL 2012).

Clinical experts recommended that TVUS, performed by an appropriately trained operator, and outpatient EB with a Pipelle® sampler or similar device precede hysteroscopy with D&C in the assessment of AUB. Alternative diagnostic procedures include SHG and magnetic resonance imaging, although SHG is more commonly performed in Australia than magnetic resonance imaging for this indication. While SHG does not provide tissue samples for histology, it does indicate the likelihood that pathology is present, which is particularly useful in elderly patients who are at higher risk of a poor operative outcome.

Limitations associated with alternative diagnostic procedures

The limitations associated with alternative diagnostic procedures for investigating AUB were identified from five CPGs (AAGL 2012; Munro 2013; Munro 2014; Singh et al. 2013; University of Texas 2012), an overview of SRs and CPGs (Van Hanegem et al. 2011) and a randomised, crossover diagnostic cohort study (Katsetos et al. 2013). EB should be conducted in postmenopausal women who undergo TVUS and have an EEC of more than 4 mm, localised thickening or an indistinct EEC (Munro 2014). Women experiencing AUB while receiving adjuvant tamoxifen therapy for breast cancer were also

advised to undergo EB because TVUS is neither sensitive nor specific for detecting neoplasia (Munro 2014). SHG was not recommended for first-line diagnostic assessment (University of Texas 2012). European CPGs recommended EB be used only when endometrial thickness is at least 5 mm, in possible combination with SHG, to distinguish between diffuse and focal pathology (Van Hanegem et al. 2011). EB was useful in cases of chronic anovulation, prolonged exposure to unopposed oestrogen or tamoxifen, obesity or a family history of increased risk for endometrial neoplasia (Munro 2013). Office EB should replace D&C as the first-line endometrial assessment for premenopausal women with AUB (Singh et al. 2013). Blind D&C or biopsy should not be used to diagnose endometrial polyps as it has a low sensitivity compared with hysteroscopically guided biopsy (AAGL 2012).

Expert opinion suggested that hysteroscopy with D&C is the gold standard diagnostic procedure for AUB in Australia. The establishment of outpatient hysteroscopy clinics may be limited by the availability of resources, including office space, equipment and appropriately skilled clinicians and nursing staff. If ultrasound replaced hysteroscopy, it would have to be performed in a tertiary level hospital by an appropriately trained ultrasonologists.

Limitations of the evidence

Evidence on the effectiveness of diagnostic hysteroscopy for AUB was derived from four CPGs (Munro 2013; Munro 2014; Singh et al. 2013; University of Texas 2012) and an overview of SRs and CPGs (Van Hanegem et al. 2011). There was potential for publication bias and missing information as neither the CPGs nor the overview cited a formal systematic search for grey literature; only two electronic literature sources were searched in the overview. There was potential for bias in the selection of evidence used to develop the recommendations as all four CPGs failed to report the method by which evidence was selected for inclusion (Munro 2013; Munro 2014; Singh et al. 2013; University of Texas 2012), and one CPG failed to report the methods used to formulate the recommendations (Singh et al. 2013). Recommendations regarding the use of diagnostic hysteroscopy may be difficult to implement and monitor because patient preferences were not sought in developing the guidelines, barriers to implementation were not discussed and monitoring and audit criteria were not reported (Singh et al. 2013; University of Texas 2012).

Four CPGs (AAGL 2012; Munro 2014; Singh et al. 2013; University of Texas 2012), an overview of SRs and CPGs (Van Hanegem et al. 2011) and a randomised, crossover diagnostic cohort study (Katsetos et al. 2013) provided information about the effectiveness, safety and quality of alternative diagnostic procedures for AUB. While diagnostic accuracy was reported for SHG, TVUS and EB (AAGL 2012; Katsetos et al. 2013; Van Hanegem et al. 2011), adverse events and complications were seldom reported. The quality of a test, in terms of patient preference was only reported in one randomised, crossover diagnostic cohort study (Katsetos et al. 2013). The overview of SRs (level I evidence) concluded that TVUS, EB, SHG and hysteroscopy were all

accurate in excluding or diagnosing endometrial cancer, but the sequence in which different procedures should be implemented could not be determined. None of the evidence sources considered implementing combinations or sequences of diagnostic procedures for assessing AUB.

The limitations associated with alternative diagnostic procedures for investigating AUB were identified from five CPGs (AAGL 2012; Munro 2013; Munro 2014; Singh et al. 2013; University of Texas 2012), an overview of SRs (Van Hanegem et al. 2011) and a randomised, crossover diagnostic cohort study (Katsetos et al. 2013). There was potential for selection bias and missing information regarding the limitations associated with diagnostic procedures for investigating AUB because most of the guidelines failed to report searching for grey literature or the methods used to select the evidence. Adverse events, complications and patient preferences were not reported in most of the evidence used to inform this research question, so the findings may not reflect all the limitations associated with these procedures.

This report was limited in that even after systematically searching the literature and contacting clinical experts, little information was found regarding the safety and limitations of alternative diagnostic procedures in terms of adverse events and patient-related factors. No relevant Australian CPGs were identified. The included CPGs were developed in the United States and Canada, and there may be inherent differences between the populations and healthcare contexts that the limit transferability of the recommendations. Information regarding the quality of alternative diagnostics in terms of patient-related factors was only reported in relation to pain and procedure length in one diagnostic cohort study that compared 3D SHG with hysteroscopy.

The evidence included in the review did not consider combination or sequential diagnostic procedures, which may be a limitation. In clinical practice, tests are commonly combined in sequences and disease probabilities are estimated by combining information from the history and physical examination, followed by additional diagnostic procedures (Cancer Australia 2011). While experts provided information regarding the setting, equipment, expertise and availability of alternative diagnostic procedures for AUB, information was not gathered on the adverse events or limitations of alternative diagnostic procedures with respect to patient characteristics or conditions.

7. Conclusions and Implications for Policy

There was consensus in the evidence that hysteroscopy is an effective diagnostic procedure for investigating AUB and diagnosing endometrial cancer. Hysteroscopy also detected uterine cavity abnormalities in postmenopausal women with a sensitivity of 96 per cent and a specificity of 90 per cent. Hysteroscopy should accompany D&C in evaluating AUB in non-pregnant women who are inappropriate for, unresponsive to or contraindicated for medical therapy. Expert opinion suggested that while hysteroscopy can be performed in a clinic setting under cervical block, conducting diagnostic hysteroscopy in a hospital setting in combination with D&C under local anaesthesia allows for the removal of endometrial polyps or fibroids, and may be particularly effective in older women when pathology is likely to be present.

While hysteroscopy remains the gold standard for assessing the uterine cavity, the less invasive alternatives of TVUS, EB and SHG may be used in the following circumstances.

- TVUS was recommended as the first-line imaging procedure for measuring endometrial thickness in premenopausal and postmenopausal women with AUB, and is the test of choice for detecting polyps.
- EB was highly sensitive for diagnosing endometrial carcinoma and hyperplasia. Office-based EB should:
  - replace D&C as the first-line assessment for AUB in premenopausal women
  - be the first test offered to women with AUB who are over 40 years of age, have been unresponsive to medical therapy and are at risk of endometrial cancer.
  - be used in women who have undergone TVUS and have endometrial thickening.
- SHG was sensitive for detecting polyps, fibroids and an abnormal endometrium. Even though a pathology sample cannot be collected during SHG, it can indicate the likelihood of pathology. When the biopsy sample is inadequate, SHG can be used to distinguish between focal and diffuse pathology.

The alternative diagnostic procedures for evaluating AUB were associated with some limitations. Postmenopausal women who have undergone TVUS and have an EEC of more than 4 mm, localised thickening or an indistinct EEC should undergo EB. Women experiencing AUB while receiving adjuvant tamoxifen therapy were advised to undergo EB because TVUS is neither sensitive nor specific for detecting neoplasia. SHG was not recommended as a first-line diagnostic procedure. European guidelines recommended that EB be used (possibly in combination with SHG) to distinguish between diffuse and focal pathology only when endometrial thickness is at least 5 mm. Blind D&C or biopsy

should not be used to diagnose polyps because it has a low sensitivity compared with hysteroscopically guided biopsy.

Adverse events were not reported in the included evidence; however, diagnostic procedures such as hysteroscopy are associated with the risk of perforation, infection, cervical laceration and fluid overload. While pain may be comparable for some procedures, there can be a marked difference in terms of patient preference. For example, there was a marked patient preference for SHG over hysteroscopy (68% versus 15%) even though the mean pain scores were comparable between the procedures.

While these results suggested that hysteroscopy, TVUS, EB and SHG have a place in the diagnostic assessment of women with AUB, there may be variation in the sequence by which these procedures are implemented. Although it was suggested that hysteroscopy be used as the final step in the diagnostic pathway of women with AUB, the included evidence did not consider the sequencing or combination of the diagnostic procedures. Disease probabilities are estimated by combining information from the history and physical examination and additional diagnostic procedures. Decision makers should consider that tests are commonly combined in diagnostic sequences in clinical practice, but the optimal sequencing and combination of hysteroscopy, TVUS, EB and SHG that provides the best results for particular subgroups of women with AUB is currently unclear. A review of the availability of services provided in Victoria may be needed to ensure that women with AUB receive appropriate diagnostic assessment without undergoing unnecessarily invasive or unpleasant procedures.

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Appendix A: Literature Search and Retrieval

The search was developed and carried out prior to the study selection process.

Databases searched and search terms

The databases and resources searched are shown in Table A.1. Searches were restricted to studies published in English from January 2005 (January 2008 for CPGs) to January 2015. A focused internet search for HTA reports and CPGs on diagnostic hysteroscopy for AUB was also conducted. In addition, the websites of relevant specialist societies were also searched (Table A.1).

Table A.1: Databases and resources searched

Database	Edition/Date Searched
Ovid MEDLINE (including In-Process & Other Non-Indexed Citations)	2005 to 2015, January 23, 2015
EMBASE	2005 to 2015, January 23, 2015
The Cochrane Library	Issue 7, 2005 to 2015, January 23, 2015
HTA agencies	
Agency for Healthcare Research and Quality (AHRQ) http://search.ahrq.gov/	January 27, 2015
Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/en/	January 27, 2015
Medical Services Advisory Committee (MSAC) http://www.msac.gov.au/	January 27, 2015
National Institute for Health and Care Excellence http://www.nice.org.uk/	January 27, 2015
Clinical practice guidelines	
BMJ Best Practice http://bestpractice.bmj.com	January 27, 2015
Guidelines International Network (G-I-N) http://www.g-i-n.net/library/international-guidelines-library	January 27, 2015
National Guideline Clearinghouse http://www.guideline.gov/	January 27, 2015
National Health and Medical Research Council Guidelines https://www.nhmrc.gov.au/guidelines	January 27, 2015
National Institute for Health and Care Excellence guidance http://guidance.nice.org.uk/	January 27, 2015
New Zealand Guidelines Group http://www.health.govt.nz/about-ministry/ministry-health-websites/new-zealand-guidelines-group	January 27, 2015

Database	Edition/Date Searched
NHS Evidence in Health and Social Care https://www.evidence.nhs.uk/	January 27, 2015
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/search.html	January 27, 2015
World Health Organization http://www.who.int/publications/guidelines/en/	January 27, 2015
Targeted internet search	
Association for Improvements in Maternity Services http://www.aims.org.uk/	January 23, 2015
American Congress of Obstetricians and Gynaecologists http://www.acog.org/	January 23, 2015
British Society for Gynaecological Endoscopy www.bsge.org.uk	January 23, 2015
International Federation of Obstetrics and Gynecology http://www.figo.org/societies/chinese-society-obstetrics-and-gynecology	January 23, 2015
International Society of Ultrasound in Obstetrics and Gynecology www.isuog.org	January 23, 2015
National Association of Specialist Obstetricians and Gynaecologists http://www.nasog.org.au/	January 23, 2015
Royal Australian and New Zealand College of Obstetricians and Gynaecologists http://www.ranzcog.edu.au/	January 23, 2015
Royal College of Obstetricians and Gynaecologists https://www.rcog.org.uk/	January 23, 2015
Society of Obstetricians and Gynaecologists of Canada http://sogc.org/	January 23, 2015

Search terms

For MEDLINE, searches on the key concepts for hysteroscopy as a diagnostic test for AUB are detailed in Table A.2. This search was conducted using the Ovid SP platform and was restricted by language, year and study type. The search strategy was also translated and run in EMBASE, *The Cochrane Library* and the Centre for Reviews and Dissemination databases; searches were restricted by language, year and, where appropriate, publication type. In addition, a NOT MEDLINE limiter was applied to the EMBASE searches.

Table A.2: Ovid MEDLINE search

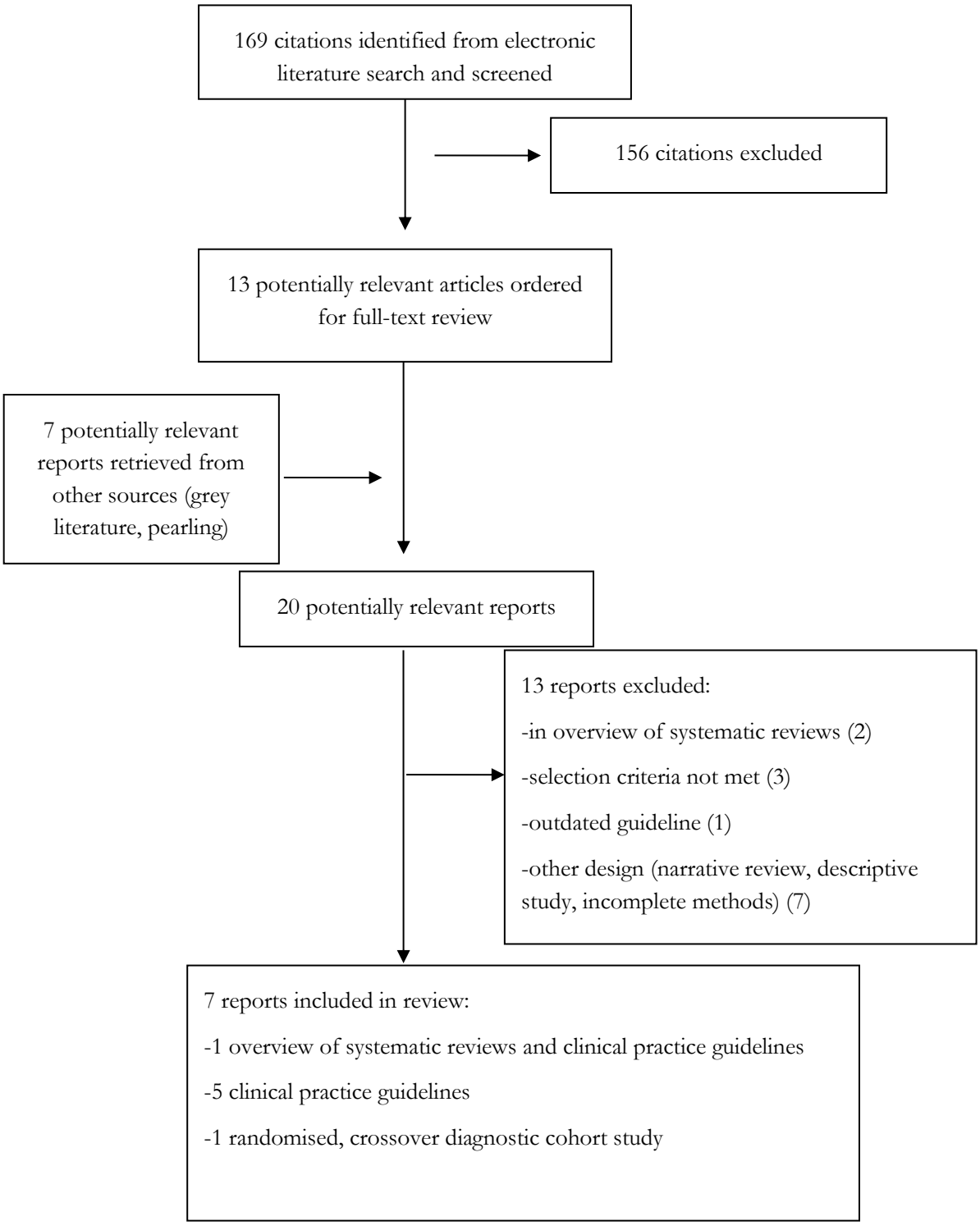
Search ID	Search
1	Uterine Hemorrhage [MeSH]
2	uterus
3	uterine
4	womb
5	vagina*
6	endometr*
7	2 OR 3 OR 4 OR 5 OR 6
8	Hemorrhage [MeSH
9	bleed*
10	haemorrhage
11	hemorrhage
12	8 OR 9 OR 10 OR 11
13	7 AND 12
14	1 OR 13
15	Hysteroscopy [MeSH]
16	Hysteroscop*
17	Uteroscop*
18	15 OR 16 OR 17
19	14 AND 18
	(limits 2005-current; SR, meta-analysis and RCT)

RCT: randomised controlled trial; SR: systematic review

Note: Ovid SP platform was used to search MEDLINE, EMBASE, The Cochrane Library and the Centre for Reviews and Dissemination databases; EMBASE searches were limited to non-MEDLINE journals.

Study selection

Figure A.1: Flow diagram of the study selection process



Appendix B: Evidence Hierarchy

Table B.1: National Health and Medical Research Council evidence hierarchy (Merlin et al. 2009)

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening Intervention
I	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	A prospective cohort study	A prospective cohort study	A randomised controlled trial
III-1	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation	All or none	All or none	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomised, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study ▪ Interrupted time series without a parallel control group	Diagnostic case-control study	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Appendix C: Excluded Studies

Included in overview of systematic reviews

Angioni, S, Loddo, A, Milano, F, Piras, B, Minerba, L & Melis, GB 2008, 'Detection of benign intracavitary lesions in postmenopausal women with abnormal uterine bleeding: A prospective comparative study on outpatient hysteroscopy and blind biopsy', *Journal of Minimally Invasive Gynecology*, vol.15(1), pp. 87-91.

Van Dongen, H, De Kroon, CD, Jacobi, CE, Trimbos, JB & Jansen, FW 2007, 'Diagnostic hysteroscopy in abnormal uterine bleeding: A systematic review and meta-analysis', *BJOG: An International Journal of Obstetrics and Gynaecology*, vol.114(6), pp. 664-75.

Selection criteria not met

American College of Obstetricians and Gynecologists (ACOG) 2012, *Diagnosis of abdominal uterine bleeding in reproductive-aged women*, ACOG, Washington DC, viewed March 2015, < http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Gynecologic-Practice/Management-of-Acute-Abnormal-Uterine-Bleeding-in-Nonpregnant-Reproductive-Aged-Women>.

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Remondi, C, Sesti, F, Bonanno, E, Pietropolli, A & Piccione, E 2013, 'Diagnostic accuracy of liquid-based endometrial cytology in the evaluation of endometrial pathology in postmenopausal women', *Cytopathology*, vol.24(6), pp. 365-71.

Outdated guidelines

National Institute for Health and Care Excellence (NICE) 2013, *Heavy menstrual bleeding: NICE quality standard 47*, NICE, London, viewed March 2015, <http://www.nice.org.uk/guidance/qs47>.

Other design or not available

American College of Radiology 2014, *ACR Appropriateness Criteria*®, viewed March 2015, <http://www.acr.org/Quality-Safety/Appropriateness-Criteria>.

Cancer Australia 2011, *Abnormal vaginal bleeding in pre- and peri-menopausal women: A diagnostic guide for general practitioners and gynaecologists*, Cancer Australia, Canberra, viewed March 2015, <http://canceraustralia.gov.au/sites/default/files/publications/ncgc-vaginal-bleeding-flowcharts-march-20111_504af02038614.pdf>.

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Nieuwenhuis, LL, Hermans, JRF, Bij de Vaate, MAJ, Leeflang, MGM, Brolmann, AMH, Mol, WB, Clark, JT & Huirne, AFJ 2014, 'Three-dimensional saline infusion sonohysterography for the diagnosis of focal intracavitary lesions', *Cochrane Database of Systematic Reviews*, vol.6, CD011126.

Sweet, MG, Schmidt-Dalton, TA & Weiss, PM 2012, 'Evaluation and management of abnormal uterine bleeding in premenopausal women', *American Family Physician*, vol.85(1), pp. 35-43.

Appendix D: Summary of Evidence

Table D.1: Grading of recommendations and levels of evidence

Study, Country	Recommendation Grading	Evidence Categories/Grading
CPGs on diagnostic procedures for AUB		
Munro (2014) Munro (2013) United States	A. Strong recommendation for routine provision: intervention improves important health outcomes, based on good evidence, and the GDG concludes that benefits substantially outweigh harms and costs. B. Recommendation for routine provision: intervention improves important health outcomes based on: 1) good evidence that benefits outweigh harms and costs; or 2) fair evidence that benefits substantially outweigh harms and costs. C. No recommendation for or against routine provision: evidence is sufficient to determine the benefits, harms and costs of an intervention, and there is at least fair evidence that the intervention improves important health outcomes. However, the GDG concludes that the balance of the benefits, harms and costs is too close to justify a general recommendation. D. Recommendation against routine provision: GDG found at least fair evidence that the intervention is ineffective or that harms or costs outweigh benefits. E. Insufficient evidence to recommend for or against routine provision: evidence that the intervention is effective is lacking, of poor quality or conflicting and the balance of benefits, harms and costs cannot be determined.	1a: Meta-analysis of RCTs 1b: RCT 2: Meta-analysis of studies that are not randomised 3: Non-randomised but internally controlled trials. Controls are considered to be "internal" if they are included in the original design of the study. Post hoc or historical comparisons are not considered internal controls. Comparisons of otherwise uncontrolled clinical series are not considered internal controls. 4: Case-control studies 5: Cohort studies 6: Clinical series without internal comparison 7: Expert opinion without available clinical studies
SOGC Singh et al. (2013) Canada	A. There is good evidence to recommend the clinical preventive action. B. There is fair evidence to recommend the clinical preventive action. C. The existing evidence is conflicting and does not allow a recommendation for or against use of the clinical preventive action; however, other factors may influence decision making. D. There is fair evidence to recommend against the clinical preventive action. E. There is good evidence to recommend against the clinical preventive action. F. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision making.	I: At least one properly designed RCT II-1: Well-designed controlled trials without randomisation II-2: Well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group II-3: Comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments could also be included in this category. III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees

Table D.1: Grading of recommendations and levels of evidence (cont'd)

Study, Country	Recommendation Grading	Evidence Categories/Grading
AAGL (2012) United States	A. Recommendations are based on good and consistent scientific evidence. B. Recommendations are based on limited and inconsistent scientific evidence. C. Recommendations are based primarily on consensus and expert opinion.	I: At least one properly designed RCT II-1: Well-designed controlled trials without randomisation II-2: Well-designed cohort or case-control analytic studies, preferably from more than one centre or research group II-3: Multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence. III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
University of Texas (2012) United States	A. Strong recommendation that clinicians provide the service to eligible patients based on good evidence that the service improves important health outcomes and that benefits substantially outweighs harms. B. Recommendation that clinicians provide the service to eligible patients based on at least fair evidence that the service improves important health outcomes and that benefits outweigh harms. C. No recommendation is made for or against routine provision of service based on at least fair evidence that the service can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation. D. Recommendation against routinely providing the service to asymptomatic patients based on at least fair evidence that the service is ineffective or that harms outweigh benefits. E. Evidence is insufficient to recommend for or against routinely providing the service. Evidence that the service is effective is lacking, of poor quality or conflicting and the balance of benefits and harms cannot be determined.	High: available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is unlikely to be strongly affected by the results of future studies. Moderate: available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by factors such as: number, size or quality of individual studies; limited generalisability of findings to routine primary care practice; and lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion. Low: available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of: the limited number or size of studies; important flaws in study design or methods; inconsistency of findings across individual studies; gaps in the chain of evidence; and lack of information on important outcomes.

AAGL: American Association of Gynecologic Laparoscopists; AUB: abnormal uterine bleeding; CPG: clinical practice guideline; GDG: guideline development group; RCT: randomised controlled trial; SOGC: Society of Obstetricians and Gynaecologists of Canada

Table D.2: Summary of critical appraisal of clinical practice guidelines

Study, Country	Strengths	Limitations
CPGs on diagnostic procedures for AUB		
Munro (2014) United States	The objective was to develop an evidence-based CPG to assist health professionals in the evaluation and management of PMB in women in the KPSC region. Research question, target patient population, users, interventions and outcomes were specified. The GDG included physicians and nurse practitioners and clinicians with expertise in family medicine, internal medicine, obstetrics and gynaecology, radiology, pathology and oncology. Evidence was identified by systematically searching MEDLINE and the Cochrane Database of Systematic Reviews from 2005 to 2012. Websites of the ACOG, the SOGC, the New Zealand Guidelines Group, NICE and the Geneva Foundation for Medical Education and Research were also searched. Evidence was classified using the system developed by the Kaiser Foundation adopted from the United States Preventive Services Task Force of the Agency for Healthcare Research and Quality, but modified by adding subgroups for meta-analysis of RCTs and expert opinion. Recommendations were formulated through expert and informal consensus. Key action items identified, appraised and summarised with an explicit link between evidence and recommendations. Evidence-based recommendations reflect the quality of evidence. All working group members reviewed final recommendations and regional chiefs of obstetrics and gynaecology approved the CPG. All authors reported no conflicts of interest to disclose.	While the GDG met to review the methods of guideline development, the method by which evidence was selected for inclusion was not reported. The views and preferences of the target population were not sought. Key review criteria for monitoring or audit were not clearly reported. Procedures for updating the guideline were not reported. Barriers and implementation strategies were not reported. The funding source was not reported.
Munro (2013) United States	The purpose was to update evidence-based guidelines, augmented with consensus where evidence was limited or conflicting, to assist healthcare professionals in the evaluation and management of non-pregnant women with AUB requiring immediate medical intervention in the KPSC region. Research question, target population, users, interventions and outcomes were specified. AUB was defined as bleeding that is sufficient in volume as to require urgent intervention in the opinion of the treating clinician. The GDG included physicians and nurse practitioners and clinicians with expertise in family medicine, internal medicine, obstetrics and gynaecology, radiology, pathology and oncology. Evidence was identified by systematically searching MEDLINE and the Cochrane Register of Controlled Trials from 2005 to 2012. Websites of the ACOG, the SOGC, the RCOG, the New Zealand Guidelines Group, NICE and the Geneva Foundation for Medical Education and Research were also searched.	While the GDG met to review the methods of guideline development, the method by which evidence was selected for inclusion was not reported. The views and preferences of the target population were not sought. Key review criteria for monitoring or audit were not reported. Procedures for updating the guideline were not reported. Barriers and implementation strategies were not reported. The primary author was a consultant for various medical companies. The funding source was not reported.

(Cont'd over page)

Table D.2: Summary of critical appraisal of clinical practice guidelines (cont'd)

Study, Country	Strengths	Limitations
CPGs on diagnostic procedures for AUB		
Munro (2013) United States *(cont'd)*	Guidelines were developed using the best available evidence or a consensus process when evidence was insufficient or absent. Evidence was classified using the system developed by the Kaiser Foundation and adopted from the United States Preventive Services Task Force of the Agency for Healthcare Research and Quality, but modified by adding subgroups for meta-analysis of RCTs and expert opinion. Key action items identified, appraised and summarised with an explicit link between evidence and recommendations. Evidence-based recommendations reflect the quality of evidence. All working group members reviewed final recommendations and regional chiefs of obstetrics and gynaecology approved the CPG.	
SOGC Singh et al. (2013) Canada	The objective was to provide current evidence-based guidelines for the diagnosis and management of AUB among premenopausal women. Research questions, target population, users, interventions and outcomes were specified. The guideline was developed by the Clinical Practice-Gynaecology Committee, reviewed by the Canadian Paediatric and Adolescent Gynaecology/Obstetrics Committee and approved by the Executive and Council of the SOGC. Evidence was identified by systematically searching MEDLINE and *The Cochrane Library* from 1999 to February 2013. Grey literature was identified through searching websites of HTA agencies, CPG collections, clinical trial registries and specialty societies. Evidence was rated for quality using the criteria described in the Report of the Canadian Task Force on Preventive Health Care. Recommendations were based on best available data published up to 2013; the strengths and limitations of the evidence were clearly described.	The method used to select evidence for inclusion was not reported. Methods used to formulate recommendations were not reported. The views and preferences of the target population were not sought. Criteria for monitoring, audit and updating were not reported. Barrier and facilitators to implementation were not discussed. The economic cost of implementing the guidelines in the Canadian healthcare system was not considered. Funding and conflicts of interest were not reported.
AAGL (2012) United States	The objective was to provide clinicians with evidence-based information about the management of endometrial polyps to guide clinical management. The GDG comprised of members of the AAGL with expertise in minimally invasive gynaecology and laparoscopy. The research question, target population and end users were specified. Evidence was identified by systematically searching MEDLINE, PubMed, CINAHL, *The Cochrane Library*, Current Contents and EMBASE from 1951 to 2010. Key recommendations were easily identifiable, explicitly linked to supporting evidence and took into consideration health benefits and risks.	Methods on how studies were selected for inclusion were not reported. Methods used to formulate recommendations were not reported. The views and preferences of the target population were not sought. Facilitators and barriers to implementation were not discussed. Resource implications and criteria for monitoring and auditing were not reported. Members of the GDG reported some financial interest or affiliation with corporations. The funding source was not reported.

Table D.2: Summary of critical appraisal of clinical practice guidelines (cont'd)

Study, Country	Strengths	Limitations
CPGs on diagnostic procedures for AUB		
University of Texas (2012) United States	The objective was to present a national guideline on the evaluation and management of HMB in primary care that included evaluation, diagnosis, medical management, pharmacological management, indications for referral to secondary care and patient educational interventions for women with HMB The GDG comprised members of the University of Texas at Austin School of Nursing, Family Nurse Practitioner Program. The research question, target population, end users and interventions were specified. Evidence was identified by systematically searching UpToDate, PubMed, CINAHL, the Cochrane Database of Systematic Reviews and MEDLINE published between 2007 and 2012. Evidence was graded for quality based on the United States Preventive Services Task Force grading system. Recommendations were formulated through expert and informal consensus. Key recommendations were easily identifiable, explicitly linked to supporting evidence and took into consideration health benefits and risks. The guideline was validated through internal review and expert external review prior to publication. Implementation tools included a clinical algorithm. Funded through the University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program.	Methods used to select and analyse the evidence were not stated. The views and preferences of the target population were not sought. Facilitators and barriers to implementation were not discussed. Resource implications and criteria for monitoring and audit were not reported. Financial disclosures and conflicts of interest were not stated.

AAGL: American Association of Gynecologic Laparoscopists; ACOG: American College of Obstetricians and Gynecologists; AUB: abnormal uterine bleeding; CPG: clinical practice guideline; GDG: guideline development group; CINAHL: Cumulative Index to Nursing and Allied Health Literature; HMB: heavy menstrual bleeding; HTA: health technology assessment; KPSC: Kaiser Permanente Southern California; NICE: National Institute for Health and Care Excellence; PMB: postmenopausal bleeding; RCT: randomised controlled trial; SOGC: Society of Obstetricians and Gynaecologists of Canada

Table D.3: CPG recommendations on diagnostic procedures for AUB

Guideline, Author, Year, Country	Recommendations
Recommendations on diagnostic procedures for AUB	
Munro (2014) United States	Women with spontaneous PMB should be primarily evaluated with either EB or TVUS to measure the thickness of the EEC [Grade A evidence-based recommendation]. Women with spontaneous PMB and an EEC>4 mm should be further evaluated with EB [Grade A evidence-based recommendation]. Women with persistent spontaneous PMB require further evaluation of the endometrial cavity for focal lesions with one or a combination of office-based contrast sonography and hysteroscopy. Such an approach is necessary even if there is adequate EB without evidence of hyperplasia and regardless of the EEC thickness [Grade B evidence-based recommendation]. Operating room-based D&C of women with PMB should be performed only when office-based EB: is indicated; cannot be performed for patient comfort or technical reasons; or is inconclusive and the results of TVUS or SHG are not reassuring [Grade B evidence-based recommendation]. Hysteroscopy is not contraindicated in the evaluation of women with PMB, including those cases suggestive of cancer [Grade B evidence-based recommendation]. Women experiencing uterine bleeding while receiving tamoxifen as adjuvant therapy for breast cancer should be assessed with EB because TVUS is neither sensitive nor specific for neoplasia [Grade A evidence-based recommendation].
Munro (2013) United States	When performed in the evaluation or treatment of patients with acute AUB, D&C should be accompanied by hysteroscopy [Grade A Evidence-based Recommendation]. EB is not considered mandatory in all instances of acute uterine bleeding; however it should be considered when risk factors are present such as chronic anovulation, obesity, prolonged exposure to unopposed oestrogens or tamoxifen or a family history of increased risk of endometrial neoplasia. There is no consensus regarding a specific age at which sampling is considered mandatory [Grade B evidence-based recommendation].
SOGC Singh et al. (2013) Canada	If imaging is indicated, TVUS should be the first-line imaging modality for AUB [Grade A recommendation]. SHG and diagnostic hysteroscopy should be used in the diagnosis and characterisation of discrete intrauterine abnormalities such as submucosal fibroids [Grade A recommendation]. EB should be considered in bleeding premenopausal women over age 40 years or in those with bleeding who are not responsive to medical therapy, as well as in younger women with risk factors for endometrial cancer [Grade A recommendation]. Office EB should replace D&C as the initial assessment of the endometrium for premenopausal women with AUB [Grade A recommendation]. Focal lesions of the endometrium that require biopsy should be managed through hysteroscopically guided evaluation [Grade A recommendation].
AAGL (2012) United States *(Cont'd over page)*	TVUS provides reliable information for the detection of endometrial polyps and should be the investigation of choice where available [Grade B recommendation]. TVUS in the proliferative phase of the menstrual cycle is likely to provide the most reliable results. TVUS has a reported sensitivity of 19% to 96%, a specificity of 53% to 100%, a PPV of 75% to 100% and a NPV of 87% to 97% to diagnose endometrial polyps, compared with hysteroscopy with guided biopsy based on level I evidence from studies involving few patients. A single large, level II-2 study reported sensitivity, specificity, PPV and NPV of TVUS as 86%, 94%, 91% and 90%, respectively. The addition of colour or power Doppler increases the capacity of TVUS to diagnose endometrial polyps [Grade B recommendation]. Power Doppler is reported to increase sensitivity to 91% and 97% in patients with and without symptoms, respectively. Specificity and NPV may be increased to 95% and 94%, respectively, when colour-flow Doppler is added to grey-scale TVUS to identify the feeding vessel. Limited data supported colour-flow or power Doppler aiding in the differentiation of hyperplasia and malignancy in polyps, with no difference in the histological grading of polyps.

Table D.3: CPG recommendations on diagnostic procedures for AUB (cont'd)

Guideline, Author, Year, Country	Recommendations
Recommendations on diagnostic procedures for AUB	
AAGL (2012) United States *(cont'd)*	Adding intrauterine contrast to sonography (with or without 3D imaging) improves the diagnostic capacity for endometrial polyps [Grade B recommendation]. When compared with hysteroscopically guided biopsy, SHG has a sensitivity of 58% to 100%, a specificity of 35% to 100%, a PPV of 70% to 100% and a NPV of 83% to 100%. Several level II studies reported no significant difference between SHG and diagnostic hysteroscopy in diagnosing endometrial polyps. Advantages of SHG include assessment of both the uterine cavity and other pelvic structures and the potential to assess tubal patency in patients with infertility. Disadvantages of SHG include an inability to determine final endometrial disease, a slower learning curve compared with non-contrast TVUS and patient discomfort caused by fluid leakage or pain during examination. Studies with non-contrast 3D TVUS showed limited improvement in diagnosis when compared with two-dimensional TVUS, with a sensitivity of 100%, a specificity of 71% to 99%, a PPV 89% to 99% and NPV of 100%. Adding saline solution contrast to 3D sonography increases specificity to 88% to 99%, PPV to 97% to 100% for endometrial polyps, sensitivity to 92% to 95% and NPV to 97%, compared with 3D ultrasonography. Blind D&C or biopsy should not be used for diagnosing endometrial polyps [Grade B recommendation]. Blind D&C has a specificity and PPV of 100% but a low sensitivity of 8% to 46% and NPV of 7% to 58% when compared with hysteroscopically guided biopsy. Hysteroscopy with guided biopsy is the most common comparator for other techniques to diagnose polyps as it offers the highest sensitivity and specificity for conservative measures. Diagnostic hysteroscopy only allows subjective assessment of the size and characteristics of the lesion, with a sensitivity of 58% to 99%, a specificity of 87% to 100%, a PPV of 21% to 100% and a NPV of 66% to 99% when compared with hysteroscopically guided biopsy.
University of Texas (2012) United States	A biopsy should be taken to exclude endometrial cancer or atypical hyperplasia: if there is persistent intermenstrual bleeding or no definite cause of HMB; in women aged 35 years or older; or when treatment fails [Grade B recommendation]. Imaging should be undertaken if the uterus is palpable abdominally, vaginal examination reveals a pelvic mass of uncertain origin or pharmaceutical treatment fails [Grade B recommendation]. Ultrasound is the first-line diagnostic tool for identifying structural abnormalities [Grade A recommendation]. Referral for hysteroscopy should be used as a diagnostic tool only when ultrasound results are inconclusive, for example, to determine the location of a fibroid or the nature of the abnormality [Grade A recommendation]. SHG should not be used as first-line diagnostic tool [Grade A recommendation].

3D: three-dimensional; AAGL: American Association of Gynecologic Laparoscopists; AUB: abnormal uterine bleeding; D&C: dilation and curettage; EB: endometrial biopsy; EEC: endometrial echo complex; HMB: heavy menstrual bleeding; NPV: negative predictive value; PMB: postmenopausal bleeding; PPV: positive predictive value; SHG: sonohysterography; SOGC: Society of Obstetricians and Gynaecologists of Canada; TVUS: transvaginal ultrasound;

Table D.4: Summary of study characteristics of the included studies on diagnostic procedures for AUB

Study, Country	Study Design	Patient Characteristics	Intervention	Comparator	Outcomes Measured
Overview of SRs and CPGs					
Van Hanegem et al. (2011) The Netherlands	Overview of nine SRs (four on TVUS, two on EB, one on SHG and two on hysteroscopy) (Clark et al. 2001; Clark et al. 2002; de Kroon et al. 2003; Dijkhuizen et al. 2000; Gupta et al. 2002; Smith-Bindman et al. 1998; Tabor et al. 2002; Timmermans et al. 2010; van Dongen et al. 2007) and five CPGs (two from the United States and three from Europe) (ACOG 2009; Dutch Society of Obstetrics and Gynecology 2003; Epstein 2004; Goldstein et al. 2001; SIGN 2002) Literature search: up to 2010 Participants: 15,454	Women with PMB Mean age: Not reported	TVUS, outpatient endometrial biopsy, SHG or hysteroscopy	Endometrial histological findings from inpatient endometrial biopsy, D&C or hysterectomy	Accuracy with which endometrial cancer and/or hyperplasia were diagnosed, sensitivity, specificity, likelihood ratios, pre-test probability of endometrial cancer or hyperplasia
Randomised, crossover diagnostic cohort study					
Katsetos et al. (2012) United Kingdom	Prospective, randomised, crossover diagnostic cohort study Setting: Teaching hospital, day surgery Participants: 49 (44 completed) Follow-up: Not reported	Women with AUB Mean age: 44.8 years (range 26 to 63) Average duration of symptoms: 14.8 months Mean parity: 1.8	3D SHG followed by hysteroscopy	Outpatient hysteroscopy followed by 3D SHG	Diagnostic accuracy, procedure time, patient discomfort

3D: three-dimensional; ACOG: American College of Obstetricians and Gynecologists; AUB: abnormal uterine bleeding; CPG: clinical practice guideline; D&C: dilation and curettage; EB: endometrial biopsy; PMB: postmenopausal bleeding; SHG: sonohysterography; SIGN: Scottish Intercollegiate Guidelines Network; SR: systematic review; TVUS: transvaginal ultrasonography

Table D.5: Summary of critical appraisal of the included studies on diagnostic procedures for AUB

Study, Country	Strengths	Limitations
Overview of SRs and CPGs		
Van Hanegem et al. (2011) The Netherlands	Inclusion and exclusion criteria were predefined. Two reviewers selected studies and reported the process in a PRISMA flow chart. References cited in the selected reviews were checked for further relevant articles not identified by electronic searching. Methodological quality was assessed using the Cochrane checklist for SRs of diagnostic studies. Reasons for exclusion of studies were reported and a list of excluded studies was available from the corresponding author. Study quality was considered in formulating results and conclusions. Authors reported no conflicts of interest.	Evidence may be incomplete; only two electronic literature sources were searched. Risk of source and time lag bias as the authors did not report searching for grey literature. It was unclear whether data extraction and quality assessment were performed in duplicate or whether guidelines were assessed for quality. Funding source was not reported.
Randomised, crossover diagnostic cohort study		
Katsetos et al. (2012) United Kingdom	All women attending a one-stop menstrual problem clinic for AUB requiring investigation were included. Patients were randomly assigned to hysteroscopy or SHG first. Interventions were clearly described. Sealed, opaque envelopes that were numbered were opened on recruitment and patients were assigned to group 1: hysteroscopy followed by sonography or group 2: sonography followed by hysteroscopy. Investigators were blinded to the results. Patient dropouts were reported.	Adverse events were not reported. The funding source and conflicts of interest were not reported.

AUB: abnormal uterine bleeding; CPG: clinical practice guideline; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; SHG: sonohysterography; SR: systematic review

Table D.6: Summary of findings from included studies on diagnostic procedures for AUB

Study, Country	Main Study Findings	Authors' Conclusions
Overview of SRs and CPGs		
Van Hanegem et al. (2011) The Netherlands	**TVUS versus EB, D&C or hysterectomy for detecting endometrial carcinoma** (4 SRs involving 11,952 women with PMB; 2 CPGs) TVUS was accurate in excluding endometrial cancer; a cut-off value of 3 mm was recommended. Smith-Bindman et al. (1998) reported a sensitivity of 96% and a specificity of 61% at 5 mm endometrial thickness; pre-test probability of 10% for endometrial cancer and post-test probability (for a negative test) of 1%. Tabor et al. (2002) reported a sensitivity of 96% and a specificity of 50% at multiples of the median endometrial thickness; pre-test probability of 10% for endometrial cancer and post-test probability for a negative test of 1%. Gupta et al. (2002) reported a sensitivity of 92% and a specificity of 66% at 5 mm endometrial thickness; likelihood ratio of 0.16 implied that a patient with a negative test result (endometrial thickness ≤5 mm) and a pre-test probability of 10% would have a post-test probability of 2.5%, concluding that TVUS can be used to rule out endometrial hyperplasia or carcinoma using an endometrial thickness of ≤5 mm. Timmermans et al. (2010) reported a lower diagnostic accuracy for TVUS; a meta-analysis of individual patient data suggested a sensitivity of 95% and a specificity of 47% at 4 mm endometrial thickness; post-test probability for a negative test of 1.2%; sensitivity of 98% and specificity of 35% at ≤3 mm endometrial thickness with a likelihood ratio for a negative test result of 0.06. A cut off of ≤3 mm reduced a pre-test probability of 10% to a 0.7% post-test probability, therefore a cut off of ≤3 mm endometrial thickness is justified. 2 CPGs from the United States recommended either TVUS or outpatient EB as the first step in diagnosing women with PMB based on similar sensitivities and cost-effectiveness for detecting endometrial carcinoma for an endometrial thickness of ≥5 mm (ACOG 2009; Goldstein et al. 2001). Other CPGs suggested TVUS as the first step in assessment based on the high sensitivity and non-invasive character of the procedure, though cut-off values varied from 3 mm to 5 mm (ACOG 2009; Dutch Society of Obstetrics and Gynecology 2003; Goldstein et al. 2001; Smith-Bindman et al. 1998). **EB versus histology, D&C, hysteroscopy or hysterectomy for detecting endometrial carcinoma or hyperplasia** (2 SRs involving 980 women with PMB) EB was moderately accurate in diagnosing pre-malignant endometrial pathology and highly sensitive for diagnosing endometrial carcinoma. Clark et al. (2001) reported a sensitivity of 91.9% and specificity of 99.7% for EB with different sampling devices; pre-test probability of 14% increased to a post-test probability for a positive result of 67% (95% CI 42.3% to 83.9%). Dijkhuizen et al. (2000) reported a sensitivity of 95% and a specificity of 99.5%; post-test probability for a positive was 96%.	The findings of this overview suggested that "neither in SRs nor in international guidelines is consensus found regarding the best sequence of diagnostic procedures for women with PMB; measurement of endometrial thickness, endometrial sampling and hysteroscopy have been independently shown to be accurate in excluding endometrial cancer; in relation to endometrial thickness a cut-off value of 3 mm is recommended, but cost-effectiveness has not yet been demonstrated; future research should focus on the combination of different diagnostic tests alongside patient characteristics and meta-analysis of individual patient data may be used to validate and refine previously described models". (p. 162)
(Cont'd over page)		

Table D.6: Summary of findings from included studies on diagnostic procedures for AUB (cont'd)

Study, Country	Main Study Findings	Authors' Conclusions
Van Hanegem et al. (2011) The Netherlands *(cont'd)*	United States CPGs recommended EB with a cut-off value for endometrial thickness of 5 mm and also recommended TVUS when the endometrial sampling was deemed insufficient (ACOG 2009; Goldstein et al. 2001). European CPGs recommended EB only when the endometrial thickness was above the cut-off value, possibly together with SHG, to distinguish between diffuse and focal pathology (ACOG 2009; Goldstein et al. 2001; Epstein 2004; SIGN 2002). **SHG versus hysteroscopy or hysterectomy for detecting an abnormal endometrial cavity** (1 SR involving 268 women with PMB) De Kroon et al. (2003) reported a sensitivity of 95% and a specificity of 88%, but the results were not separately described for premenopausal and postmenopausal women. CPGs suggested that SHG be used to distinguish between a diffusely thickened endometrium, for which D&C could be the next step (Goldstein et al. 2001), and a focal lesion, for which a hysteroscopy is the next step (ACOG 2009; Goldstein et al. 2001) **Hysteroscopy versus histology (different methods) for detecting endometrial carcinoma or an abnormal cavity** (2 SRs involving 2,254 women with PMB) Hysteroscopy was highly accurate when the uterine cavity is adequately visualised and was useful in diagnosing rather than excluding cancer. Clark et al. (2002) reported a sensitivity of 86% and a specificity of 99%; likelihood ratio of 61; pre-test probability of 4% and post-test probability of 72% (95% CI 67.0% to 76.6%). Van Dongen et al. (2007) reported a sensitivity of 96% and a specificity of 90%; likelihood ratio of 8; pre-test probability of 61% and post-test probability of 93% (95% CI 88.0 to 95.0%) for uterine cavity abnormality.	
Randomised controlled cohort study		
Katsetos et al. (2012) United Kingdom *(Cont'd over page)*	**Comparison of hysteroscopy with 3D SHG Diagnosis** *Diagnostic accuracy:* Hysteroscopy was considered the gold standard for investigating AUB. Intracavity lesions were noted in 26/44 (59%) women with AUB. 3D SHG missed three uterine polyps that were detected by hysteroscopy. In all cases the uterus was enlarged with intramural and subserous fibroids. The sensitivity of SHG was 72% for diagnosing polyps, 93% for detecting fibroids and 100% for diagnosing an abnormal endometrium, compared with hysteroscopy. The specificity in all three categories was 100%. *Pain ratings*: The visual analogue score for pain at hysteroscopy ranged between 0 and 10. The mean score was 2.81, with a SD of 2.65 (95% CI 2 to 3.6). The pain score for SHG ranged between 0 and 9.2, with a SD of 2.63 (95% CI 1.8 to 3.4; P=0.55).	"In the investigation of women with AUB in the outpatient setting, both hysteroscopy and SHG are comparable in the diagnosis of intracavity lesions, pain rating and procedure time. However, patient acceptability of SHG was significantly more when compared to outpatient hysteroscopy." (p. 74)

Table D.6: Summary of findings from included studies on diagnostic procedures for AUB (cont'd)

Study, Country	Main Study Findings	Authors' Conclusions
Katsetos et al. (2012) United Kingdom *(cont'd)*	*Procedure duration*: Hysteroscopy procedure duration varied from 1 to 13 minutes, with a mean of 6 minutes (SD 2.86, 95% CI 5.119 to 6.881). SHG procedure duration varied between 10 and 30 minutes, with a mean of 17.3 (SD 4.43, 95% CI 15.76 to 18.81; P≤0.001). *Patient satisfaction*: 30/44 (68%) patients would choose SHG if given the choice again. In contrast, only of 44 (15.2%) would choose hysteroscopy again. Three patients (6.8%) had no specific preference and three (6.8%) did not respond to the question. Despite the pain being comparable in both procedures, there was a marked patient preference for SHG.	

3D SHG: three-dimensional sonohysterography; ACOG: American College of Obstetricians and Gynecologists; AUB: abnormal uterine bleeding; CI: confidence interval; CPG: clinical practice guidelines; D&C: dilation and curettage; EB: endometrial biopsy; LR: likelihood ratio; PMB: postmenopausal bleeding; SD: standard deviation; SR: systematic review; TVUS: transvaginal ultrasound