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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Date: Aug 13, 2021
To: "Rodolfo Carvalho Pacagnella" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1505

RE: Manuscript Number ONG-21-1505

Pessary plus progesterone to prevent preterm birth: a randomized controlled trial

Dear Dr. Pacagnella:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

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 Sep 03, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This is a prospective RCT comparing a particular pessary with vaginal progesterone to vaginal progesterone without pessary for women with a short cervix on second trimester vaginal ultrasound. The primary outcome was a composite of neonatal morbidity and mortality. Several clarifications are in order:

1. Why were twin pregnancies included? This group has a higher incidence of preterm delivery as well as the primary outcome and appears to be less responsive to interventions to prevent spontaneous preterm birth than singletons. This could lead to potential error in not identifying a difference if one exists.
2. Why was 30 mm used as a "short" cervix length? At this gestational age, the current literature supports <25 mm as this appears to have the greatest benefit from intervention. Adding those with a cervical length of 25-30 mm could also lead to error in not identifying a difference where one exists.
3. Many readers will be unfamiliar with the Ingamed AM pessary. How does this pessary compare with the more thoroughly evaluated Arabin pessary? Perhaps a photo or drawing of the pessary and an explanation of either comparison of this pessary with Arabin or explaining the reasons for using this pessary including references would help.
4. In the Methods section, the paragraph of lines 77-82 is redundant as this technique is referenced in the preceding paragraph.
5. Were there any issues with insertion or expulsion of progesterone in those with a pessary?
6. The reasons for the power calculations are unclear. The proposed reductions appear to be based on intervention vs placebo in a highest risk group of singletons related to early preterm birth rather than the study populations used and the primary outcome.
7.1146/8168 appears to be a high percentage of subjects with a short cervix. What do the authors attribute this to?
8. In Figure 1, only 2 of 1146 pregnancies had a major fetal anomaly. What do the authors attribute this very low rate to?
9. In Figure 1, the authors describe the number of subjects who completed or did not complete their treatment for all study subjects. How do the authors know these data for all study subjects when some were lost to follow up?
10. In Table 1, the mean CL for both groups is 25.0 mm. In the text it is 23.1 and 23.4. Which are correct?
11. Why do the authors propose there is a significant difference in cesarean delivery and stillbirth rates between the pessary and non-pessary groups?
12. One of the key findings of this trial is the effect on early preterm birth in those with a singleton and second trimester CL<25. This might have been anticipated from prior trials. Why was this not the planned primary outcome?

Reviewer #2:

This is a multicenter, randomized, controlled trial of vaginal progesterone vs vaginal progesterone plus pessary in women with a short cervix (<3cm) at midgestation. Primary outcome is a neonatal composite morbidity and mortality. Overall, thorough description of methodology with clear acknowledgement of limitations. Although similar RCTs have been previously published, the question of pessary utility is incompletely answered. Thus, this study is helpful.

1. Methods, line 83: the choice of 30mm as cutoff for short cervix is likely limiting given that you are including a lower risk group. I understand you can't go back and change this, but I'm interested to know why you chose this cutoff given that progesterone is most efficacious <25mm.
2. Methods, line 136: what is the predicted primary outcome incidence based on? Internal data?
3. Methods, lines 174-175: I understand this may be how your national guideline defines ethnicity, but I don't think skin color categories as listed are acceptable for this publication.
4. Methods, lines 180-182: were p-values corrected for interim analyses?
5. Results, lines 226-227: what do you make of the increased Cesarean rate in the P+P group? Simply due to less periviable/extreme preterm birth? Please address this in discussion.
6. Discussion: I know you are trying to not overstate your conclusions, which I appreciate. However, I think it's reasonable to highlight that multiparous women who are not on baseline progesterone (an exclusion criterion) are by definition lower risk due to a likely history of previous full term birth. This may explain why an effect is seen in the nulliparous group but not the overall group.
7. Discussion: There is a significant difference in side effect profile between groups (worse with pessary). Please add this to the discussion section.

Reviewer #3:

The investigator present the results of a large, multicenter randomized, controlled trial of vaginal progesterone vs vaginal progesterone and cervical pessary for the prevention of preterm birth in women with singleton or twin gestations and a cervical length of 30 mm or less. In an intent to treat analysis, neonatal morbidity and mortality, as well as delivery less than 37 weeks, was similar between groups. Delivery < 34 weeks was 34% less frequent in the progesterone and pessary group, but there was an increased frequency in side effects including vaginal discharge, bleeding and pain.

1. In line 52, the authors state "there is consensus the progestogens reduce spontaneous preterm birth in women with a short cervix and …previous preterm birth." Given the constant evolution of these data, this remains a controversial statement. Consideration should be given to also referencing the data from the EPPPIC meta-analysis that was recently published.
2. The authors point out the conflicting results of the pessary studies, but it is unclear from the introduction why there may be such divergent results. While not necessary to delve into details here, it would be useful to explain why this current study is going to be different. Since some of the studies that demonstrated benefit of pessary had no or very infrequent concomitant progesterone use and compared pessary to no treatment, the authors should explain why in this study they chose two treatment arms as opposed to including a no treatment arm.
3. Why was 30 mm chosen as the threshold for definition of short cervix? Was there consideration of a different threshold in singletons vs twins? Most would consider 30 mm a normal cervical length in singletons and then argue that there reason there was no difference seen in groups was that the patients with cervical length between 25 and 30 mm, at least singletons, did not need treatment.
4. What was the time interval from cervical length measurement to randomization? Was it same day?
5. Is the Ingamed pessary similar to the pessary used I other studies? If so that should be stated. If different, that should be explained.
6. How was the neonatal composite chosen? Why was 10 weeks chosen as the time point?
7. Approximately 14% of patients had a cervical length of 30 mm or less. Is this typical for this patient population? In singleton gestations, 30 mm typically approximates the 25th percentile in other studies.
8. Were there any specific criteria in the protocol allowing for cerclage placement or was it aat physician discretion?
9. There was a reduction in PTD < 34, 32, 30 and 28 weeks. The way the abstract is written it does not emphasize the reduction at all of these time points. Consideration should be given to emphasizing the reduction at these earlier points as well as this may be where the value in treatment is.
10. In the post hoc analysis, the authors included nulliparous, singletons with CL 25 mm or less and found reduction in key outcomes with pessary plus progesterone. Was an analysis including only singletons and cervical length 25 mm or less conducted? While interesting to include nulliparas, from a clinical standpoint, cervical length and singleton gestation alone is a more useful decision point. The authors should explain why they included this nulliparous subgroup as opposed to including multiparas as well.

11. The final paragraph of the discussion section seems out of place. It seems like it belongs earlier in the discussion section.

STATISTICS EDITOR COMMENTS:

Abstract needs to conform to our RCT template.

lines 123-127, 135-142: The primary outcome was neonatal, but since both singletons and twins were included, the outcomes for twins cannot be considered as statistically independent events. Need to either adjust for intra class correlation within twin pairs (which effectively decreases the sample size of neonates), randomly select one of each twin pair or omit twins altogether from the analysis as a separate cohort. Also, The comparison of adverse neonatal rates was evaluated for two cohorts: one consisting of those with maternal CL ≤ 25 mm. The specified rates were 22% vs 12% and 17.3% vs 8.65% for the two groups. The results in Abstract, Tables etc should first state those primary outcomes, then all the secondary ones. In present format, both neonatal and maternal outcomes are aggregated as the primary outcome in Table 2 and the subset of results for the cohort with CL ≤ 25 mm is in Table 4 with other secondary outcomes. Need to more clearly separate and emphasize the primary outcomes, then all the secondary ones.

Fig 1: The flowchart has a typo, since the next to last level has labelled both the N = 475 and N = 461 as receiving pessary +
progesterone treatment.

Fig 2: Need to include in the figure or its legend a concise summary of the statistical test of the K-M curves.

Table 2: Should include a column of unadjusted RRs for contrast with the aRRs. The column of p-values is redundant, since CIs are shown. Should omit the p-values. Need to include as footnote to Table the variables included in the adjustment model.

EDITOR COMMENTS:

1. Thank you for submitting your work to Obstetrics and Gynecology. If you opt to submit a revision, we require additional documentation regarding clinical trial registration. The authors provided documentation that the Brazilian trial registry sent an email requesting a response to some errors/issues with the initial submission (not confirmation that the trial had been registered) in June 2015. Please provide documentation that the trial protocol did not change from the time of the initial submission that was incomplete to the time that the trial was documented as registered in Sept 2016. This will also need to be addressed transparently in the methods section of the manuscript.

2. Please pay close attention to the need to emphasize the primary outcome of this study and be clear about what are primary and what are secondary outcomes.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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. 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:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* 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 uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

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, 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.

5. 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).

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 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, 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).
* 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]."

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

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

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

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

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

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14. 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.

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

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

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

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

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If the reference you are citing has been updated and 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.

18. Figure 1: In the exclusion box where n=28, are items not mutually exclusive? Please upload as a figure file on Editorial Manager.
Figure 2: Please upload as a figure file on Editorial Manager.

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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 as a Microsoft Word document. 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 Sep 03, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD
Associate Editor, Obstetrics

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

Dwight J. Rouse
Editor in chief
Obstetrics & Gynecology

AND
Torri D. Metz, MD
Associate Editor, Obstetrics
Obstetrics & Gynecology

10th of September 2021

Dear Doctor,

Thank you for reviewing our manuscript (ONG-21-1505,) entitled "Pessary plus progesterone to prevent preterm birth: a randomized controlled trial" and for giving us the opportunity to provide a revised version for publication in The *Obstetrics & Gynecology.*

We have read your comments and the comments of the reviewers with interest and tried to adjust the manuscript accordingly. Included you will find two revised drafts of the manuscript. In one of these versions the adjustments have been highlighted.

Our point-by-point reply to the comments of the referees is summarised below.
All authors have read and approved the revised version of the manuscript.

We hope that our adjustments make the manuscript suitable for publication in the journal, and we are looking forward to your final decision on the manuscript.

Yours sincerely,

On behalf of the authors

Rodolfo Pacagnella, MD, Ph.D.

[redacted]

REVIEWER COMMENTS:

Reviewer #1:

1. Why were twin pregnancies included? This group has a higher incidence of preterm delivery as well as the primary outcome and appears to be less responsive to interventions to prevent spontaneous preterm birth than singletons. This could lead to potential error in not identifying a difference if one exists.
We decided to include twins as the twin population had not been extensively studied and the proposed intervention had not been tested in this population.
Considering that this group has indeed a higher incidence of preterm delivery as well as the primary outcome, in theory, the presence of twins in the sample could affect the results by reducing the effect of the intervention, leading us to be more conservative in identifying a group difference. However, in the prespecified subgroup analysis regarding singleton and twin pregnancies (Table 4), we did not find a significant difference for the primary outcome between the two subgroups, suggesting that the effect of this issue is small. Also, the number of twins was relatively small.
Change in the manuscript: no change.

2. Why was 30 mm used as a "short" cervix length? At this gestational age, the current literature supports <25 mm as this appears to have the greatest benefit from intervention. Adding those with a cervical length of 25-30 mm could also lead to error in not identifying a difference where one exists.
For clinical practice, 25 mm is currently used to define 'short cervix', but since the Iams' study, we know that there is a higher risk of preterm birth from the 25% percentile of cervical length. In our population, the 25th percentile occurred at 32.3mm. Indeed, the only way to find out if the proposed intervention (in this case a combination of Pessary plus Progesterone) is effective in women with a cervical length of 25-30 mm is to randomize them.
At design stage, we considered that the sample size should be powered to show differences in a subgroup of short cervical length (≤25 mm). In this prespecified and power tailored subgroup analysis, we also did not find a significant effect for pessary in terms of the primary outcome. (Table 4)
Change in the manuscript: no change We primarily intended to study a high-risk group of women (CL ≤25 mm) but was also interested in estimating the effect of pessary in women with CL between 25 and 30 mm, who also have an elevated risk but there is no available treatment. LINES 139-141

3. Many readers will be unfamiliar with the Ingamed AM pessary. How does this pessary compare with the more thoroughly evaluated Arabin pessary? Perhaps a photo or drawing of the pessary and an explanation of either comparison of this pessary with Arabin or explaining the reasons for using this pessary including references would help.

The Ingamed AM pessary is highly similar to the large size ARABIN® Cerclage Pessary perforated. At the moment the trial was designed, this was the only approved device in Brazil.
In the revised version, we included a full description of the Ingamed AM pessary, a comparison with the Arabin pessary for readers to be familiar with the device.

Change in the manuscript: 'We used the Ingamed AM® silicone pessary (unique size: outer diameter 70 mm, height 25 mm and inner diameter 40 mm with indentations – similar to the largest ARABIN® Cerclage Pessary perforated). LINES 110-111

4. In the Methods section, the paragraph of lines 77-82 is redundant as this technique is referenced in the preceding paragraph.
Indeed, however we prefer, if you agree, to keep this information to explain to readers the exact technic in the text.
No changes were made.

5. Were there any issues with insertion or expulsion of progesterone in those with a pessary?
There were no difficulties reported by women or by local researchers regarding the insertion or expulsion of progesterone in those with a pessary
Change in the manuscript: There were no difficulties reported by women or by local researchers regarding the insertion or expulsion of progesterone in those with a pessary. LINES 221-223

6. The reasons for the power calculations are unclear. The proposed reductions appear to be based on intervention vs placebo in a highest risk group of singletons related to early preterm birth rather than the study populations used and the primary outcome.
At the time the study was designed, there were no reliable information on the primary outcome to calculate the sample size. We primarily intended to study a high-risk group of women (CL ≤25 mm) but were also interested in estimating the effect of pessary in women with CL between 25 and 30, who have an elevated risk according to the literature but there is no available treatment.
The sample size calculation was primarily based on the literature reported rates in the subgroup of CL ≤25 mm and amplified according to the proportion of this subgroup in the overall study population.
Change in the manuscript: 'We primarily intended to study a high-risk group of women (CL ≤25 mm) but was also interested in estimating the effect of pessary in women with CL between 25 and 30 mm, who also have an elevated risk but there is no available treatment. To demonstrate or refute a reduction in the primary outcome from 17.3% to 8.65% in a subgroup analysis for CL ≤25 mm[22,23], we needed to include 468 women for this subgroup (234 per arm, power 80%, type I error 5%). We assumed half of the women had CL ≤ 25 mm. Thus, the final sample should be composed of 936 women (468 per arm).' LINES 139-142

7.1146/8168 appears to be a high percentage of subjects with a short cervix. What do the authors attribute this to?
In fact, we did not find a prevalence of 'short cervix' very different from the literature. The 'short cervix' using 25 mm as a cut-off was observed in around 6.6% of the sample. Cervices below 30 mm was observed in about 14% of the screened population, whose average was 36.9 mm, consistent with the literature on the subject.

Change in the manuscript: no change.

References for cervical length distribution

1. Iams JD, Goldenberg RL, Meis PJ, Mercer BM, Moawad A, Das A, et al. The length of the cervix and the risk of spontaneous premature delivery. National Institute of Child Health and Human Development Maternal Fetal Medicine Unit Network. N Engl J Med. 1996;334(9):567-72.
2. Silva SV, Damião R, Fonseca EB, Garcia S, Lippi UG. Reference ranges for cervical length by transvaginal scan in singleton pregnancies. J Matern Fetal Neonatal Med. 2010;23(5):379-82
3. Andrade SGA, Andrade FM, Araujo Júnior E, Pires CR, Mattar R, Moron AF. Assessment of Length of Maternal Cervix between 18 and 24 weeks of Gestation

in a Low-Risk Brazilian Population. Rev Bras Ginecol Obstet. 2017;39(12):647-52.
4. Heath VC, Southall TR, Souka AP, Novakov A, Nicolaides KH. Cervical length at 23 weeks of gestation: relation to demographic characteristics and previous obstetric history. Ultrasound Obstet Gynecol. 1998;12(5):304-11.
5. Bligard K TL, Stout MJ, Tuuli MG, Macones GA, Cahill AG. Performance of cervical length screening in african american women. American Journal of Obstetrics & Gynecology. 2020.
6. Thain S, Yeo GSH, Kwek K, Chern B, Tan KH. Spontaneous preterm birth and cervical length in a pregnant Asian population. PLoS One. 2020;15(4):e0230125.18.

8. In Figure 1, only 2 of 1146 pregnancies had a major fetal anomaly. What do the authors attribute this very low rate to?
In this flowchart we show that there were 2 pregnancies with **major** fetal anomaly with cervical length ≤30 mm out of 1146. Considering that major fetal anomalies are a rare condition, these anomalies in women with cervical length under 30 mm are even more rare and we consider this according to what should be expected. For example, the rate of gastroschisis is around 2 per 10,000 live births in Brazil.
Change in the manuscript: no change.

References for major fetal anomalies
Calderon, M.G., Santos, E.F.d.S., Abreu, L.C.d. et al. Increasing prevalence, time trend and seasonality of gastroschisis in São Paulo state, Brazil, 2005–2016. Sci Rep 9, 14491 (2019). https://doi.org/10.1038/s41598-019-50935-1

9. In Figure 1, the authors describe the number of subjects who completed or did not complete their treatment for all study subjects. How do the authors know these data for all study subjects when some were lost to follow up?
We used intention-to-treat analysis where only those who were lost to follow-up were excluded from the analysis. Participants who did not complete the allocated intervention were analyzed according to their initial allocation. We followed up those who violated the assigned treatment as long as they were not lost to follow-up.
Change in the manuscript: no change.

10. In Table 1, the mean CL for both groups is 25.0 mm. In the text it is 23.1 and 23.4. Which are correct?
CL is heavily skewed so it should not be presented with mean and sd. Table 1 is correct and the text was changed to describe median for CL. LINES 211

11. Why do the authors propose there is a significant difference in cesarean delivery and stillbirth rates between the pessary and non-pessary groups?
Brazil has one of the higher rates of C-section and a high prevalence of provider-initiated preterm birth. Early spontaneous preterm births are more likely to be delivered by vaginal birth than late preterm births. The fact that we had more late preterm birth in the pessary plus progesterone group may have influenced the higher rates of C-section.
Change in the manuscript: We also identified a significant difference in C-section rates between the pessary and non-pessary groups. Brazil has one of the higher rates of C-section and a high prevalence of provider-initiated preterm birth. Early spontaneous preterm births are more likely to be delivered by vaginal birth than late preterm births. The fact that we had more late preterm birth in the pessary plus progesterone group may have influenced the higher rates of C-section. LINES 305-310

References for C-section and preterm delivery

1. Barros FC, Rabello Neto DL, Villar J, Kennedy SH, Silveira MF, Diaz-Rossello JL, Victora CG. Caesarean sections and the prevalence of preterm and early-term births in Brazil: secondary analyses of national birth registration. BMJ Open. 2018 Aug 5;8(8):e021538. doi: 10.1136/bmjopen-2018-021538. PMID: 30082353; PMCID: PMC6078248.
2. Thanh BYL, Lumbiganon P, Pattanittum P, et al. Mode of delivery and pregnancy outcomes in preterm birth: a secondary analysis of the WHO Global and Multi-country Surveys. Sci Rep. 2019;9(1):15556. Published 2019 Oct 29. doi:10.1038/s41598-019-52015-w
3. Leal MdC, Esteves-Pereira AP, Nakamura-Pereira M, Torres JA, Domingues RMSM, Dias MAB, et al. (2016) Provider-Initiated Late Preterm Births in Brazil: Differences between Public and Private Health Services. PLoS ONE 11(5): e0155511. https://doi.org/10.1371/journal.pone.0155511

12. One of the key findings of this trial is the effect on early preterm birth in those with a singleton and second trimester CL<25. This might have been anticipated from prior trials. Why was this not the planned primary outcome?
We consider that regardless of gestational age at birth, studies on preterm birth prevention should eventually look for deliver healthy babies. Therefore, we aimed to investigate neonatal consequences, rather than to improve gestational age at birth. Also, a reduction of preterm birth does not automatically mean healthy neonates. Nevertheless, we consider, since the study designing, gestational age at birth as a secondary outcome.
We are in accordance with the published statement “CROWN initiative and preterm birth prevention: researchers and editors commit to implement core outcome sets” that provides a set of outcomes that should be considered in the design of preterm birth prevention studies.

Change in the manuscript: According to the CROWN initiative and preterm birth prevention, the primary outcome was a composite of neonatal adverse events that occurred within 10 weeks after birth. LINES 126-127

Reference

van 't Hooft J, Alfirevic Z, Asztalos EV, Biggio JR, Dugoff L, Hoffman M, Lee G, Mol BW, Pacagnella RC, Pajkrt E, Saade GR, Shennan AH, Vayssière C, Khan KS. CROWN initiative and preterm birth prevention: researchers and editors commit to implement core outcome sets. BJOG. 2018 Jan;125(1):8-11. doi: 10.1111/1471-0528.14987. PMID: 29055092.

Reviewer #2:

This is a multicenter, randomized, controlled trial of vaginal progesterone vs vaginal progesterone plus pessary in women with a short cervix (<3cm) at midgestation. Primary outcome is a neonatal composite morbidity and mortality. Overall, thorough description of methodology with clear acknowledgement of limitations. Although similar RCTs have been previously published, the question of pessary utility is incompletely answered. Thus, this study is helpful.

1. Methods, line 83: the choice of 30mm as cutoff for short cervix is likely limiting given that you are including a lower risk group. I understand you can't go back and

change this, but I'm interested to know why you chose this cutoff given that progesterone is most efficacious <25mm.
Please refer to our response to Q2 of reviewer 1.

2. Methods, line 136: what is the predicted primary outcome incidence based on? Internal data?
Please refer to our response to Q6 of reviewer 1.

3. Methods, lines 174-175: I understand this may be how your national guideline defines ethnicity, but I don't think skin color categories as listed are acceptable for this publication.
Brazil has a unique mixed population in the world and there is a “myth of racial democracy” which is not at all the truth. Race/skin color have complex social, behavioral and biological aspects related to maternal health indicators. The racial component is related to high levels of inequality in Brazilian society mainly associated with usually subtle forms of racial discrimination. Black, brown, and white people have great disparities regarding socioeconomic and demographic conditions, as well as inequalities in health indicators with, for example infant mortality twice as higher among black children compared to white ones.
Regarding preterm birth, we know that Black women have a higher risk of having a premature birth than white women. The skin color approach is the chosen strategy to address this issue in health studies as it is powerful enough to highlight the subtle differences in health care among different groups, which is more related to social disparities than to biological aspects.

Change in the manuscript: In Brazil, Race/skin color have complex social, behavioral, and biological aspects related to maternal health indicators. The skin color approach was the chosen strategy to address this issue in health studies as it is powerful enough to highlight the subtle differences in health care among different groups, which is more related to social disparities than to biological aspects. LINES 180-185

References for skin color approach

1. Fernandes KG, Costa ML, Haddad SM, Parpinelli MA, Sousa MH, Cecatti JG; The Brazilian Network For Surveillance Of Severe Maternal Morbidity Study Group. Skin Color and Severe Maternal Outcomes: Evidence from the Brazilian Network for Surveillance of Severe Maternal Morbidity. Biomed Res Int. 2019 Jul 30;2019:2594343. doi: 10.1155/2019/2594343. PMID: 31467877; PMCID: PMC6699272.
2. Oliveira KA, Araújo EM, Oliveira KA, Casotti CA, Silva CALD, Santos DBD. Association between race/skin color and premature birth: a systematic review with meta-analysis. Rev Saude Publica. 2018 Apr 9;52:26. doi: 10.11606/S1518-8787.2018052000406. PMID: 29641651; PMCID: PMC5893270.
3. Fonseca JM, Silva AAM, Rocha PRH, Batista RLF, Thomaz EBAF, Lamy-Filho F, Barbieri MA, Bettiol H. Racial inequality in perinatal outcomes in two Brazilian birth cohorts. Braz J Med Biol Res. 2021 Jan 22;54(1):e10120. doi: 10.1590/1414-431X202010120. PMID: 33503156; PMCID: PMC7822460.

4. Methods, lines 180-182: were p-values corrected for interim analyses?
We changed table 2 to include only crude and relative risk according to the Editor suggestion.

5. Results, lines 226-227: what do you make of the increased Cesarean rate in the P+P group? Simply due to less periviable/extreme preterm birth? Please address this in discussion.

We think this is the main hypothesis for this unbalancing in C-section. Brazil has one of the higher rates of C-section and a high prevalence of provider-initiated preterm birth. Early spontaneous preterm births are more likely to be delivered by vaginal birth than late preterm births. The fact that we had more late preterm birth in the pessary plus progesterone group may have influenced the higher rates of C-section.

Change in the manuscript: We also identified a significant difference in C-section rates between the pessary and non-pessary groups. Brazil has one of the higher rates of C-section and a high prevalence of provider-initiated preterm birth. Early spontaneous preterm births are more likely to be delivered by vaginal birth than late preterm births. The fact that we had more late preterm birth in the pessary plus progesterone group may have influenced the higher rates of C-section. LINES 305-310

6. Discussion: I know you are trying to not overstate your conclusions, which I appreciate. However, I think it's reasonable to highlight that multiparous women who are not on baseline progesterone (an exclusion criterion) are by definition lower risk due to a likely history of previous full term birth. This may explain why an effect is seen in the nulliparous group but not the overall group.
We agree with this point and have added this in the discussion.
Change in the manuscript: This may be explained by a higher prevalence of term deliveries among multiparous women, reducing the incidence of PTB in the present pregnancy. The history of a previous preterm birth is well balanced between groups with a non-statistical higher frequency in the P+P group, however we observed 40% with preterm birth history among multiparous, which means 60% with term births only. LINES 323-28

7. Discussion: There is a significant difference in side effect profile between groups (worse with pessary). Please add this to the discussion section.
Thank you for raising this point. We included a paragraph in the discussion section:
Change in the manuscript: There was a significant difference in the side effect profile between groups. Women using cervical pessary had more vaginal discharge and pain than those not using the device but there were no severe side effects compromising the safety of the treatment. This is in accordance with other studies [10,12] and should be considered in the treatment option. LINE 329-33

Reviewer #3:

1. In line 52, the authors state "there is consensus the progestogens reduce spontaneous preterm birth in women with a short cervix and …previous preterm birth." Given the constant evolution of these data, this remains a controversial statement. Consideration should be given to also referencing the data from the EPPPIC meta-analysis that was recently published.
Thank you for highlighting this. We changed the paragraph and included the EPPPIC citation.
Change in the manuscript: While there is evidence that vaginal progestogens reduces spontaneous preterm birth in women with a short cervix and women with previous preterm birth[8,9]. LINE 52-54

2. The authors point out the conflicting results of the pessary studies, but it is unclear from the introduction why there may be such divergent results. While not necessary to delve into details here, it would be useful to explain why this current study is going to be different. Since some of the studies that demonstrated benefit of pessary had no or very infrequent concomitant progesterone use and compared pessary to no

treatment, the authors should explain why in this study they chose two treatment arms as opposed to including a no treatment arm.
Given the divergence in the results, we've hypothesized that a mechanical (pessary) treatment would add to the reduction of preterm birth in combination with a biochemical (progesterone). We included this argument in the introduction.
The decision to compare two treatment arms as opposed to including a no treatment arm was built based on this argument and the fact that at that time in Brazil, there was suggestion in the national guideline considering the prescription of progesterone for women with preterm birth risk and this was widely used across the country.
Change in the manuscript: In view of this divergence, and hypothesizing that a mechanical (pessary) treatment would add to the reduction of preterm birth in combination with a biochemical (progesterone), we conducted a multicentre randomized controlled trial (RCT) comparing cervical pessary plus vaginal progesterone (P+P) vs. vaginal progesterone only (P-only) in women with a short cervix in mid-pregnancy. LINES 57-62

3. Why was 30 mm chosen as the threshold for definition of short cervix? Was there consideration of a different threshold in singletons vs twins? Most would consider 30 mm a normal cervical length in singletons and then argue that there reason there was no difference seen in groups was that the patients with cervical length between 25 and 30 mm, at least singletons, did not need treatment.
Please refer to our response to Q2 of reviewer 1 and Q1 of reviewer 2.

4. What was the time interval from cervical length measurement to randomization? Was it same day?
The protocol allowed inserting the pessary from the cervical length measurement up to three days after. Most pessaries were placed on the same day. This information is in line 108.

5. Is the Ingamed pessary similar to the pessary used I other studies? If so that should be stated. If different, that should be explained.
We agree and corrected in the text.

Change in the manuscript: We used the Ingamed AM® silicone pessary (unique size: outer diameter 70 mm, height 25 mm and inner diameter 40 mm with indentations – similar to the largest ARABIN® Cerclage Pessary perforated). LINE 110-111

6. How was the neonatal composite chosen? Why was 10 weeks chosen as the time point?
In accordance with the published statement "CROWN initiative and preterm birth prevention: researchers and editors commit to implement core outcome sets" that provides a set of outcomes that should be considered in the design of preterm birth prevention studies, we consider that regardless of gestational age at birth, studies on preterm birth prevention might look for deliver healthy babies. We, therefore, aimed to reduce neonatal consequences more than to improve gestational age at birth.
We choose 10 weeks after birth considering the restauration of the physiological function of a normal condition after pregnancy. After 10 weeks, the mother-baby binomial should be healthy. Also, some neonatal diagnosis needs some time to be defined, as leukomalacia.

Change in the manuscript: no changes

Reference
van 't Hooft J, Alfirevic Z, Asztalos EV, Biggio JR, Dugoff L, Hoffman M, Lee G, Mol

BW, Pacagnella RC, Pajkrt E, Saade GR, Shennan AH, Vayssière C, Khan KS. CROWN initiative and preterm birth prevention: researchers and editors commit to implement core outcome sets. BJOG. 2018 Jan;125(1):8-11. doi: 10.1111/1471-0528.14987. PMID: 29055092.

7. Approximately 14% of patients had a cervical length of 30 mm or less. Is this typical for this patient population? In singleton gestations, 30 mm typically approximates the 25th percentile in other studies.

In our sample the 25th percentile was 32.3 mm. This is different from other studies from different populations but in accordance with the argument that there is a difference of cervical length across populations.1

Iams et al. were among the pioneers in proposing reference values for CL. For women at 22-week's gestation, we found very similar measurements for the 5th, 10th and 25th percentiles. Studies have proposed cervical distributions curves for the Brazilian population considering population characteristics. In general, the 50th and 95th percentiles are similar to those of our study; however, for the lower percentiles, we obtained slightly different values than others for the lower percentiles (2,3)

Even within a single country, it is also necessary to be aware of the importance of intra-population differences. A prospective cohort found that Afro-Caribbean women had a shorter cervices than did Caucasian women.15 Similar findings were identified in a retrospective cohort conducted in the US involving 16,598 women in the second trimester of pregnancy, suggesting that a short cervix definition should differ between ethnic groups within the same population.(4)

In 2020, a prospective Asian cohort study involving 1013 women found significant difference between the mean cervical measurement by population group (Chinese 32.2 ± 0.77 mm, Malay 31.3 ± 0.69 mm, Indian 29.7 ± 0.70, Others 33.3 ± 0.82 mm).(5)

1. Bortoletto TG, Silva TV, Borovac-Pinheiro A, Pereira CM, Silva AD, França MS, Hatanaka AR, Argenton JP, Passini R Jr, Mol BW, Cecatti JG, Pacagnella RC. Cervical length varies considering different populations and gestational outcomes: Results from a systematic review and meta-analysis. PLoS One. 2021 Feb 16;16(2):e0245746. doi: 10.1371/journal.pone.0245746. PMID: 33592005; PMCID: PMC7886126.
2. Silva SV, Damião R, Fonseca EB, Garcia S, Lippi UG. Reference ranges for cervical length by transvaginal scan in singleton pregnancies. J Matern Fetal Neonatal Med. 2010;23(5):379-82
3. Andrade SGA, Andrade FM, Araujo Júnior E, Pires CR, Mattar R, Moron AF. Assessment of Length of Maternal Cervix between 18 and 24 weeks of Gestation in a Low-Risk Brazilian Population. Rev Bras Ginecol Obstet. 2017;39(12):647-52.15. Heath VC, Southall TR, Souka AP, Novakov A, Nicolaides KH. Cervical length at 23 weeks of gestation: relation to demographic characteristics and previous obstetric history. Ultrasound Obstet Gynecol. 1998;12(5):304-11.
4. Bligard K TL, Stout MJ, Tuuli MG, Macones GA, Cahill AG. Performance of cervical length screening in african american women. American Journal of Obstetrics & Gynecology. 2020.
5. Thain S, Yeo GSH, Kwek K, Chern B, Tan KH. Spontaneous preterm birth and cervical length in a pregnant Asian population. PLoS One. 2020;15(4):e0230125.18.

Change in the manuscript: no changes

8. Were there any specific criteria in the protocol allowing for cerclage placement or was it at the physician's discretion?

Cerclage was not considered in the protocol. Indication was at physician's discretion.

Change in the manuscript: no changes

9. There was a reduction in PTD < 34, 32, 30 and 28 weeks. The way the abstract is written it does not emphasize the reduction at all of these time points. Consideration should be given to emphasizing the reduction at these earlier points as well as this may be where the value in treatment is.
Thank you for bringing this to the discussion. We included this information in the abstract.
Change in the manuscript: Spontaneous preterm delivery rates <37 weeks were 29.1% vs. 31.4% (aRR 0.86, CI 0.72 to 1.04), and delivery rates <34 weeks were 9.9% vs. 13.9% (aRR 0.66, CI 0.47 to 0.93). Also, overall delivery rates were reduced for under 28 (aRR 0.19, 95% CI 0.07 to 0.54), 32 (aRR 0.48, 95% CI 0.26 to 0.88) and 34 (aRR 0.61, 95% CI 0.39 to 0.96) weeks of gestation. LINES 67-71

10. In the post hoc analysis, the authors included nulliparous, singletons with CL 25 mm or less and found reduction in key outcomes with pessary plus progesterone. Was an analysis including only singletons and cervical length 25 mm or less conducted? While interesting to include nulliparas, from a clinical standpoint, cervical length and singleton gestation alone is a more useful decision point. The authors should explain why they included this nulliparous subgroup as opposed to including multiparas as well.
Thank you for the interest. Yes, we performed this analysis. The results are in the table below included in the appendix 4.

High- effect subgroup: singleton, cervix length <25mm, (n=464)

Outcome	Progesterone + Pessary		Progesterone		Adjusted RR (95% CI)	Adjusted p-value
	n/N	%	n/N	%		
Primary outcome (maternal level)	47/230	20.4	52/215	24.2	0.85 (0.61 - 1.19)	0.344
Overall preterm delivery < 37 weeks	64/233	27.5	73/228	32.0	0.87 (0.66- 1.14)	0.317
Overall preterm delivery < 34 weeks	24/233	10.3	42/228	18.4	0.57 (0.36 - 0.89)	**0.014**
Overall preterm delivery < 32 weeks	16/233	6.9	31/228	13.6	0.51 (0.29 - 0.89)	**0.017**
Overall preterm delivery < 30 weeks	12/233	5.2	23/228	10.1	0.51 (0.27 - 0.98)	**0.045**
Overall preterm delivery < 28 weeks	6/233	2.6	15/228	6.6	0.38 (0.16 - 0.93)	**0.034**

We intent to show at first the results for the higher-effect subgroup: nulliparous, cervix length <25mm, singleton. Considering your point, we decided to also present this result in the appendix.

We changed the text:
In a posthoc subgroup analysis, there was a trend that the effects of the P+P group on overall preterm deliveries under 28, 30, 32, and 34 weeks of gestation were more prominent in women with a singleton pregnancy who had CL ≤ 25 mm (Appendix 4). In nulliparous women with a singleton pregnancy and CL ≤ 25 mm, there were also lower frequencies of the composite neonatal outcome in the P+P group (15.8% vs. 27.5%; aRR 0.59, 95% CI 0.37 to 0.94). Overall preterm birth rates under 37, 34, 32, 30, and 28 weeks were also significantly lower for P+P in this subgroup of women (Appendix 5). LINES 267-274

11. The final paragraph of the discussion section seems out of place. It seems like it belongs earlier in the discussion section.
We agree and changed for earlier in the text. LINES 307-14

STATISTICS EDITOR COMMENTS:

Abstract needs to conform to our RCT template.
We corrected the Abstract to conform to RCT template (http://edmgr.ovid.com/ong/accounts/authors.pdf. PAGE 10)

lines 123-127, 135-142: The primary outcome was neonatal, but since both singletons and twins were included, the outcomes for twins cannot be considered as statistically independent events. Need to either adjust for intra class correlation within twin pairs (which effectively decreases the sample size of neonates), randomly select one of each twin pair or omit twins altogether from the analysis as a separate cohort.
The primary outcome was presented at both the mother level and the neonatal level. For the mother level, neonatal events in any of the two babies of one pregnancy was considered to be an event for the mother, so there is no issue of intra-class correlation. For the neonatal level, we considered intra-class correlation and use generalized estimating equations to counteract non-independence among neonates from the same pregnancy.
We described these in the manuscript: “For the comparisons of the primary outcome at the mother level (experiencing neonatal adverse events in at least one baby if multiple pregnancy), we used a generalized linear model (GLM), with Poisson log link function and robust variance estimate. For the primary outcome at the neonatal level, to account for possible non-independence among neonates from the same pregnancy, we used generalized estimating equations (GEEs).” LINES 151-156

Also, The comparison of adverse neonatal rates was evaluated for two cohorts: one consisting of those with maternal CL ≤ 25 mm. The specified rates were 22% vs 12% and 17.3% vs 8.65% for the two groups.
For the sample size calculation, please refer to our response to Q6 of reviewer 1.

The results in Abstract, Tables etc should first state those primary outcomes, then all the secondary ones. In present format, both neonatal and maternal outcomes are aggregated as the primary outcome in Table 2 and the subset of results for the cohort with CL ≤ 25 mm is in Table 4 with other secondary outcomes. Need to more clearly separate and emphasize the primary outcomes, then all the secondary ones.

The primary outcome was presented at both the mother level and the neonatal level. For the mother level, neonatal events in any of the two babies of one pregnancy was considered to be an event for the mother, so there is no issue of intra-class correlation. For the neonatal level, we considered intra-class correlation and use generalized estimating equations to counteract non-independence among neonates from the same pregnancy.

Fig 1: The flowchart has a typo, since the next to last level has labelled both the N = 475 and N = 461 as receiving pessary + progesterone treatment.
Thank you. We corrected.

Fig 2: Need to include in the figure or its legend a concise summary of the statistical test of the K-M curves.
Included

Table 2: Should include a column of unadjusted RRs for contrast with the aRRs.

Included

The column of p-values is redundant, since CIs are shown. Should omit the p-values.
Excluded
Need to include as footnote to Table the variables included in the adjustment model.

EDITOR COMMENTS:
1. Thank you for submitting your work to Obstetrics and Gynecology. If you opt to submit a revision, we require additional documentation regarding clinical trial registration. The authors provided documentation that the Brazilian trial registry sent an email requesting a response to some errors/issues with the initial submission (not confirmation that the trial had been registered) in June 2015. Please provide documentation that the trial protocol did not change from the time of the initial submission that was incomplete to the time that the trial was documented as registered in Sept 2016. This will also need to be addressed transparently in the methods section of the manuscript.

We have already formally asked the Brazilian Registry to correct this information. And we are waiting for a formal change in this information.

2. Please pay close attention to the need to emphasize the primary outcome of this study and be clear about what are primary and what are secondary outcomes.

We clearly indicate what was our primary outcome in the text, in methods results and discussion (LINES 127, 223, 280), and also in abstract.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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.

OK

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:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
* 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.

OK

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

OK

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, 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.

OK

5. 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).

OK

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.

OK

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 5,500 words. Stated word limits include the title page, précis, abstract, text,

tables, boxes, and figure legends, but exclude references.

OK.

Word count 5500.

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).
* 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]."

OK

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

OK

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

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

OK

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

OK

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

OK

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

OK

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