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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.
RE: Manuscript Number ONG-21-10

Fractional CO2 Laser for the Treatment of Vulvar Lichen Sclerosus: a Double-Blind, Sham-Controlled Randomized Trial.

Dear Dr. Goldstein:

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 Feb 26, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Introduction:
Line 103: Could add that treatments in addition to topical corticosteroids are needed because these require regular long-term use and compliance

Methods:
Line 136: It is stated here that women with VLS were recruited from one center, however it is stated in the results section (line 204) that women in a database were screened for eligibility. Selecting eligible participants from a database should be added to the methods section. Were all women who met inclusion criteria contacted for participation? Or how were those that were contacted selected from the larger group in the database?
Line 164: Is there a reference for this histopathology scale? Or was this created by the authors?
Line 189: It should be stated that the potential confounding factors (age, race, years since symptoms, and baseline scores) were selected a priori. How was years since symptoms determined? Did patients complete a questionnaire or was this determined by chart review?

Results:
Lines 212-214: It is inappropriate to remove participants from the analysis due to exacerbation of symptoms, as this is a clinically meaningful outcome. These women should be included in the analysis. The analysis would then be an "intention to treat" analysis, rather than a "per-protocol" analysis.
Line 221: This reviewer is not familiar with the term "model-based mean." This is not defined in the methods section. Is this the adjusted mean referred to in line 198?
Line 229: Similarly, it is not clear what "based on the model-based mean" means. Does this term mean "In the adjusted model"?
Lines 240-242: How do these results differ from the results reported above (in lines 229-231)? It appears that the same results are reported twice, but with slightly different numbers?
Table 1: Were any other standard demographic characteristics collected, such as income, insurance type, education, or other markers of SES? These are important to help readers identify whether their patients are similar to those in the study/whether the results could apply to their patient population.
Is any information available on why these women with long-standing VLS had active disease? What treatment were they using at the time of enrollment (prior to the washout period)? Which treatments had they tried and/or failed in the past?
How complaint they were with treatment? Was their disease well-controlled prior to stopping their meds to allow participation in the study?
Table 2: In the first line, second column (Patient CSS, active treatment, crude model), the pretreatment mean is 24.3 and
the posttreatment mean is 7.5, but the difference is reported as -6.8. How is this possible? Shouldn't this difference by -16.8?

Discussion:
Very good discussion of prior research, how this study differs from prior work, and how this study is relevant and important.

Reviewer #2:

Review of Manuscript ONG-21-10 "Fractional Co2 laser for the treatment of vulvar lichen sclerosus: a double-blind, sham-controlled randomized trial"

Mitchell and colleagues have submitted the results from a small RCT that evaluated outcomes in women with biopsy proven vulvar lichen sclerosus that were treated, following a seemingly appropriate washout period of 4 weeks, with either active laser therapy or a sham "laser" therapy" that was designed to at least mimic active laser therapy in order to protect masking. As noted by the authors, outcomes was based on histopathologic findings in this study although also incorporated the Clinical Scoring System for Vulvar Lichen Sclerosus (CSS) as a secondary endpoint. A CONSORT checklist is included. I have the following questions and comments.

Title - No comments

Précis - I did not see one.

Abstract - Consider noting in the abstract that this is for biopsy (histopathological) proven LS.
Line 73 - Consider noting that 50 signed consent with 40 enrolled and ultimately 35 evaluated for outcomes.
Consider noting median age and/or racial distribution in the abstract if space allows.

Introduction - Overall reasonable summary of the background information including the current limitation as it relates to the lack of controlled studies.
Line 110 - Although Figure 1 may often be a flow diagram for a study, I think that you should reverse the order since you mention figure 2 first in this line.
Slightly revise the last sentence as it relates to the objective of the study (model after the abstract). "The purpose of this study was to evaluate...."

Methods - Line 129-130 - Do you mean in terms of designing and/or interpreting the outcomes?
Line 145 - Was block randomization used?
Line 146 - How was the initial biopsy recorded in order to ensure the repeat was in the same general location?
Line 149-151 - Presumptively the research associate now who received what. How was the laser set and who did this?
Line 158 - Were patients awake and able to 'smell the smoke? If not, I think this masking would be directed more at the surgeon.
Line 167 - The abbreviation CSS is represented several times later in the manuscript as CCS, which I think is an error. Please correct.
Line 198 - confidence is misspelled

Results - Line 205 - See previous comment about figure 1 and 2.
Line 209 - As noted above, can you modify abstract to note what actually happened in the study - 35 women treated and analyzed and not 40.
Line 219 - Are there any other important covariates that needed to be tracked - prior surgery, prior h/o other vulvar issues, hormonal levels, and family history?
Line 221-3 - Minor issues but I would list results for treatment group first.
Line 236 - you can just list the p value and it is clear that it is not a significant without having half a sentence to explain this finding.

Did you consider having histopathology from the 2 groups demonstrating the lack of change from pre-treatment to post- in the FxCO2 as well as sham?

Discussion - Line 295 - May want to soften this as it sounds a bit accusatory to say the least.

Tables - Table 1 - See previous comments about other variables which could have been collected.
Table 2 - Need to spell out CSS and HS so that the table stands on its own.
Table 3 - Agree this should be supplementary. Do you have more info that the laser settings "appeared" the same for the surgeon regardless of treatment arm?

Figures - Figure 2 - not beneficial in my opinion.

Reviewer #3:

Abstract
Line 59 - "with biopsy who [missing 'were'] abstaining from topical...
Line 74 - 0.1 should be 0.10 (maintain one or two decimals throughout)

Introduction
Strong explanation for the problem at hand and how their research fits into the broader literature on this topic. We were able to follow it clearly and have an understanding of the reason why this study was preformed. The only thing is adding a bit more about the traditional treatment with CO2 laser is with corticosteroids: how many sessions are done and how is further surveillance preformed.

Methods -
Very clear explanation of the funding, enrollment, randomization and histopathology process.
Why was 40% chosen as clinically significant? They tried to factor in all variables that could confound the data. They were different in including objective data; physician clinical assessment and also histological changes. I do like how they added patient perception in the data; it gives an interesting twist to the data. Some of the limitations I noted was race and the decrease in population size. I'm also not sure if any use of steroids makes a difference; they have a flush out period but unsure if the outcome would have been different if they never used steroids in the first place. Since it was stated that it worked in GSM due to the recruitment of inflammatory changes and vascular changes but does the previous steroid use decreased those local factors needed for that.

Results
I think they were significant in the sense it allows us to see that laser treatment alone is not necessarily beneficial but its the combination with steroids that it is helpful for treatment.
Their population size was low and not very diverse which is hard to assess racial discrepancies.

Tables/Figures -
Table 1 - in document used the other categories but did not list as other. Would have the same as consistency
Table 2 - Any way to condense this down?
Table 3 - not sure if this is needed
Figure 1 - fine
Figure 2 - What is the purpose of the vulvar picture?

Conclusion -
Was concise and went through the findings and the implications. I liked how they also went through some of the downfalls of previous studies to allow us to understand why this study was preformed and why some variables were changed.
They mention that there is a placebo affect in patient perspective - is that meaningful to patients and worth offering in conjunction with topical steroids?
Not sure if they need paragraph starting in 262 - would focus more about the findings and significant within VLS vs role of laser.
Interesting consideration in line 295 about payment.
Good rationale in paragraph starting in 317
Good summary statement at the end.

Originality / Contribution - Original with strong study design. They spoke on other similar studies that were preformed but knowing about their limitations helps us understand why this study was preformed.

Fit for journal - I believe it would be helpful to be in a journal. I think it sparks interest in the field and may allow other people to replicate the study on a larger scale.
STATISTICS EDITOR COMMENTS:

Abstract: Should conform to our template for RCTs, esp regarding the power/sample size calculation, statement of primary outcome and the restatement of primary outcome in the same format as stated in power/sample size. That is, the primary outcome is the difference in histopathology scale (16%, assuming 17% was the SD). The other results are all secondary ones.

Table 1: Since the groups were randomized, there is no need to statistically compare the groups, any difference is due to random chance.

Table 2: Need to present both the Intention to treat and Per protocol analysis. Need to clearly separate the primary outcome from all secondary ones. Since the groups were randomized, why is the adjusted analysis included? If age, race or years since symptoms were thought to be important variables regarding the outcome, then the study design should have been different and factored those into the randomization process.

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

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

4. 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 (e.g., 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).

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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revalidate-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revalidate-gynecology-data-definitions. 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); Case Reports should not exceed 8 typed, double-spaced pages (2,000 words); Review articles should not exceed 25 typed, double-spaced pages (6,250 words); Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words); Clinical Practice and Quality articles should not exceed 22 typed, double-spaced pages (5,500 words); Procedures and Instruments articles should not exceed 8 typed, double-spaced pages (2,000 words); Personal Perspectives essays should not exceed 12 typed, double-spaced pages (3,000 words); Clinical Conundrums articles should not exceed 6 pages (1,500 words); Questioning Clinical Practice articles should not exceed 6 pages (1,500 words); Research Letters articles should not exceed 2.5 pages (600 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.

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. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

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

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

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

11. 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.

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

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

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

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

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%.

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

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

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the 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 at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

18. Figures 1-2: Please make sure that the numbering of the figures matches the order in which they appear in the manuscript.

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.

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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 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. Do not omit your responses to the Editorial Office or Editors’ comments.

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 26, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

John O. Schorge, MD
Associate Editor, Gynecology

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.
March 5, 2021

Dwight J. Rouse, MD, MSPH
Editor-in-Chief, Obstetrics and Gynecology

Dear Dr. Rouse:

We would like to submit a revision of our manuscript ONG-21-10 entitled “Fractional CO2 Laser for the Treatment of Vulvar Lichen Sclerosis: A Double-Blind, Sham-Controlled Randomized Trial” for consideration in Obstetrics and Gynecology.

We greatly appreciate the reviewers’ comments and feel that we have addressed them adequately. In so doing, we feel that the paper has been considerably improved.

Our changes are listed below highlighted in yellow.

Sincerely,

Andrew T. Goldstein MD, FACOG IF

REVIEWER COMMENTS:

Reviewer #1:

Introduction:
Line 103: Could add that treatments in addition to topical corticosteroids are needed because these require regular long-term use and compliance.

We agree and have added the following sentence: “Additionally, adequate treatment requires compliance with a regimen of long-term corticosteroid use.”

Methods:
Line 136: It is stated here that women with VLS were recruited from one center, however it is stated in the results section (line 204) that women in a database were screened for eligibility. Selecting eligible participants from a database should be added to the methods section. Were all women who met inclusion
criteria contacted for participation? Or how were those that were contacted selected from the larger group in the database?

We have further clarified this by adding the following: “Women with a diagnosis of biopsy-proven active VLS were recruited from a database of a center that specializes in the treatment of vulvar disorders. Women in the database were contacted by a clinical researcher via email and/or phone. At that time, the eligibility of each woman was determined using the inclusion and exclusion criteria. Women who were eligible were offered screening visits for the trial. Additionally, new patients with lichen sclerosus who presented to the center during the recruitment phase of this trial were offered inclusion in the trial if they met eligibility requirements.”

Line 164: Is there a reference for this histopathology scale? Or was this created by the authors?

The HS scale has been used in previous randomized, controlled trials (now cited). In addition, in communications between the U.S. FDA and the senior author (ATG), the FDA requires change in histopathology for any Investigational New Drug (IND) application for the treatment of lichen sclerosus.

Line 189: It should be stated that the potential confounding factors (age, race, years since symptoms, and baseline scores) were selected a priori. How was years since symptoms determined? Did patients complete a questionnaire or was this determined by chart review?

These confounding factors were not controlled for and, therefore, statistical analysis that including these factors has been removed.

Results:

Lines 212-214: It is inappropriate to remove participants from the analysis due to exacerbation of symptoms, as this is a clinically meaningful outcome. These women should be included in the analysis. The analysis would then be an "intention to treat" analysis, rather than a "per-protocol" analysis.

We agree and have now included an intent-to-treat (ITT) analysis as well as a per protocol analysis of the data.

Line 221: This reviewer is not familiar with the term "model-based mean." This is not defined in the methods section. Is this the adjusted mean referred to in line 198?
At the suggestion of the journal’s statistician, this type of analysis has been removed.

Line 229: Similarly, it is not clear what "based on the model-based mean" means. Does this term mean "In the adjusted model"?

As above.

Lines 240-242: How do these results differ from the results reported above (in lines 229-231)? It appears that the same results are reported twice, but with slightly different numbers?

This has been corrected

Table 1: Were any other standard demographic characteristics collected, such as income, insurance type, education, or other markers of SES? These are important to help readers identify whether their patients are similar to those in the study/whether the results could apply to their patient population.

Unfortunately, these data were not obtained and, therefore, cannot be included.

Is any information available on why these women with long-standing VLS had active disease? What treatment were they using at the time of enrollment (prior to the washout period)? Which treatments had they tried and/or failed in the past? How complaint they were with treatment? Was their disease well-controlled prior to stopping their meds to allow participation in the study?

The patient population was highly variable. Some women had no prior treatment, other had been non-compliant with treatment regimens, and other had used steroids but were still symptomatic. To address this important comment, we added the following to the discussion section of the paper: “Another weakness is the variability in patient population in regard to prior treatments for lichen sclerosus. Some of the women had never received treatment for their VLS, others had used corticosteroids but were non-compliant with treatment regimens (or had adverse reactions to steroids), and others had used corticosteroids but continued to be symptomatic. However, as mentioned in the methods section, all women had to have active VLS on biopsy in order to qualify for participation in the treatment phase of the trial and 10 women were excluded after they had signed informed consent because their biopsies did not confirm active VLS.”
Table 2: In the first line, second column (Patient CSS, active treatment, crude model), the pretreatment mean is 24.3 and the posttreatment mean is 7.5, but the difference is reported as -6.8. How is this possible? Shouldn't this difference by -16.8?

The post treatment mean was 17.5 and this has been corrected in the new table 2.

Discussion:
Very good discussion of prior research, how this study differs from prior work, and how this study is relevant and important.

We thank the reviewer for this positive assessment of our discussion.

Reviewer #2:

Review of Manuscript ONG-21-10 "Fractional Co2 laser for the treatment of vulvar lichen sclerosus: a double-blind, sham-controlled randomized trial"

Mitchell and colleagues have submitted the results from a small RCT that evaluated outcomes in women with biopsy proven vulvar lichen sclerosus that were treated, following a seemingly appropriate washout period of 4 weeks, with either active laser therapy or a sham "laser" therapy" that was designed to at least mimic active laser therapy in order to protect masking. As noted by the authors, outcomes was based on histopathologic findings in this study although also incorporated the Clinical Scoring System for Vulvar Lichen Sclerosus (CSS) as a secondary endpoint. A CONSORT checklist is included. I have the following questions and comments.

Title - No comments

Précis - I did not see one.

Abstract - Consider noting in the abstract that this is for biopsy (histopathological) proven LS.

The sentence now is “The study participants were forty women with active VLS confirmed with biopsy who…”
Consider noting that 50 signed consent with 40 enrolled and ultimately 35 evaluated for outcomes.

We have changed the abstract to report on an ITT population: “forty women were randomized to participate in the trial, and thirty-seven women (19 FXCO₂, 18 sham) were included in an intention-to-treat (ITT) analysis. Three women were excluded from the ITT analysis because they did not have post-treatment biopsies and, therefore, a post-treat HS score could not be obtained.”

Consider noting median age and/or racial distribution in the abstract if space allows.

Unfortunately, it does not.

Introduction - Overall reasonable summary of the background information including the current limitation as it relates to the lack of controlled studies.
Line 110 - Although Figure 1 may often be a flow diagram for a study, I think that you should reverse the order since you mention figure 2 first in this line.

We have changed the order.

Slightly revise the last sentence as it relates to the objective of the study (model after the abstract). "The purpose of this study was to evaluate….."

Methods - Line 129-130 - Do you mean in terms of designing and/or interpreting the outcomes?

Line 145 - Was block randomization used?

No, simple randomization because this was a small study. We have now included this in the text.

Line 146 - How was the initial biopsy recorded in order to ensure the repeat was in the same general location?

We have added the following: “Using photo-documentation as a guide, a repeat biopsy was performed adjacent to the original biopsy site 8 weeks after the final treatment.”

Line 149-151 - Presumptively the research associate now who received what. How was the laser set and who did this?
We have added the following: “The laser’s settings were set by a research associate and these setting were obscured so that the treating physician could not see them.”

Line 158 - Were patients awake and able to "smell the smoke? If not, I think this masking would be directed more at the surgeon.

Yes, they were awake and able to smell the smoke.

Line 167 - The abbreviation CSS is represented several times later in the manuscript as CCS, which I think is an error. Please correct.

Corrected.

Line 198 - confidence is misspelled

Corrected

Results - Line 205 - See previous comment about figure 1 and 2.

Corrected.

Line 209 - As noted above, can you modify abstract to note what actually happened in the study - 35 women treated and analyzed and not 40.

The abstract has now been changed to show the ITT population.

Line 219 - Are there any other important covariates that needed to be tracked - prior surgery, prior h/o other vulvar issues, hormonal levels, and family history?

Unfortunately, we did not track additional covariates.

Line 221-3 - Minor issues but I would list results for treatment group first.

Changed.
Line 236 - you can just list the p value and it is clear that it is not a significant without having half a sentence to explain this finding.

**Changed.**

Did you consider having histopathology from the 2 groups demonstrating the lack of change from pre-treatment to post- in the FxCO2 as well as sham?

We are not sure we understand this comment. Pre and post treatment histopathology was examined for both the FXCO2 group as well as the sham group.

Discussion - Line 295 - May want to soften this as it sounds a bit accusatory to say the least.

**Changed.**

Tables - Table 1 - See previous comments about other variables which could have been collected.

**Unfortunately, no additional demographic data was not obtained.**

Table 2 - Need to spell out CSS and HS so that the table stands on its own.

**Corrected.**

Table 3 - Agree this should be supplementary. Do you have more info that the laser settings "appeared" the same for the surgeon regardless of treatment arm?

**The settings were complete obscured from the physicians’ view. The authors believe this table is necessary as it provides the information necessary to repeat the study if desired.**

Figures - Figure 2 - not beneficial in my opinion.

**The authors believe that this photo shows the “dots” from a fractional laser, with which many readers may not be familiar, and illustrates that only a small fraction of the tissue is affected by the laser. We leave it up to the editors to decide if this photo adds value to the paper.**
Reviewer #3:

Abstract
Line 59 - "with biopsy who [missing 'were'] abstaining from topical…

Corrected.

Line 74 - 0.1 should be 0.10 (maintain one or two decimals throughout)

Corrected.

Introduction
Strong explanation for the problem at hand and how their research fits into the broader literature on this topic. We were able to follow it clearly and have an understanding of the reason why this study was preformed. The only thing is adding a bit more about the traditional treatment with CO2 laser is with corticosteroids: how many sessions are done and how is further surveillance preformed.

The authors do not believe that the use of lasers, with or without corticosteroids, are traditionally used for lichen sclerosus. We do not believe there is any standard of care in regards to the number of sessions or surveillance and the use of steroids has never been endorsed in any consensus treatment guidelines.

Methods -
Very clear explanation of the funding, enrollment, randomization and histopathology process.
Why was 40% chosen as clinically significant?

The choice of 40% is somewhat arbitrary but corticosteroids (the gold standard treatment) have been shown to completely reverse the histopathologic changes. As such, and given that lichen sclerosus is a premalignant process, it seems reasonable that a smaller effect would not be clinically significant.

They tried to factor in all variables that could confound the data. They were different in including objective data; physician clinical assessment and also histological changes. I do like how they added patient perception in the data; it gives an interesting twist to the data. Some of the limitations I noted was race and the decrease in population size. I'm also not sure if any use of steroids makes a difference; they have a flush out period but unsure if the outcome would have been different if they never used steroids in the first place. Since it was stated that it worked in GSM due to the recruitment of inflammatory changes and vascular changes but does the previous steroid use decreased those local factors needed for that.
As most women with lichen sclerosus have used corticosteroids at some point in time, often before they had a definitive diagnosis, it seemed unreasonable to exclude women who have ever used this treatment. However, this is one reason why we did the pre-treatment biopsy to confirm that they have active lichen sclerosus before any laser treatments.

Results
I think they were significant in the sense it allows us to see that laser treatment alone is not necessarily beneficial but its the combination with steroids that it is helpful for treatment. Their population size was low and not very diverse which is hard to assess racial discrepancies.

The authors are not necessarily in agreement with the reviewer that the data presented here (or in any other peer reviewed publication) that the combination of laser plus steroids is better than steroids alone.

We agree that a lack of racial diversity is a weakness of the study and have added the following sentence to the discussion: “An additional weakness was the relatively racially homogenous population which may affect applicability in non-Caucasian populations of women.”

Tables/Figures -
Table 1 - in document used the other categories but did not list as other. Would have the same as consistency

Table 2 - Any way to condense this down?

Unfortunately, the authors do not see how to do this without losing data which is potentially valuable to readers.

Table 3 - not sure if this is needed

The authors believe this table is necessary as it provides the information necessary to repeat the study if desired.

Figure 1 - fine
Figure 2 - What is the purpose of the vulvar picture?
The authors believe that this photo shows the “dots” from a fractional laser, with which many readers may not be familiar, and illustrates that only a small fraction of the tissue is affected by the laser. We leave it up to the editors to decide if this photo adds value to the paper.

Conclusion -
Was concise and went through the findings and the implications. I liked how they also went through some of the downfalls of previous studies to allow us to understand why this study was preformed and why some variables were changed.
They mention that there is a placebo affect in patient perspective - is that meaningful to patients and worth offering in conjunction with topical steroids?

The authors believe that any treatment, especially one that is costly and somewhat uncomfortable, that does not add benefit beyond a placebo effect, is not appropriate to offer to patients. We are not sure if adding this into the paper is useful.

Not sure if they need paragraph starting in 262 - would focus more about the findings and significant within VLS vs role of laser.
Interesting consideration in line 295 about payment.
Good rationale in paragraph starting in 317
Good summary statement at the end.

Originality / Contribution - Original with strong study design. They spoke on other similar study was preformed.

Fit for journal - I believe it would be helpful to be in a journal. I think it sparks interest in the field and may allow other people to replicate the study on a larger scale.

STATISTICS EDITOR COMMENTS:

Abstract: Should conform to our template for RCTs, esp regarding the power/sample size calculation, statement of primary outcome and the restatement of primary outcome in the same format as stated in power/sample size. That is, the primary outcome is the difference in histopathology scale (16%, assuming 17% was the SD). The other results are all secondary ones.
We have rewritten the abstract to conform to the *Obstetrics and Gynecology* template for power and sample size and have now only included results of the primary endpoint in the abstract. Additionally, we have now given the results of an ITT analysis instead of the PP analysis.

Table 1: Since the groups were randomized, there is no need to statistically compare the groups, any difference is due to random chance.

*We have removed P values.*

Table 2: Need to present both the Intention to treat and Per protocol analysis. Need to clearly separate the primary outcome from all secondary ones. Since the groups were randomized, why is the adjusted analysis included? If age, race or years since symptoms were thought to be important variables regarding the outcome, then the study design should have been different and factored those into the randomization process.

*We have now given both the ITT and PP analysis and have differentiated between the primary out from the secondary outcome. Lastly, we have removed any statistical adjustment for age, race, and duration of symptoms.*