



Effective Health Care

Effectiveness and Harms of Endometrial Ablation

Results of Topic Selection Process & Next Steps

The nominator, American College of Obstetrics and Gynecology (ACOG), is interested in a new evidence review on Effectiveness and harms of endometrial ablation (EA) to inform clinical practice.

We identified three review(s) and a protocol that cover parts of this nomination. A feasibility search determined that the literature has not expanded enough to warrant a new review of medical options, or comparisons between EA techniques. No further activity on this nomination will be undertaken by the Effective Health Care (EHC) Program.

Topic Brief

Topic Name: Effectiveness and harms of endometrial ablation, #0777

Nomination Date: 03/01/2018

Topic Brief Date: 04/30/2018

Authors

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report

Summary

- This nomination meets the selection criteria of appropriateness and importance.
- A new review would be duplicative of an existing product. Three recent reviews cover the literature on the topic. We found recent systematic reviews that covered the parts of the nomination, and a planned systematic review of EA vs. levonorgestrol (LNG) is registered in PROSPERO
- A new systematic review has limited potential impact. Although the current recommendations are based on older literature and expert opinion, these could be updated with the existing systematic reviews.
- A new review is not feasible. The evidence base is likely small.

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Background

Abnormal uterine bleeding (also called menorrhagia or heavy menstrual bleeding) is a common problem for women in the US, which negatively impacts quality of life and consumes healthcare resources. Endometrial ablation (EA) refers to a number of minimally invasive intrauterine surgical procedures performed to treat abnormal uterine bleeding. Endometrial ablation is indicated for the treatment of menorrhagia in premenopausal women with normal endometrial cavities who have no desire for future fertility. In general, such patients will have failed medical therapy, and hope to avoid a more expensive and invasive hysterectomy. A wide variety of EA techniques are available, and the relative benefits and harms of these options are not well understood. In addition, a comparison of EA vs medical therapies is lacking. The American College of Obstetrics and Gynecology (ACOG) nominated this topic to inform practice guidelines

Nominator and Stakeholder Engagement: ACOG reviewed the PICOTs and Key Questions, which were adjusted based on their feedback. (We excluded comparisons to the Levonorgestrel- intrauterine system (LNG-IUS).)

The key questions for this nomination are:

Key Questions:

1. In premenopausal women with heavy menstrual bleeding, what is the effectiveness of endometrial ablation on outcomes?
 - a. Does effectiveness differ by patient characteristics?
 - b. Does effectiveness differ between specific devices used for endometrial ablation?
2. In premenopausal women with heavy menstrual bleeding, what are the harms of endometrial ablation?
 - a. Do harms differ by patient characteristics
 - b. Do harms differ between specific devices used for endometrial ablation?
3. In premenopausal women with heavy menstrual bleeding, what is the comparative effectiveness of endometrial ablation vs. non-ablative therapy on outcomes?
 - a. Does effectiveness differ by patient characteristics
 - b. Does effectiveness differ between specific devices used for endometrial ablation?
4. In premenopausal women heavy menstrual bleeding, what are the comparative harms of endometrial ablation vs. non-ablative therapy?
 - a. Do harms differ by patient characteristics
 - b. Do harms differ between specific devices used for endometrial ablation?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, outcomes, timing, and setting (PICOTS) of interest (Table 1).

Table 1: Key Questions and PICOTS

PICOTS	KQ	
Population:	KQ 1-4	<ul style="list-style-type: none"> • Premenopausal women with heavy menstrual bleeding who have no desire for future fertility <p>KQ 1a, 2a, 3a, and 4a: Subgroups include age, prior therapy, presence of fibroids/ endometrial cavity distortion, pre-treatment, prior tubal ligation)</p>
Intervention(s):	KQ 1-4	<ul style="list-style-type: none"> • Endometrial Ablation (EA) <p>KQ 1b: subgroups are specific devices such as Cryotherapy (Her Option), Heated Free Fluid (e.g. Hydro ThermAblator), Microwave (e.g. Microwave Endometrial Ablation System), Radiofrequency (e.g. NovaSure, Minerva), Thermal Balloon (e.g. ThermoChoice)</p>
Comparator(s):	KQ 1-2	<ul style="list-style-type: none"> • Placebo/no treatment
	KQ 3-4	<ul style="list-style-type: none"> • INCLUDE: Non-ablative intervention (medical therapy only) • EXCLUDE: bipolar radiofrequency vs. thermal balloon (prior review); LNG-IUS (prior review); hysterectomy, myomectomy (not in scope)
Outcome(s):	KQ 1, KQ 3	<ul style="list-style-type: none"> • Reduced bleeding (Pictorial Blood Loss Assessment Chart (PBLAC)) • Patient satisfaction (Quality of Life, QoL) • Resource utilization
	KQ 2, KQ 4	<ul style="list-style-type: none"> • Procedural complications • Adverse events of treatments • Need for subsequent procedures, including hysterectomy • Delayed diagnosis of malignancy
Timing:	KQ 1-4	<ul style="list-style-type: none"> • Short term (e.g., post-operative), longer term (e.g., 12 months, till menopause)
Setting	KQ 1-4	<ul style="list-style-type: none"> • Any

Methods

We assessed nomination #0777, Effectiveness and harms of endometrial ablation, for priority for a systematic review or other AHRQ EHC report with a hierarchical process using established selection criteria (Appendix A). Assessment of each criterion determined the need for evaluation of the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years on the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in OVID/PubMed from 1946 to April 2018. We focused on literature since 2015, the end date of the searches of the recently published systematic reviews. We reviewed all identified titles and abstracts for inclusion and classified them by study design, to assess the size and scope of a potential evidence review.

See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

Compilation of Findings

We constructed a table with the selection criteria and our assessments (Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic.

The prevalence of menorrhagia, or heavy menstrual bleeding, is difficult to assess precisely. It is usually defined subjectively, by patient report, since objective measures (such as anemia) may take years to develop. However, in recent reports, about 30 % of women in the US report bothersome menorrhagia, which impacts their quality of life (**Bruinvels et al. 2016; Dorsey 2013; Farquhar and Steiner 2002; Karlsson, Marions, and Edlund 2014; Marsh et al. 2014**)

Hysterectomy is the most common gynecologic surgical procedure performed in the United States with approximately 600,000 cases per year, accounting for over \$5 billion health care dollars. In two recent reviews, about 50% of women undergoing hysterectomy reported menorrhagia. (**Cohen et al. 2017; Mehta et al. 2017**)

EA allows women to defer or avoid hysterectomy. Since the introduction of EA, hysterectomy rates have decreased in some areas. (**Farquhar, Naoom, and Steiner 2002**) EA procedures typically cost from \$2500 to \$6000. In contrast, hysterectomy costs range from \$30,000 to \$50,000. (**Wright et al. 2012**)

Desirability of New Review/Duplication

A new evidence review on Effectiveness and harms of endometrial ablation is partially duplicative of existing products.

For KQ 1a (differences in effectiveness by EA technique) we found two reviews. A 2016 review from Italy compared “first generation” resectoscopic techniques and “2nd generation” proprietary techniques performed without a resectoscope. **(Angioni et al. 2016)** Search dates ended in September 2015. The full details of the review and details of the studies included could not be assessed: the full report was not available. A 2018 metanalysis (six studies) compared EA via bipolar radiofrequency or thermal balloon to reduce menstrual loss and improve quality of life. **(Zhai et al. 2018)** Search date ended in November 2016.

For KQ 3 (comparative effectiveness vs. non ablative techniques), we found one recent review and a published protocol. A 2016 Cochrane review compared surgical to medical approaches for heavy menstrual bleeding. **(Marjoribanks, Lethaby, and Farquhar 2016)** Of the 15 included studies, 13 compared EA to medication (one) or LNG (12). The search concluded in January 2016. We found one protocol that plans to compare EA to LNG-IUS in PROSPERO. The primary outcome is a “harm” (need for subsequent hysterectomy), and the secondary outcome is a benefit (bleeding outcome). **(Bergeron 2018)** The research is slated to begin in February 2018. The author reports that the results will be publically available in the winter of 2018. [Personal communication].

KQ 2 (harms) and KQ 4 (comparative harms) were not easily assessed from the literature. We found a single review of a rare harm (pregnancy complications) after EA. **(Kohn et al. 2018)**

In summary, there is significant overlap with some existing reviews especially for the comparative effectiveness of EA versus LNG IUD.

A feasibility search might help determine if the literature has expanded enough to warrant a new review of medical options, or comparisons between EA techniques.

See Table 2, Duplication column.

Impact of a New Evidence Review

A new systematic review on the effectiveness and harms of endometrial ablation may have a moderate level of impact. ACOG published a practice bulletin in 2007. However, only two of 12 recommendations are backed by high quality evidence, seven are based on expert opinion. Also, the bulletin is based on literature before 2006. ('ACOG Practice Bulletin. Clinical management guidelines for obstetrician-gynecologists. Number 81, May 2007' **2007**) ACOG is well poised to impact provider practice. However, they could update their guidance based on the existing systematic reviews.

Feasibility of a New Evidence Review

A new evidence review examining effectiveness and harms of endometrial ablation is not feasible. The search yielded only a single study (related to KQ 1) published since the last search date of the existing SRs. This is one year follow up of a prospective observational study (n=105 women) of the efficacy/harms of a single EA system.**(Laberge et al. 2015)** A review of Clinical Trials.gov produced a previously undetected study related to KQ3. This small trial (n=76) compared medications to EA. **(Famuyide et al. 2017)** This suggests that there is insufficient literature to warrant a new review at this time. See Table 2, Feasibility column.

Table 2. Key questions and Results for Duplication and Feasibility

Key Question	Duplication (03/29/2015-03/29/2018)	Feasibility (4/20/2015-4/20/2018)
KQ 1: effectiveness	Total number of identified systematic reviews: Two <ul style="list-style-type: none"> SR from Italy compared effectiveness of 1st and 2nd generation EA. Full text not available, number of studies is unclear. Search date end September 2015. (Angioni et al. 2016) Metanalysis of bipolar EA (1st generation) and thermal balloon (2nd generation). 6 studies. Search date end November 2016. (Zhai et al. 2018) 	<u>Size/scope of review</u> Relevant Studies Identified: One <ul style="list-style-type: none"> Type: prospective observational (Laberge et al. 2015) <u>Clinicaltrials.gov</u> <ul style="list-style-type: none"> Recruiting: One Active: Four Complete: Five- no published results
KQ 2: harms	Total number of identified systematic reviews: # 1 <ul style="list-style-type: none"> Kohn 2018 published a review of pregnancy complications reported after EA. (Kohn et al. 2018) 	<u>Size/scope of review</u> Relevant Studies Identified: None <u>Clinicaltrials.gov</u> <ul style="list-style-type: none"> Recruiting: 0 Active: 0 Complete: 1- no results
KQ 3: comparative effectiveness	Total number of identified systematic reviews: One published, One protocol <ul style="list-style-type: none"> Most cross over: Cochrane review of surgery vs meds for heavy bleeding. 13 of 15 studies compared EA to medication or LNG. Search date end January 2016. (Marjoribanks, Lethaby, and Farquhar 2016) PROSPERO protocol. EA vs. LNG-IUS (Bergeron 2018) 	<u>Size/scope of review</u> Relevant Studies Identified: None <u>Clinicaltrials.gov</u> <ul style="list-style-type: none"> Recruiting: 1 Active: 0 Complete: 5- no results for 4; One published study (Famuyide et al. 2017)
KQ 4: comparative harms	Total number of identified systematic reviews: Three (same as above)	<u>Size/scope of review</u> Relevant Studies Identified: None <u>Clinicaltrials.gov</u> <ul style="list-style-type: none"> Recruiting: 0 Active: 0 Complete: 0

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question;

Summary of Findings

- Appropriateness and importance: The topic is both appropriate and important.
- Duplication: A new review would be duplicative of an existing product. Three recent reviews cover the literature on the topic.
- Impact: A new systematic review has limited potential. Although the current recommendations are based on older literature and expert opinion, these could be updated with the existing systematic reviews.
- Feasibility: A new review is not feasible. The evidence base is likely small.

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Appendix A. Selection Criteria Summary

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes
1b. Is the nomination a request for a systematic review?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes. Heavy menstrual bleeding, also known as menorrhagia, is a common gynecological problem.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes. Heavy menstrual bleeding impacts quality of life for many women and uses substantial healthcare resources.
2c. Represents important uncertainty for decision makers	Yes. Currently, it is unclear if EA is better than medical approaches, or if specific EA approaches differ in effectiveness or harms.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. EA allows women to defer or avoid hysterectomy. EA procedures typically cost from \$2500 to \$6000. In contrast, hysterectomy costs range from \$30,000 to \$50,000.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	Duplicative. There are three recent reviews of effectiveness, plus one of rare harms (pregnancy outcomes) A PROSPERO protocol plans to evaluate EA vs. LNG-IUS for both harms and effectiveness. There is very little in these reviews on effectiveness of EA vs. oral medications, and only one trial identified since 1997. A single 2018 review compares older (bipolar) to a single newer EA technique (thermal balloon). No review discusses patient characteristics. Search dates end between September 2015 and November 2016.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. ACOG published a practice bulletin in 2007. However, 7 of 12 recommendations are backed by expert opinion, and older literature.

Selection Criteria	Assessment
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Unsure
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: <ul style="list-style-type: none"> - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies) 	The search yielded only two new studies since 2015. (Famuyide et al. 2017; Laberge et al. 2015) ClinicalTrials.gov. identified ten recently completed trials, most relating to KQ1; none of these had published results.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; KQ=Key Question

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

Search date: January 1, 2015 to March 30, 2018
AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/

Appendix C. Search Strategy (Feasibility)

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations,

Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Date Searched: April 20, 2018

Searched by: Robin Paynter, MLIS

1. Menorrhagia/co, dt, su, th
2. ((Menorrhagi* or "abnormal uterine bleeding" or "heavy menstrua*") adj5 (ablat* or cryosurg* or cryotherap* or drug* or medical* or medication* or medicine* or microwave or non-ablat* or non-drug or non-pharm* or non-surg* or pharm* or surger* or therap* or treat*)).tw,kf.
3. or/1-2
4. ("adverse effect*" or "adverse event*" or complication* or harm* or "Her Option" or "Heated Free Fluid" or "Hydro ThermAblator").tw,kf. or ae,co,dt,su,th.fs.
5. and/3-4
6. limit 5 to (adaptive clinical trial or clinical trial, all or clinical trial or controlled clinical trial or pragmatic clinical trial or randomized controlled trial)
7. limit 5 to (meta analysis or systematic reviews)

Clinicaltrials.gov

Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation
Studies | Interventional Studies | Menorrhagia | ablation | Studies with Female
Participants | Adult

https://clinicaltrials.gov/ct2/results?cond=Menorrhagia&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&recrs=e&age_v=&age=1&gndr=Female&intr=ablation&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&lupd_s=&lupd_e=