Date: Nov 15, 2018
To: "Vinh Q Dang" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1970

RE: Manuscript Number ONG-18-1970

Pessary versus vaginal progesterone in women with a twin pregnancy and a cervix <38 mm: a randomized clinical trial

Dear Dr. Dang:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Dec 06, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

Pessary versus vaginal progesterone in women with a twin pregnancy and a cervix <38 mm: a randomized clinical trial, single center

1. Exclusion criteria: previous PTB? why not, you had 6 in the progesterone group and none in the pessary group, you did exclude cervical surgeries? What was your thinking ?

2. In setting the power calculation you state that the delivery rate at <34 weeks' gestation in twin pregnant women with a CL <38 mm and 176 treated with 400 mg progesterone at My Duc Hospital was 28.4% Was this over the past year or two ? was that standard of care prior to the study? can you explain. How do you explain the difference between the base rate of 28% and the study rate of 22%?

3. Can you discuss why you chose 38mm as the cutoff, Why not use 28-25 mm, This would match clinical practice as opposed to research methodology. Understand that you planned a post randomized sub analysis. By most clinical standards (NOT research standards) an acceptable cervical length >3.0 cm is normal, I don't know that anyone would treat a 38 mm cervix in real life medicine. Wont treating a normal cervix dilute out any potential effect? There are statistical cervical lengths and pragmatic cervical lengths. Please discuss.

4. When you discussed generalizability or external validity, you discussed the high rate of IVF as a potential weakness. I would add Body mass index of 21and that 80-90% were nulliparous

5. Why do you think there was more low birth weight in the progesterone group? Did a sub analysis give you any hints

6. Table 1: Although you have a single sentence in the results that state no difference, either showing p values or having some foot note would be helpful for reader

7. Do you know what is driving the significant difference in perinatal outcomes: My glance at Table 3 tells me it may be RDS? Since you have data on antenatal steroid and Magnesium for fetal neuro protection, these two are important enough to be included in Table 2 instead of Appendix

8. Given that RDS was the most common neonatal complication I ask that you give the defintion in amore practical understandable way. Your current defintion is "Respiratory distress syndrome Grade 2 or worse, diagnosed as described by Giedion et al.,1973." Most papers are able to give the clinician a little more guidance. I thought your other definitions were

OK and easily understood

REVIEWER #2:

1. You are comparing the difference in outcome in women with twins and a CL < 38 mm. You never stated why that threshold was chosen. In your paper, you note ~ 40% of your enrolled patients met that threshold ! Please state why researchers or readers would be interested in studying a problem that almost half of the patients have.

2. Objectives or Hypotheses are typically best stated as a null hypothesis -- would it not be best to state yours this way, too ?

3. The primary outcome is listed as PTB < 34 weeks -- nowhere, that I can see, in the paper does it specify whether this delivery had to be spontaneous, iatrogenic / indicated or both. Please specify.

4. In line 78, for the sample size calculation, you looked to detect a 14% difference in the primary outcome -- is this an ABSOLUTE difference or a RELATIVE difference ? Please specify.

5. One of my concerns is generalizability -- your patients are older (average age ~ 32 yrs), highly educated (two thirds with university education OR higher), have low BMIs (average ~ 21) and have a high degree of nulliparity (~85% to 90%). This does NOT match well (I believe) with cohorts elsewhere in developed countries.

6. Similarly -- ~ 95% conceived via IVF and ~ 95% were DC twins. This also would be a hard cohort to match.

7. Compliance with the progesterone therapy was > 95% -- would not find that in other populations. Was compliance with pessary use assessed ? If so, how?

8. The pre-planned, subgroup analysis is reasonable but would only serve as a source for hypothesis generation and future studying. I would downplay the amount of coverage you've given to it in the paper.

9. Post-hoc analyses are, as you know, not worth very much -- again, they can serve as a basis for future study. I would give this one or two lines in the paper.

REVIEWER #3:

General comments: This is a well-written manuscript of a clinical trial with hypothesis that pessary would be superior to vaginal progesterone in reduction of early preterm birth <34 weeks in twin pregnancies with CL < 38 mm. I have some critiques regarding the description of the methodology and sample size estimates, but overall it appears to be a properly performed clinical trial. The interpretation of the results may require some revision. Otherwise this is a strong submission for publication.

Specific comments:
1. Introduction: Well-written, and is a fair summary of the published literature on the topic. It is true that there is conflicting evidence regarding the efficacy of both pessary and vag progesterone for twins with short cervix. Therefore, the introduction fails to clearly present why the authors chose to pursue this investigation, which hypothesizes that pessary would result in a 50% reduction in early PTB compared to vaginal progesterone.

2. The objective could be more clearly stated as a comparison of pessary "to" vaginal progesterone, since progesterone is being considered the normal or referent group for comparison.

Methods:

3. The most significant critique is the lack of explanation why CL <38 mm was chosen as the study population. The introduction implies the study is of women with twins and "short cervix". However, there is no presentation of literature to support that <38 mm would be considered short or "at risk" in twins.

4. The second most significant critique is the description of the sample size. The authors start with an estimate of 28% PTB rate <34 weeks in twins with CL <38 mm. This sounds reasonable. They then say they hypothesize a 10% decrease with pessary, which would be a reduction to an absolute rate of 26% and would require a sample size of 7000 in each group. I suspect what the authors meant to say is they wanted to observe a 36% decrease in (which would be an absolute rate difference of 10%) from 28% to 18%. That is a reasonable estimate of a clinically relevant reduction in risk. However, based on prior published data on efficacy of pessary it is questionable why the authors thought they might observe a 36% reduction a priori. Then, due to slow recruitment, they did something that you are not supposed to do after a study starts - they changed their hypothesis. Now they decided they could see a larger effect size of 50% from rate of 28.4% to 14.4% (although they describe it incorrectly as 14% difference). It does not seem reasonable based on available clinical evidence that a 50% reduction in risk would be possible with pessary compared to progesterone. But, in effort to minimize sample size, this is what the authors chose to do. I do applaud them for being transparent and sharing this information, but it was

wrong nonetheless. However, it does not negate the findings of the study.

Results

5. 39% of the study population ad a CL <38 mm. Again, this raises the question why this length was chosen as the entry criteria

6. The observed rate of PTB <34 weeks in the prog group was 22%, which was lower than estimated at 28%. Starting from this observation, the study is underpowered for primary outcome unless a >50% reduction in risk is observed. If 50% reduction was observed, a sample size of 362 (181 in each group) would be needed.

7. There were many statistical comparisons performed, which can influence risk of alpha error.

8. Surprisingly, there were large effect sizes observed for reduction in risk of important perinatal outcomes with pessary. These effects were larger in the higher risk groups, which further supports the premise these were true effects.

Discussion:

The first sentence should say that the study was underpowered to detect at 50% reduction in the primary outcome. Other outcomes with larger effect sizes were significantly reduced with pessary, which are noteworthy findings. However, the remarkable reduction in risk observed in this study compared to other studies with no improvement with pessary warrants further discussion.

STATISTICAL EDITOR'S COMMENTS:

1. lines 78-80 and 175-179: Should explicitly state in abstract the expected proportion of PTB among the referent group, since the power/sample size calculation is defined by both the difference and the referent baseline proportion.

2. Given the expected referent proportion of 28%, why were the expected proportions of the treatment group set at either 14% or 10%? Seems like a high threshold.

3. lines 142-144 and 147-149: The treatments were not initiated at the same times in gestation, since the pessaries were inserted "within one week of randomization", while the progesterone was applied "starting from the day of randomization". What were the precise delays in insertion of pessaries with respect to randomization and were the actual GA at initiation of treatments statistically different? Could this difference have modified the difference in PTB rates?

4. Table 2: Since there were two perinatal outcomes per delivery and there would be correlation within each twin pair, the analyses for perinatal outcomes need to account for this correlation, with resultant decrease in the effective sample sizes. Many of the comparisons have low counts and their NS findings cannot be generalized.

5. Table 3: Same issues with perinatal outcomes.

6. In Table 2, the Authors have appropriately separated their primary from the secondary outcomes. They should also label the outcomes in Table 3 as all being secondary outcomes, lest the reader misinterpret the results.

7. Fig 2A, 2B: Should cite the results of stats test for difference in survival methods analyses for the two figures, either in legends or on the graph itself.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. 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:
   1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
   2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. This statement must appear at the end of your Materials and Methods section. 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). Examples of statements can be found online at http://www.icmje.org/news-

and-editorials/data_sharing_june_2017.pdf.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

5. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:
a. - Was this also presented at the 28th World Congress on Ultrasound in Obstetrics and Gynecology? If so, please disclose the name, date, and location of the meeting on the title page of your manuscript.

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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.

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

Please limit your Introduction to 250 words and your Discussion to 750 words.

8. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

9. 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 limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

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

sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

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

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

14. 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.

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If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 Dec 06, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

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Dr Nancy Chescheir
Editor-in-Chief
Obstetrics & Gynecology

3 December 2018

Dear Dr Chescheir,

Thank you for your consideration on our manuscript entitled "**Pessary versus progesterone in women with a twin pregnancy and a cervix <38 mm: a randomized clinical trial**" submitted to *Obstetrics & Gynecology* (ONG-18-1970).

The authors are grateful to the reviewers and editors for their review and valuable comments. Point-by-point responses to each editor and reviewer comment are provided below.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

If you require any further information, please do not hesitate to contact us. We hope that the adjustments make the manuscript suitable for publication in *Obstetrics & Gynecology*.

Sincerely yours,

On behalf of all co-authors
Vinh Q Dang, MD

Point-by-point response to the comments of reviewers and editor

Reviewer #1:

1. Exclusion criteria: previous PTB? why not, you had 6 in the progesterone group and none in the pessary group, you did exclude cervical surgeries? What was your thinking?

RESPONSE: Thank you for your question. A history of preterm birth (PTB) is a risk factor of new PTB. Since women with a history of PTB are at increased risk as compared to women with a twin pregnancy without such history, and since both cervical pessary and vaginal progesterone are applicable in these women, we did not see a reason to exclude them.

We could not foresee the skewed distribution between the pessary and the progesterone group. The fact that there was no patient with previous PTB in pessary group as compared with six in progesterone group is due to chance, since the number of patients with previous PTB was low. In these six women, CL measured at 16 – 24 weeks' gestation was 32 mm (n=2); 31 mm (n=3) and 29 mm (n=1). The reason for previous PTB were severe pre-eclampsia (n=1), PPROM (n=4) and unstable GDM (n=1).

Women with a history of cervical surgery are also at increased risk of PTB (Kyrgiou et al, 2014). However, for those with a history of cervical surgery and a short cervix, cervical pessary is not feasible, and we perform cerclage as a preventive method for PTB in our current practice. Therefore, in this trial, these women were not included. No adjustments were made in the revised manuscript.

2. In setting the power calculation you state that the delivery rate at <34 weeks' gestation in twin pregnant women with a CL <38 mm and treated with 400 mg progesterone at My Duc Hospital was 28.4%. Was this over the past year or two? Was that standard of care prior to the study? Can you explain. How do you explain the difference between the base rate of 28% and the study rate of 22%?

RESPONSE: We appreciate the question. It was our clinical practice that women with a twin pregnancy were advised to use 400 mg vaginal progesterone, started from 10 weeks' gestation until 36 weeks' gestation. A CL measurement was performed routinely from 16 – 24 weeks' gestation. For those with a short cervix (<30 mm), cerclage could be applied, based on the preference of clinicians and patients.

Indeed, our observed PTB rate <34 weeks was lower than anticipated. Firstly, the base rate of 28.4% was found through a retrospective data; therefore, it could be different from what we found in this RCT. Secondly, the study might be underpowered to detect a 50% relative risk reduction in the primary outcome.

The text has been updated in the Discussion section. It now reads "Our data showed that pessary did not significantly reduce PTB <34 weeks as compared to 400 mg progesterone in twin pregnant women with a CL <38 mm. However, the study was underpowered to detect a 50% relative risk reduction in the primary outcome.". Please see line 269 - 270, page 12 of the revised manuscript.

3. Can you discuss why you chose 38mm as the cut-off? Why not use 28-25 mm, this would match clinical practice as opposed to research methodology. Understand that you planned a post randomized sub analysis. By most clinical standards (NOT research standards) an acceptable cervical length >3.0 cm is normal, I don't know that anyone

would treat a 38 mm cervix in real life medicine. Won't treating a normal cervix dilute out any potential effect? There are statistical cervical lengths and pragmatic cervical lengths. Please discuss.

RESPONSE: Thank you for your question. We chose the 38 mm as a cut-off based on the result of the Dutch study (Liem et al, 2013), that reported that in patients with a CL <25th percentile (<38 mm), the pessary significantly reduced preterm delivery and improved perinatal outcome. We want to stress that this cut-off was set in the context of our research, and not in the context of clinical practice. Only by including women below a cut-off as high as 38 mm, we were able to study where the relevant clinical cut-off should be. Our data show that a difference between cervical pessary and progesterone is maybe present below a CL of 30 mm. This could also have been 28 or 32 mm. We could only explore this by including women with a higher cut-off. We felt this was ethical, since in women with unselected twin pregnancies both progesterone and cervical pessary have been found to do no harm.

The text has been updated in Materials and Methods section to clarify this. It now reads "The 38-mm cut-off in this trial was based on the result of the Dutch study, that reported that in patients with a CL <25th percentile (<38 mm), the pessary significantly reduced preterm delivery and improved perinatal outcomes as compared with no intervention.[9] As this was a randomized clinical trial in a research setting, such a relatively high cut-off would allow us to assess a potential clinical relevant cut-off that will probably be lower than 38 mm". Please see line 133 - 138, page 6 of the revised manuscript.

4. When you discussed generalizability or external validity, you discussed the high rate of IVF as a potential weakness. I would add Body mass index of 21 and that 80-90% were nulliparous.

RESPONSE: Thank you for your suggestion. The text has been updated in the Discussion section. It now reads "Firstly, the study was conducted at a single center in Asia, with most twins occurred after ART. Moreover, most patients in the study were nulliparous, highly educated, with low BMI and at old age, which might compromise the external validity of our study.". Please see line 314 - 316, page 13 of the revised manuscript.

5. Why do you think there was more low birth weight in the progesterone group? Did a sub analysis give you any hints?

RESPONSE: Differences in birth weight can be related to the duration of pregnancy. While not statistically significant, the difference in PTB <34 weeks was 16.2% versus 22.1%. Since there are two babies per pregnancy, differences between children do reach earlier statistical significance, even after correction for a cluster effect.

The difference in low birth weight was even larger and statistically significant in women with a CL ≤28 mm (pre-specified subgroup analysis), and also here it followed the difference in PTB rate <34 weeks. No changes were made to the revised manuscript.

6. Table 1: Although you have a single sentence in the results that state no difference, either showing p values or having some foot note would be helpful for reader.

RESPONSE: Thank you for your remark. We politely disagree. Since this is a randomized clinical trial, any differences in baseline characteristics are only due to chance, hence the p-value expressing the probability that any of the baseline

characteristics is due to chance by definition. No adjustments were made in the revised manuscript.

7. Do you know what is driving the significant difference in perinatal outcomes? My glance at Table 3 tells me it may be RDS? Since you have data on antenatal steroid and Magnesium for fetal neuro protection, these two are important enough to be included in Table 2 instead of Appendix.
RESPONSE: It is our standard treatment to give antenatal corticosteroids to patients at risk of PTB, like for twins, starting from 28 weeks' gestation. Should patients develop preterm labour symptoms, they will be admitted to the hospital. At My Duc Hospital, Atosiban is the standard tocolytic treatment. In case the patients admitted to hospital for PTB at gestational age less than 30 weeks' gestation, magnesium sulfate will be used for neuroprotection of the newborn.
The significant difference in perinatal outcomes can be related to the duration of pregnancy. While not statistically significant, the difference in PTB <34 weeks was 16.2% versus 22.1%. Since there are two babies per pregnancy, differences between children do reach earlier statistical significance, even after correction for a cluster effect.
The difference in perinatal outcomes was even larger and statistically significant in women with a CL ≤28 mm (pre-specified subgroup analysis), and also here it followed the difference in PTB rate <34 weeks.
Data on antenatal steroids and Magnesium for fetal neuroprotection were included now the Table 2, instead of Appendix, as per your suggestion.

8. Given that RDS was the most common neonatal complication I ask that you give the definition in a more practical understandable way. Your current definition is "Respiratory distress syndrome Grade 2 or worse, diagnosed as described by Giedion et al.,1973." Most papers are able to give the clinician a little more guidance. I thought your other definitions were OK and easily understood.
RESPONSE: Thank you for your suggestion. The definition for RDS has been updated in Appendix 1. It now reads "The presence of tachypnea >60/minute, sternal recession and expiratory grunting, need for supplemental oxygen, and a radiological picture of diffuse reticulogranular shadowing with an air bronchogram (Hjalmarson, 1981)".

Reviewer #2:
1. You are comparing the difference in outcome in women with twins and a CL <38 mm. You never stated why that threshold was chosen. In your paper, you note ~ 40% of your enrolled patients met that threshold! Please state why researchers or readers would be interested in studying a problem that almost half of the patients have.
RESPONSE: Thank you for your comment. Please see our response to reviewer 1, comment 3. We want to add two arguments. First, the PTB rate in twins is very high, and thus a higher treatment rate as compared to singletons is potentially justified in these women. Second, the decision for treatment should not be based on a percentage, but on the balance between benefit and harm from treatment. If expected benefit outweighs expected harm, treatment is justified. Only by studying a group as large as 40%, we will

be able to see the treatment can be justified in which patient group (10%, 20% or maybe 30%).

2. Objectives or Hypotheses are typically best stated as a null hypothesis -- would it not be best to state yours this way, too?
RESPONSE: Thank you for your suggestion. We have adjusted this in the revised manuscript, Materials and Methods section. It now reads "The null hypothesis was that there was no difference in delivery rate <34 weeks' gestation between the two groups. Our original alternative hypothesis was that the absolute risk difference in delivery rate at <34 weeks' gestation between the two groups was 10%, based on a clinically relevant reduction in risk. Therefore, a sample size of 520 women (power 80%, alpha-error 5%, loss to follow up rate 10%) was required.". Please see line 184 - 192, page 8 - 9 of the revised manuscript.

3. The primary outcome is listed as PTB <34 weeks -- nowhere, that I can see, in the paper does it specify whether this delivery had to be spontaneous, iatrogenic / indicated or both. Please specify.
RESPONSE: Thank you for your comment. Our primary outcome was PTB <34 weeks, including those with spontaneous or iatrogenic PTB <34 weeks' gestation. The word "spontaneously" in the sentence "The cumulative percentage of patients who did not give birth spontaneously at <34 weeks" in the original manuscript was a typo.
The text has been updated in the Materials and Methods and Results sections to clarify this. It now reads "The primary outcome was PTB <34 weeks' gestation, including spontaneous or iatrogenic PTB" and "The cumulative percentage of patients who did not give birth at <34 weeks was not statistically significant different between the two groups…". Please see line 169, page 8 and line 243, 258, page 11 of the revised manuscript.

4. In line 78, for the sample size calculation, you looked to detect a 14% difference in the primary outcome -- is this an ABSOLUTE difference or a RELATIVE difference? Please specify.
RESPONSE: In our trial, sample size was calculated based on an absolute risk reduction (14%) of the primary outcome.
The text has been updated, in Materials and Methods and Abstract sections to clarify this. It now reads "Our original alternative hypothesis was that the absolute risk difference in delivery rate at <34 weeks' gestation between the two groups was 10%, based on a clinically relevant reduction in risk. Therefore, a sample size of 520 women (power 80%, alpha-error 5%, loss to follow up rate 10%) was required." and "…we re-calculated the sample size to detect a 14% absolute risk difference in the primary outcome between the two treatment groups (power 80%, alpha-error 5%)..." and "A sample size of 290 women was required to detect a 14% absolute risk difference in the primary outcome between the two groups…". Please see line 185 - 198, page 8 - 9 and line 79 page 4 of the revised manuscript.

5. One of my concerns is generalizability -- your patients are older (average age ~ 32 yrs), highly educated (two thirds with university education OR higher), have low BMIs

(average ~ 21) and have a high degree of nulliparity (~85% to 90%). This does NOT match well (I believe) with cohorts elsewhere in developed countries.
RESPONSE: Thank you for your comment. The text has been updated in the Discussion section to clarify this. It now reads “Firstly, the study was conducted at a single center in Asia, with most twins occurred after ART. Moreover, most patients in the study were nulliparous, highly educated, with low BMI and at old age, which might compromise the external validity of our study.”. Please see line 313 - 317, page 13 of the revised manuscript.

6. Similarly -- ~ 95% conceived via IVF and ~ 95% were DC twins. This also would be a hard cohort to match.
RESPONSE: Thank you for your comment. The text has been updated as mentioned above.

7. Compliance with the progesterone therapy was >95% -- would not find that in other populations. Was compliance with pessary use assessed ? If so, how?
RESPONSE: This is a critical point; thank you for raising this. Participant compliance was assessed in both groups at every visit (at least every one month). For patients in the progesterone group, compliance was documented by checking the patient diary and drug purchasing records from the hospital pharmacy. The compliance rate was calculated by dividing the number of progesterone doses used since the last visit by the number of progesterone doses that should have been used since the last visit. Women were defined as compliant when the compliance rate was over 80%.
For patients in the pessary group, compliance was assessed by the presence of the pessary in the vagina and by asking any side effects happened since the last visit. In fact, vaginal discharge was more frequent in the pessary group compared to that in the progesterone group.
There are two possible explanations for a high compliance to progesterone in our trial. Firstly, patients might be familiar with the use of vaginal progesterone. More than 90% of our patients conceived from IVF treatment, in which luteal support with vaginal progesterone has been used up to 7 – 8 weeks’ gestation. Secondly, activities to maximize the retention of patients in the trial (consultations, hotline, brochures, leaflets) and a strict follow-up program have been set up. No adjustments were made to the revised manuscript.

8. The pre-planned, subgroup analysis is reasonable but would only serve as a source for hypothesis generation and future studying. I would downplay the amount of coverage you've given to it in the paper.
RESPONSE: Thank you for your suggestion. The text has been updated to downplay the amount of coverage to the subgroup analysis in the Discussion section.
It now reads “As an exploratory analysis, we compared the effectiveness of both treatments in a pre-specified subgroup according to the CL percentile. In women with a CL in the 25–50th percentile, pessary might be more effective than progesterone. This effect is more profound in women with a CL <25th percentile. A similar ‘dose-response’ effect was also seen in the study of Liem et al.[9] These findings should be confirmed in other trials.”. Please see line 304 - 308, page 13 of the revised manuscript.

9. Post-hoc analyses are, as you know, not worth very much -- again, they can serve as a basis for future study. I would give this one or two lines in the paper.
RESPONSE: Thank you for your suggestion. The text has been updated in the Discussion section to clarify this. It now reads “Lastly, the composite of poor perinatal outcomes was not pre-specified and there were many statistical comparisons performed, which can influence risk of alpha error. Therefore, findings from these analyses should be confirmed in other studies.”. Please see line 337 - 339, page 14 of the revised manuscript.

Reviewer #3:
General comments: This is a well-written manuscript of a clinical trial with hypothesis that pessary would be superior to vaginal progesterone in reduction of early preterm birth <34 weeks in twin pregnancies with CL < 38 mm. I have some critiques regarding the description of the methodology and sample size estimates, but overall it appears to be a properly performed clinical trial. The interpretation of the results may require some revision. Otherwise this is a strong submission for publication.
RESPONSE: Thank you for your kind comments.

Specific comments:
1. Introduction: Well-written, and is a fair summary of the published literature on the topic. It is true that there is conflicting evidence regarding the efficacy of both pessary and vaginal progesterone for twins with short cervix. Therefore, the introduction fails to clearly present why the authors chose to pursue this investigation, which hypothesizes that pessary would result in a 50% reduction in early PTB compared to vaginal progesterone.
RESPONSE: Thank you for your comment. The reason for this was mainly due to the limit number of words in the Introduction section (250 words). However, the text has been updated in the Materials and Methods to clarify this.
It now reads “The 38-mm cut-off in this trial was based on the result of the Dutch study, that reported that in patients with a CL <25th percentile (<38 mm), the pessary significantly reduced preterm delivery and improved perinatal outcomes as compared with no intervention.[9] As this was a randomized clinical trial in a research setting, such a relatively high cut-off would allow us to assess a potential clinical relevant cut-off that will probably be lower than 38 mm.”. Please see line 133 - 138, page 6 of the revised manuscript.

2. The objective could be more clearly stated as a comparison of pessary "to" vaginal progesterone, since progesterone is being considered the normal or referent group for comparison.
RESPONSE: Thank you for your suggestion. The text has been updated in Abstract section and in Discussion section to clarify this. It now reads “To compare the effectiveness of cervical pessary to vaginal progesterone for the prevention of preterm birth (PTB) in women with a twin pregnancy and a short cervix” and “Our data showed that pessary did not significantly reduce PTB <34 weeks as compared to 400 mg

progesterone in twin pregnant women with a CL <38 mm.". Please see line 70, page 4 and line 268, page 12 of the revised manuscript.

3. The most significant critique is the lack of explanation why CL <38 mm was chosen as the study population. The introduction implies the study is of women with twins and "short cervix". However, there is no presentation of literature to support that <38 mm would be considered short or "at risk" in twins.
RESPONSE: The rationale why CL <38 mm was chosen as the study population has been added in the Materials and Methods section due to the limit of number of words in the Introduction (250 words).
It now reads "The 38 mm cut-off in this trial was based on the result of the Dutch study, that reported that in patients with a CL <25th percentile (<38 mm), the pessary significantly reduced preterm delivery and improved perinatal outcomes as compared with no intervention.[9] As this was a randomized clinical trial in a research setting, such a relatively high cut-off would allow us to assess a potential clinical relevant cut-off that will probably be lower than 38mm.". Please see line 133 - 138, page 6 of the revised manuscript.

4. The second most significant critique is the description of the sample size. The authors start with an estimate of 28% PTB rate <34 weeks in twins with CL <38 mm. This sounds reasonable. They then say they hypothesize a 10% decrease with pessary, which would be a reduction to an absolute rate of 26% and would require a sample size of 7000 in each group. I suspect what the authors meant to say is they wanted to observe a 36% decrease in (which would be an absolute rate difference of 10%) from 28% to 18%. That is a reasonable estimate of a clinically relevant reduction in risk. However, based on prior published data on efficacy of pessary it is questionable why the authors thought they might observe a 36% reduction a priori. Then, due to slow recruitment, they did something that you are not supposed to do after a study starts - they changed their hypothesis. Now they decided they could see a larger effect size of 50% from rate of 28.4% to 14.4% (although they describe it incorrectly as 14% difference). It does not seem reasonable based on available clinical evidence that a 50% reduction in risk would be possible with pessary compared to progesterone. But, in effort to minimize sample size, this is what the authors chose to do. I do applaud them for being transparent and sharing this information, but it was wrong nonetheless. However, it does not negate the findings of the study.
RESPONSE: Thank you for your comment. The 10% decrease in the initial sample size calculation and also the 14% decrease in the adjusted sample size calculation were all based on the absolute risk reduction.
The text has been updated in the Materials and Methods section to clarify this. It now reads "Our original alternative hypothesis was that the absolute risk difference in delivery rate at <34 weeks' gestation between the two groups was 10%, based on a clinically relevant reduction in risk. Therefore, a sample size of 520 women (power 80%, alpha-error 5%, loss to follow up rate 10%) was required." and "…we re-calculated the sample size to detect a 14% absolute risk difference in the primary outcome between the two treatment groups…". Please see line 185 - 192, line 195 – 196, page 8 - 9 of the revised manuscript.

5. 39% of the study population had a CL <38 mm. Again, this raises the question why this length was chosen as the entry criteria.
RESPONSE: Thank you for your comment. We refer to the response to your comment 3.

6. The observed rate of PTB <34 weeks in the progesterone group was 22%, which was lower than estimated at 28%. Starting from this observation, the study is underpowered for primary outcome unless a >50% reduction in risk is observed. If 50% reduction was observed, a sample size of 362 (181 in each group) would be needed.
RESPONSE: Thank you for your comment. Please see our response to reviewer 1, comment 2.
The text has been updated to clarify this in the Discussion section. It now reads "Our data showed that pessary did not significantly reduce PTB <34 weeks as compared to 400 mg progesterone in twin pregnant women with a CL <38 mm. However, the study was underpowered to detect a 50% relative risk reduction in the primary outcome.". Please see line 268 - 270, page 12 of the revised manuscript.

7. There were many statistical comparisons performed, which can influence risk of alpha error.
RESPONSE: Thank you for your comment. Although all the statistical comparisons were pre-planned (except for one post-hoc analysis in the composite of poor perinatal outcomes), it is true that the risk of alpha error could be influenced.
The text has been updated to clarify this in the Discussion section. It now reads "Lastly, the composite of poor perinatal outcomes was not pre-specified and there were many statistical comparisons performed, which increases the risk of alpha errors. Therefore, findings from these analyses should be confirmed in other studies.". Please see line 337 – 339, page 14 of the revised manuscript.

8. Surprisingly, there were large effect sizes observed for reduction in risk of important perinatal outcomes with pessary. These effects were larger in the higher risk groups, which further supports the premise these were true effects.
RESPONSE: Thank you for your comments. As stated above, all the statistical comparisons were pre-planned, except for one post-hoc analysis in the composite of poor perinatal outcomes. The reasons for the large effect sizes observed could be due to either the true effects or the small number of patients in the subgroup analysis. This remains to be elucidated in further studies. No adjustments were made to the revised manuscript.

9. Discussion: The first sentence should say that the study was underpowered to detect at 50% reduction in the primary outcome. Other outcomes with larger effect sizes were significantly reduced with pessary, which are noteworthy findings. However, the remarkable reduction in risk observed in this study compared to other studies with no improvement with pessary warrants further discussion.
RESPONSE: Thank you for your suggestion. The text has been updated in the Discussion section. It now reads "Our data showed that pessary did not significantly reduce PTB <34 weeks as compared to 400 mg progesterone in twin pregnant women with a CL <38 mm. However, the study was underpowered to detect a 50% relative risk reduction in the

primary outcome. Secondary outcomes with larger effect sizes were significantly reduced with pessary. However, other studies evaluating pessary have shown heterogeneous effects,[8,9,10,13] which could be due to differences in insertion of the pessary, strict control of correct placement of the pessary. The remarkable reduction in risk observed in our study warrants further discussion.". Please see line 268 - 274, page 12 of the revised manuscript.

Statistical editor:

1. Lines 78-80 and 175-179: Should explicitly state in abstract the expected proportion of PTB among the referent group, since the power/sample size calculation is defined by both the difference and the referent baseline proportion.

RESPONSE: Thank you for your suggestion. The text has been updated in the Abstract section to clarify this. It now reads "The PTB <34 weeks' gestation in twin pregnant women with a CL <38 mm and treated with 400 mg progesterone at My Duc Hospital was 28.4%.". Please see line 77 - 79, page 4 of the revised manuscript.

2. Given the expected referent proportion of 28%, why were the expected proportions of the treatment group set at either 14% or 10%? Seems like a high threshold.

RESPONSE: Thank you for your question. In the original sample size calculation, the 10% absolute risk difference was set based on a clinically relevant reduction in risk. However, due to the low speed of recruitment, the 14% absolute risk difference was used in the adjusted sample size calculation.

The text has been updated in Materials and Methods section. It now reads "Our original alternative hypothesis was that the absolute risk difference in delivery rate at <34 weeks' gestation between the two groups was 10%, based on a clinically relevant reduction in risk. Therefore, a sample size of 520 women (power 80%, alpha-error 5%, loss to follow up rate 10%) was required.". See line 185 - 192, page 8 - 9, of the revised manuscript.

3. Lines 142-144 and 147-149: The treatments were not initiated at the same times in gestation, since the pessaries were inserted "within one week of randomization", while the progesterone was applied "starting from the day of randomization". What were the precise delays in insertion of pessaries with respect to randomization and were the actual GA at initiation of treatments statistically different? Could this difference have modified the difference in PTB rates?

RESPONSE: Thank you for your question. We are aware that the delay in the pessary insertion within one week of randomization might result in the difference in the initiation of intervention between the two groups. However, pessary is considered as a more invasive intervention compared with vaginal progesterone. It is our experience that patients might need some times to discuss with their husbands.

In this trial, out of 150 participants allocated to pessary group, 57 women were inserted a pessary on the same day of randomization, 65 patients were inserted a pessary one day after and 28 women were inserted a pessary two days after randomization. No adjustments were made to the revised manuscript.

4. Table 2: Since there were two perinatal outcomes per delivery and there would be

correlation within each twin pair, the analyses for perinatal outcomes need to account for this correlation, with resultant decrease in the effective sample sizes. Many of the comparisons have low counts and their NS findings cannot be generalized.
RESPONSE: We used cluster analysis, taking into account the dependency between the twins for neonatal outcomes, as suggested by Gates and Brocklehurst (Gates and Brocklehurst, 2004). This has been stated in the Materials and Methods section, line 197 – 198 of the original manuscript.
We agree with the reviewer that many outcomes occurred less frequent which might affect the non-significant findings. No adjustments were made to the revised manuscript.

5. Table 3: Same issues with perinatal outcomes.
RESPONSE: Thank you for your comment. No adjustments were made to the revised manuscript.

6. In Table 2, the Authors have appropriately separated their primary from the secondary outcomes. They should also label the outcomes in Table 3 as all being secondary outcomes, lest the reader misinterpret the results.
RESPONSE: Thank you for your suggestion. Table 3 has been already updated to clarify this.

7. Fig 2A, 2B: Should cite the results of stats test for difference in survival methods analyses for the two figures, either in legends or on the graph itself.
RESPONSE: Thank you for your suggestion. The results of the statistical test have been mentioned in the legend of figure, Appendix 8 of the original Appendix.

Editorial office:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. 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:
1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.
RESPONSE: Thank you for your comment. We choose “OPT-IN”

2. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. This statement must appear at the end of your Materials and Methods section. 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). Examples of statements can be found online at http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf.
RESPONSE: The text has been updated, with the data sharing statement as required, in the Materials and Methods section. It now reads "Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices) and study protocol will be available, upon request from investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose to achieve aims in the approved proposal. Data will be available at the beginning 9 months and ending 36 months following article publication. Proposals should be directed to bsvinh.dq@myduchospital.vn. To gain access, data requestors will need to sign a data access agreement. Data are available for 5 years at https://www.project-redcap.org/.". Please see line 221 – 228, page 10 of the revised manuscript.

3. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.
If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.
RESPONSE: The transparency declaration statement from the lead author has been added in the cover letter. It now reads "The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained."

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.
RESPONSE: The complete name of the IRB has been already updated in the Materials and Methods section. It now reads "The trial was approved by the institutional ethics

committee of My Duc Hospital (IEC, 09/15/ĐĐ-BVMĐ)…". Please see line 119, page 6 of the revised manuscript.

5. All submissions that are considered for potential publication are run through CrossCheck for originality. The following lines of text match too closely to previously published works. Variance is needed in the following sections:
a. - Was this also presented at the 28th World Congress on Ultrasound in Obstetrics and Gynecology? If so, please disclose the name, date, and location of the meeting on the title page of your manuscript.
RESPONSE: Thank you for your comment. The text has been updated to clarify this. It now reads "**Presented at:** SMFM's 38th Annual Pregnancy Meeting, January 29 - February 3, 2018, Hilton Anatole, Dallas, Texas (Late Breaking Session, Abstract number LB3); RCOG World Congress 2018, 21-24 March, 2018, Suntec Singapore Convention and Exhibition Centre, Singapore (2nd Best oral presentation, Abstract ID 6315); The 28th World Congress on Ultrasound in Obstetrics and Gynecology, 20 – 24 October, Sands Expo and Convention Centre, (Award Lectures and Top abstracts, Abstract number 2995217)". Please see line 31 - 33, page 2 of the revised manuscript.

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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at http://links.lww.com/AOG/A515, and the gynecology data definitions are available at http://links.lww.com/AOG/A935.
RESPONSE: Thank you for your remark. No adjustments were made in the revised manuscript.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).
Please limit your Introduction to 250 words and your Discussion to 750 words.
RESPONSE: The revised manuscript was in 22 page long, with 5118 words in total.

8. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).
RESPONSE: No adjustments were made in the revised manuscript.

9. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.
RESPONSE: A short title with 42 characters has been added in line 22, page 1. It now reads “Pessary vs. progesterone in twin pregnancy”.

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 limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.
RESPONSE: No adjustments were made in the revised manuscript.

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.
RESPONSE: No adjustments were made in the revised manuscript.

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.
RESPONSE: No adjustments were made in the revised manuscript.

13. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.
RESPONSE: No adjustments were made in the revised manuscript.

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.
RESPONSE: Thank you for your suggestion. No adjustments were made in the revised manuscript.

***

If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

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 Dec 06, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Daniel Mosier

From: BS Vinh [redacted]
Sent: Friday, December 14, 2018 6:04 PM
To: Daniel Mosier
Subject: Re: Manuscript Revisions: ONG-18-1970R1
Attachments: 18-1970R1 ms (12-12-18v2) Vinh14Dec18.docx

Dear Ms/Mr Mosier,

Thank you for your email and your revision of our manuscript.

We hereby attach the revised manuscript that addressed all the remaining issues as you pointed out.

For the Comment 6 (regarding the Appendixes), we would like to have the Appendix 1-8 published. The protocols (Appendixes 9, 10) will be available upon request as already stated in "Author's data sharing statement"

We also updated the reference list, since the reference number 11 and 14 have been removed in the Introduction.

There is only one issue remained in Table 2. The congenital anomalies occurred in 1 (0.3%) in Arabin group. How do we round up the figure, to 1%?

Thank you again for your valuable support and please feel free to contact us for further information.

Vinh

> On Dec 12, 2018, at 9:00 PM, Daniel Mosier <dmosier@greenjournal.org> wrote:
>
> Dear Dr. Dang,
>
> Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:
>
> 1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
> 2. LINE 5: Please see the email from Denise Shields dated 12/7/18 regarding providing your co-author email addresses. We will need to receive this information so your co-authors can confirm their authorship.
> 3. LINE 28: What year?
> 4. LINE 79: Table 3 says 45.7%. Which is correct?
> 5. LINE 208: For articles submitted to O&G after July 1, 2018, we require a data sharing statement indicating what we've listed here. Your answers may be different from what I've listed here. If so, please edit the responses accordingly.
> 6. LINE 247: Appendixes 9–16 were removed from your appendixes file, since they aren't cited in the text. How many of your appendixes did you want us to consider for publication? Have Appendixes 9 and 10 been published before?
> 7. TABLES 2 AND 3: Please add Cesarean Delivery as a row in both tables.
> 8. TABLE 2:

    a. Of vagina?
    b. Of what?
    c. What kind of pain
9. TABLE 3:
    a. Please give percentages as whole numbers only
    b. Please provide weight thresholds for this and the next row as done in Table 2

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Friday, December 14th.**

Sincerely,

-Daniel Mosier

Daniel Mosier
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Web: http://www.greenjournal.org

<18-1970R1 ms (12-12-18v2).docx>

From: [redacted]
To: Stephanie Casway
Subject: Re: O&G Figure Revision: 18-1970
Date: Thursday, December 13, 2018 8:19:11 PM

Dear Ms Casway,

Thank you for your email.

In Fig. 1, the block “Excluded: Lost to follow-up” should be “Excluded: Loss to follow-up”. Others are fine.

Thank you again and regards,

Vinh

> On Dec 12, 2018, at 10:23 PM, Stephanie Casway <SCasway@greenjournal.org> wrote:
>
> Good Morning Dr. Dang,
>
> Your figures and legend have been edited, and PDFs of the figures and legend are attached for your review. Please review the figures CAREFULLY for any mistakes.
>
> PLEASE NOTE: Any changes to the figures must be made now. Changes at later stages are expensive and time-consuming and may result in the delay of your article’s publication.
>
> To avoid a delay, I would be grateful to receive a reply no later than Friday, 12/14. Thank you for your help.
>
> Best wishes,
>
> Stephanie Casway, MA
> Production Editor
> *Obstetrics & Gynecology*
> American College of Obstetricians and Gynecologists
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>
> <18-1970 Legend.pdf><18-1970 Fig 1 (12-11-18 v1).pdf><18-1970 Fig 2 (12-11-18 v1).pdf>