OBSTETRICS & GYNECOLOGY

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- 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: Dec 17, 2021
To: "Quaker E Harmon" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-2309

RE: Manuscript Number ONG-21-2309

Depot medroxyprogesterone acetate and uterine leiomyoma development using prospective ultrasounds

Dear Dr. Harmon:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

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 Jan 07, 2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS

1. Please consider modification of the title to "Depot Medroxyprogesterone Acetate Use and the Development and Progression of Uterine Leiomyoma" or something similar.

REVIEWER COMMENTS:

Reviewer #1: The authors performed a prospective, longitudinal analysis of 1,693 AA women without a prior diagnosis of uterine fibroids. They evaluated ever use, recent use, and cumulative use of DMPA on fibroid incidence, growth and loss every 20 months by ultrasound over up to 5 years of follow-up. The had a high retention rate with 79% attending all 4 study visits.

1. Abstract, Methods: Based upon my reading of the supplemental materials, this study was not designed to assess the impact of DMPA use on uterine fibroids. The study was powered "based on 3 hypotheses unrelated to DMPA use". It is important to clarify that this is a sub study in the manuscript.

2. Introduction: Concise and appropriately representative of the manuscript.

3. Study Population, line 51: The reference is redacted, which may be part of the issue, but there needs to be clarity on the initial goal and design of the study cohort (which was not specific to DMPA) versus the goal of the current study/manuscript (as noted in #1 above).

4. Study Population, line 58: I recommend briefly outlining the "baseline activities".

5. Study Population, lines 64-65: This was a bit unclear. Potentially change to "91% attended visit #4…".

6. Fibroid Outcomes, lines 73-75: Recommend adding that the 6 largest fibroids were measured. Additionally, it is not stated but I assume both abdominal and vaginal imaging was used? Additionally, were the ultrasonographers blinded to the patient's demographic variables and DMPA use?

7. Fibroid Outcomes, line 81: I feel it would be beneficial to include supplemental figure 2 (flow chart of participants) in the main article (not supplemental).

8. Fibroid Outcomes, lines 82-88: I assume the fibroid growth analysis also excluded any intervals including or following a myomectomy, hysterectomy, or UAE as is noted in for the fibroid loss section (lines 92-93).

9. DMPA Use Variables, line 104: How was use of other forms of hormonal contraception controlled for in the study? Was use of a GnRH analogue also taken into account?

10. Discussion, lines 246-252: Another important limitation is the variability in ultrasound assessment, particularly for such small fibroids (0.5cm). Also important to include recall bias for use and length of use of DMPA and other hormone modifying medications.

Reviewer #2: Thank you for this opportunity to review this manuscript entitled "Depot medroxyprogesterone acetate and uterine leiomyoma development using prospective ultrasounds"

This is a prospective cohort study of fibroid incidence and growth that enrolled 1693 participants from 2010 to 2012.

Comments:

General:

- This manuscript presents a large dataset with large number of variables, understanding the effort behind this work cannot be totally grasped without reviewing the supplemental material. On the other hand, the writing style is hard to follow to the average reader.
- The biggest question I have is the relevance of the findings to clinical practice as all the fibroids are really small, participants are asymptomatic.

Material & Methods:
- Enrollment was restricted to African-American women only, this will limit the generalizability of the results.
- All participants had no clinical diagnosis of fibroids, this limits how much the findings are relevant to symptomatic patients
- More explanation on how the sample size was calculated specifically in regards of ratio between case (920) and control (690) [some explanation of the sample size calculation was mentioned in the supplemental material, I encourage the authors to include it is the main M&M section]
- More explanation about how the ultrasonographers were blinded to the exposure of DMPA is needed to prevent information bias
- More explanation about the utilization of controls to prevent confounding bias is needed, examples: pregnancy vs non-pregnancy, duration since last pregnancy, duration of use of DMPA, smoking, utilization of other hormonal contraceptives vs never user of any hormonal contraceptives (line 120: the referent group includes participants who have only ever used non-DMPA hormonal contraception, as well as those who have never used any hormonal contraception.)

Discussion:
- Is very well written, supported by the results, tries to find a biological plausibility for the findings.

Reviewer #3: Though years in the making, the authors present a timely study assessing fibroid development in the setting of DMPA use. While there are many components to the methodology, the authors had a sound statistical analysis and sensitivity analyses leant support to their findings.

Comments to the authors:
1. The abstract is specific and representative of the article. It is clear to the reader the exposure and intended outcomes of the study.

2. The introduction clearly states the scope of the problem, the current gaps in the literature and some of the limitations in prior assessment of fibroid development.

3. The methods are comprehensive; however, the reader can get lost in the current format. More clarification is needed on why fibroid growth was performed for a subset of fibroids (lines 82-83). Is this subset specific to the fibroids or to the individual subject? This needs some clarification. The description on selection for covariates is helpful

4. The results of this study support the conclusion that recent DMPA exposure did impact fibroid development (lower growth rates and fibroid shrinkage). Their findings suggest that DMPA within 2 years demonstrates greatest benefit with regard to growth. The tables are helpful in concisely presenting their findings, though figure 1 is perhaps more convincing with regard to the impact and the justification of using DMPA 8+ years prior as nearly equivalent to never DMPA users—the greatest benefit is within 2 years and decreasing benefit with more time passing from DMPA exposure.

5. The discussion is clearly written. The authors do highlight the limitations of their study. They comment on fibroids that could be tracked over time. Given the number of ultrasounds, a second review of all images would be overly burdensome, but perhaps the authors could address here (or in methods) if any effort was made for subjects to have the same sonographer for follow up imaging (which would potentially limit variability in image quality and fibroids detected).

6. All references appear to be appropriate for the manuscript.

7. The supplemental material was reviewed and while helpful, likely in excess of what is need for the average reader.

STATISTICAL EDITOR COMMENTS:

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

Table 2 and line 22: Need to clarify whether the HR 0.6 (0.4-1.0) includes 1.0, ie, is NS per line 159. Should embolden or otherwise demarcate for the reader which HRs and aHRs were statistically significant. Need to include a column of median follow-up with IQR for the various row entries.

Table 3: Should indicate for reader which differences were statistically significant. Need to include a column of median follow-up with IQR for the various row entries.

Table 4: Need to clarify whether the HR 1.3(1.0-1.6) includes 1.0, ie, is NS. Need to indicated for reader which differences were statistically significant. Need to include a column of median follow-up with IQRs for the row entries.

Supplementary figures 1 and 2 are important re: any loss to follow-up in this long term study and should be in main text.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the

manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

5. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Methods section of the body text, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

6. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

8. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

9. 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).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

10. Precis: Please edit this sentence to remove the data. It isn't necessary here.

11. 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 limit for Original Research articles is 300 words. Please provide a word count.

12. 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.

13. 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.

14. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

15. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

16. 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.

17. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, 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 references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and 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.

18. Figure 1: Please upload as a figure file on Editorial Manager.

19. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

20. 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 https://wkauthorservices.editage.com/open-access/hybrid.html.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. 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. Do not omit your responses to the Editorial

Office or Editors' comments.

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 Jan 07, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason Wright, MD
Editor-in-Chief, Elect

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

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RE: Manuscript Number ONG-21-2309

Depot Medroxyprogesterone Acetate Use and the Development and Progression of Uterine Leiomyoma

Dear Editor and Reviewers,

Thank you for the quick review and the opportunity to revise our manuscript. We affirm that we have fully reviewed the instructions to authors. We have included a point-by-point response to the reviewers below.

EDITOR COMMENTS

1. Please consider modification of the title to "Depot Medroxyprogesterone Acetate Use and the Development and Progression of Uterine Leiomyoma" or something similar.

Author Response: The title has been edited as suggested

REVIEWER COMMENTS:

Reviewer #1: The authors performed a prospective, longitudinal analysis of 1,693 AA women without a prior diagnosis of uterine fibroids. They evaluated ever use, recent use, and cumulative use of DMPA on fibroid incidence, growth and loss every 20 months by ultrasound over up to 5 years of follow-up. The had a high retention rate with 79% attending all 4 study visits.

1. Abstract, Methods: Based upon my reading of the supplemental materials, this study was not designed to assess the impact of DMPA use on uterine fibroids. The study was powered "based on 3 hypotheses unrelated to DMPA use". It is important to clarify that this is a sub study in the manuscript.

   Author Response: We have edited the abstract and the methods to reflect that SELF is an observational study with the primary aims of investigating reproductive tract infections, vitamin D insufficiency, and genetic ancestry, but that the original proposal emphasized that a broad range of exposures would be examined, including hormonal exposures.

   Manuscript Edits:
   Abstract (Line 7): For this sub-study, years since last use of DMPA was ascertained from questionnaire data at every visit.
   Methods (Lines 46-47): The Study of Environment, Lifestyle & Fibroids (SELF) is a prospective cohort study of fibroid incidence and growth[11] with collection of a broad range of exposures, not limited to the primary factors of interest: reproductive-tract infections, vitamin D insufficiency and genetic ancestry.

2. Introduction: Concise and appropriately representative of the manuscript.

   Author Response: Thank you

3. Study Population, line 51: The reference is redacted, which may be part of the issue, but there needs to be clarity on the initial goal and design of the study cohort (which was not specific to DMPA) versus the goal of the current study/manuscript (as noted in #1 above).

   Author Response: With redaction removed, we now include the reference which we hope will provide interested readers with a full description of the aims and design of SELF. We have also added a line to the methods section to highlight the primary goals

   Manuscript Edits:
   Line 46-47: The Study of Environment, Lifestyle & Fibroids (SELF) is a prospective cohort study of fibroid incidence and growth[11] with collection of a broad range of exposures, not limited to the primary factors of interest: reproductive-tract infections, vitamin D insufficiency and genetic ancestry.

4. Study Population, line 58: I recommend briefly outlining the "baseline activities".

   Author Response: These activities are included in the next paragraph and are not repeated in this paragraph for brevity.

   Manuscript Edits:
   Lines 57-59: Visits included collection of data via questionnaires, interviews, and a clinical visit for ultrasound examination and measurement of weight and height

5. Study Population, lines 64-65: This was a bit unclear. Potentially change to "91% attended visit #4…".

   Author Response: We have edited this paragraph to improve clarity.

   Manuscript Edits:
   Line 59-64: Visits were delayed for pregnant participants until 3-4 months post-pregnancy. Active engagement of participants through newsletters and an excellent study staff, resulted in a high retention rate. Participants who missed a follow-up were invited to the next follow-up. At the final study visit (Visit #4) 91% completed data collection. Over the course of the study 95% attended at least 2 visits, and 79% attended all 4 study visits) (Appendix 1).

6. Fibroid Outcomes, lines 73-75: Recommend adding that the 6 largest fibroids were measured. Additionally, it is not stated but I assume both abdominal and vaginal imaging was used? Additionally, were the ultrasonographers blinded to the patient's demographic variables and DMPA use?

   Author Response: A transvaginal approach was attempted for all ultrasounds. If the transvaginal approach was not tolerated by the participant, or visualization was not optimal, a transabdominal approach was also attempted. We did not include ultrasound results when they came from a transabdominal exam only (<1% of ultrasounds).

   The sonographers had no access to participant study data but were aware of apparent demographic features.

   We have edited this section to include the maximum number of fibroids measured.

Manuscript Edits:
Lines 73-75: Experienced sonographers followed a study protocol[11,13] for ultrasound examinations (Appendix 1) and were unaware of exposure status. Ultrasound was conducted using a transvaginal approach, with the addition of a transabdominal approach if needed. The six largest fibroids ≥0.5 cm in any diameter were counted, localized, and measured, but most women had no more than 2 or 3.

7. Fibroid Outcomes, line 81: I feel it would be beneficial to include supplemental figure 2 (flow chart of participants) in the main article (not supplemental).

   Author Response: We are happy to include if supported by the editor. We have included a publication ready Figure and would be happy to edit the text and Supplemental Materials as needed.

8. Fibroid Outcomes, lines 82-88: I assume the fibroid growth analysis also excluded any intervals including or following a myomectomy, hysterectomy, or UAE as is noted in for the fibroid loss section (lines 92-93).

   Author Response: You are correct. We have edited the text in the methods section.

   Manuscript Edits:
   Lines 88-89: No fibroids imaged after procedures such as myomectomy or uterine artery embolization were included.

9. DMPA Use Variables, line 104: How was use of other forms of hormonal contraception controlled for in the study? Was use of a GnRH analogue also taken into account?

   Author Response: Given that this was a non-clinical population with mostly small fibroids, there were no participants who reported using a GnRH analogue. Use of oral contraceptives was common. We explored its potential role and found no confounding effects for incidence or loss, but it was potentially influential for growth, so was included in those models. We also explored effects of the hormonal IUD, though it was used much less frequently; we did not find evidence for confounding effects. We have edited the text as shown below.

   Manuscript Edits:
   Lines 127-129: Given these patterns, the referent group includes participants who have only ever used non-DMPA hormonal contraceptives, as well as those who have never used any hormonal contraceptive. Current use of birth control pills, the other frequently used contraceptive, was explored as a potential confounder but was only retained for the fibroid growth outcome.

10. Discussion, lines 246-252: Another important limitation is the variability in ultrasound assessment, particularly for such small fibroids (0.5cm). Also important to include recall bias for use and length of use of DMPA and other hormone modifying medications.

Measurement error

Author Response: Sonographers were trained in the study protocol to identify and measure such small fibroids, but we found early in the study that despite training, the measurement error for small fibroids was greater than for large (Moshesh M, Peddada SD, Cooper T, Baird D. Intraobserver variability in fibroid size measurements: estimated effects on assessing fibroid growth. J Ultrasound Med. 2014;33(7):1217-24). To account for this extra variability, our growth models included a term for measurement error by fibroid size. Although this information is included in the supplement, we have edited the limitations section to include this information.

Manuscript Edits:

Lines 266-268: Thirdly, ultrasound introduces measurement error that is greater for smaller fibroids[13]. We address this limitation by accounting for differences in measurement error by fibroid size in our model (Appendix 1).

Recall bias

Author Response: We recognize that there is measurement error in the time since last use of DMPA variable due to both recall error and the use of age, and not specific dates, to calculate the time since last use. Although we are not aware of a literature on the accuracy of recall of DMPA, use of oral contraception has been reported to be quite accurately recalled, especially when collected using a detailed telephone interview as we did (Hunter DJ, Manson JE, Colditz GA, et al. Contraception, 1997). We collected history of use for all forms of hormonal contraceptives at enrollment, including age starting and age of last use, so participants were encouraged to think through their use history. The time-dependent DMPA data collected during the study required much shorter recall since at each follow-up visit they were asked about use "since the last interview that occurred XX months ago" [XX refers to participant-specific listing of # months since her last interview]. Most importantly, as might be expected, we found little association with fibroid development for DMPA use several years in the past, suggesting that recall of recent use is most important. We have edited the discussion to include a reference for recall accuracy and measurement error.

Manuscript Edits:

Lines 255-263: Our study has limitations. First, we lack accurate data on duration of the last episode of DMPA use. However, we have reasonably good data on time since last DMPA use. Recall accuracy of hormonal contraceptive use has been reported to be high and we collected these data using a detailed telephone interview which enhances data quality[30]. Measurement error in the time since last DMPA use is unavoidable because we collected age at last use instead of date at last use. Nevertheless, the exposure showing strong associations with fibroid development was recent use, which is likely to be well-remembered. Further study with prospective follow-up of first-time DMPA users who will continue to use for variable periods of time would be valuable for evaluating the importance of length of DMPA use.

Reviewer #2: Thank you for this opportunity to review this manuscript entitled "Depot medroxyprogesterone acetate and uterine leiomyoma development using prospective ultrasounds"

This is a prospective cohort study of fibroid incidence and growth that enrolled 1693 participants from 2010 to 2012.

Comments:

General:

1. This manuscript presents a large dataset with large number of variables, understanding the effort behind this work cannot be totally grasped without reviewing the supplemental material. On the other hand, the writing style is hard to follow to the average reader.

   Author Response: We hope that the revisions made have improved the readability.

2. The biggest question I have is the relevance of the findings to clinical practice as all the fibroids are really small, participants are asymptomatic.

   Author Response: Although the participants in this study have mostly small fibroids and are asymptomatic, we think that the results have important clinical ramifications. An exposure, such as DMPA, which delays fibroid development, increases fibroid loss and reduces fibroid growth will delay the onset of symptoms and the need for medical or surgical interventions. As the larger, symptomatic fibroids have the most adverse health impacts, this delay could have profound impacts on long-term quality of life.

Material & Methods:

3. Enrollment was restricted to African-American women only, this will limit the generalizability of the results.

   Author Response: We designed the study with a focus on African-American women because they are at the highest risk of major medical interventions to treat fibroids and thus have the highest burden of disease. Although few studies have looked at DMPA and fibroids, the earliest report on this association was from a clinical population in Thailand which suggests that this exposure is relevant to other ethnic groups. Of course, similar studies in more diverse populations are needed.

4. All participants had no clinical diagnosis of fibroids, this limits how much the findings are relevant to symptomatic patients.

   Author Response: The newly developed fibroids identified during the study were small, of course, but by the end of the study 20% of those with fibroids had a fibroid ≥4cm, though we have not explored how many of these participants were symptomatic.

5. More explanation on how the sample size was calculated specifically in regards of ratio between case (920) and control (690) [some explanation of the sample size calculation was mentioned in the supplemental material, I encourage the authors to include it is the main M&M section].

Author Response: As a prospective cohort study we did not consider the ratio of cases and controls in the study design. As outlined in the Supplement, SELF was powered based on plausible incidence rates for uterine fibroids, based on prior models of cumulative incidence by age. We prefer to leave the power calculation as written in the supplement as they were formulated for the SELF study's primary goals.

6. More explanation about how the ultrasonographers were blinded to the exposure of DMPA is needed to prevent information bias.

   Author Response: You are correct, sonographers were unaware of exposure status. The text has been edited in the methods section.

   Manuscript Edits:
   Lines 72-73: Experienced sonographers followed a study protocol[11,13] for ultrasound examinations (Appendix 1) and were unaware of exposure status.

7. More explanation about the utilization of controls to prevent confounding bias is needed, examples: pregnancy vs non-pregnancy, duration since last pregnancy, duration of use of DMPA, smoking, utilization of other hormonal contraceptives vs never user of any hormonal contraceptives (line 120: the referent group includes participants who have only ever used non-DMPA hormonal contraception, as well as those who have never used any hormonal contraception).

   Author Response: For our cohort study, we controlled for confounding by the inclusion of covariates in our statistical models. The covariates included those mentioned in the comment as well as others found to be important in the modelling process. For all outcomes the differences in the estimate from the minimally adjusted and fully adjusted models were of small magnitude suggesting that measured confounding is not playing a large role. While unmeasured confounding is always a possibility, we explored some threats to bias in our sensitivity analysis and did not find evidence of this.

   We have expanded our discussion about possible confounding by use of oral contraceptives (see response to Reviewer #1, comment #9).

   Manuscript Edits:
   Lines 127-129: Current use of birth control pills, the other frequently used contraceptive, was explored as a potential confounder but was only retained for the fibroid growth outcome.

Discussion:

8. Is very well written, supported by the results, tries to find a biological plausibility for the findings.

   Author Response: Thank you

Reviewer #3: Though years in the making, the authors present a timely study assessing fibroid development in the setting of DMPA use. While there are many components to the methodology, the authors had a sound statistical analysis and sensitivity analyses leant support to their findings.

Comments to the authors:

1. The abstract is specific and representative of the article. It is clear to the reader the exposure and intended outcomes of the study.

   Author Response: Thank you

2. The introduction clearly states the scope of the problem, the current gaps in the literature and some of the limitations in prior assessment of fibroid development.

   Author Response: Thank you

3. The methods are comprehensive; however, the reader can get lost in the current format. More clarification is needed on why fibroid growth was performed for a subset of fibroids (lines 82-83). Is this subset specific to the fibroids or to the individual subject? This needs some clarification. The description on selection for covariates is helpful.

   Author Response:
   - We have edited the methods section and we hope this improves readability.
   - Regarding the matching of fibroids, we were not able to determine matches for all fibroids. When fibroids were in a similar location in the uterus from one visit to the next without competing fibroids in that same area, these were considered to be the same fibroid. We have updated the methods section to provide more information on the matching process.

   Manuscript Edits:
   Lines 84-89: Fibroid growth (change in the natural logarithm of the tumor volume) was calculated for fibroids <u>that could be matched across two successive visits</u>. <u>Matching individual fibroids across visits</u> was completed by the lead sonographer (TC) and one author (DDB) based on archived images and fibroid location. <u>Without a clear 'match' at successive visits, a fibroid was considered 'unmatched' and was not included in the analysis.</u> <u>No fibroids imaged after procedures such as myomectomy or uterine artery embolization were included</u>.

4. The results of this study support the conclusion that recent DMPA exposure did impact fibroid development (lower growth rates and fibroid shrinkage). Their findings suggest that DMPA within 2 years demonstrates greatest benefit with regard to growth. The tables are helpful in concisely presenting their findings, though figure 1 is perhaps more convincing with regard to the impact and the justification of using DMPA 8+ years prior as nearly equivalent to never DMPA users—the greatest benefit is within 2 years and decreasing benefit with more time passing from DMPA exposure.

   Author Response: Thank you.

5. The discussion is clearly written. The authors do highlight the limitations of their study. They comment on fibroids that could be tracked over time. Given the number of ultrasounds, a second review of all images would be overly burdensome, but perhaps the authors could address here (or in

methods) if any effort was made for subjects to have the same sonographer for follow up imaging (which would potentially limit variability in image quality and fibroids detected).

Author Response: Thank you. The same group of sonographers worked on the study throughout data collection. Training specific to the study protocol (an initial training and two refresher trainings) was the same for all sonographers. There was an ongoing review process of archived images that included an oversample of participants with fibroids to identify any issues over time. It was not possible however to schedule participants with the same sonographer for every study visit. Given word constraints we have added a statement about scheduling and sonographer training in the supplement.

Supplemental Material Edits:
Ultrasound examinations were conducted throughout the study with Phillips IU-22s, with the exception of 1 GE Logic 9 machine with a consistent group of sonographers. The initial and refresher study trainings of sonographers included care in distinguishing fibroids from other pathologic changes in the uterus including adenomyosis and polyps, protocol for conducting the exam, and recording the data. If any fibroids with at least one diameter of 0.5 cm or greater were detected, the largest six were measured in three separate passes through the uterus. At each pass the 3 perpendicular diameters were measured and recorded for each fibroid, and caliper placement was from outer border to outer border. It was not logistically feasible to schedule study participants with the same sonographer at every visit. Ongoing quality control throughout the study by the lead sonographer included the review of archived video and still images for every sonographer each month.

6. All references appear to be appropriate for the manuscript.

   Author Response: Thank you

7. The supplemental material was reviewed and while helpful, likely in excess of what is need for the average reader.

   Author Response: We recognize the supplemental material is detailed but believe that the material will be important for readers who wish to evaluate our procedures, given that is the first epidemiologic study to prospectively follow fibroid incidence and growth.

STATISTICAL EDITOR COMMENTS:

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

1. Table 2 and line 22: Need to clarify whether the HR 0.6 (0.4-1.0) includes 1.0, ie, is NS per line 159. Should embolden or otherwise demarcate for the reader which HRs and aHRs were statistically significant. Need to include a column of median follow-up with IQR for the various row entries.

   Author Response (Significance): The p-value for this estimate is 0.08, the confidence interval with additional decimal places is 95% CI: 0.406, 1.054. The p-value has been demarcated with a superscript and added as a footnote in Table 2 and in the Results Section (Line 187).

   Author Response (Median Follow-Up): For Tables 2-3 median follow-up by exposure status is not as informative in our prospective cohort study as it would be in an RCT. We have time varying exposures such that participants will change exposure groups over time. Additionally, eligibility for an outcome does not always start at enrollment. These two factors will result in differences in median follow-up time that are not a result of bias (competing risks, loss to follow-up). Please see below for some examples of how follow-up time will vary.

   In order to demonstrate follow-up time overall by exposure group, we have now included the median length of study participation with IQR in Table 1 for the sample as a whole and by baseline DMPA use. The length of study participation was the same by baseline exposure status with a range from first to third quartile of 4.7 years—5.0 years for those never exposed to DMPA and those ever exposed to DMPA. Given the tight range around the study protocol (5 years of follow-up) we choose not to report these values in the abstract as it would be redundant. We do report them in the results section.

   Manuscript Edits:

   Lines 176-178: Participants had a median length of study participation of 4.8 years (25^{th}-75^{th} percentiles: 4.7-5.0 years) with no difference by exposure to DMPA at baseline.

   Table 1: Now includes median (IQR) Follow-Up Time

Author Response:

Examples of DMPA use across study visits:

	Visit	DMPA Use	Ever/Never	Time Since Last Use
Participant #1	Visit 1	Never use	Never	Never
	Visit 2	Current use	Ever	Within 1.9Y
	Visit 3	Stops use	Ever	Within 1.9Y
	Visit 4	Not using	Ever	Within 2-4 Years
Participant #2	Visit 1	Last use 1 year before enrollment	Ever	Within 1.9Y
	Visit 2	Not using	Ever	Within 2-4 Years
	Visit 3	Not using	Ever	Within 2-4 Years
	Visit 4	Not using	Ever	Within 4-8 years
Participant #3	Visit 1	Last use 8 years before enrollment	Ever	8+ years since last use
	Visit 2	Not using	Ever	8+ years since last use
	Visit 3	Starts use	Ever	Within 1.9Y
	Visit 4	Continues use	Ever	Within 1.9Y

Because we have a time-varying exposure measure, participants contribute to multiple time since last use intervals and Participant #1 will contribute to both Never use of DMPA and Ever Use of DMPA.

- For **Table 2** we provide Person Years of follow-up as a measure of follow-up time which reflects the relative amount of at-risk time participants spend in each of the exposure categories. As the example above illustrates, there is movement between exposure categories over time. While the movement for time since last use can be in any direction, never users can only become ever users.

- For **Tables 3 and 4** we present the intervals at risk for each exposure category as an indicator of the distribution of the exposure and the sample size for each contrast. For both of these outcomes participants only enter the analysis when they develop a fibroid. Therefore, median follow-up time will reflect, in part, how long it takes to develop a fibroid. For instance, if a participant enters the study fibroid-free and develops a fibroid at visit 3, they will only be eligible for the final interval of analysis (approx. 1.5 years). This shorter follow-up time will not necessarily be a result of their DMPA exposure. Therefore, differences in median follow-up time by DMPA exposure for these analyses will not necessarily reflect bias (competing risks, loss to follow-up).

- If we have misunderstood this request, we are happy to work with the statistical editor to provide a more suitable measure.

2. Table 3: Should indicate for reader which differences were statistically significant. Need to include a column of median follow-up with IQR for the various row entries.

   Author Response (Significance): As none of the confidence intervals include the null value of 0% as an upper or lower limit (where the strict significance may be in question as in Comment #1) we choose to omit the p-values as recommended by the Editor (Comment #16).

   Author Response (Median Follow-Up): Please see response above

3. Table 4: Need to clarify whether the HR 1.3(1.0-1.6) includes 1.0, ie, is NS. Need to indicate for reader which differences were statistically significant. Need to include a column of median follow-up with IQRs for the row entries.

   Author Response (Significance): The p-value for this estimate is 0.0486; the 95% CI showing more decimal places is: 1.001, 1.583. The p-value has been demarcated with a superscript and added as a footnote in Table 4 (with 2 significant figures to clarify a value <0.05).

   Author Response (Median Follow-Up): Please see response above

4. Supplementary figures 1 and 2 are important re: any loss to follow-up in this long term study and should be in main text.

   Author Response: We do report that 91% of enrolled participants attended the final follow-up visit, but we are happy to include these figures in the main text if supported by the editor. We have included publication ready images and are happy to edit the supplement and text if required. We are close to our word limit however, so we prefer not to include these additional figures, but we leave this choice to the editor.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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.

   Author Response: I OPT-IN please publish my point-by-point response letter

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

Author Response: The manuscript has been unblinded.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

   Author Response: Co-authors have been alerted to complete the eCTA and report no conflicts of interest.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes). Race/ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases, missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

   Author Response: Our methods section describes the way in which race was collected and the rationale for restricting study enrollment to participants who identify as Black or African American.

   Use "Black" and "White" (capitalized) when used to refer to racial categories. The nonspecific category of "Other" is a convenience grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

   Author Response: We have changed the terminology to “Black” and “White” as requested. We retain “African American” in our description of our collection of race and ethnicity classification because that was used in the recruitment materials and eligibility determinations. We do not classify any individual as “Other” in this study.

5. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Methods section of the body text, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

   Author Response: Our IRB information is included in the Methods section and we report here that this study was approved by the IRBs of the National Institute of Environmental Health Sciences and Henry Ford Health Systems.

6. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

   Author Response: We have reviewed the reVITalize definitions and have changed contraception to contraceptives throughout the manuscript. We see no other definitions that require editing, but this list is new to us and we are happy to make additional edits if we missed something.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

   Author Response: The title page, precis, abstract, text, tables and figure legends are 5,399 words. The legends for the supplemental figures would add 16 words (Study Visits and Retention) and 181 words (Flow chart for fibroid incidence and fibroid loss analyses).

8. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

   Author Response: We have edited the title as requested. It is 97 characters including spaces

9. 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).

* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

Author Response: Funding support is acknowledged on the title page. We had no manuscript preparation assistance that is not acknowledged. We have written permission from the individuals we acknowledge. These results were present at the Annual Meetings of the Society of Epidemiologic Research and the Society for Perinatal and Pediatric Epidemiologic Research (noted on the title page). No preprints of this work have been posted

10. Precis: Please edit this sentence to remove the data. It isn't necessary here.

    Author Response: The precis has been edited as requested

    Manuscript Edits:
    Precis: Current or recent use of depot medroxyprogesterone acetate was associated with lower fibroid incidence, reduced fibroid growth and increased fibroid loss.

11. 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.

    Author Response: We confirm that the abstract matches the data presented in the manuscript.

12. In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words. Please provide a word count.

    Author Response: Abstract word count is 300.

13. 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.

    Author Response: We note that DMPA is an approved abbreviation. We do not see the abbreviations for statistical measures of effect (RR, HR, CI) but we assume they are permitted. We are happy to edit if we are in error.

14. 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.

    Author Response: We have edited out the virgule symbol. We note that this restriction does not allow the inclusion of “race/ethnicity” in the text. We have edited our methods to indicate that race is a social construct.

15. ACOG avoids using "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

    Author Response: “Provider” is not used in the manuscript.

16. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

    Author Response: At the request of the statistical editor we have added p-values where the null value is included at the limit of a confidence interval to provide information on statistical significance.

    Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

    Author Response: Percentages are presented with fewer than 1 decimal place and p-values do not exceed 3 decimal places.

17. 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.

    Author Response: Tables have been reviewed.

18. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

    Author Response: Reference style has been checked and updated where necessary.

    In addition, 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 references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

    Author Response: ACOG Practice Bulletin 96 has be replaced with Practice Bulletin 228 for Reference #6. Clinical Opinion No.602 (Reference #36) has not been withdrawn.

If the reference you are citing has been updated and 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.

Author Response: The newer Practice Bulletin (No. 228) continues to support the statement in the manuscript.

19. Figure 1: Please upload as a figure file on Editorial Manager.

    Author Response: Figure 1 and Supplemental Figures 1 and 2 have been uploaded as TIFFs and in the original PPTX format.

20. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

    Author Response: The supplemental material has been re-formatted

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