Date: Mar 31, 2020
To: "Emily Spencer Lukacz"
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-413

RE: Manuscript Number ONG-20-413
Sexual Activity and Dyspareunia One Year After Surgical Repair of Pelvic Organ Prolapse

Dear Dr. Lukacz:

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).

***Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Apr 30, 2020, we will assume you wish to withdraw the manuscript from further consideration.***

REVIEWER COMMENTS:

Reviewer #1: Thank you for submitting you work for peer review.
Overall comment: this is a well written paper. The topic is important and timely.
Introduction: well written.
Methods: well written . Due to the multiple studies cited it is slightly wordy, I have no recommendation though about making it any better.

Results: It is slightly difficult to follow the flow of patients in the study. I would recommend adding a diagram similar to a prospective trial to follow the flow from evaluation, to inclusion and exclusion and then final number with data analysis. line 200-204 I was unable to access the supplemental table, it becomes difficult to follow when the 710 come into play (you only had paired data on 932 why mention the rest at all...) if any I would compare the 932 to the remainder in terms of baseline demographic and surgical data. did any of the 101 women who were not sexually active and became sexually active experience dyspareunia? Table 1 is too long , I would group when possible and split the table into two with the surgical data separate... Again keeping in mind the ease for the reader to follow and remain engaged.

discussion: well written but long. lines 288-296 Not sure what the first two lines mean... the entire paragraph is not well supported by the study data and results and introduces more uncertainty than answers. under these circumstances I would consider removing it or significantly revising.

Reviewer #2: Authors performed a secondary analysis of pooled data from 4 past trials to evaluate the risks of dyspareunia after pelvic organ prolapse surgery. They reported overall, 20% of women had dyspareunia or fear of dyspareunia prior to surgery and presence of pre-operative dyspareunia is predictive of occurrence of post-operative dyspareunia.

A couple of major concerns that threaten the internal validity of authors' findings; first, a formal meta-analysis using the MOOSE or PRISMA guidelines will instill more confidence in the study's conclusions. As it is, readers have little insight into the quality of included studies- especially since none of the studies set out primarily to evaluate sexual dysfunction in women having POP surgery.
Further, there likely is marked heterogeneity in terms of patients' demographics, important clinical factors, and types of validated questionnaire used, types of surgery performed (with likely varying impact on dyspareunia) and of course variability in outcomes data for each included study. Quantifying heterogeneity will be important for determining confidence in the pooled analyses results.

Secondly, the study is likely not representative of the overall cohort since a) analysis is based on <50% of the available cohort and b) the excluded cohort differed significantly from the included cohort.

Thirdly, the study findings has limited generalizability- practice has evolved significantly in this field, such that significant proportions of procedures that constituted the analysis are no longer performed (use of mesh) or rarely performed (open sacrocolpopexy)

Additional comments;
1. Lines 76-7; it would appear authors have already published the same study on a subset of patients included in the OPTIMAL trial (citation #8). This needs to be acknowledged.
2. Lines 96-99; general readers would be more interested in understanding the impact of mesh augmented repairs or of transvaginal multi-compartment repair on sexual dysfunction. Is there any expectation or evidence that abdominal sacrocolpopexy would have similar-if any- impact when compared to transvaginal mesh use or multi-compartment repairs? Inability to evaluate the impact of type of surgery on dyspareunia is a major weakness.
3. Lines 147-9; how was chronic pelvic pain evaluated? It would be important to differentiate acute pain from chronic since only the latter will be expected to have impact on long term pain complaints? Was your assessment reliable in teasing this out?
4. Lines 152-161; it would appear several validated questionnaire were in use over the period of time of these studies-how comparable were the PFIQ (used in CURE) and the 31 item PISQ (OPUS) vs. PISQ-12? Clearly if the primary objective was to evaluate sexual dysfunction, would the 31 item PISQ not be the most ideal questionnaire to use across the board? Also, why was this analysis limited to 12 months when data is available up to 24 months for these studies?
5. Further, important details are lacking, for example, not knowing why patients reported dyspareunia before after surgery is problematic- is it related to bulge or incontinence or both??
6. Lines 247-9 & 270-2; how many patients were included in the analysis that had mesh augmentation? Likely not many, since only 1 arm of the 4 studies (n=94/1345) had mesh? Perhaps numbers are too small to detect any impact?? What would be the sample size needed to see a clinically significant difference?

Reviewer #3:
1. Although this study focuses on rates of dyspareunia, it would be interesting to know more about the women who reported they were not sexually active prior to surgery who then became active after repair. This was a fairly significant proportion (25%) and seems like an encouraging finding. Perhaps it is an indicator that in addition to dyspareunia, prolapse has a negative impact on sexual function via alterations in body image, libido, confidence, etc. One could consider mentioning this in your discussion.
2. The group of women who had de novo dyspareunia are of particular interest for preoperative counseling. The small number in this group essentially precludes any meaningful statistical analysis, but nonetheless, it would be useful to know the demographics and the types of repairs they had. Did they have mesh implanted? Did they have complications? This could be done in chart form.
3. In a previous study by Lukacz et. al. (reference 8), rates of de novo dyspareunia did double from 5% to 10% in the second year following prolapse repair. Understandably, you are limited to 12 month follow up data in this secondary analysis, but I wonder about the longer term sexual outcomes and whether they would continue to be as favorable. Of course, the etiology of dyspareunia 2 or 3 years, or longer, after surgery may or may not be related to the repair itself. Regardless, this may be worth mentioning in the discussion as it can be important for counseling patients.
4. One limitation of this study is the heterogeneity in the types of prolapse repair that were performed. There was a small number of women within each group and therefor this study would not reliably tease out the risk of dyspareunia based on the type of prolapse procedure performed, the approach, or the presence of mesh.
STATISTICAL EDITOR’S COMMENTS:

1. General (lines 59-64): Since not all women had outcome to determine dyspareunia status, need to compare the cohorts with vs without data to address issue of selective bias in interpretation of outcome conclusions. Also, need to include a flow diagram to make interpretation of the various subsets more transparent to the reader.

2. Tables 1,3 : The columns labelled "Dyspareunia" has N = 63 and labelled "persistent Dyspareunia" has N = 46, , so all %s should be rounded to nearest integer %, not to 0.1% precision. The NS p-values should all be rounded to nearest 0.01 precision. I presume dyspareunia is at the 12 month time point, not at baseline, in Table 1, so need to clarify for reader.

3. Tables 2, 4: Need to include the crude ORs to contrast with the aORs. Need to list as footnote the variables included in the aOR model. Need to include the data from which the crude ORs were calculated, when that data was not present in Tables 1 or 2. Again, the NS p-values should be rounded to 0.01 precision. Many of the counts in subsets are small and there is insufficient power to generalize those NS findings. For both Tables, but esp Table 4, the NS aORs may be due to low power, since the counts and frequencies are low in some subsets, so the NS findings may not be generalizable.

4. Table 5: The column with N=43 should have all %s rounded to nearest integer %. The NS p-values should be rounded to nearest integer %. Some of the p-values are incompatible with the corresponding CIs. For instance, the OR = 5.6 with CI (0.8,29.4) has CI that includes 1.0, so its p-value is > .05. Similarly, if the location shift = -0.5 with CI (-0.5,0.0), that CI upper boundary = 0.0, ie, plausibly no difference, so how can the p-value be 0.0013? Also, need to clarify whether the ORs are aORs, and if so, what were the adjustors used in the model?

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:
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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:
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   (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 
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(2e) All authors have disclosed any relationships or potential competing interests relating to the research and its 
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(3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the 
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(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 
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All individuals included as authors and contributors who made substantial intellectual contributions to the research, data 
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studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in 
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6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was 
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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-
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Again, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Apr 30, 2020, we will assume you wish to withdraw the manuscript from further consideration.***

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