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.*

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

Date: Feb 21, 2020
To: "Alison Edelman" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-130

RE: Manuscript Number ONG-20-130

Treatment of Unfavorable Bleeding Patterns in Contraceptive Implant Users: A Randomized Trial

Dear Dr. Edelman:

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 Mar 13, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors present a double blinded RCT comparing Tamoxifene vs. placebo for prolonged bleeding or spotting B/S while on etonorgestrel implant contraception. The authors should be applauded for addressing a common clinical problem and barrier to continued implant contraceptive use.

Abstract:

1. Line 61 The objective implies the primary outcome but this should be stated in the abstract before the secondary outcomes.

2. Line 69 Was this a cross over? It is not clear the way it is worded.

Introduction:

1. This was an excellent review of the problem and prior studies along with the rationale for sustained improved bleeding profiles.

Methods:

1. Line 105 What was the purpose of using < 18 y.o and how was this addressed from a consent stand point, IRB and parental consent?

2. Line 106 Why was 30 days of use vs 90 used? AUB is should be clearly discussed and general recommendations of concerns are usually put at 90 days or 3 mths. There should also be further discussion of whether patients had the implant placed postpartum and if they were breast feeding. It looks like this was addressed in line 110.

3. Line 115 The washout period is important and glad it was included.

4. Line 118 Was there assessment of the cavity with TVUS or sonohystogram? This would not be detected by PE.

5. Line 126 Describe specifics of randomization such as permuted blocks or opaque envelopes etc. This is addressed in lines 137-140.

6. Line 129 The second phase was all tamoxifene. Why was it not a cross over study? Ie placebo group then got SERM.

7. Line 142 Was there further assessment of use by pill counts or other biomarkers if available?

8. Line 145-146 I would suggest not combining amenorrhea and spotting. The assumption is reasonable but more detailed data on spotting vs. amenorrhea is still useful clinically for some patients.

9. Line 155 The assumptions on missing data is reasonable however analysis with and without these participants would be helpful and a cleaner analysis.

10. Line 178-181 It is not clear what is meant by censor vs. analysis intention to treat. The very reason for drop out may be directly related to the primary outcome. Descriptively including this information addresses this limitation.

Results:

11. Line 183-184 There was a relatively low drop out. Can you clarify the power analysis and recruitment. Was it 66 per arm or total?

Table 1

12. What was included under other for race? Break it down further if able

13. Why was marital status included?

14. Is there any demographics related to other comorbidities or medications that could impact hepatic clearance or blood levels of etonorgesterol

15. Table 2 clarify the open label portion of the study. It states those on placebo got tamoxifen but were they still blinded? What was done with the original cohort on Tamoxifen?

16. Table 3 The satisfaction rate at the end of the study is not clear from the table. I assume this is after the open end phase. If so it would be interesting to see satisfaction with and without those who dropped out.

17. Figure 1 the cross over open label portion of the study strengthens the study design and glad to see it was included. My only comments previously mentioned were why it was not done as a pure blinded cross over. The range is quite large 1-69 days

18. Line 206 The sustained effect in the open label portion of the study for those originally on tamoxifen is interesting and clinically relevant.

19. Line 230 What were the side effects causing drop out?

Discussion:

1. Line 250-251 The review of short and long term bleeding with OCP vs. tamoxifen is important and possible opens RCT comparing the 2 options.

2. Line 187 The 30 day enrolment is an acknowledged limitation.

3. Line 296 Was the prior contraceptive trial looking at blood levels?

Reviewer #2: This is a well designed, well executed study examining the role of tamoxifen in the management of unscheduled bleeding associated with the etonogestrel contraceptive implant.

Introduction:
1. [Line 83-84]: Consider rephrasing the sentence "Clinicians lack guidance..." as the CDC Selected Practice Recommendations provides evidence-based guidelines for the management of bleeding irregularities, among other sources.
2. [Line 91 -93]: Please restate or provide additional references to support the statement "...as prior studies of other pharmacologic therapies... have only demonstrated improvement during maintenance therapy"

Discussion:
1. Line 244: The authors state "During the open label phase, satisfaction with bleeding improved in the placebo group after these women commenced active tamoxifen treatment. Taken together, these results support a positive benefit..." Care must be taken not to overstate the conclusions. Without a comparison group, it is difficult to negate the improved bleeding pattern that occurs over time, with or without therapy.
2. Line 255: Similarly, care must be taken not to overstate the conclusions. The classify the increased amenorrhea days as

"clinically-important". The length of time without bleeding or spotting that can be considered important is likely to differ between users and this was not asked (or reported) by the authors.
3. Line 261 - 269: This paragraph seems out of place and does not flow with the rest of the discussion. Consider moving to introduction or incorporating in the paragraph starting at Line 277.

Table 1:
1. While it is argued that using statistical significance testing to compare baseline characteristics is inappropriate, if the testing is done, the results should be presented. Otherwise, remove references to the statistical tests.

Table 4:
1. Consider separating the "reason for withdrawal" and "adverse event" table into two separate tables for clarity

Reviewer #3: General Comments:
The treatment of unscheduled bleeding associated with etonogestrel implants is of great clinical relevance to the practicing gynecologist. This placebo controlled, randomized trial address one possible treatment strategy. I appreciate the completion of the consort guideline checklist.

Specific Comments:
Line 85: My limited review of the literature did not reveal "several" studies - just the ones mentioned here. I would consider changing this to just "prior studies"
Line 112: How was "bleeding dyscrasia" determined? A known diagnosis or just a patient reported bleeding disorder?
Line 121-122: Baseline bleeding pattern was determined retrospectively, which may or may not be accurate. This is unlikely to change your results as they were similar between the groups, and bleeding information was collected prospectively during the trial.
Line 218 as compared with Table 3: Is satisfied with the implant 'for contraception' the same as satisfied overall?
Line 261-269: This paragraph is much more "background" than "discussion" and can likely be eliminated all together.
Line 294-296: The reassurance about tamoxifen not interfering with contraception is very important.
Line 301: How did you determine that this is a clinically important reduction in the number of bleeding days? Clearly it is a reduction, but what makes it clinically important?

Discussion overall: It seems very difficult to determine what is a "meaningful" reduction in unscheduled bleeding. The satisfaction data may be the most important outcome presented here.

Possible future directions:
- Determine if tamoxifen use could decrease implant discontinuation rates.
- RCT of tamoxifen vs OCP

STATISTICAL EDITOR'S COMMENTS:

1. lines 65-68, 160, 168-172 and Table 2: Need to clearly separate the primary outcome (number of consecutive days of amenorrhea), from a ll secondary outcomes. Also, need to conform the Abstract to our RCt template.

2. lines 168-172: Need to specifically cite the pooled estimate for SD (appears to be ~ 22 days). Also, is the difference of 15 days chosen as an arbitrary number or does it have some clinical importance? In any event, since the difference was actually ~10 days and the difference has statistical significance based on the smaller pooled SD (~ 13 days), did the mean difference of ~ 10 demonstrate a weaker clinical difference than would be clinically important, although it was statistically significant?

3. Table 1: The columns had N = 52 and N = 55, so the %s should be rounded to nearest integer %, not to nearest 0.1% precision. Need units for age.

4. Table 2: Need to clearly identify the primary outcome and label all others as secondary outcomes.

5. lines 63-64, Table 3, S-1, Fig 3: The rates of follow-up are mostly satisfactory, but should show the demographic/clinical profile of those who did not respond/follow-up at the end of 90 days or end of study vs those who did to help the reader understand whether there could be bias in the results obtained. Also, the rates of completion at 90 days (79%) and at 180 days (71%) should be explicitly cited in the Abstract and Results and addressed as potential limitation.

6. Fig 3: Need to identify the number of women in each group at various time points Should include 10, 20, 30, 40, 50 day marks.

7. Table 4: The column totals are few and the %s should be rounded to nearest integer %, not to nearest 0.1%.

EDITORIAL OFFICE 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. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

4. Obstetrics & Gynecology follows the Good Publication Practice (GPP3)* guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.

(1) Adherence to the GPP3 guideline should be noted in the cover letter.

(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:
(2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.
(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.
(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.
(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.
(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s).

(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:

"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above).

*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med 2015;163:461-4.

5. Was this study presented at ASRM in 2019? If so, please disclose the name of the meeting, the dates, and location on the title page of your 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 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.

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 22 typed, double-spaced pages (5,500 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.

8. 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).

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: Original Research articles, 300 words. Please provide a word count.

10. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

11. 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.

12. 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.

13. 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.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

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%").

14. 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.

15. The Journal's Production Editor had the following comments about the figures in your manuscript:

"Figure 1: Please confirm or explain n values for those who completed treatment 1. Where there any other exclusions other than early termination? (57-2=55 and 55-3=52)"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

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.

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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 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 Mar 13, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

_____

[redacted]

March 1, 2020

Dear Editor,

Please find attached our **resubmission** to Obstetrics & Gynecology, titled "Treatment of unfavorable bleeding patterns in contraceptive implant users: a randomized trial." We have responded to all the reviewer comments below.

This manuscript has not been submitted to any other publication, and I do not intend to submit this manuscript to any other publication while it is under review at Obstetrics & Gynecology. A portion of the data was presented as a poster at ASRM, 2019.

All those named in the acknowledgements have given written permission. All individuals meet criteria for authorship.

The trial was registered to clinicaltrials.gov. NCT**02903121** and received IRB approval by the Oregon Health & Science University (OHSU) IRB. The study was also conducted University of Hawaii and the UH IRB waived authority to OHSU. Informed written consent was obtained from all participants and these are filed with other study materials.

The lead author* (below) 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.

This work was funded by an investigator initiated grant through Merck. The authors designed and executed the study, analyzed the results, and prepared the manuscript. The sponsor had no involvement in these activities but was given quarterly updates on the research progress and was provided a copy of the manuscript as a courtesy prior to submission. We have adhered to GPP3:

- All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings. In fact, the authors are in ownership and control of the study findings and were responsible for the analysis and interpretation.

- All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.

- The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.
- The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.
- All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

Please contact me with any outstanding questions or concerns.

Alison Edelman, MD, MPH
Professor, OB/GYN
Director, Family Planning Fellowship
Oregon Health & Science University
[redacted]

REVIEWER COMMENTS: Author responses in blue text

Reviewer #1: The authors present a double blinded RCT comparing Tamoxifene vs. placebo for prolonged bleeding or spotting B/S while on etonogestrel implant contraception. The authors should be applauded for addressing a common clinical problem and barrier to continued implant contraceptive use. Thank you – we appreciate the attention you have given to the review of our paper.

Abstract:

1. Line 61 The objective implies the primary outcome but this should be stated in the abstract before the secondary outcomes. We have added the sentence "Our primary outcome was the total number of consecutive amenorrhea days following the first treatment" to line 65 of the abstract.

2. Line 69 Was this a cross over? It is not clear the way it is worded. The design was not a cross over but an RCT for the first 90 days and then all participants, no

matter the study arm, entered an open label portion. The term 'open label' is specific to a study design in which participants are aware of the treatment they are receiving. We have included the study design in Line 56 "double-blind randomized control trial" and Line 62 where we have added some wording to help clarify that it is not a cross over study which reads "Participants then entered a 90-day open label study where all received active tamoxifen treatment if needed every 30 days (maximum 3 treatments)."

Introduction:

1. This was an excellent review of the problem and prior studies along with the rationale for sustained improved bleeding profiles. Thank you. We did make some minor changes to the introduction based on Reviewer 2 &3's comments (see below).

Methods:

1. Line 105 What was the purpose of using < 18 y.o and how was this addressed from a consent stand point, IRB and parental consent? The contraceptive implant is popular in teens and young women. These women can choose to use an implant without consent of their parent/guardian. We wanted to ensure generalizability of our study to the population that utilizes the method. Women under 18 were accompanied by an adult who also needed to co-sign the consent form. We have added a sentence to the Methods, line 115 "Women under the age of 18 were consented in tandem with a parent/guardian who cosigned the consent form."

2. Line 106 Why was 30 days of use vs 90 used? AUB is should be clearly discussed and general recommendations of concerns are usually put at 90 days or 3 mths. There should also be further discussion of whether patients had the implant placed postpartum and if they were breast feeding. It looks like this was addressed in line 110. We are utilizing a study eligibility criteria to determine if women were experiencing a known side effect of the implant which is different than the clinical evaluation of a woman with AUB. In regard to pregnancy and breastfeeding, women could not be less than 6 months postpartum or breastfeeding. We have included information on our eligibility criteria starting on line 119.

3. Line 115 The washout period is important and glad it was included. Thank you – this information with all the additional edits from earlier has now shifted to Line 114.

4. Line 118 Was there assessment of the cavity with TVUS or sonohystogram? This would not be detected by PE. We did not include a pelvic ultrasound as part of our eligibility criteria. It is more common for STIs to be the cause of irregular bleeding in this

population than a structural abnormality. We did include STI screening prior to study entry. If a concern for a structural abnormality was found on PE or history, then we would refer for usual clinical care and delay enrollment until ruled out. We did add a sentence to the discussion section to address this weakness line 335 "We did not extensively rule out other sources for the bleeding, other than testing for the presence of chlamydia, as the likelihood of a structural abnormality in this reproductive age population would be rare."

5. Line 126 Describe specifics of randomization such as permuted blocks or opaque envelopes etc. This is addressed in lines 137-140. We clarified this in Line 150: We performed a 1:1 randomization in a 2 block sequence

6. Line 129 The second phase was all tamoxifene. Why was it not a cross over study? Ie placebo group then got SERM. At the onset, we were unsure if tamoxifen would have a 'duration of effect'. This was the major weakness of the Simmons et al study and one of the original reasons we did this study. Also based on our clinical experience, we did not think that study participants with persistent prolonged bleeding would 'hang in there' for 6 months if they were getting placebo with no improvement. Thus we chose the design of an RCT followed by an open label where they would have the opportunity to get tamoxifen.

We added the following to the discussion (lines 329-336): *We chose to have all participants move into an active "open label" treatment phase for the second three month phase of the study rather than switch allocations in a crossover design. While a crossover design provides a powerful approach to assess response to treatment with each participant serving as her own control, we did not know how long the benefit of one or more active treatments with tamoxifen might last. As we hypothesized that tamoxifen treatments would have a carryover effect, a crossover design may have diluted our ability to demonstrate a difference in the second three months. We also felt that the opportunity for all participants to receive an active treatment after 90 days would reduce drop out.*

7. Line 142 Was there further assessment of use by pill counts or other biomarkers if available? We performed pill counts during the study visits. We have now included this information in line 145 "At follow up visits, participants returned unused drug, counts were compared to reports, and a new supply was provided (if indicated), and reported side effects."

8. Line 145-146 I would suggest not combining amenorrhea and spotting. The assumption is reasonable but more detailed data on spotting vs. amenorrhea is still useful clinically for some patients. We a priori planned to do both as sometimes we can identify important trends by combining these two categories. However, we understand the reviewer's concern, which is why we generally

have separated amenorrhea and spotting results when reporting it in the paper including in Table 2.

9. Line 155 The assumptions on missing data is reasonable however analysis with and without these participants would be helpful and a cleaner analysis. Language has been added to clarify the extent of imputation and the results of exclusion from analysis starting at Line 169. "…, updating data for 9 participants. Seven of the 9 participants had data updated for 1-2 days, one had data updated for 3 days, and one had data updated for 15 days out of the 180-day study period. Excluding participants with recoded missing data from analysis did not change the results of any primary or secondary bleeding outcomes."

10. Line 178-181 It is not clear what is meant by censor vs. analysis intention to treat. The very reason for drop out may be directly related to the primary outcome. Descriptively including this information addresses this limitation. The term "censored" is specific to the Kaplan-Meier time-to-event analysis, implying that the participant contributed data up to the point at which they were no longer in the study. The distinction is made between the Kaplan-Meier analysis where we were able to use as much data as a participant provided, and the 30- and 90-day analyses, in which we had to exclude participants who did not complete the reference period. Language has been added to specifically define censoring Line 200" i.e. they contributed data up to the point at which they discontinued," and to clarify our reasoning for excluding participants lost to follow-up during a reference period Line 205: "in order to avoid estimates of bleeding outcomes that were artificially biased toward low values."

Results:

11. Line 183-184 There was a relatively low drop out. Can you clarify the power analysis and recruitment. Was it 66 per arm or total? We have included information about the power analysis and sample size in Line 177 and have added wording to clarify that 66 was total "Based on Simmons et al.,[3] we estimated that a total sample size of 66 women (33 per group)…." On line 175, we also included information that we increased the sample size to 106 to account for drop outs.

Table 1

12. What was included under other for race? Break it down further if able Table 1 has been changed to break down race in detail. Participants formerly categorized as "other" are now categorized as Hispanic, Asian, Black, more than one race, or Other/Unspecified. Please let us know if you would like us to collapse any categories or if this level of detail is desired.

13. Why was marital status included? Partner status is a standard demographic variable included in contraceptive studies of reproductive age women. We can

remove it if desired but have currently left that demographic variable as part of Table 1.

14. Is there any demographics related to other comorbidities or medications that could impact hepatic clearance or blood levels of etonorgesterol. We are not aware any additional comorbidities or medications to the exclusion list we already had for tamoxifen (which was extensive). Our simplified eligibility criteria condensed this long list into 'other contraindications to tamoxifen'. In order to clarify this further, we have changed Line 124 (eligibility criteria) to read ".....or other contraindications including medication interactions or precautions to tamoxifen".

15. Table 2 clarify the open label portion of the study. It states those on placebo got tamoxifen but were they still blinded? What was done with the original cohort on Tamoxifen? All participants, no matter their original study arm allocation, received tamoxifen during the open label phase. We have changed the legend to Table 2 to read "All participants received tamoxifen during the open label phase (days 91-180)." The definition of an open label study design is that participants are not blinded to treatment. We have not further clarified this in the paper but if we need to define what an open label study design is further – then we can add that.

16. Table 3 The satisfaction rate at the end of the study is not clear from the table. I assume this is after the open end phase. If so it would be interesting to see satisfaction with and without those who dropped out. Table 3 has been updated to separate satisfaction and acceptability levels at the end of study according to early termination status, and relabeled to clarify the point at which satisfaction was reported. However, we would recommend not including it in the table and just keeping the language that has also been added to the text in the results section Line 256: "Participants who terminated the study prior to completion reported lower satisfaction and acceptability levels, with no significant differences between treatment groups."

17. Figure 1 the cross over open label portion of the study strengthens the study design and glad to see it was included. My only comments previously mentioned were why it was not done as a pure blinded cross over. The range is quite large 1-69 days. As mentioned earlier, we did not conduct a crossover study as we were unsure if tamoxifen would have a 'duration of effect'. This was the major weakness of the Simmons et al study and one of the original reasons we did this study. Also based on our clinical experience, we didn't think that women with persistent prolonged bleeding would 'hang in there' for 6 months if they were getting placebo and getting no improvement. Thus we chose the design of an RCT followed by an open label. See discussion, lines 329

18. Line 206 The sustained effect in the open label portion of the study for those originally on tamoxifen is interesting and clinically relevant. Yes, this trend toward a sustained effect is interesting; participants in the tamoxifen

group during the open label phase continued to experience more amenorrhea days and fewer spotting days, but we prefer to remain cautious in our interpretation of this claim. We prefer to let the data speak for itself. We have not made any changes to the manuscript at this time.

19. Line 230 What were the side effects causing drop out? We had one participant that noted her reason for drop out was side effects. Her reported side effect was mood changes. We have included this information in line 261.

Discussion:

1. Line 250-251 The review of short and long term bleeding with OCP vs. tamoxifen is important and possible opens RCT comparing the 2 options. Thank you, we agree that an RCT would be interesting. However, this would be a very large study. In the interest of brevity, we have not added this to discussion.

2. Line 187 The 30 day enrolment is an acknowledged limitation. We believe this is referring to line 287 and not 187? We have included this as a weakness in the study line 337. We had no women that were within 30 days of their implant use and only 9 that were within 90 days of their implant use. The range of days of implant use has also been added to Table 1 for further clarification.

3. Line 296 Was the prior contraceptive trial looking at blood levels? This prior study did not look at levels of tamoxifen or ENG but a portion of the study looked at urine hormone metabolites for evidence of ovulation – which were not found. In the interest of brevity, we have not added any additional information to the discussion, but are happy to provide more details if needed.

Reviewer #2: This is a well designed, well executed study examining the role of tamoxifen in the management of unscheduled bleeding associated with the etonogestrel contraceptive implant.

Introduction:

1. [Line 83-84]: Consider rephrasing the sentence "Clinicians lack guidance..." as the CDC Selected Practice Recommendations provides evidence-based guidelines for the management of bleeding irregularities, among other sources. While the CDC SPR are evidence based guidelines, the management of bleeding irregularities for implants contains very little guidance that is known to result in any real benefit and the recommendations contained were based on expert opinion and lower grade evidence. We have added this information to Lines 87-89

2. [Line 91 -93]: Please restate or provide additional references to support the statement "...as prior studies of other pharmacologic therapies... have only

demonstrated improvement during maintenance therapy" We had added an additional reference to this sentence (Hou et al) line 99.

Discussion:

1. Line 244: The authors state "During the open label phase, satisfaction with bleeding improved in the placebo group after these women commenced active tamoxifen treatment. Taken together, these results support a positive benefit..." Care must be taken not to overstate the conclusions. Without a comparison group, it is difficult to negate the improved bleeding pattern that occurs over time, with or without therapy. Our RCT portion with a placebo comparator does provide this comparison group both within the RCT and also when looking at the open label portion like a prospective cohort. We view the inclusion of the control group in our RCT during phase 1 of the study to provide high quality evidence of improved satisfaction with tamoxifen compared to placebo, and not a time effect. No changes made.

2. Line 255: Similarly, care must be taken not to overstate the conclusions. The classify the increased amenorrhea days as "clinically-important". The length of time without bleeding or spotting that can be considered important is likely to differ between users and this was not asked (or reported) by the authors. While we believe that over a week of a bleeding reprieve is clinically important, the reviewer is correct in that we didn't ask women what different in bleeding would make a difference to them. We have removed 'a clinically important difference' from this sentence (now line 287).

3. Line 261 - 269: This paragraph seems out of place and does not flow with the rest of the discussion. Consider moving to introduction or incorporating in the paragraph starting at Line 277. We believe it is important to discuss the potential mechanisms for bleeding on progestin therapy as this may be helpful in understanding the treatment, treatment failures, and future research. As the reviewer has suggested an alternative from removing, we have moved this paragraph to after the one starting on line 277 (now line 312 in the track changed version).

Table 1:

1. While it is argued that using statistical significance testing to compare baseline characteristics is inappropriate, if the testing is done, the results should be presented. Otherwise, remove references to the statistical tests. Thank you for pointing this out. We have removed all references to p values from Table 1.

Table 4:

1. Consider separating the "reason for withdrawal" and "adverse event" table into two separate tables for clarity. We have added to the Table 4 legend "Reasons for withdrawal (upper table) from the study and adverse events (lower table)" in order to clarify the contents and where to find them.

Reviewer #3: General Comments:
The treatment of unscheduled bleeding associated with etonogestrel implants is of great clinical relevance to the practicing gynecologist. This placebo controlled, randomized trial address one possible treatment strategy. I appreciate the completion of the consort guideline checklist. We have updated the consort guideline to match the correct track change resubmission manuscript version.

Specific Comments:
Line 85: My limited review of the literature did not reveal "several" studies - just the ones mentioned here. I would consider changing this to just "prior studies" We have changed this to prior studies (now line 97).

Line 112: How was "bleeding dyscrasia" determined? A known diagnosis or just a patient reported bleeding disorder? It was both. We have added to the eligibility critera to state "bleeding dyscrasia (known or patient reported)" Line 121.

Line 121-122: Baseline bleeding pattern was determined retrospectively, which may or may not be accurate. This is unlikely to change your results as they were similar between the groups, and bleeding information was collected prospectively during the trial. You are correct but then participants had to have a current bleeding episode once enrolled to start treatment or they were discontinued after 30 days of enrollment so we really had both a retrospective and a prospective aspect to understanding their bleeding pattern prior to taking treatment.

Line 218 as compared with Table 3: Is satisfied with the implant 'for contraception' the same as satisfied overall? We asked several satisfaction questions including "are you satisfied with your bleeding", "are you satisfied with your implant as an overall method of contraception", and "how acceptable is your bleeding pattern". We have entitled Table 3 "Satisfaction with bleeding and implant as contraception and acceptability of bleeding". Please let us know if that is not clear regarding how we represented the data and we can make changes.

Line 261-269: This paragraph is much more "background" than "discussion" and can likely be eliminated all together. We have moved the paragraph as suggested by Reviewer 2 in hopes that it now fits better into the discussion.

Line 294-296: The reassurance about tamoxifen not interfering with contraception is very important. Agreed which is why we included these studies in the initial study by Simmons et al. and then did not have to include it in this study.

Line 301: How did you determine that this is a clinically important reduction in the number of bleeding days? Clearly it is a reduction, but what makes it clinically important? We removed this portion of the sentence as suggested by Reviewer 2 as they are correct in that we did not ask participants what was meaningful to them but we still feel that the satisfaction of bleeding data supports this claim.

Discussion overall: It seems very difficult to determine what is a "meaningful" reduction in unscheduled bleeding. The satisfaction data may be the most important outcome presented here. Agreed and it likely depends on what makes the woman satisfied with the method and that she continues it. Likely individual to the individual. We have removed this phrasing (see prior comment & answer).

Possible future directions:
- Determine if tamoxifen use could decrease implant discontinuation rates.
- RCT of tamoxifen vs OCP
Thank you for these suggestions. In the interest of brevity, no changes made.

STATISTICAL EDITOR'S COMMENTS:

1. lines 65-68, 160, 168-172 and Table 2: Need to clearly separate the primary outcome (number of consecutive days of amenorrhea), from a ll secondary outcomes. Also, need to conform the Abstract to our RCt template. Our primary outcome was the parametric test of consecutive amenorrhea days after the first treatment and results are only reported in the text. We have tried to clarify this whenever referring to this outcome. All results in Table 2 are secondary outcomes. Text in the methods section has been rearranged to more clearly separate discussions of the primary and secondary outcomes, and additional language “primary outcome” or “secondary outcomes” has been added in the abstract, results, and Table 2 to clarify whether a discussed outcome was primary or secondary.

2. lines 168-172: Need to specifically cite the pooled estimate for SD (appears to be ~ 22 days). Also, is the difference of 15 days chosen as an arbitrary number or does it have some clinical importance? In any event, since the difference was actually ~10 days and the difference has statistical significance based on the smaller pooled SD (~ 13 days), did the mean difference of ~ 10 demonstrate a weaker clinical difference than would be clinically important, although it was statistically significant? The pooled SD for the sample size calculation has been added line 181: “(tamoxifen 28.8±24.5 days, placebo 13.6±19.2 days, pooled SD = 21.2 days)”. The 15-day effect size was based on previously reported effect of tamoxifen treatment on implant-related bleeding by Simmons et al. (2017) rather than a clinical assessment of significance. We believe the difference of ~10 days still represents a meaningful (although weaker) improvement in breakthrough bleeding. Language has been added to the discussion addressing

this issue in more detail line 288: "While this difference is not as large as the 15.2 days reported by Simmons et al. that our study was powered to detect, due to our larger sample size and lower variability, our results are still statistically significant and we believe they represent a meaningful improvement in bleeding patterns."

3. Table 1: The columns had N = 52 and N = 55, so the %s should be rounded to nearest integer %, not to nearest 0.1% precision. Need units for age. Column percentages in Table 1 have been rounded to the nearest integer and years specified as the unit for age.

4. Table 2: Need to clearly identify the primary outcome and label all others as secondary outcomes. All results in Table 2 represent secondary outcomes (see comment 1, above). The legend for Table 2 has been changed to clarify this point: added "secondary outcomes"

5. lines 63-64, Table 3, S-1, Fig 3: The rates of follow-up are mostly satisfactory, but should show the demographic/clinical profile of those who did not respond/follow-up at the end of 90 days or end of study vs those who did to help the reader understand whether there could be bias in the results obtained. Also, the rates of completion at 90 days (79%) and at 180 days (71%) should be explicitly cited in the Abstract and Results and addressed as potential limitation. Percentages of completion have been added to the abstract and results section. Percentages have also been added to the number of treatments taken in the results section. Tabulation of demographics/clinical profiles for non-responders/early terminations is shown below. We did not feel the lengthy table enhanced an understanding of the reasons for non-response/leaving the study, but would be happy to include it in supplemental materials (see table below). Text has been added to the results section addressing differences by non-response/early termination status line 244: "No significant differences were identified between the demographic and clinical profiles of those who responded to treatment and those who did not. When combined with participants who were lost to follow-up, those who did not respond to treatment/did not complete the study were younger and had their implant in place for a shorter period than those who responded to all treatments and completed the study (data not shown)."

	Overall			RCT (Days 1 – 90)			Open Label (Days 91-180)		
	Completed/ Responded	Lost to follow-up/Non-responders	p-value	Completed/ Responded	Lost to follow-up/Non-responders	p-value	Completed/ Responded	Lost to follow-up/Non-responders	p-value
n	73	34		80	27		74	8	
Age (years)	24.6 ± 4.8	22.5 ± 4.5	0.039	24.3 ± 4.8	22.7 ± 4.6	0.147	24.5 ± 4.9	21.4 ± 4.0	0.084
Race/Ethnicity			0.191			0.233			0.290
White	42 (58)	20 (58)		46 (57)	16 (59)		42 (57)	5 (64)	
Hispanic	14 (19)	4 (12)		15 (19)	3 (11)		14 (19)	1 (12)	
Asian	7 (10)	4 (12)		7 (9)	4 (15)		8 (11)	0 (0)	
Black	1 (1)	2 (6)		1 (1)	2 (7)		1 (1)	0 (0)	
More than one race	9 (12)	2 (6)		10 (13)	1 (4)		9 (12)	1 (12)	
Other/Unspecified	0 (0)	2 (6)		1 (1)	1 (4)		0 (0)	1 (12)	
Marital status			0.078			0.166			0.425
Single/Divorced	25 (34)	6 (18)		26 (32)	5 (19)		25 (34)	1 (12)	
Partnered/Married	48 (66)	28 (82)		54 (68)	22 (81)		49 (66)	7 (88)	

Nulliparity	64 (88)	27 (79)	0.265	69 (83)	22 (81)	0.544	49 (66)	7 (88)	0.425
BMI (kg/m²)	27.3 ± 7.5	27.6 ± 7.2	0.842	27.5 ± 7.5	26.8 ± 7.3	0.672	27.4 ± 7.6	29.1 ± 6.7	0.533
Education			0.364			0.762			0.332
High School or less	10 (14)	7 (21)		12 (15)	5 (19)		10 (14)	2 (25)	
College (any or more)	63 (86)	27 (79)		68 (85)	22 (81)		64 (86)	6 (75)	
Days of implant use	458.2 ± 278.6	333.6 ± 247.6	0.028	454.4 ± 275.6	312 ± 245.1	0.019	456.3 ± 277.1	388.9 ± 251.0	0.512

6. Fig 3: Need to identify the number of women in each group at various time points Should include 10, 20, 30, 40, 50 day marks. The number of participants in each treatment group at the beginning of each treatment number has been added to Figure 3. Because the goal of the study was to determine how long amenorrhea would last after treatment, each participant's treatment schedule was based on their individual bleeding patterns, and therefore treatment numbers did not align with the study day in a clean way. For example, at day 75, some participants would have already taken treatment 3, some would have taken treatments 1 & 2, and a small number would only have taken treatment 1 because they had not yet restarted bleeding. This variability makes it impossible to include day marks on the graph in any meaningful way. However, we have added a label to the y-axis of Figure 3 specifying that it represents treatment number for additional clarification. Please let us know if you would like us to include any other additional information to make this clear to the reader.

7. Table 4: The column totals are few and the %s should be rounded to nearest integer %, not to nearest 0.1%.We have changed the Column totals in Table 4 to reflect the full cohort and percentages have been rounded to the nearest integer.

EDITORIAL OFFICE 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.
A – we opt-in.

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.
We will confirm with our coauthors that their disclosures match our title page.

3. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).
We have included an Authors' Data Sharing statement in our revised manuscript

Authors' Data Sharing Statement

- **Will individual participant data be available (including data dictionaries)?** ***Yes.***
- **What data in particular will be shared?** ***All de-identified individual participant data collected during the trial.***
- **What other documents will be available?** ***Study protocol.***
- **When will data be available (start and end dates)?** ***Immediately following publication and ending 3 years after article publication.***
- **By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)?** ***Researchers who provide a methodologically sound proposal and rationale for use of the data set, their proposed analyses and results through academically established means. Oregon Health & Science University maintains a high community standard for the free release of data and materials. Transfer of resources is subject to the acceptance of a Materials Transfer Agreement as required by policy at Oregon Health & Science University. Oregon Health & Science University understands and agrees to comply with the NIH policy on Sharing Research Data and on Sharing Model Organisms.***

4. Obstetrics & Gynecology follows the Good Publication Practice (GPP3)* guideline for manuscripts that report results that are supported or sponsored by

pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.

(1) Adherence to the GPP3 guideline should be noted in the cover letter.

(2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:
(2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.
(2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.
(2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.
(2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.
(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.
We abide by the GPP3 and have included these in the cover letter

(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s). Have moved the funding source from the title page to after the abstract.

(4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a detailed description of the sponsor's role as well as the following language:

"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of

the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above). Do we still include this for an investigator initiated grant from a sponsor? If so we can add.

*From Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med 2015;163:461-4.

5. Was this study presented at ASRM in 2019? If so, please disclose the name of the meeting, the dates, and location on the title page of your manuscript. We have added the following to the end of the title page: A portion of this research was presented as a poster at the following meeting: ASRM 2019, Philadelphia, PA. Simmons KB, Kaneshiro B, Hauschildt J, Bond K, Jensen JT, Edelman AB. Treatment of unfavorable bleeding patterns in contraceptive implant users. Fertil Steril Sept 2019 Supplement e305.

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 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. **We will abide by the revitalize definitions.**

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 22 typed, double-spaced pages (5,500 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. We have 15 pages of manuscript minus the references and a page break.

8. 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).
Our acknowledgements follow the rules as governed by the journal.

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. We have complied with this.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count. Our word count minus the abstract subtitles is 300.

10. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed. **The manuscript was reviewed and is compliant**

11. 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. **The manuscript was reviewed and is compliant.**

12. 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. **The manuscript was reviewed and the virgule symbol in the revised manuscript is used only to express data or a measurement.**

13. 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.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

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%"). **Where possible (specifically for our primary outcome), results have been reported as effect size and confidence interval. All other group comparisons were based on extremely skewed data distributions, making parametric testing inappropriate and reporting of effect size challenging. Options for non-parametric effect size estimates either rely on assumptions about the distributions that were violated by our data, or produce relatively obscure correlation values that are not easily interpretable. We therefore reported the medians and ranges for each group in order to make the results easy to understand and clinically relevant. P values reporting meets the journal's requirements.**

14. 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 have reviewed the tables and they comply to the journal's style.**

15. The Journal's Production Editor had the following comments about the figures in your manuscript:

"Figure 1: Please confirm or explain n values for those who completed treatment 1. Where there any other exclusions other than early termination? (57-2=55 and 55-3=52)" We have updated Figure 1 to include numbers for early terminations during and between treatment periods to further clarify the participant flow.

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint. When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file). If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program. Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines. Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce. We have complied with the recommendation.