OBSTETRICS & GYNECOLOGY

NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

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

Date: Jun 18, 2019
To: "James A Simon" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-939

RE: Manuscript Number ONG-19-939

Long-Term Safety of Bremelanotide for Hypoactive Sexual Desire Disorder

Dear Dr. Simon:

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 Jul 09, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Overall Comments: The authors describe outcomes of a 52-week open-label extension study performed in women participating in 2 separate randomized cohorts of women undergoing subcutaneous active medication (1.75mg) vs placebo for 24 weeks after an initial 4-week screening and 4 week placebo run-in. The results of the index primary trial (referred to in the current paper) were not available thus limiting the ability to scrutinize the level 1 data, but a look at the literature revealed that the results of dose-finding studies revealed efficacy (although unclear whether the improvements in sexual function met the minimal clinically important difference [MID]). The current paper title addresses long-term safety, but there appears to be a significant amount of efficacy data as well. Before this paper is accepted anywhere, the primary paper should be peer-reviewed and published.

Specific Comments:

Title: Should reflect efficacy and safety

Précis: Readers may not know what the RECONNECT studies are.

Abstract: Objective reflects safety and efficacy-which is the primary and secondary outcome? Methods do not need a commentary regarding the results of the primary study, especially as it is not yet published. Lines 42-44 should reflect where these subjects originated and that after participating in a randomized trial, they were offered participation in an open-label extension study. Is there a reason why the cohorts could not be combined? Methods should describe the definition of efficacy and which expected and unexpected adverse events were collected. Analysis methods should be provided. Results: Need actual results. What were efficacy results in those going from placebo to open-label medication group ie at baseline and 24 weeks versus 76 weeks and those in the active medication group, same time-points? What were the type and number of adverse events (AE) and proportion of subjects sustaining AE. Conclusion: What is the definition of "favorable safety profile"?
There is inherent bias in this study secondary to authors from the company manufacturing the drug played a significant role in the design, execution, analysis, reporting and study funding.

Introduction: The enthusiasm for the results of this study are dampened by not having the results of the 2 index RCTS.

Methods: Comments as noted above. Is there any reason why the results of the open-label subjects not be combined and stratified by original randomization group if there were no significant difference between the 2 RECONNECT RCTs? What was the primary outcome? Secondary outcomes? Cannot refer to measures being used as described in a paper submitted for peer review ie not published. Provide measures in results with ranges and MIDs noted. Although key efficacy outcomes time-points were not formalized for the open-label extension (OLE), there are some evident, obvious time-points to report

that should be described in the Methods. What specific AEs were collected a priori? No statistical methods reported.

Results: What were the differences in baseline clinical and demographic factors in subjects participating in the OLE versus those opting out? I wonder if a combined patient flow diagram would be possible for the open label if there are no differences in baseline clinical/demographic variables? Tables 1 and 2-any significant differences between cohorts as noted? Figures 2A, B and C data need standard deviations and primary results presented in the text. How was safety defined? Did treatment results meet minimal clinically important differences? Overall the results do not flow well from participant description to primary and secondary outcomes. Appendix 2 should be considered for main patient flow diagram if the cohorts cannot be combined.

Discussion: The Discussion should succinctly reflect the results, relate them to other current literature, provide strengths and limitations and clinical applications.
Without the results of the primary trial, it is difficult to appreciate the content of this report.

Tables/Figures: Tables 1 and 2 as above. Figure 1-should be patient flow. Current Figure 1 provides perspective and could be supplementary. The OLE results of Figure 2A,B,C should be in a table with marked time-points and should be specifically described in the Results.

Reviewer #2: The authors define HSDD in the introduction and cite 3 references to support their definition. Their definition is quite broad and a review of the references used to support their definition make it clear that the definition put forth in the manuscript is actually an amalgam of definition(s) used or accepted in epidemiological reviews and expert opinion panels. Reference 3 is a review of the epidemiology, biopsychology, diagnosis and treatment of HSDD that relies on HSDD as it is referenced in the DSM-IV-TR and 4 peer reviewed articles. Reference 4 is the result of a consensus panel brought together specifically to develop a concise, clinically relevant, evidence-based review of the epidemiology, physiology, pathogenesis, diagnosis, and treatment of hypoactive sexual desire disorder (HSDD); while it reviewed different definitions/criteria of HSDD the panel did not set forth which definition it preferred or used and so a variety of definitions were accepted in its review. Reference 5 reflects the outcome of a nomenclature conference sponsored by International Society for the Study of Women's Sexual Health (ISSWSH) held, in part, to develop standardized definitions for female desire, arousal, and orgasm disorder. Acknowledging the controversy around a universal definition for HSDD is one thing; creating a definition by simply 'mashing' them all together creates a female sexual dysfunction almost any woman will likely experience at some point in her is another.

While there is commercial interest in developing a pharmacological treatment for HSDD, it is disingenuous, at best, to discuss or present HSDD as a singular, well defined disorder whose primary pathophysiology is chemically based. The role of biology, or even neurobiology, in influencing or even driving female desire is extraordinarily scant. It is important to note, quite clearly, that if desire is not fundamentally a biological process, then pharmacological interventions to address it are unlikely to be successful. There is a plethora of research demonstrating the profound impact and roles that social, cultural, and psychological factors play in female sexual desire. At a minimum, current evidence based models for female sexuality (the circular model of response and the incentive model) and the insights they provide into female desire and sexuality should be discussed to avoid the reductionistic assertion that female desire results primarily from a chemical or neuro-chemical deficiency.

The authors note that preclinical studies (plural) with bremelanotide act on "neurobiological components of female sexual dysfunction and is postulated [my emphasis] to modulate pathways involved in sexual desire and arousal." Only one (singular) reference is cited for this assertion and it involves the use of female rats. The neurobiological components of female sexual dysfunction in human females are in the most nascent stages of being understood. In the conclusion of the reference article, it states: "To the extent that solicitations indicate the desire of female rats to engage in sexual activity, bremelanotide appears to possess the behavioral, pharmacological, and neuroanatomical specificity required of a drug in the treatment of hypoactive sexual desire disorders." While I am not a veterinary or rodent specialist, I am not aware that HSDD is a common problem among female rats.

As the findings of the two phase 3 RCTs for bremelanotide have not been published, I find it premature, and a demonstration of hubris, for the author to ask the reviewer to take on faith that the results clearly and unequivocally demonstrated statistical and clinical significance of improvements in low sexual desire and related distress.

Please review all of the GPP3 guidelines; a simple disclosure of financial and non-financial interests does not satisfy all of the requirements, particularly when a commercial writing entity is involved and the role of each author in the trial, as well as the creation of the manuscript, are left undisclosed.

A total of 7 questionnaires were used in the RCTs: FSEP-R, FSDS-DAO, FSFI, EDQ, GAQ, WITS-9. The specific reasons for including so many questionnaires, as well as the role each played in the enrollment, monitoring, or analysis of the trials are not discussed. At the last visit during the study, the Beck Scale for Suicide Ideation was administered and while the reasons for this are not stated, they should be discussed.

In the published dose finding study for bremelanotide, the primary efficacy end point was each patient's change, from baseline to the end of the study (EOS), in the number of sexually satisfying encounters (Available at

https://journals.sagepub.com/doi/pdf/10.2217/whe-2016-0018. Accessed June 1, 2019). Interestingly, this was measured by a response of 'Yes' to question 10 (Q10) of the Female Sexual Encounter Profile-Revised, regardless of whether the study drug was used or not. In that dosing trial, the only other questionnaires used were the FSFI and the FSDS-DAO, and they were used for secondary endpoint analysis. While the authors note that measures used during the CSP were continued during the OLE, they should be discussed and reviewed (especially if more or different measures were sued) in lieu of summarizing things in an appendix.

As the results of the two phase 3 trials are not available, one is left to review the outcomes of the published dosing trial. In that study, the population that provided data after 4 weeks of treatment were assessed for changes in SSE- a population that included women suffering from HSDD and/or FSAD- "the mean (SD) change in number of SSEs from baseline to EOS was +0.7 (2.4) events/month for BMT 1.25/1.75 mg pooled, compared with +0.2 (2.3) for placebo (p = 0.0180)." While this may be a statistically significant change, its clinical relevance is questionable although publication of the phase 3 trials will yield more insights into clinical efficacy.

It is not clear why only descriptive analysis is available for safety and efficacy results in the OLE "as there were no comparator arms". It seems plausible that after all of the women in the OLE study had been participating for at least 4 weeks, a baseline of their scores could have been obtained and then used as the baseline for comparison after the >52 weeks of use. It would be useful to know if the changes claimed to be seen in the phase 3 trials were sustained over time, if they waxed and waned, as well as the patterns of drug use by participants.

Please address the high drop-out rates overall as well as why the drop-out rate was higher in the Study 301 subjects continuing in the OLE in the first 20 weeks compared to the 'steady' drop-out rate noted among participants in the Study 302 trail who continued in the OLE trial.

The vast majority of participants were white; please address this.

The fourth most common adverse event was 'sunburn' which is an unusual AE. Was it a rash or was it truly a burn of the skin caused by UV sun exposure and if the latter, why was there such increased photosensitivity.

Please comment on what contraceptive precautions were in place for the study, in light of the fact that 10 subjects became pregnant while using an investigational drug.

While it 'nice' that an expert panel of hepatologists concluded the case of hepatitis we unlikely due to the bremelanotide, this is a concerning adverse effect, particularly since after 6 months of drug discontinuation, the subject continued to have elevated liver enzymes. This should remain a prominent area for concern if the drug is approved for use in the general population and post-marketing surveillance studies should be planned to monitor for this. Are they?

Please explain how a single question on the GAQ served as the "dynamic anchor" (whatever that means) for the co-primary endpoints of the CSP.

The discussion section notes the differences between drug and placebo in effect size for improving desire and reducing distress but does not say if these differences are statistically significant or even clinically significant. Commenting on the analysis of effect sizes of drugs vs placebo for generalized anxiety disorder is irrelevant as general anxiety disorder is a completely distinct entity (in diagnosis, treatment and evaluation of response to treatment) than HSDD. The sentence on this needs to be deleted; it is superfluous and entirely non-contributory.

There are small, transient increased in BP with accompanying changes in heart rate noted in several clinical studies of bremelanotide and while these may not be "anticipated" to have any long term adverse cardiovascular effects, the fact is this trial was done in healthy pre-menopausal women and, if approved for commercial release, will be utilized by unhealthy pre-menopausal women and, likely even postmenopausal women. Please discuss these findings further and what they may portend in a general population of women. This too should remain a prominent area for concern if the drug is approved for use in the general population and post-marketing surveillance studies should be planned to monitor for this. Are they? Even the manuscript states that the incidence of AEs is likely higher in the 'real world' compared with the study population. Unless the efficacy of this drug is profound and robust (which remains to be conclusively seen), some comment on the decision to either try to expand inclusion criteria and continue with an ongoing clinical trials or acknowledgement of the need for a robust post-marketing surveillance program should be made.

Given the high drop-out rate of this trial it is not just 'likely' that non-responders are underrepresented, ti is extremely likely.

The conclusion that the OLE study confirms and highlights the "robust data from the double-blind CSP and provide additional support for use of bremelantoide in the treatment of HSDD in premenopausal women" is arrogant and unfounded given the lack of published data from the phase 3 clinical RCTs.
There are huge potential conflicts of interest in this manuscript and full adherence to GGP3 guidelines are lacking. This manuscript glosses over the still unsettled definition of HSDD and the implications of a lack of universal definition, ignores the vast amount of research demonstrating that female sexual desire is definitively more than just a lack of a chemical compound effect on the brain, skirts past the real possibility of long term hepatic issues or CVS issues if used in a non-healthy or older population, does not address the biases inherent relying only on self-reporting, albeit validated,

questionnaires in assessing treatment effects, and only tacitly acknowledges the high drop-out rate and the possible ramifications of this. Given the length of time it took to complete this OLE after the phase 3 trials were completed, it is not readily apparent why those phase 3 RCT results are still unpublished.

Reviewer #3:

The authors have submitted results from an open label extension study of a new medication for treating hypoactive sexual desire disorder, a common and often distressing condition for premenopausal women.

Precis: appropriate.

Abstract: Lines 52 and 53: can delete "PBO/BMT." The statement that "the only severe TEAE experienced by >1 participants in both studies was nausea" is too vague. Please clarify that this refers to the CSP/OLE combination. Also, the authors excluded the case of hepatotoxicity.

Introduction: appropriate for manuscript.

Methods:

Lines 112-119. The authors report that several questionnaires, adverse event monitoring, vital signs and other measurements were obtained at "the last visit of the CSP." Were these also measured during the OLE, and, if so, when? There appears to be conflicting information, as lines 140-142 report that "safety was assessed throughout the study…." Please clarify.

Results:

Safety:

Lines 198-200. The discontinuation rate described here seems discordant with the data presented in line 177. If so, this should also be adjusted in Appendix 2. Also please rewrite lines 198-199 for clarity.

Line 216: can delete "comprehensive" or "extensive."

Discussion:

In the methods section the authors note that participants could return to the clinic for more of the study drug. Do they believe this is a limitation on the number of dosages used, as it presumably required driving to a clinic to pick up medications?

Lines 264-270: There are advantages to describing effect size. However, casual readers may not be aware of these. Please include a brief description of why you are reporting effect size.

Lines 270-272: can probably delete this.

Line 297: This sentence states "several" studies have characterized the effects of bremelanotide on BP. However, there is only 1 reference. Also, if the authors do not believe that there are any cardiac conditions that would contraindicate using the medication, please state that here.

Lines 311-316: I would like further analysis of study discontinuation rates. A 60% discontinuation rate seems high, and readers will want more information. Also please clarify why almost 1/5 patients withdrew consent. Further, do they authors have a theory as to why so many patients in the 301 study arm discontinued the medication during the first 20 weeks (one would assume adverse events, and, if so, do they believe a "ramp up" process or some other method of alleviating nausea and flushing symptoms would be useful to increase compliance)?

Tables:

Please confirm that table data matches data in text.

Figures:

Figure 2: This can be split into 3 separate figures with individual figure headings. For Figure 2A (FSFI-D) what is the range of possible results? For Figure 2C (GAO Question 3) please report the possible range of results. Consider adding a horizontal line in the figure at 5 to show where benefit occurs. Also for 2C, patients reported a screening result of a little over 4. How does that work? If the question asks about the difference between starting and taking the drug (or placebo, because during the core phase this was blinded), how can patients start with a score for medication usage before they ever

take the medication? Please elaborate.

References:

Appear contemporaneous and appropriate for manuscript.

STATISTICAL EDITOR'S COMMENTS:

1. lines 48-49: Should also include the "n" of those who completed the OLE (n = 272).

2. Table 2: Several things are apparent from this Table: (1) although the initial allocation (core phase) into BMT vs placebo was balanced, the placebo group (core) was more likely to continue into the OLE phase (430 vs 254, or 63% placebo vs 37% BMT). (2) the incidence of TEAEs in the OLE phase were consistently higher in the placebo-BMT vs the BMT-BMT cohorts. That is, assuming the groups were randomized for the core phase, there was a selective loss of BMT core subjects before the OLE phase was started. Also, that selection bias was reflected in the rates of TEAEs, in that women who had been in the core BMT group who elected to continue were more likely the ones who did not have a previous adverse event. For example for nausea: Placebo-BMT: 109+84= 193 events vs 237 non-events (44.9%); BMT-BMT: 46+37=83 events vs 171 non-events (32.7%), Chi-square = 9.87, p = .002

3. Figs 2A, 2B and 2C: Need to include at each time point along the x-axes, the number remaining in each cohort

4. Appendix figures re: Disposition of OLE subjects in studies 301 and 302: Only a minority of patients elected or were allowed to continue for the OLE phase of the study. Excluded were any women who had a previous adverse event or who withdrew consent, among other reasons. Overall, about 40% of those in the initial core study phase completed the OLE phase.

5. Therefore, the safety and efficacy profiles relate to a select subset of the initial cohorts. That is, women who had a previous adverse reaction may not have the same subsequent incidence of adverse reactions had they continued the treatment. Also, women who had a satisfactory clinical response might be more inclined to continue treatment into the OLE phase.

6. That is, the results herein may be biased towards fewer adverse reactions and better clinical responses compared to a longer study of the initial cohort. The section on page 16 of discussion should be expanded to point these out for the reader.

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.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

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 Methods 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. 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.

6. 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, tables, boxes, figure legends, and print appendixes) but exclude references.

7. 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).

8. 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.

9. 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.

10. 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.

11. 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.

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

13. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Figure 2: It is recommended to use different colors for the graphs rather than grayscale. Another concern is that the text is very small and I am not sure if it will be legible on print."

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.

14. 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.

***

If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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 Jul 09, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

_____