

OBSTETRICS & GYNECOLOGY



NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:
obgyn@greenjournal.org.

Date: Jul 25, 2019
To: "Pleun Beelen" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1222

RE: Manuscript Number ONG-19-1222

Prognostic factors for the failure of endometrial ablation: a systematic review and meta-analysis

Dear Dr. Beelen:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 15, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors present a meta analysis of risk factors for failure of endometrial ablation. This is a very germane topic given the number of women undergoing this procedure as an alternative to hysterectomy. Overall this is a reasonably well written manuscript with a clear and cogent hypothesis that is substantiated by the literature review. I don't believe the conclusions are over stretched though I think there is some work to be done here on condensing the data. I have the following comments.

- 1) The authors should include either in the body of the work or in supplemental data the terms used for the data extraction.
- 2) Line 157- what was the logic in choosing at least 30 patient reviews? does this introduce bias into your data?
- 3) Line 168- I am concerned that three different sets of authors did the data review/extraction to decide which studies were included. If it isn't the same two authors, this introduces some bias as well as further complicates the data evaluation process. Why did the authors choose to do this?
- 4) Lines 212- 214; How did the incorporation of different types of trials affect your data? By pooling retrospective/case control trials with randomized control trials you are combining studies with different controls/measures and different types of bias. Did you consider separating these out?
- 5) The results section is way too long and verbose. I had difficulty getting through it given the volume of information that is presented. This should/could be condensed down into a table particularly the variables were not found to be associated with failure.
- 6) Lines 462- Please refrain from using terms like "this is the first" as you do not know this to be definitively true.
- 7) The weaknesses of this study need to be expanded upon in more than just the cursory way in which they are presented in this manuscript.

Reviewer #2: This interesting metaanalysis by Beelen colleagues examines various prognostic factors for reintervention following second generation meta-analyses. The paper conforms to the PRISMA guidelines and appears to be

methodologically sound. The findings are clinically useful and do provide guidance to clinicians. Likewise, this study points out the need for consistent collection and predefined outcomes; a process that the study points out is already under way. The following points are intended to strengthen the manuscript:

Major suggestions:

- * Though the study addresses the issue of HR vs OR- it is somewhat dissatisfying to not see this addressed numerically. The study only includes women with at least 12 months of follow up but understanding the distribution of re-intervention would be helpful. If most occur in the first year this approach is very helpful but if most of the reinterventions occur at beyond this time period there may be an underappreciation of the total risk.
- * Definitions of key exposures could be better defined. E.g. Uterine Length (I assume this is uterine length by sound at procedure but it is unclear) and Tubal ligation (is this only at the time of procedure or can it occur at the time of the procedure which is indicated if the woman is not either with a partner with a vasectomy or not sexually active).
- * There has been a lot of controversy about technique (balloon vs. RFA vs HTA)- I would encourage the authors to consider this exposure as well.
- * I would ask that the total number of number of patients included appear in the abstract
- * The tables would markedly benefit from either the number of participants and the prevalence of interventions.
- * I would ask that the results be written. The paper is very long (5231 and the results are iteratively repeated for the 10 exposures lines 228 to 410. The authors should make the tables more robust and work to condense the commentary for the reader.
- * Age is variably discussed using cutoffs of 35, 40 and 45 all of which were statistically significant. This nuance is not presented in the abstract and should be better captured as many readers do not stray beyond the abstract.
- * The authors attempt to address other issues like satisfaction, composite outcomes etc. This paper is already too complex and these issues should not be addressed.

Minor suggestions:

- * Line 81 clarify if the tubal ligation was prior to the ablation
- * Line 249 no should be not (this error occurs multiple times e.g. 376)
- * None the supplementary material is available.
- * The authors reference two tools for assessment of bias and no data is available.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Fig 2 (forest plots): It is not necessary and in fact, redundant, to include both the OR(CIs) with the log (OR) and their SE. Instead, should include columns of the counts that led to those ORs. Also, without actual counts, the reader cannot decide whether some of the NS associations may simply be due to inadequate statistical power.

lines 474-478: This acknowledged limitation, that is, that the studies mostly represent unadjusted ORs and those that included aORs were often adjusted for different variables, should be emphasized more as a potential limitation. From this review, younger age (replicated by several age thresholds), obesity, hx of tubal ligation and dysmenorrhea were each strongly associated with recurrence risk, so it is possible that these univariate OR results may be due to confounding, or that an interaction may magnify some associations.

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the

revision letter will be posted. Please reply to this letter with one of two responses:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."
*The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

6. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

7. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

8. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Reviews, 300 words. Please provide a word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. Line 462: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

14. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at <https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance>.

15. Figures

Figure 1: This figure may be resubmitted as-is with the revision.

Figure 2: Please provide high-res versions of these figures (eps, tiff, jpeg, etc.). Please update legend to include the differences between each forest plot (will be relabeled 2A-2I).

16. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifauth.htm>.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

17. If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

- * A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and
- * A point-by-point response to each of the received comments in this letter.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 15, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

N. C. Chescheir, MD
Editor-in-Chief
The Green Journal: Obstetrics & Gynecology

Veldhoven, 8/15/2019

Dear Nancy C. Chescheir,

Thank you for reviewing our manuscript entitled *Prognostic factors for the failure of endometrial ablation: a systematic review and meta-analysis* (number ONG-19-1222), which we have submitted for publication to The Green Journal: Obstetrics & Gynecology. We have read your comments and the comments of the reviewers with interest and have tried to adjust our manuscript appropriately. The revised manuscript is uploaded. Our alterations are indicated with track changes. Our reply to the comments of the referees and editors is summarized below. We agree to publish this point-by-point response as supplemental digital content.

The short title which can be used as a running foot is '*Prognostic factors for endometrial ablation*'.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

We have read the Author Guidelines before submitting the cover letter with point-by-point response.

We look forward to hearing from you regarding our resubmission and to respond to any further questions and comments you may have.

Yours sincerely,

On behalf of all co-authors,

Pleun Beelen

REVIEWER COMMENTS:

Reviewer #1: The authors present a meta analysis of risk factors for failure of endometrial ablation. This is a very germane topic given the number of women undergoing this procedure as an alternative to hysterectomy. Overall this is a reasonably well written manuscript with a clear and cogent hypothesis that is substantiated by the literature review. I don't believe the conclusions are over stretched though I think there is some work to be done here on condensing the data. I have the following comments.

Thank your for reviewing our manuscript. We have read your comments with interest and tried to answer the questions as good as possible. We adjusted our manuscript based on your suggestions.

1) The authors should include either in the body of the work or in supplemental data the terms used for the data extraction.

We included the terms used for data extraction in the body of the work ('methods'- 'data collection process', page 7 of the revised manuscript, lines 173-177):

"The following data were extracted for each selected study: names of the authors, year of publication, study design, used ablation technique, follow-up time, prevalence of surgical re-interventions, other reported outcome measures, described prognostic factors, and the results of the prognostic factors (raw data and measures of association)."

Our exact search strategy is given in the Supplementary Appendix (Appendix 1, page 2):

"Search Medline 11-02-2019

((("EA Techniques"[Mesh]) AND "Prognosis"[Mesh])) OR (((endometri[tiab] AND (ablat*[tiab] OR destruct*[tiab] OR resect*[tiab]))) AND (prognos*[tiab] OR long term[tiab] OR outcome*[tiab] OR late onset[tiab])))"*

2) Line 157- what was the logic in choosing at least 30 patient reviews? does this introduce bias into your data?

Endometrial ablation is a frequently performed procedure so there are many studies in which the outcomes of large study populations are described. Therefore, we chose to exclude studies with a small study population. Most studies with a small study population are case reports and case series in which only unique cases are described. With these studies nothing can be told about prognostic factors, because you need a bigger population for these analyses. After discussion with all authors we agreed to a margin of at least 30 patients. Eventually we only excluded one study, which examined

prognostic factors, due to a small study population (Figure 1, Flow diagram of study selection). Therefore, we do not think that this margin introduced bias to our data.

3) Line 168- I am concerned that three different sets of authors did the data review/extraction to decide which studies were included. If it isnt the same two authors, this introduces some bias as well as further complicates the data evaluation process. Why did the authors choose to do this?

The reviewer is right that data extraction is done by different sets of authors. The assessment of eligibility of full-text studies was done by two independent reviewers to ensure accuracy of the selection. The subsequent data extraction was done by two independent authors as well however in three different combinations (PB/IR; PB/WS; IR/WS) because of efficiency reasons. We could not find any information (e.g. the Cochrane Collaboration Guidelines for conducting Systematic Reviews) whether the authors for data extraction, should be the same authors as of the study selection. During pilot-testing of data extraction, we performed an assessment of agreement between the authors on twenty studies to ensure that the process is reproducible and reliable. Between the authors there was a high rate of agreement. In case of disagreement there was a discussion between the authors, which resulted in more consensus in the data extraction of the subsequent studies.

4) Lines 212- 214; How did the incorporation of different types of trials affect your data? By pooling retrospective/case control trials with randomized control trials you are combining studies with different controls/measures and different types of bias. Did you consider separating these out?

This is a relevant point raised by the reviewer. We did consider to separate the different types of studies before we performed the analyses. However, the studies which could be included in the meta-analysis are all observational studies. The randomized controlled trials included in our review did not describe our primary outcome (surgical re-intervention). They analysed the prognostic factors for the secondary outcomes (post-ablation pain, menstrual pattern, and patient satisfaction). We added this to the Results-section, page 8 of the revised manuscript, line 208-209:

“21 studies provided results that could be included in the meta-analysis (Figure 1). These studies were cohort studies and case-control studies.”

5) The results section is way too long and verbose. I had difficulty getting through it given the volume of information that is presented. This should/could be condensed down into a table particularly the variables were not found to be associated with failure.

We appreciate the comment of the reviewer, and adjusted our manuscript accordingly. We designed a new table with an overview of the data of our primary outcome (Table 1. Overview of included data for the primary outcome (surgical re-intervention)).

Because of the new table, the results section is shortened. The word count of the Results section was 3,039 words. In the revised manuscript the Results section counts 2,119 words. Page 8-17 of the revised manuscript, line 201-452.

6) Lines 462- Please refrain from using terms like "this is the first" as you do not know this to be definitively true.

As suggested by the reviewer we removed the sentence.

7) The weaknesses of this study need to be expanded upon in more than just the cursory way in which they are presented in this manuscript.

We expanded the limitations of this study in the discussion section, page 19 of the revised manuscript, line 513-531.

"Some limitations also have to be acknowledged. Although only limited exclusion criteria were applied and an extended systematic search was performed, we did not search for gray literature in this review. This could have led to an overestimation of the results. Furthermore, the included studies differed in study design, outcome measures, measures of effect size, follow-up duration, and ablation device that was used. Besides, different units and cut-off values were used for the same outcome measures. Due to this clinical and methodological heterogeneity the available literature was difficult to compare and we were not able to include all studies in the meta-analysis. Eventually we could combine the results of 21 of the 56 studies, enabling us to draw a more accurate conclusion about the influence of certain prognostic factors on the effect of endometrial ablation. To prevent selective reporting, we descriptively presented the results of the studies which used different outcome measures. Another limitation is that most studies included in this review only presented unadjusted ORs. The studies who did present adjusted ORs, adjusted for different sets of variables. The unadjusted ORs were pooled in the meta-analysis. It is therefore possible that the found association of the prognostic factors and re-intervention, might be due to confounding. To roughly examine the influence of confounders on the measured effect we performed sensitivity analyses in which we included studies who presented adjusted ORs. The pooled adjusted ORs only slightly differed from the pooled unadjusted ORs and it did not change the outcome. Nevertheless, it is still possible that the results are influenced by confounding."

Reviewer #2: This interesting metanalysis by Beelen colleagues examines various prognostic factors for reintervention following second generation meta-analysis. The paper conforms to the PRISMA guidelines and appears to be methodologically sound. The findings are clinically useful and do provide guidance to clinicians. Likewise, this study points out the need for consistent

collection and predefined outcomes; a process that the study points out is already under way. The following points are intended to strengthen the manuscript:

Thank you for reading our manuscript and your suggestions to improve it.

Major suggestions:

*** Though the study addresses the issue of HR vs OR- it is somewhat dissatisfying to not see this addressed numerically. The study only includes women with at least 12 months of follow up but understanding the distribution of re-intervention would be helpful. If most occur in the first year this approach is very helpful but if most of the reinterventions occur at beyond this time period there may be an underappreciation of the total risk.**

Unfortunately, the first suggestion is not completely clear to us. All the mentioned HRs and ORs of the included studies are written down in Appendix 6. Can you clarify this suggestion if it is still eligible to add this to our manuscript?

In several studies with at least 5 years follow-up, it is reported that most re-interventions occurred within 2 years after the initial ablation. In a cohort-study of Cooper et al, which included 14,078 women who underwent endometrial ablation, it was shown that 19.7% of these women went on to have a hysterectomy, with a median time of 1.25 years between both interventions.⁽¹⁾ Only 15 (27%) of the included studies in our review had a follow-up which was less than 24 months. Three of these studies (Julian, Kreider and Iglesias) were included in one of the meta-analysis. They reported re-intervention rates of 10.7%-18.3%, which is comparable with the other included studies. Therefore, it is unlikely that the chosen follow-up period of at least 12 months resulted in underappreciation of the total risk of re-intervention.

*** Definitions of key exposures could be better defined. E.g. Uterine Length (I assume this is uterine length by sound at procedure but it is unclear) and Tubal ligation (is this only at the time of procedure or can it occur at the time of the procedure which is indicated if the woman is not either with a partner with a vasectomy or not sexually active).**

Unfortunately, the method of measuring the length of the uterus was not always described in the included studies. It was mostly performed by ultrasound or by uterine sounding. In some studies, the length of the whole uterus (including myometrium) was used, in others the total sounding length, or the sounding length from the internal os until the fundus was used. We added this to the revised manuscript on page 16, line 440-441:

“Uterus length was measured with ultrasound or by uterine sounding and different measuring points were used.”

We only included studies in which tubal ligation in history was described. In some studies, the feasibility of concurrent tubal ligation and endometrial ablation is examined, but these studies were excluded. To clarify this point we added the following to the revised manuscript on page 9, line 230-231:

“These prognostic factors are; age, myomas, tubal ligation prior to endometrial ablation (no concurrent intervention), BMI, parity, pre-existing dysmenorrhea, caesarean delivery, bleeding pattern, uterus position, and uterus length.”

* **There has been a lot of controversy about technique (balloon vs. RFA vs HTA)- I would encourage the authors to consider this exposure as well.**

We appreciate the suggestion of the reviewer however we feel that this technical distinction falls outside the scope of this study in which we focus on the patient characteristics instead of the technique. Moreover, a recent systematic review about this topic is published in the Cochrane Library on 22 January 2019 by Bofill Rodriguez et al.⁽²⁾ They conclude that there is no evidence for a convincing difference between the second-generation techniques in terms of satisfaction or bleeding pattern.

* **I would ask that the total number of number of patients included appear in the abstract**

Thank you for this suggestion. We now added the total number of patients included in this review in the abstract of the revised manuscript on page 3, line 78.

“In these 56 studies 157,830 women were included.”

* **The tables would markedly benefit from either the number of participants and the prevalence of interventions.**

As suggested by the reviewer we now added a table with this information (Table 1. Overview of included data for the primary outcome (surgical re-intervention)).

* **I would ask that the results be written. The paper is very long (5231 and the results are iteratively repeated for the 10 exposures lines 228 to 410. The authors should make the tables more robust and work to condense the commentary for the reader.**

The same point was raised by reviewer 1 (point 5). We now shortened the results section and added Table 1. Overview of included data for the primary outcome (surgical re-intervention).

* **Age is variably discussed using cutoffs of 35, 40 and 45 all of which were statistically significant. This nuance is not presented in the abstract and should be better captured as many readers do not stray beyond the abstract.**

We acknowledge the advice of the reviewer, and integrated this feedback. We added the pooled odds ratios of the other categories (≤ 40 years and ≤ 45 years) to the abstract of the revised manuscript on page 3, line 82 as follows:

“Younger age ($age \leq 35$ OR 1.68; $age \leq 40$ OR 1.58; $age \leq 45$ OR 1.63), tubal ligation (OR 1.46), and pre-existing dysmenorrhea (OR 2.12) were associated with an increased risk of surgical re-intervention.”

* **The authors attempt to address other issues like satisfaction, composite outcomes etc. This paper is already too complex and these issues should not be addressed.**

In our opinion surgical re-intervention is an important outcome measure in heavy menstrual bleeding studies. As it is an objective outcome measure it gives reliable information about the influence of possible prognostic factors. Therefore, we chose this outcome as the primary outcome measure. However, we knew before the beginning of this study that a wide variety of treatment outcomes are being used in heavy menstrual bleeding studies. Therefore, we chose to also include studies which used post-ablation pain, menstrual pattern and patient satisfaction as outcome measures. If we had only focused on surgical re-intervention as an outcome measure, we would have had to exclude half of the studies which reported on prognostic factors. In our opinion, this would have led to selective reporting of the results. We agree that this design causes complexity of the review, so alternatively we shortened our results section and more information about the secondary outcomes can be collected from Appendix 5.

Fortunately, The COMET initiative (<http://www.comet-initiative.org/studies/details/789>) is working on a core outcome set for heavy menstrual bleeding (*reference 77 in the revised manuscript*). This will hopefully be used in all future HMB studies, which will make it easier to combine the different heavy menstrual bleeding studies

Minor suggestions:

* **Line 81 clarify if the tubal ligation was prior to the ablation**

As requested by the reviewer, we adjusted the text on page 9 of the revised manuscript, line 230-231 as follows:

“Tubal ligation prior to endometrial ablation (no concurrent intervention)”

* **Line 249 no should be not (this error occurs multiple times e.g. 376)**

Thank you for this comment. We adjusted the text on page 10, line 264; page 11, line 279; page 13, line 335, page 14, line 378 of the revised manuscript.

*** None the supplementary material is available.**

We apologize for this inconvenience, and hope the reviewer is able to see the supplementary material in the revised manuscript.

*** The authors reference two tools for assessment of bias and no data is available.**

Again we apologize for this inconvenience. The data of the assessment of bias were added in the supplementary material (Appendix 3).

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Fig 2 (forest plots): It is not necessary and in fact, redundant, to include both the OR(CIs) with the log (OR) and their SE. Instead, should include columns of the counts that led to those ORs. Also, without actual counts, the reader cannot decide whether some of the NS associations may simply be due to inadequate statistical power.

We changed our forest plots by using the raw data presented in the studies (with actual counts of re-intervention and prognostic factors). Because of this, some ORs changed a little, as in the first version we used the ORs mentioned in the studies. Three studies did not report the raw data for some prognostic factors, so they were excluded from the meta-analysis (Wishall et al (4 prognostic factors), El-Nashar et al (2 prognostic factors) and Peeters et al (1 prognostic factor)). With the inverse variance method, it was possible to include these studies to the forest plots.

Because the new forest plots give more information, we chose to include these in the new version. If you prefer the old forest plots, we are willing to undo this change.

We added information to the data synthesis section on page 8 of the revised manuscript, line 197:

“Raw data was used to compute ORs of the studies included in the meta-analysis.”

lines 474-478: This acknowledged limitation, that is, that the studies mostly represent unadjusted ORs and those that included aORs were often adjusted for different variables, should be emphasized more as a potential limitation. From this review, younger age (replicated by several age thresholds), obesity, hx of tubal ligation and dysmenorrhea were each strongly associated with recurrence risk, so it is possible that these univariate OR results may be due to confounding, or

that an interaction may magnify some associations.

We described this limitation in the discussion section, page 19-20 of the revised manuscript, line 523-531 as follows:

“Another limitation is that most studies included in this review only presented unadjusted ORs. The studies who did present adjusted ORs, adjusted for different sets of variables. The unadjusted ORs were pooled in the meta-analysis. It is therefore possible that the found association of the prognostic factors and re-intervention, might be due to confounding. To roughly examine the influence of confounders on the measured effect we performed sensitivity analyses in which we included studies who presented adjusted ORs. The pooled adjusted ORs only slightly differed from the pooled unadjusted ORs and it did not change the outcome. Nevertheless, it is still possible that the results are influenced by confounding.”

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

A. OPT-IN: Yes, please publish my point-by-point response letter.

B. OPT-OUT: No, please do not publish my point-by-point response letter.

We agree with publishing our point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

This is checked with all the co-authors.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

We guarantee that this manuscript is honest, accurate, and transparent. The statement is included in the cover letter.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

All the used gynecological terms were checked with the reVITALize definitions. No problems occurred.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

The manuscript counts 19 pages (excluding refereces). The word count of the manuscript is 4,451 words.

6. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

*** All financial support of the study must be acknowledged.**

*** Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.**

*** All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.**

*** If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).**

We meet the above stated requirements.

7. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

'Prognostic factors for endometrial ablation' can be used as running foot.

8. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

The précis is incorporated in the manuscript.

9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Reviews, 300 words. Please provide a word count.

The abstract was checked carefully after implementing the revisions. The total word count of the abstract is 300 words.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online at <http://edmgr.ovid.com/ong/accounts/abbreviations.pdf>. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

Some abbreviations were spelled out after checking the selected list (endometrial ablation (EA) and heavy menstrual bleeding (HMB)).

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

We rephrased the sentences in which the virgule symbol was used.

12. Line 462: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

As suggested by the editor and reviewer we removed this sentence.

13. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here:http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

We included a table in this revised version (Table 1. Overview of included data for the primary outcome (surgical re-intervention)). This table meets the requirements of the Table Checklist.

14. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear

replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at <https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance>. The version of the ACOG document (Management of Abnormal Uterine Bleeding Associated with Ovulatory Dysfunction) we cited is still available.

15. Figures

Figure 1: This figure may be resubmitted as-is with the revision.

We resubmitted this figure as-is.

Figure 2: Please provide high-res versions of these figures (eps, tiff, jpeg, etc.). Please update legend to include the differences between each forest plot (will be relabeled 2A-2I).

We uploaded high-resolution versions of the figures as pdf-files. The figures are relabeled as Figure 2A-2I. In case another type of file is preferred, we can supply this.

16. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifaauth.htm>.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

We will keep an eye out for this e-mail if our manuscript is accepted for publication.

17. If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

*** A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and**

*** A point-by-point response to each of the received comments in this letter.**

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

All the co-authors were involved in writing the revised manuscript and this cover letter with point-by-point response. The Instructions for Authors have been read.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Aug 15, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Thank you for the suggestions in this cover letter to improve our manuscript. Our reply to the comments of the reviewers and editors is summarized above.

References

1. Cooper K, Lee A, Chien P, Raja E, Timmaraju V, Bhattacharya S. Outcomes following hysterectomy or endometrial ablation for heavy menstrual bleeding: retrospective analysis of hospital episode statistics in Scotland. *BJOG : an international journal of obstetrics and gynaecology*. 2011;118(10):1171-9.
2. Bofill Rodriguez M, Lethaby A, Grigore M, Brown J, Hickey M, Farquhar C. Endometrial resection and ablation techniques for heavy menstrual bleeding. *The Cochrane database of systematic reviews*. 2019;1:Cd001501.