OBSTETRICS & GYNECOLOGY

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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

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

Date: Dec 18, 2020
To: "Linda Burkett" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-3046

RE: Manuscript Number ONG-20-3046

A Randomized Controlled Trial of Clobetasol vs Fractionated CO2 Laser for Lichen Sclerosus (CuRLS)

Dear Dr. Burkett:

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 Jan 08, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

The authors provided a nice study to compare steroid use and CO2 fractionated laser treatment for lichen sclerosus. All parameters are well studied and well reported. However, this would have been a much cleaner study if all patients had been prior treatment naïve. Please report the outcomes in treatment naive patients. The authors provide an explanation that they have distributed "clobetasol non-responders" equally between the groups, but it would be difficult to ascertain if they were non-responders or if they were non-compliant with the treatment despite response initially. This is the basic premise that is concerning in this study and potentially biases the results.
Why did the authors not follow the patients til one year? Are there plans to continue to report outcomes at one year?
Line 128 - typo - "…two pilot case studies…"
Line 147 - it is interesting that exclusion criteria included those patients planning a pregnancy when they were all post-menopausal.
Line 148 - please clarify if the exclusion was for current and/or prior treatment with systemic immunomodulators

Reviewer #2:

This paper describes a randomized controlled trial of CO2 laser therapy compared to standard topical steroid therapy for biopsy proven, symptomatic, vulvar lichen sclerosus. To date this has only been evaluated in case studies. The primary outcome was measured with scales that captured patient reported acute skin symptoms.

Abstract:
1. The abstract is specific to the manuscript.
2. Lines 83-84: May not need to state "subjective" twice (e.g. Secondary outcomes included validated subjective and objective measures...)

Introduction:
3. Well described background.

Methods:
4. Methods seem suitable to the design.

5. Consider including all surveys used as supplemental material.

Results:

6. Lines 222-224: What was the main reason (or reasons) for the large number of women who declined?
7. Lines 223-224: Consider the term "none were lost to follow-up" instead of "without drop out".
8. Lines 226-228: Does the 74% compliance rate apply to the entire study group as whole?
9. Lines 236-242: This section could benefit from restructuring some of the sentences. For example:

The primary outcome was the mean change in Skindex-29 scores between baseline and six-months. The Skindex-29 is a validated questionnaire for assessing acute dermatologic symptoms over a 4 week period with more negative scores indicating greater improvement. In the intention to treat analysis, greater improvement was noted for laser group compared to the steroid group (table 2). Similar results were seen in the per protocol analysis.....

Discussion:

10. The data support the conclusions.
11. Lines 305-306: Please clarify the meaning of this sentence.
12. Lines 306 -308: What is the effect that was only maintained in those with prior steroid use?
13. Lines 318-319: Why does the current clinical climate warn against energy based treatments?
14. Can the authors comment on practicality of CO2 laser treatment (cost, access)?

Reviewer #3: ONG-20-3046_review

The authors have undertaken an important project, conducting a randomized clinical trial (RCT) of a potential emerging therapy for lichen sclerosus (LS), comparing fractional CO2 laser to the standard treatment of high-potency topical steroids. It should be recognized that an RCT about LS is an ambitious undertaking, as research tools are sparse that provide an adequate foundation for high quality studies.

The stated objective: "hypothesized that it is a safe alternative treatment" differs from the hypothesis that is tested. The primary outcome variable, the Skindex-29 score, is a dermatology-specific quality of life instrument and not a measure of safety. At best, this paper measures no serious adverse events in 27 women after 6 months of follow up, which is encouraging, but insufficient for concluding that laser therapy of the vulva is safe. Since the laser treatment was given in 3 sessions, 4-6 weeks apart, the actual follow up time is even shorter, 3-4 months.

Assuming that the actual objective is measuring treatment efficacy, the trial has resulted in important findings, but findings that do not yet support the conclusions of the manuscript. The authors astutely posited that previously-treated women might respond differently than treatment-naïve women but unfortunately, did not power the study to assess this stratification. This was indeed true—when stratified, both groups improved with both treatments, but the treatment effect was larger and only significant in the previously treated group. Because of the smaller sample size after stratification, we don't know if laser is superior to clobetasol in treatment naïve women, and if the effect size is actually smaller in this group.

In the previously treated group, the residual treatment effect of the previous clobetasol therapy would be expected to lower the measured benefit in the clobetasol group, thus enhancing the comparison to the laser group. An 8-week washout might be inadequate, with at least one study showing that symptoms and exam findings had not returned to baseline 3 months after follow up.1 For all analyses, the baseline values of the outcome measures should be reported as well as the treatment differences, for the overall and stratification results.

Further, the baseline values of the outcome measures should be reported in order to determine whether the randomization resulted in LS cases with similar severity as best as can be measured. This would also allow readers to assess the generalizability of the study. Figure 2 provides some baseline information for the Skindex, but not for the stratification and not for the other outcomes.

LS is a highly variable condition with respect to symptoms and physical changes—some women are very symptomatic with minimal physical changes while others experience marked architectural changes with a dearth of symptoms. It is possible that LS cases identified in a Urogyn practice may represent the latter, a less symptomatic sample compared to women who present to a general gynecologist or dermatologist with LS as the primary reason for the visit. The LS cases seen in a Urogyn practice are often "incidental" diagnoses that are relatively asymptomatic for the level of architectural changes. This variability is rarely addressed in LS research and there are no tools for measuring this. In the absence of tools, more detailed descriptions are needed.

Table 2 should include effect sizes and confidence intervals for all variables.

The primary outcome variable, the Skindex-29, one of the few/only validated instruments that could be used for LS studies, and it is a quality of life instrument. While important to patients, quality of life is remote from direct treatment effects. It is notable that the quality of life improvement that occurs with both treatments is much greater than the smaller and nonsignificant changes in symptoms and clinical findings. This contrasts to the other RCT that utilizes the Skindex-29 (comparing clobetasol to UV-A1),1 in which both groups have similar improvement in symptoms and findings,

but the improvement in Skindex-29 is much greater in the clobetasol vs. the UV-A1 treatment. Perhaps quality of life instruments indirectly measure satisfaction with the treatment approach. The UV-A1 treatment is more cumbersome for women, requiring 5-minute phototherapy sessions to the vulva, 4 times weekly for 12 weeks compared to daily application of topical steroids. In this study, perhaps the laser offers "space-age" therapy with hope for a "cure," in comparison to lifetime topical therapy for a chronic condition. The investigators in the Ogrinc RCT noted a difficulty in gaining compliance for the steroid arm, stating: "We found it very difficult to motivate patients in the control group to adhere to the study protocol. This was in part because of the recurrence of symptoms and in part because of the negative attitude of the patients to the control treatment."2 A sham-control for the laser will likely be required in future studies to allow blinding to control for such effects.
The Skindex-29 in not well known to OB/GYN clinicians and should be described to readers in the methods section, not the results section.
In the comments section, the authors state that their findings with regard to the Skindex are similar to those in the Ogrinc study, but the Ogrinc study did not use the Skindex as an outcome measure.
There is a typo in Table 1, Prior Clobetasol Use is "11", not "1" in the steroid group. I don't understand the categories of "Living Situation:" "Alone, Home."

The strengths of this study are its rigorously planned design with sample size analysis, intention-to-treat and per protocol analysis, and use of the best available outcome measures, with blinded analysis where possible. The rigor of this trial is superior to the only other published RCT evaluating laser therapy to LS. I recommend revision of the manuscript attending to the flaws noted above, and I suspect that this will result in a final result of an inconclusive trial. These results will provide important evidence to support much needed research by gynecologists about lichen sclerosus and the vulva more generally.

Of note, in 2004, Dr. Kenneth Noller published an editorial in "Obstetrics and Gynecology" titled "Vulva: the forgotten pelvic organ,"3 noting the lack of attention to vulvar disorders and offering hope for improved gynecologic research regarding vulvar diseases. Unfortunately, a PubMed search of RCTs for LS resulted in 21 studies, with a majority published in dermatology journals and none in major OB/GYN journals. These gynecologic investigators have focused considerable attention of this forgotten organ. This study represents an important gynecologic contribution to the science of vulvar studies and an opportunity raise awareness regarding older women's health.

1. Terras S, Gambichler T, Moritz RK, Stücker M, Kreuter A. UV-A1 phototherapy vs clobetasol propionate, 0.05%, in the treatment of vulvar lichen sclerosus: a randomized clinical trial. JAMA Dermatol. 2014;150(6):621-627.
2. Bizjak Ogrinc U, Senčar S, Luzar B, Lukanović A. Efficacy of Non-ablative Laser Therapy for Lichen Sclerosus: A Randomized Controlled Trial. J Obstet Gynaecol Can. 2019;41(12):1717-1725.
3. Noller KL. Vulva: the forgotten pelvic organ. Obstet Gynecol. 2004;104(5 Pt 1):913-914.

STATISTICS EDITOR COMMENTS:

Abstract: Needs to conform to our RCT template.

lines 96-98: The sample size was insufficient to generalize conclusions re: occurrence of serious safety or adverse events (n = 27 in the laser treatment arm). For example, a serious event occurring 0/27 instances has 95% CI = 0-13%.

Table 1: Need units for BMI. Parity can only have integer values, so should cite as median(range or IQR). Should verity whether the duration of diagnosis nor duration of estrogen replacement were normally distributed. If not, then should format as median(range or IQR), rather than as mean±SD.

Table 2: Need to clearly separate the primary from all secondary outcomes. The strata with mean difference in Skindex-29 were not separately calculated in the sample size/power calculations. They should be listed as secondary outcomes. Were the differences normally distributed? If not, then should test non-parametrically, particularly since the sample sizes were relatively modest.

Table 3: These are also secondary outcomes. The sample size/power calculation did not factor in subsets and the study was not powered to evaluate the clobetasol naïve comparison, so that NS finding cannot be generalized.

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 (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).

5. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works.

Disclose oral AJOG presentation or provide citation for Abstract (09: A randomized controlled trial of clobetasol propionate versus fractionated CO2 laser for the treatment of lichen sclerosus (CURLS)).

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 words. Please provide a word count.

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

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

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

13. 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.

14. 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%").

15. Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

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. Figure 1: Please check n values (205-150 doesn’t equal 52). Please upload as a figure file on Editorial Manager.
Figure 2: Please upload as a figure file on Editorial Manager.
Figure 3: Please upload a version without labels, these will be added back per journal style. Please upload as a figure file on Editorial Manager.

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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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 Jan 08, 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

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January 7, 2021

Dear Editors of *Obstetrics and Gynecology*,

Thank you for your review of our submission Manuscript Number ONG-20-3046 entitled: “A Randomized Controlled Trial of Clobetasol vs Fractionated CO2 Laser for Lichen Sclerosus (CuRLS).” We have carefully addressed each comment by the reviewers and editors below and made changes to the submitted manuscript. We again appreciate your consideration.

Please also be aware that written permission must be obtained from all individuals named in the acknowledgments and are on file by the corresponding author.

Below are the individual responses to the reviewer and editor comments.

Reviewer #1:
Point 1: All parameters are well studied and well reported. However, this would have been a much cleaner study if all patients had been prior treatment naïve. Please report the outcomes in treatment naive patients. The authors provide an explanation that they have distributed "clobetasol non-responders" equally between the groups, but it would be difficult to ascertain if they were non-responders or if they were non-compliant with the treatment despite response initially. This is the basic premise that is concerning in this study and potentially biases the results.

Response: Thank you for this comment. We agree that all naïve patients would be a cleaner group to study with less potential for bias based on non-responder and poor compliance. However, it is important to further understand if the laser treatment works in patients with a long history of lichen sclerosus as well. We chose not to exclude these women but rather to stratify them between groups to allow generalization to all women with lichen sclerosus. However, as the statistician pointed out it is important to note that we did not power to these groups and it is difficult to make robust conclusions. We are planning a follow up study with only naïve patients. We had good compliance with Clobetasol treatment.

We have added a table 2 and table 5 to show the naïve vs exposed patients values for comparison. You can see that the outcomes were not significantly different between groups for the majority of measures. There are not significant differences between these groups which should minimize some of the potential bias.

New wording: Line 549-550. “Further research utilizing placebo and sham lasers for treatment blinding, and a naive population is needed.”

Lines 388-389. “The change in outcomes at six-months were similar between Clobetasol naïve and exposed groups, table 5.”
See Table 5.

Point 2: Why did the authors not follow the patients til one year? Are there plans to continue to report outcomes at one year?

Response: Thank you for the comment, we did follow patients until one year and do plan to report these findings in a separate manuscript. We present the six-month outcomes as they were designed as the primary outcome. Patients were given the ability to crossover into another treatment group at six months and therefore the 12-month outcomes will report four groups and

become underpowered. We choose to limit this manuscript to the six-month outcomes for simplicity of methods and robustness of sample size. However, we did add comment into manuscript about prolonged observation.

New wording: Line 282-284. “Data collection was completed at baseline, 6-months, and 12 months with multiple validated scales, surveys, and photo documentation providing reproducible measures of vulvar symptoms and appearance as primary and secondary outcomes.”
Line 286-287. “The primary outcome was change in mean Skindex-29 score at six-months and the six-month outcomes are presented in this manuscript.”

Point 3. Line 128 - typo - "…two pilot case studies…"

Response: Thank you for the comment. Typo was addressed and updated as a newly published study was added to references.

New wording: Line 217. “Three case series”

Point 4. Line 147 - it is interesting that exclusion criteria included those patients planning a pregnancy when they were all post-menopausal.

Response: Thank you for the comment, we agree that this does not make sense however was request by IRB and submitted on ClinicalTrials.gov so we included it.

Point 5. Line 148 - please clarify if the exclusion was for current and/or prior treatment with systemic immunomodulators

Response: Thank you for the comment, the exclusion criteria was for current treatment with immunomodulators. As with current Clobetasol use all patients were eligible if they agreed to an eight week wash out period.

New wording: Lines 263-264. “Subjects completed an 8-week washout period prior to enrollment if currently using clobetasol propionate or other topical or systemic immunomodulator.”

Reviewer #2:
Point 1. Abstract Lines 83-84: May not need to state "subjective" twice (e.g. Secondary outcomes included validated subjective and objective measures...)

Response: Thank you for the comment, we agree it is clearer without, word removed.

New wording: Lines 134-136. “Secondary outcomes included validated subjective and objective measures. Intention-to-treat, per protocol, and regression analysis based on prior steroid exposure were performed.”

Point 2. Consider including all surveys used as supplemental material

Response: Thank you for the comment. Unfortunately, the Skindex-29 is a copyrighted survey and we purchased the copies needed to for study and the scoring materials. The VSQ-Vulvovaginal Symptom Questionnaire and VHI- vaginal health index are validated questionnaires previously published and used with author permissions and the original studies

with surveys are referenced. The remaining visual analog scale and global impression of improvement scale are described as simple scaled measured and questions reported within the tables. If these questionnaires are further requested by the reviewers and or editors we can include them but we are not sure they would add to understanding in this case.

Point 3. Lines 222-224: What was the main reason (or reasons) for the large number of women who declined?

Response: Thank you for the comment. We reviewed our patient log and the majority of patients declined due to the travel requirements which were not funded by the study. We had wide geographic interest from the clinicaltrials.gov posting. The second most common reason was disinterest in the randomization and research process. Several patients also initial expressed interest during outpatient visit who then declined by non-communication with study personal.

Point 4. Lines 223-224: Consider the term "none were lost to follow-up" instead of "without drop out".

Response: Thank you for the comment, we agree and the change was made.

New wording: Line 225-226. “subjects completed laser treatment and six-month follow-up none were lost to follow-up.”

Point 5. Lines 226-228: Does the 74% compliance rate apply to the entire study group as whole?

Response: Thank you for the comment. We agree this is not clear. The compliance rate is reported for the steroid arm. Patients in the laser group were all compliant as the laser treatment was completed by researchers and none were lost to follow up.

New wording: Line 229-231. “At six-months, 74% of patients reported complete compliance with treatment, one partial compliance, 4 without report, and one patient reported stopping treatment for lack of efficacy in the steroid group.”

Point 6. Lines 236-242: This section could benefit from restructuring some of the sentences. For example:
The primary outcome was the mean change in Skindex-29 scores between baseline and six-months. The Skindex-29 is a validated questionnaire for assessing acute dermatologic symptoms over a 4 week period with more negative scores indicating greater improvement. In the intention to treat analysis, greater improvement was noted for laser group compared to the steroid group (table 2). Similar results were seen in the per protocol analysis.....

Response: Thank you for the comment and time to generate a clearer structure. We agree and reworked this portion. Per request of Reviewer 3, we did move the explanation of the Skindex to the methods.

New wording: Lines 242-244 “The primary outcome was the mean change in Skindex-29 scores between baseline and six-months. In the intention to treat analysis, greater improvement was noted for laser group compared to the steroid group (laser –16.83 ±18.09 vs steroid -5.92

±5.81; p=0.007), table 3. Similar results were seen in the per protocol analysis with laser (n=26) versus steroid (n=19), (-16.46±17.21 vs -5.79±5.29; p=0.007) with size effect -10.66 (CI -18.93 to -2.39).

Point 7. Lines 305-306: Please clarify the meaning of this sentence.

Response: Thank you for the comment. We included this sentence about a patient whom had protocol deviation requiring oral steroids. We agree that the diagnoses of West Nile virus is distracting and removed it from the sentence. We included this explanation as part of the per protocol analysis.

New wording: Line 472-473. "Another patient in the steroid group deviated study protocol and started oral steroids."

Point 8. Lines 306 -308: What is the effect that was only maintained in those with prior steroid use?

Response: Thank you for the comment. When the subjects were examined based on prior Clobetasol treatment verses those naïve to treatment there was statistical difference still seen between laser and steroid treatment groups in those with prior Clobetasol treatment. Patients who were naïve to Clobetasol still had greater improvement in the laser group but not to the level of statistical significance. We attempted to clarify this point with rewording. Table 4 allows readers to visualize this data. We have also presented the secondary outcomes between these groups, see response Reviewer 1, point 1 and the newly added Table 5.

New wording: Lines 512-514. "Linear mixed model analysis based on prior clobetasol propionate use showed that the greater improvement in the laser group effect was only maintained on the subjects with prior use as opposed to naïve patients, table 4"

Point 9. Lines 318-319: Why does the current clinical climate warn against energy based treatments?

Response: Thank you for the comment. We were referring to statements issued by ACOG, IUGA, and several other national organizations with concerns about laser technology in gynecology being used under an FDA 510k clearance without significant literature support. These devices were quickly cleared using data from similar technology in the predicate devices. In addition, many manufacturers are marketing for cosmetic applications which are unsupported by national organizations. We used the Mona Lisa platform which is the originally cleared device and one with the most literature support. Our statement was meant to indicate that we are aware of legitimate safety concerns surrounding new technology especially with only FDA clearance required. However, treatment of defined pathology (lichen sclerosus) is a very reasonable use for this technology and is covered under the clearance indications. ACOG has issued a new committee opinion this year and has called for more research. We hope to present of our findings as a way to enrich the literature. All patients in the study were made aware of the risk and benefits of this technology in informed consent.

New wording: line 527-529. "The current clinical climate cautions the use of energy based for non-Food and Drug Administration approved indications, however lichen sclerosus is a defined gynecologic pathology."

Point 10. Can the authors comment on practicality of CO2 laser treatment (cost, access)?

Response: Thank you for your comment. We added an explanation about implementation of this technology into gynecology practice.

New wording: Lines 531-535. "Fractionated CO_2 technology is currently offered by a range of providers including gynecologist, plastic surgeons, dermatology, and aesthetic providers. At this point, treatments are not covered by insurance and out-of-pocket cost may limit this resource for patients. We hope by continuing investigation, insurance providers will consider coverage of this technology and more gynecologist may consider offering this treatment option.

Reviewer #3:
Point 1. The stated objective: "hypothesized that it is a safe alternative treatment" differs from the hypothesis that is tested. The primary outcome variable, the Skindex-29 score, is a dermatology-specific quality of life instrument and not a measure of safety.

Response: Thank you for your comment. We agree that the objective and hypothesis could be clearer and new wording is presented.

New wording. Lines 237-239. 'We sought to compare fractional CO_2 laser treatment to clobetasol propionate and observe safety. We hypothesized that it is an effective alternative treatment for patients with symptomatic vulvar lichen sclerosus."

Point 2. At best, this paper measures no serious adverse events in 27 women after 6 months of follow up, which is encouraging, but insufficient for concluding that laser therapy of the vulva is safe. Since the laser treatment was given in 3 sessions, 4-6 weeks apart, the actual follow up time is even shorter, 3-4 months.

Response: Thank you for the comment. You are correct that six months follow up only provides short term conclusions about safety. We did follow patients to 12 months and plan to present these findings in another manuscript. We adjusted our conclusion statement. The six months follow up is from the first treatment and you are correct it would be 3-4 month after the third treatment. We did offer this a weakness in the discussion section lines 350-351.

New wording: Line 149. "or adverse events at six months."
Line 524-525. "Fractionated CO_2 laser treatment did not demonstrate significant safety concerns or adverse events during the trial six month time period."

Point 3. Assuming that the actual objective is measuring treatment efficacy, the trial has resulted in important findings, but findings that do not yet support the conclusions of the manuscript. The authors astutely posited that previously-treated women might respond differently than treatment-naïve women but unfortunately, did not power the study to assess this stratification. This was indeed true—when stratified, both groups improved with both treatments, but the treatment effect was larger and only significant in the previously treated group. Because of the smaller sample size after stratification, we don't know if laser is superior to clobetasol in treatment naïve women, and if the effect size is actually smaller in this group.

Response: Thank you for these comments. You are correct that the objective was to measure efficacy. We are not powered to report conclusions about the stratification results. Of course, we could not predict these findings at this time of study design. However, as discussed by Reviewers 1 point 1 and Reviewer 2 point 8, we still feel these findings in an understudied area are important to present to readers. To improve understanding of this information and generalizability of the study, we will now present tables 2 and 5 of stratified results. We understand a study of all naïve patients would provide a cleaner comparison but did not want to exclude patients previously treated as this may be an important treatment option for them and would have further limited our recruitment pool.

New wording: See Table 5.
Lines 388-389: "The change in outcomes between baselines and six-months were similar between Clobetasol naïve and exposed groups, table 5."
Lines 507-510: "Baseline characteristics were similar between clobetasol exposed and naïve patients indicating comparable disease severity prior to treatment, table 2, and majority of change outcomes at six-months were similar decreasing the risk of bias based on clobetasol exposure status, table 5."

Point 4. Further, the baseline values of the outcome measures should be reported in order to determine whether the randomization resulted in LS cases with similar severity as best as can be measured. This would also allow readers to assess the generalizability of the study. Figure 2 provides some baseline information for the Skindex, but not for the stratification and not for the other outcomes.

Response: Thank you for this comment. The baseline values between study group were not significantly different and the randomization effect appear to hold. We initially choose not to report the baseline outcomes in order to condense results.

New wording: See Table 2.

Point 5. In the previously treated group, the residual treatment effect of the previous clobetasol therapy would be expected to lower the measured benefit in the clobetasol group, thus enhancing the comparison to the laser group. An 8-week washout might be inadequate, with at least one study showing that symptoms and exam findings had not returned to baseline 3 months after follow up. For all analyses, the baseline values of the outcome measures should be reported as well as the treatment differences, for the overall and stratification results.

Response: Thank you for the comment. We choose the eight week wash out period based on treatment patterns for Clobetasol propionate. Eight weeks is the median value for 6-12 week treatment regiments recommended for patients with lichen sclerosus. In addition, only a handful of patients required a washout period. The majority of patients with prior Clobetasol use had been off for many months. We tried to balance the physiologic effect with maintaining patient interest in the research trial.

Point 6. LS is a highly variable condition with respect to symptoms and physical changes—some women are very symptomatic with minimal physical changes while others experience marked architectural changes with a dearth of symptoms. It is possible that LS cases identified in a Urogyn practice may represent the latter, a less symptomatic sample compared to women who present to a general gynecologist or dermatologist with LS as the primary reason for the visit. The LS cases seen in a Urogyn practice are often "incidental" diagnoses that are relatively asymptomatic for the level of architectural changes. This variability is rarely addressed in LS

research and there are no tools for measuring this. In the absence of tools, more detailed descriptions are needed.

Response: Thank you for this comment. You keenly point out another limitation of this study. Patients limited to a Urogynecology practice and could represent a different patient population. We attempted to overcome this limitation in a few ways. First, we advertised the study among all general gynecology practices in our network to try to capture a diverse subject group. Patients did have to come to the Urogynecology office for the actual treatment if randomized to laser. We should have made this clearer and have adjusted the text. Second, we required patient to have symptomatic lichen sclerosus based on the Skindex-29 score of at least 21 for enrollment in the study. Third, we measured both symptomatic measures and objective (appearance) measures within the study to capture both of these features.

New wording: Lines 243-244. "Patients were recruited from urogynecologic and gynecology academic medical center office visits."

Point 7. Table 2 should include effect sizes and confidence intervals for all variables.

Response: Thank you for this comment. We have adjusted Table 2 now named Table 3.

New wording: Table 3.

Point 8. The primary outcome variable, the Skindex-29, one of the few/only validated instruments that could be used for LS studies, and it is a quality of life instrument. While important to patients, quality of life is remote from direct treatment effects. It is notable that the quality of life improvement that occurs with both treatments is much greater than the smaller and nonsignificant changes in symptoms and clinical findings. This contrasts to the other RCT that utilizes the Skindex-29 (comparing clobetasol to UV-A1), 1 in which both groups have similar improvement in symptoms and findings, but the improvement in Skindex-29 is much greater in the clobetasol vs. the UV-A1 treatment. Perhaps quality of life instruments indirectly measure satisfaction with the treatment approach. The UV-A1 treatment is more cumbersome for women, requiring 5-minute phototherapy sessions to the vulva, 4 times weekly for 12 weeks compared to daily application of topical steroids. In this study, perhaps the laser offers "space-age" therapy with hope for a "cure," in comparison to lifetime topical therapy for a chronic condition.

The investigators in the Ogrinc RCT noted a difficulty in gaining compliance for the steroid arm, stating: "We found it very difficult to motivate patients in the control group to adhere to the study protocol. This was in part because of the recurrence of symptoms and in part because of the negative attitude of the patients to the control treatment."2 A sham-control for the laser will likely be required in future studies to allow blinding to control for such effects.

Response: Thank you for these comments. You are absolutely correct that patient satisfaction with the laser treatment and desire for treatment effect in both Clobetasol exposed and naïve groups could make the results involving quality of life difficult to interpret. We did feel that the Skindex was one of the only options for a validated measure in lichen sclerosus despite this limitation. We were fortunate to have excellent compliance in the Clobetasol group and hope this would help decrease this effect experienced by Ogrinc et al. We moved the explanation of the instrument to the methods section. We agree that a sham laser arm should be included in future studies. We edited comments to address these concerns.

New wording: Line 540-543. “The Skindex-29 is a quality of life measure and we found significant improvement above that of the other subjective and objective measures with lesser effect size. It is possible, some of the subjective improvement was biased by ease or satisfaction with treatment and desire for novel treatment approach.”
Line 549-550. “Further research utilizing placebo and sham lasers for treatment blinding, and a broader population is needed.”

Point 9. The Skindex-29 in not well known to OB/GYN clinicians and should be described to readers in the methods section, not the results section.

Response: Thank you for the comment. We agree and moved the explanation.

New wording: Move to Line 286-290. “The Skindex-29 is a validated questionnaire for assessing acute dermatologic symptoms over a 4-week period with more negative scores indicating greater improvement.”

Point 10. In the comments section, the authors state that their findings with regard to the Skindex are similar to those in the Ogrinc study, but the Ogrinc study did not use the Skindex as an outcome measure.

Response: Thank you for your comment. We have a typo and this should read VAS scores were similar. Text was corrected.

New wording. Line 520: “Their reported VAS scores were very”

Point 11. There is a typo in Table 1, Prior Clobetasol Use is "11", not "1" in the steroid group.

Response: Thank you for this comment, you are correct and it was corrected.

New wording: Table 1.

Point 12. I don't understand the categories of "Living Situation:" "Alone, Home."

Response: Thank you for this comment. We agree this is confusing. We believe some understanding was lost while trying to simplify the table. Additional description was added to the table. Home, not alone is the actual category.

New wording: Table 1.

Point 13. The strengths of this study are its rigorously planned design with sample size analysis, intention-to-treat and per protocol analysis, and use of the best available outcome measures, with blinded analysis where possible. The rigor of this trial is superior to the only other published RCT evaluating laser therapy to LS. I recommend revision of the manuscript attending to the flaws noted above, and I suspect that this will result in a final result of an inconclusive trial. These results will provide important evidence to support much needed research by gynecologists about lichen sclerosus and the vulva more generally.

Of note, in 2004, Dr. Kenneth Noller published an editorial in "Obstetrics and Gynecology" titled "Vulva: the forgotten pelvic organ,"3 noting the lack of attention to vulvar disorders and offering hope for improved gynecologic research regarding vulvar diseases. Unfortunately, a PubMed search of RCTs for LS resulted in 21 studies, with a majority published in dermatology journals

and none in major OB/GYN journals. These gynecologic investigators have focused considerable attention of this forgotten organ. This study represents an important gynecologic contribution to the science of vulvar studies and an opportunity raise awareness regarding older women's health.

1. Terras S, Gambichler T, Moritz RK, Stücker M, Kreuter A. UV-A1 phototherapy vs clobetasol propionate, 0.05%, in the treatment of vulvar lichen sclerosus: a randomized clinical trial. JAMA Dermatol. 2014;150(6):621-627.
2. Bizjak Ogrinc U, Senčar S, Luzar B, Lukanović A. Efficacy of Non-ablative Laser Therapy for Lichen Sclerosus: A Randomized Controlled Trial. J Obstet Gynaecol Can. 2019;41(12):1717-1725.
3. Noller KL. Vulva: the forgotten pelvic organ. Obstet Gynecol. 2004;104(5 Pt 1):913-914.

Response: Thank you very much for these comments. We agree it is a forgotten organ and hope to add to the literature.

STATISTICS EDITOR COMMENTS:

Point 1. Abstract: Needs to conform to our RCT template. on line 82-83: The sample size calculation criteria are incomplete; need to include the power and p-value and stipulate that the latter was for a two tailed test.

Response: Thank you for this comment. We have expanded the details of the power calculation in the abstract.

New Wording: Line 133-134. “A total sample size of 52 subjects were recruited to detect a mean difference of 16 points on the Skindex-29 (SD ±22) with 80% power between the study groups based on a one-sided two-sample t-test with alpha=0.05, accounting for 10% attrition.”

Point 2. Lines 96-98: The sample size was insufficient to generalize conclusions re: occurrence of serious safety or adverse events (n = 27 in the laser treatment arm). For example, a serious event occurring 0/27 instances has 95% CI = 0-13%.

Response: Thank you for this comment. You are correct that we are not powered to detect adverse outcomes as a primary outcome. Reviewer 3 in point 1 also noted that the explanation of the hypothesis and objective was misleading. We have reworded these to clarity. We powered the study to detect efficacy between the laser and steroid groups measured by the Skindex-29.

New wording: Lines 237-339 “We sought to compare fractional CO_2 laser treatment to clobetasol propionate and observe safety. We hypothesized that it is an effective alternative treatment for patients with symptomatic vulvar lichen sclerosus.”

Point 3. Table 1: Need units for BMI. Parity can only have integer values, so should cite as median(range or IQR). Should verity whether the duration of diagnosis nor duration of estrogen replacement were normally distributed. If not, then should format as median(range or IQR), rather than as mean±SD.

Response: Thank you for these comments. Adjustments were made to Table 1.

New wording: Table 1.

Point 4. Table 2: Need to clearly separate the primary from all secondary outcomes. The strata with mean difference in Skindex-29 were not separately calculated in the sample size/power calculations. They should be listed as secondary outcomes. Were the differences normally distributed? If not, then should test non-parametrically, particularly since the sample sizes were relatively modest.

Response: Thank you for your comment. We separated the table with another line. We are not able to add another heading within the table due to journal policies. We have edited the text to make this point clearer. Regarding normality, The two sample t test is generally robust to small deviations from normality. In any case, we ran the data through D'Agostino test for normality, and assessed non-normal Kruskal test p values. They were consistent with the t test significance and thus we presented the data as t-test outcomes.

New wording: Line 291-293. "Secondary outcomes of subjective symptoms included a validated visual analog scale (subjective VAS), the Vulvovaginal Symptoms Questionnaire (VSQ), Skindex-29 subscores, and patient satisfaction and global impression of improvement (PGI-S and PGI-I)."
Line 379. "A similar trend was seen for secondary Skindex-29 subscores including emotion."
Line 320. "D-Agostino test was used to assess normality."

Point 5. Table 3: These are also secondary outcomes. The sample size/power calculation did not factor in subsets and the study was not powered to evaluate the clobetasol naïve comparison, so that NS finding cannot be generalized.

Response: Thank you for this comment. You are correct these are a secondary outcome and therefore we are not powered to make conclusions or generalizations. However, given the importance in this patient phenotype. All of the reviewers requested more information about these subgroups to be expressed. For the stratified analysis, it was conducted using regression model with interaction term between treatment and exposure variable. For regression model, it's not the actual differences that need to be normally distributed but the residuals resulting from the regression model need to be normal. We did not run normality tests on these residuals as they may not be normal cause these tests are very sensitive, especially with small sample size with small deviation from normality can throw them off. We inspected visually q-q plots and histogram and they appear normal. There is no non-normal regression analysis that can be done.

New wording: Lines 357-362. "The clobetasol propionate naïve group tended to have less improvement than those who had used Clobetasol, while the previously exposed laser group had the most improvement, table 4. Two-way ANOVA for mean Skindex-29 overall score improvement showed no effect of prior clobetasol exposure while treatment group had a significant effect without interaction effect. The change in outcomes at six-months were similar between Clobetasol naïve and exposed groups, table 5."
See Table 5.

Point 5: Also (and not necessarily part of the Abstract itself), the mean difference of 16 point was chosen as having clinical significance in the sample size calculation, but the actual mean difference was 10.9 (lines 88-89). The authors need to state that the difference was statistically significant, but did not meet the prespecified margin of clinical significance. Or in some other way, explain this discrepancy.

Response: Thank you for this comment. You are correct the study was powered to detect a 16 point difference on the Skindex-29 as this was a clinically meaningful difference of two health quality of life categories (figure 2) illustrates. We did not find a 16 point difference between groups but we did find a statistically significant differences. As you know, this is secondary to the narrower standard deviation in our study than used in the power calculation from the literature. We have tried to carefully word our conclusions. We have tried to further emphasize this point in the results.

New wording: Line 396-397. “However, the size effect between treatment groups was <16 points for primary outcome, overall Skindex-29 score.”

EDITORIAL OFFICE COMMENTS:

Point 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.

Response: Thank you for the opportunity. We will opt-in.

Point 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.

Response: Thank you will we make sure the disclosures match.

Point 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.

Response: Thank you for this comment. Race was assessed as part of baseline subject characteristics. Participants were asked to select from investigator provided options. We had no blank or missing items. Ethnicity was not assessed. Due to limited options for race categories we have chosen to remove this variable from the manuscript.

New wording: Deleted variable from table 1.

Point 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 (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).

Response: Thank you for this clarification. We moved these responses to the proper section.

New wording: Moved to lines 655-665.

Point 5. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works.

Disclose oral AJOG presentation or provide citation for Abstract (09: A randomized controlled trial of clobetasol propionate versus fractionated CO2 laser for the treatment of lichen sclerosus (CURLS)).

Response: This is our own work and the abstract presentation of this manuscript noted on the title page.

Point 6. Standard obstetrics and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Response: Thank you for this information. Our explanation of lichen sclerosus matches this work.

Point 7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and

print appendixes) but exclude references.

Response: Thank you for the comment. We addressed this requirement by decreasing some extra text from title page and changing the font. The word count is well below the limit.

Point 8. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

Response: Thank you for this comment. We edited the acknowledgement section to simplify the reporting. A statement in this cover letter is also included regarding the disclosures for individuals in the acknowledgement section.

New wording: Lines 58-60. "**Acknowledgements:** We would like to acknowledge the hard work of additional individuals: Nemi Shah, MD; Tania Marek, NP; Andrew Sokol, MD; Lee Ann Richter, MD; Patricia Tanjutco, MD; Alyson Davidson, MD; Elizabeth Hoang, MD; and Joanna Peterson, RN, BSN."

Point 9. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 words. Please provide a word count.

Response: Thank you for this comment. We reviewed the abstract. The revised word count is 290.

Point 10. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online

here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

Response: Thank you for the comment. We have edited our abstract to include complete information about power calculation. See Statistician Point 1.

Point 11. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

Response: Thank you for the comment. We were careful to avoid abbreviations and acronyms throughout the paper. We defined the CuRLS acronym at the end of the title to provide the study short name but it is not used to define the words. This can be removed if not allowed specifically. The only other abbreviations used are those to represent the validated questionnaires. These were included to improve readability of the text.

Point 12. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

Response: Thank you for this comment. Any use of this symbol was removed from the manuscript.

Point 13. 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.

Response: Thank you for this comment. The word provider was replaced throughout the manuscript.

Point 14. 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%").

Response: Thank for you for these comments. We have provided our results primarily in the form of mean difference between our two study groups. We have added the effect size to the outcome tables. We agree that this is the best way to present the information for readers to show the clinically meaningful understanding. However, we have chosen to include p values

within our results, and tables because not all providers are familiar with these validated measures to understand the effect size differences. We added size effect to main outcome table 3.

Number need to treat or harm are not appropriate in this study.

Care was taken to review all reported values to consistency in reporting with the same number of decimal places. P values are expressed with only three decimal places.

Point 15. Your manuscript contains a priority claim. We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

Response: This claim was not based on a systemic review and was therefore removed.

New wording: Line 553-556. “Strengths of the study include the use of organized validated subjective and objective assessment tools. In addition, this adds to the lichen sclerosus literature with robust randomized controlled trial methods directly comparing a new treatment to the gold standard clobetasol treatment.”

Point 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.

Response: Thank you for the comment. The table checklist was reviewed and changes made as appropriate to tables. Table 3 is a large table and might be better in the opposite page orientation. We were not sure if we could submit tables in this format or if that is decided by the publisher

Point 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).

Response: Thank you for the comment. The references were reviewed and updated. The ACOG documents referenced were reviewed.

Point 18. Figure 1: Please check n values (205-150 doesn't equal 52). Please upload as a figure file on Editorial Manager.
Figure 2: Please upload as a figure file on Editorial Manager.
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Response: Thank you for the instructions. The error in the CONSORT diagram was corrected and the figure and text updated. The figures were uploaded per instructions.

Point 19. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at https://wkauthorservices.editage.com/open-access/hybrid.html.

Response: Thank you for this comment. We will not be utilizing this option.

Sincerely,

Linda Burkett, MD