OBSTETRICS & GYNECOLOGY

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

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

Date: Jun 23, 2022
To: "Antonio Saad" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-1042

RE: Manuscript Number ONG-22-1042

Outpatient Versus Inpatient Pre-induction Cervical Ripening Using Dilapan-S: a Randomized Clinical Trial (HOMECARE)

Dear Dr. Saad:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 14, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors present a paper regarding the use of Osmotic dilators for cervical ripening in an outpatient setting. Given the increased numbers of induced labors and the limited resource of labor floor beds, an ability to safely move cervical ripening into the outpatient setting is of major interest to the practicing OBGYN. I would ask the authors to consider the following:

1. What efforts if any were made to eliminate provider bias in the management of patients in the study?
2. Out of the 5394 patients who were candidates for the study only 339 participated. There were also a large number of patients were after initial enrollment were disqualified. I would appreciate the authors' insights as to why this occurred and did this account for the three-year time frame it took to enroll the patients for the study?
3. The authors recognize their population is not typical and the application of their findings may not be generalized. Were considerations made to enlist other institutions whose populations may better reflect the U.S. as a whole?
4. If the length of stay starts at admission, the difference in the LOS appears to be related to the approximately twelve hours of outpatient cervical ripening. That is not to say that is not meaningful. However, the authors should be making that point clear in their discussion.
5. While LOS is an important measurement, safety of outpatient cervical ripening is of paramount importance. This study admits it did not recruit sufficient numbers of patients to adequately address the outcomes that would answer the serious question of whether outpatient cervical ripening with Dilapan is safe for both mothers and infants. Without that question answered, the study while interesting cannot be used as a source to support safe outpatient cervical ripening. I would suggest the authors attempt to redesign the study with the larger more diverse population to answer these critical questions.

Reviewer #2: The authors' objective was to assess whether outpatient cervical ripening with a synthetic osmotic dilator shortens the length of hospital stay in term pregnancies undergoing labor induction. Pregnant women scheduled for labor induction at term with unfavorable cervix and not requiring inpatient maternal or fetal monitoring were consented, and synthetic osmotic dilator rods were inserted on the day of scheduled induction. After reassuring fetal heart tracing, patients randomized to the outpatient arm were asked to return 12 hours after insertion or earlier if needed. In contrast, those

randomized to the inpatient group remained in the hospital. The primary outcome was the proportion of women with hospital stay >48 hours. The proportion of women with hospital stay >48 hours was lower in the outpatient versus inpatient group. Compared with the inpatient group, patients in the outpatient group had a shorter total length of stay and time from admission to active 25 labor. They had higher 24 hours delivery rates from admission and were less likely to require analgesics during ripening. Route of delivery and other maternal and neonatal outcomes were not significantly different between groups. The authors conclude that pregnant women undergoing labor induction at term, outpatient cervical ripening with a cervical osmotic dilator decreased hospital stay compared with inpatient ripening, without significant adverse outcomes.

The following are my questions and comments:
1. Can the authors further elaborate on why they chose as their primary outcome hospital stay >48 hours. The explanation given does not seem to fully address this question?
2. Can the authors comment on whether there were any different management considerations or precautions for the GBS positive patients?
3. Can the authors be very clear in the methods section that no augmentation was performed on the inpatient arm during the first 12 hours.
4. Can the authors note whether any additional fetal monitoring was performed on the inpatient arm during the first 12 hours?
5. The study went on for 3 years it seems -- it appears that over 5,000 induction patients were screened, of which <10% were ultimately randomly assigned. Can the authors comment on the generalizability of this approach and its potential for an impactful change on labor and delivery workflows?
6. Can the authors comment on how they addressed re-entry challenges in the outpatient arm -- were rooms on labor and delivery reserved for patients in the study within the time window of outpatient care?
7. Can the authors comment more on analgesia during ripening and how they tracked this in the outpatient arm?
8. The authors mentions more daily activities in the outpatient arm -- given the other arm in in the hospital, what do the authors mean specifically by this?
9. There have been several small trials such as this one showing the feasibility of outpatient mechanical ripening -- what doe the authors consider the main contribution to the literature for this study -- is it primarily the use of an outpatient osmotic dilator as opposed to a Foley?
10. The authors need to be very clear throughout this manuscript that they did not have the power to determine maternal or neonatal safety. This needs to be highlighted as a limitation. On line 196, the authors write that the evidence supports the benefit and safety of outpatient mechanical cervical ripening. Given the absence of power to determine safety both in the current literature and in this paper, the authors may want to be more circumspect.
11. It appears that most of these patients were 39 week pure elective inductions. Can the authors make that clear both in the text and in Table 1.
12. The authors may want to present baseline cervical dilation data in addition to Bishop score
13. Can the authors comment on any baseline uterine activity in each arm and whether a given threshold of uterine activity excluded the patient?
14. Can the authors comment on the 60 minutes to the hospital threshold for enrollment -- how was this developed?

Reviewer #3: This is an open-label RCT evaluating the proportion of patients with hospital stay >48hrs after receiving inpatient vs. outpatient cervical ripening with Dilapan. Pregnancies included for randomization were singleton term pregnancies undergoing IOL after 37w0d with an unscarred uterus, no need for continuous fetal monitoring, no contraindication to vaginal delivery, and no evidence of oligo/FGR/macrosomia/chorioamnionitis/labor/fetal anomaly or any maternal indications that required inpatient management. Patients also had to be able to be within close range of the hospital, have a support person and telephone. The outpatient arm returned to the hospital for admission within 12 hours of Dilapan placement. The study found that the outpatient arm had a significantly decreased rate of stay >48hr, however the inpatient arm had markedly higher rates of stay than had been predicted. The total hospital length of stay was shorter by about 8 hours. Planned secondary analysis did not show any difference in cesarean rates, or adverse maternal/neonatal outcomes. This is the first study to evaluate the role of synthetic osmotic dilator for outpatient cervical ripening.
Comments:
1) Line 110: Why were the inpatient arm subject to continuous fetal monitoring?
2) Parity can affect several outcomes, including time to vaginal delivery, time to active labor and AROM, and length of stay. Not evaluating the primary and secondary outcomes in relation to parity is a limitation of this study and should be commented in the discussion
3) Line 129 and Line 147: The sample size was made on the assumption that the inpatient arm would have 54% with stay >48hr, however the inpatient arm had almost 89% stay >48hr, while the outpatient arm was almost 54%. Please discuss why this may have occurred and how this could affect interpretation of your results
4) Line 151-152, Line 224: Secondary analysis evaluated analgesia during ripening, and found a significant difference. Can you discuss biologic plausibility for this observation? Why would outpatient arm be more comfortable than inpatient arm?
5) Line 164: The patient satisfaction surveys note that the outpatient arm was able to walk/eat/shower more than the inpatient arm -- this seems more likely to be attributed to the inpatient arm being on continuous monitoring, which may have limited their activity, rather than necessarily location of ripening
6) Line 166: The patient survey discussing that outpatient arm thought outpatient ripening is beneficial is a difficult question to ask the inpatient arm that wasn't allowed to experience it. This question seemed biased

STATISTICAL EDITOR COMMENTS:

Table 1: Need to enumerate any missing data.

Table 2: The p-value for secondary outcome "Removal of Dilapan-S < 12 hrs" is > 0.05

Fig 2: Need to include the counts for remaining patients at time points along the x-axis. Should include more time increments (e.g., 0.25 day

Although the calculations are almost the same, should include the PP analysis (as in Table 2) in supplemental material.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. 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, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and 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.

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

6. The journal follows ACOG's Statement of Policy on Inclusive Language (https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language). When possible, please avoid using gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;" "patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."

7. Clinical trials must include a data sharing statement. Please add the following questions and your answers to the end of the manuscript after the References section:

Authors' Data Sharing Statement
Will individual participant data be available (including data dictionaries)? No.
What data in particular will be shared? Not available.
What other documents will be available? Not available.
When will data be available (start and end dates)? Not applicable.
By what access criteria will data be shared (including with whom, for what types of analyses, and by what mechanism)?

Not applicable.

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

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

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

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

(4) The title page should describe how the funder was or was not involved in the manuscript.

9. Line 67: Please add the name of the IRB that approved your study.

10. 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.

11. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

12. "Dilapan-S" appears to be a brand name. Journal style is to use the brand only once in the manuscript body text. We do not use brand names in the title, running title, abstract, precis, tables, or figures. You may leave it on line 49, but please replace "Dilapan-S" with a generic term everywhere else in your article.

13. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

* 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 or indicate whether the meeting was held virtually).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

* Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

14. Provide a short title of no more than 45 characters, including spaces, for use as a running foot. Do not start the running title with an abbreviation.

15. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

Abstracts for clinical 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 at http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf and edit your abstract as needed.

16. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

17. ACOG avoids using "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.

18. 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.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001").

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

19. Line 188: "There are no published trials evaluating this synthetic osmotic dilator in the outpatient setting." If this statement is based on a systematic search of the literature, that search should be described in the text (search engine name, 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, please delete or rephrase this statement.

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

21. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. 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 formal reference list. Please cite them on the line in parentheses.

If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

22. Figure 1: Are items in the exclusion box not mutually exclusive?

23. 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.

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 as a Microsoft Word document. Your revision's cover letter should include a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

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

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 14, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

_____