

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)*
- Email correspondence between the editorial office and the authors*

**The corresponding author has opted to make this information publicly available.*

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:

obgyn@greenjournal.org.

Date: Sep 06, 2018
To: "Eva Pajkrt" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1508

RE: Manuscript Number ONG-18-1508

Amnioinfusion versus no intervention in women with midtrimester rupture of membranes: A multicenter open-label randomized controlled trial (PPROMEXIL-III)

Dear Dr. Pajkrt:

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 Sep 27, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

This is a randomized controlled trial comparing amnioinfusion to no intervention in women with PPRM between 16 and 24 weeks. It is important to evaluate these types of interventions in a rigorous fashion before they are widely adopted.

1. Methods: Why was the window for enrollment so wide (3 days to 21 days of PPRM)? It would seem that the population that has been stable for 3 weeks with PPRM is different than the population that is only 3 days into their clinical course.
2. Methods: Was exclusion criteria of the cervical length < 25 mm an ultrasound measurement? If so, please clarify in the text.
3. Methods: In terms of blinding, why not have a blinded sonographer first determine the deepest vertical pocket after randomization so that the decision to provide amnioinfusion in the treatment arm was more protected from bias? The person performing the amnioinfusion could leave the room for the measurement.
4. Methods: Since women were enrolled at various points in their PPRM clinical course, surely some of them had already received latency antibiotics by the time they were enrolled, so was the course of erythromycin repeated in these participants? Was data regarding exposure to antibiotics collected?
5. Methods: The sample size chosen was small and could only detect a large difference in the two groups, was this chosen because of concerns for recruitment? Why not opt for a large sample size so a better estimate of the true difference between the groups could be obtained and more information on secondary outcomes? There doesn't seem to have been a plan for over-recruiting due to anticipated drop out or technical difficulties which did occur in the treatment arm.
6. Table 1: Why were vaginal cultures performed? Is this standard practice in the Netherlands?
7. Table 5: 4 participants requested induction termination before 24 weeks, essentially changing their mind about continuing the trial, shouldn't they be dropped from analysis as the delivery was per patient request, or at least the per protocol analysis?

REVIEWER #2:

1. This was a well-designed study to address a challenging problem that we encounter in MFM- primarily, are there interventions that might be helpful in cases of previable PPRM and is serial amnioinfusion one of them?
2. The abstract is clear and succinct.
3. The introduction summarizes the challenge of previable PPRM and why the authors sought to do this study well. The objective is clearly defined.
4. Methods state that amnioinfusions occurred in an outpatient setting (line 172) and then line 181 "women could be discharged from the hospital" which implies an inpatient setting. This needs to be reconciled.
5. It is difficult to understand why biometry was assessed weekly, although if this was the same for both groups then it should not impact results or interpretation of data.
6. Lines 217-219 do not align. "...described in all neonates that were still alive one week postpartum: chronic lung disease (CLD) defined as oxygen dependency at 28 days of life." One week of life would not necessarily predict oxygen dependency at 28 days of life. This should be corrected.
7. I very much appreciate the meta-analysis incorporating the AMIPROM results and the authors' comments regarding the way that this study was powered and how this may have influenced the results and conclusions. I also agree that a larger study is needed and, at minimum, these data are relevant for inclusion in a meta-analysis as it brings us closer to understanding whether this intervention might be beneficial or not. Agree with the conclusion that serial amnioinfusion should not be recommended at this point given the data that we have and that more information is needed.

REVIEWER #3:

This well designed and thoughtfully executed trial by van Kempen and colleagues demonstrates the lack of efficacy of amnioinfusion in women with previable premature rupture of membranes. The manuscript is well written, the analysis is appropriate and the conclusions are well stated. The study is also strengthened by inclusion of CRP data. The following comments are meant to strengthen the manuscript.

Major:

- 1* The greatest flaw in this paper is the small sample size which is dictated by an aggressive estimation of the effect size. This was no doubt in recognition of the challenges in performing this complex trial. Nonetheless, the authors readily acknowledge this issue in their discussion.
- 2* The other challenge in this trial that is less well explained is the median number of amniocenteses that were performed. This is a bit challenging as the median number of amnios is 2 and latency is over 6 weeks and the procedure is to be done weekly. This would infer that a significant number of women did not receive their allotted treatments. I am unable to locate a clear statement about the percentage of women who received all of their scheduled amnios or what percent of scheduled amnios were performed. Though the authors do share data on the "as treated population"; this greater clarity about protocol adherence is required.

Minor:

- 3* Line 76- "seem" is a bit of a weak conclusion. Would remove.
- 4* Line 85- include randomization ratio (1:1). Likewise the inclusion of the fact that the platform is password-protected is distracting and not necessary in the abstract.
- 5* Line 154-more clarity here would be helpful. Any visualized dilation? Likewise what percent of women had a cervical length > 25mm is not available in table 1.
- 6* Line 229- is "independent" mean blinded?
- 7* Line 277- Though this table provides additional data I would recommend treating it as a supplement. Those who are curious can then dig deeper for the data but it is distracting to the general readership.
- 8* Line 366- "We hypothesize....."- though acknowledged as a hypothesis, this statement is very speculative and I would encourage its removal.
- 9* Table 1: Other ethnic origin should be broadened.
- 10* Table 2: Because of the limited data may be better included as text and removed. Currently there are 6 tables.
- 11* Table 4 Time from PPRM to birth should express units (weeks)

STATISTICAL EDITOR'S COMMENTS:

1. Table 2, lines 201-202: The primary outcome (upon which the power analysis/sample sizes were estimated) was overall mortality, not the subsets. The Table should be modified to show the primary outcome alone, the others are of interest, but there was not sufficient power to have evaluated them and if more than one primary was intended, then the sample size and inference threshold would have to be re-calculated.
2. Table 4: One of these estimates (eg, GA and 32-37 wks) involves comparison with a zero entry and continuity assumption. It should be left blank as the counts are too small to precisely allow estimation. Could use Fisher's test. In any event, the counts are small, and there is insufficient power to generalize the NS findings.
3. Table 5, 6a, 6b: Same comment re: comparisons of "lethal anomaly" or "intrauterine fetal demise" and zero entries. Also, same comment re: low power of NS findings.
4. lines 338-340: Authors could consider including a statement as to the sample sizes required to detect a smaller difference, based on their estimate of what a clinically relevant difference might be.
5. Fig 2: Either legend or figure should include summary of stats test.

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. 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>.
4. 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.

5. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.
6. 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).

7. 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.

8. 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.

9. 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.

10. 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.

11. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Figure 2: Is this figure available at a higher resolution?"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Figures should be no smaller than the journal column size of 3 1/4 inches. Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce. Refer to the journal printer's web site (<http://cjs.cadmus.com/da/index.asp>) for more direction on digital art preparation.

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 Sep 27, 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

In response to the EU General Data Protection Regulation (GDPR), you have the right to request that your personal information be removed from the database. If you would like your personal information to be removed from the database, please contact the publication office.

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Nancy C. Chescheir, MD
Editor-in-Chief of *Obstetrics & Gynecology*

Amsterdam, September 26th 2018

Dear Dr. Nancy C. Chescheir,

Thank you very much for your comments on our manuscript number ONG-18-1508, entitled "Amnioinfusion versus no intervention in women with midtrimester rupture of membranes: A multicenter open-label randomized controlled trial (PPROMEXIL-III)" submitted to *Obstetrics & Gynecology*.

We are grateful that you allow us to address and repair these issues. We have adjusted the manuscript according to your comments. Below are our point-to-point responses to the comments. Moreover, we have adjusted the manuscript in order to adhere to the length restrictions (point 4 of the editorial office comments) and table format (point 10 of the editorial office comments), without altering the contents of the manuscript. These adjustments are indicated in the revised manuscript by the "track changes" feature. Of course, in case a more detailed point-to-point overview of these adjustments is required, we are more than willing to provide this.

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*.

On behalf of all authors,

Yours sincerely,

Eva Pajkrt, MD, PhD

A large black rectangular redaction box covering the signature and name of the author, Eva Pajkrt.

REVIEWER COMMENTS:

REVIEWER #1:

This is a randomized controlled trial comparing amnioinfusion to no intervention in women with PPROM between 16 and 24 weeks. It is important to evaluate these types of interventions in a rigorous fashion before they are widely adopted.

1. Methods: Why was the window for enrollment so wide (3 days to 21 days of PPROM)? It would seem that the population that has been stable for 3 weeks with PPROM is different than the population that is only 3 days into their clinical course.

Authors' response: Many thanks for your comment. We aimed to assess the effectiveness of amnioinfusion on reducing the perinatal mortality rate that is associated with PPROM between 16 and 24 weeks gestation. In our experience, in a clinical setting, women do not always notice that they have ruptured membranes right away. Hence, PPROM is often discovered quite some time later, for instance during (the midtrimester) ultrasound screening. Since PPROM is often retrospectively diagnosed with some delay, we kept our window for enrollment wide. Moreover, we have chosen this window for enrollment considering the limited incidence of midtrimester PPROM and keeping in mind the feasibility of the trial.

2. Methods: Was exclusion criteria of the cervical length < 25 mm an ultrasound measurement? If so, please clarify in the text.

Authors' response: The exclusion criterion of a cervical length <25 mm was indeed a (transvaginal) ultrasound measurement. We have rephrased page 7, line 149–150 of the revised manuscript (with changes accepted) to clarify this: "...cervical incompetence (cervical dilatation visualized during speculum examination or cervical length <25 mm on transvaginal ultrasound)".

3. Methods: In terms of blinding, why not have a blinded sonographer first determine the deepest vertical pocket after randomization so that the decision to provide amnioinfusion in the treatment arm was more protected from bias? The person performing the amnioinfusion could leave the room for the measurement.

Authors' response: Thank you for your suggestion. This is something that could be considered in future trials.

4. Methods: Since women were enrolled at various points in their PPROM clinical course, surely some of them had already received latency antibiotics by the time they were enrolled, so was the course of erythromycin repeated in these participants? Was data regarding exposure to antibiotics collected?

Authors' response: In case a course of antibiotics had already been administered, it was not repeated. Data regarding exposure to antibiotics were collected.

5. Methods: The sample size chosen was small and could only detect a large difference in the two groups, was this chosen because of concerns for recruitment? Why not opt for a large sample size so a better estimate of the true difference between the groups could be obtained and more information on secondary

outcomes? There doesn't seem to have been a plan for over-recruiting due to anticipated drop out or technical difficulties which did occur in the treatment arm.

Authors' response: The sample size calculation was based on the study of van der Heyden et al. (2013) that reported a perinatal mortality rate of 70% in pregnancies complicated by midtrimester PPROM and a 50% estimated reduction in perinatal mortality rate after amnioinfusion based on observational studies available at the time the PPROMEXIL-III study was designed. To show a reduction in perinatal mortality from 70% to 35%, we had to randomize 56 women (beta-error 0.20, 2-sided alpha-error 0.05). In hindsight, the 50% estimated reduction in perinatal mortality rate was too optimistic. We did not expect technical difficulties to occur that would make the amnioinfusion procedure impracticable. Hence, we did not anticipate for this while calculating the sample size. However, in our trial one woman indeed did not receive her scheduled amnioinfusion due to impracticability of the procedure.

6. Table 1: Why were vaginal cultures performed? Is this standard practice in the Netherlands?

Authors' response: Performance of vaginal cultures is indeed standard practice in The Netherlands to rule out Group B streptococcal (GBS) infection in case of PPROM. In case a woman is carrier of GBS she is treated prophylactically with antibiotics once labor starts.

7. Table 5: 4 participants requested induction termination before 24 weeks, essentially changing their mind about continuing the trial, shouldn't they be dropped from analysis as the delivery was per patient request, or at least the per protocol analysis?

Authors' response: Thank you for your very interesting comment. In line with your suggestion we have adjusted our as-treated analysis by additionally excluding the women that had requested termination of pregnancy before 24 weeks. Please see page 5, line 94–95 (Abstract) and page 12 line, 271–272 and page 14, line 305–307 (Results) of the revised manuscript (with changes accepted) for the new results: “relative risk 0.72, 95% confidence interval 0.45–1.15, *P* value 0.17”. In addition, we have adjusted figure 1 (flow chart, please see file “Figure 1 PPROMEXIL-III trial profile_revised.pptx”) to match these changes.

REVIEWER #2:

4. Methods state that amnioinfusions occurred in an outpatient setting (line 172) and then line 181 “women could be discharged from the hospital” which implies an inpatient setting. This needs to be reconciled.

Authors' response: Thank you for pointing out this inconsistency. We have corrected the manuscript accordingly: the sentence that read “Women could be discharged from the hospital if signs of premature labor or infection were absent.” (line 181–182 of the original submission) has been removed, since this was incorrect.

5. It is difficult to understand why biometry was assessed weekly, although if this was the same for both groups then it should not impact results or interpretation of data.

Authors' response: Indeed fetal biometry was assessed weekly in both groups, merely as a form of reassurance for the patients.

6. Lines 217-219 do not align. "...described in all neonates that were still alive one week postpartum: chronic lung disease (CLD) defined as oxygen dependency at 28 days of life." One week of life would not necessarily predict oxygen dependency at 28 days of life. This should be corrected.

Authors' response: Thank you, this has been corrected. It now reads "Additionally, chronic lung disease was assessed, defined as oxygen dependency at 28 days of life." and has been moved to the end of the paragraph. Please see page 10, line 216–217 of the revised manuscript (with changes accepted).

REVIEWER #3:

This well designed and thoughtfully executed trial by van Kempen and colleagues demonstrates the lack of efficacy of amnioinfusion in women with previable premature rupture of membranes. The manuscript is well written, the analysis is appropriate and the conclusions are well stated. The study is also strengthened by inclusion of CRP data. The following comments are meant to strengthen the manuscript.

Major:

1* The greatest flaw in this paper is the small sample size which is dictated by an aggressive estimation of the effect size. This was no doubt in recognition of the challenges in performing this complex trial. Nonetheless, the authors readily acknowledge this issue in their discussion.

Authors' response: Thank you very much for recognizing this. Please see our response to REVIEWER #1 point 5.

2* The other challenge in this trial that is less well explained is the median number of amniocenteses that were performed. This is a bit challenging as the median number of amnios is 2 and latency is over 6 weeks and the procedure is to be done weekly. This would infer that a significant number of women did not receive their allotted treatments. I am unable to locate a clear statement about the percentage of women who received all of their scheduled amnios or what percent of scheduled amnios were performed. Though the authors do share data on the "as treated population"; this greater clarity about protocol adherence is required.

Authors' response: Indeed not all women have received their allotted treatment weekly, since amnioinfusion was only performed if the single deepest pocket was <20 mm on transabdominal ultrasound, which was done prior to the procedure. In total 81 amnioinfusions were performed with a median number of two amnioinfusions per woman (range 0–8).

Minor:

3* Line 76- "seem" is a bit of a weak conclusion. Would remove.

Authors' response: Thank you for your suggestion. The word "seem" has been removed. Please see page 4, line 76 of the revised manuscript (with changes accepted).

4* Line 85- include randomization ratio (1:1). Likewise the inclusion of the fact that the platform is password-protected is distracting and not necessary in the abstract.

Authors' response: The 1:1 randomization ratio has been added and "password-protected" is removed from the abstract. Please see page 5, line 84 of the revised manuscript (with changes accepted).

5* Line 154-more clarity here would be helpful. Any visualized dilation? Likewise what percent of women had a cervical length >25mm is not available in table 1.

Authors' response: All women in this trial had a cervical length >25 mm, since a cervical length <25 mm was an exclusion criterion. Please see page 7, line 146–150 of the revised manuscript (with changes accepted): "We excluded women with... and cervical incompetence (cervical dilatation visualized during speculum examination or cervical length <25 mm on transvaginal ultrasound)."

6* Line 229- is "independent" mean blinded?

Authors' response: Thank you for your comment. "Independent" in this case means both blinded as well as that both neonatologists individually scored the neonatal endpoints.

7* Line 277- Though this table provides additional data I would recommend treating it as a supplement. Those who are curious can then dig deeper for the data but it is distracting to the general readership.

Authors' response: Thank you for your suggestion. This table has been moved to the supplementary section. Please see page 31, line 482 and 484, and Appendix 1 on page 32–34 of the revised manuscript (with changes accepted).

8* Line 366- "We hypothesize....."- though acknowledged as a hypothesis, this statement is very speculative and I would encourage its removal.

Authors' response: Thank you, this sentence has been removed.

9* Table 1: Other ethnic origin should be broadened.

Authors' response: Thank you very much for your suggestion. Other ethnicities were: Hindu, Middle-Eastern, North-African, African (sub-Sahara), Afro-Caribbean, and Asian. Because of the limitation of the length of the manuscript to 5,500 words, we would suggest not to include this information in the manuscript.

10* Table 2: Because of the limited data may be better included as text and removed. Currently there are 6 tables.

Authors' response: Thank you, these data have been included as text and the table has been removed accordingly. Please see page 12–13, line 276–281 of the revised manuscript (with changes accepted).

11* Table 4 Time from PPROM to birth should express units (weeks).

Authors' response: Thank you very much. We acknowledge that it is more common to express latency and gestation in units (weeks). Therefore we have now expressed these outcomes in weeks throughout the entire revised manuscript.

STATISTICAL EDITOR'S COMMENTS:

1. Table 2, lines 201-202: The primary outcome (upon which the power analysis/sample sizes were estimated) was overall mortality, not the subsets. The Table should be modified to show the primary outcome alone, the others are of interest, but there was not sufficient power to have evaluated them and if more than one primary was intended, then the sample size and inference threshold would have to be re-calculated.

Authors' response: Many thanks for your suggestion. Because of space limitations we have removed the entire table and have included the data as text. We acknowledge that the subsets should not be confused as being primary outcomes. However, since these subsets are of interest for clinicians we did include them in text. Please see page 12–13, line 276–281 of the revised manuscript (with changes accepted).

2. Table 4: One of these estimates (eg, GA and 32-37 wks) involves comparison with a zero entry and continuity assumption. It should be left blank as the counts are too small to precisely allow estimation. Could use Fisher's test. In any event, the counts are small, and there is insufficient power to generalize the NS findings.

Authors' response: Thank you, following your suggestion these columns have been left blank. Please see table 2 (page 24–25) of the revised manuscript (with changes accepted).

3. Table 5, 6a, 6b: Same comment re: comparisons of "lethal anomaly" or "intrauterine fetal demise" and zero entries. Also, same comment re: low power of NS findings.

Authors' response: Thank you, following your suggestion these columns have been left blank. Please see table 3 (page 26) and 4 (page 27–28) of the revised manuscript (with changes accepted).

4. lines 338-340: Authors could consider including a statement as to the sample sizes required to detect a smaller difference, based on their estimate of what a clinically relevant difference might be.

Authors' response: To show a reduction in perinatal mortality from 74% to 65% we would have to randomize 272 women to both groups (beta-error 0.20, 2-sided alpha-error 0.05). We would prefer not to include this estimation in the manuscript, but do keep it in mind for future research.

5. Fig 2: Either legend or figure should include summary of stats test.

Authors' response: Of course we are willing to include more information in Figure 2. However, we are sorry to inform you that we do not understand what you mean by a summary of stats test.

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.

Authors' response: OPT-IN: Yes, please 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.

Authors' response: Please find the data sharing statement of the PPROMEXIL-III study at the end of our Materials and Methods section (page 11–12, line 251–262).

3. 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>.

Authors' response: Thank you, the authors have familiarized themselves with the reVITALize definitions. For example, “primary or secondary caesarean section” (original manuscript) has been changed into “cesarean birth before or after onset of labor” (revised manuscript) accordingly. Please see page 9, line 193–194 of the revised manuscript (with changes accepted).

4. 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.

Authors' response: The manuscript now adheres to the length restrictions of an Original Research report (5.495 words in total, Introduction: 228 words, Discussion: 590 words). Please see the track changes in the revised manuscript to see what has been removed in order to shorten the manuscript.

5. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

Authors' response: We have made no adjustments to our title so far: "Amnioinfusion versus no intervention in women with midtrimester rupture of membranes" (84 characters including spaces), with subtitle: "A multicenter open-label randomized controlled trial (PPROMEXIL-III)" (68 characters including spaces). However, of course we are open to your suggestions.

6. 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.

Authors' response: Not applicable.

- * 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).

Authors' response: This information can be found on page 3, line 62–66.

7. 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. **Authors' response:** Thank you, this has been checked and the authors declare that the abstract is consistent with the rest of the manuscript.

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.

Authors' response: The abstract consists of 233 words. Please see page 5, line 78–98 of the revised manuscript (with changes accepted).

8. 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.

Authors' response: Thank you, the abbreviation checklist has been reviewed. We were not able to locate the following abbreviations in the checklists: “PPROM” (=preterm prelabor rupture of membranes), “PPHN” (=persistent pulmonary hypertension of the neonate) and “GCP” (=good clinical practice). However, these abbreviations are, in our opinion, widely accepted in the (obstetric) academic world. In order to adhere to the space limitations and assure readability of the manuscript we would suggest to keep these abbreviations as they currently appear in the manuscript, so first spelled out followed by the abbreviation within parentheses (for example: page 6, line 105). However, of course we are open to your suggestions. The abbreviation “CRF” (=case report form) has been removed (please see page 10, line 222–223 of the revised manuscript with changes accepted), since this abbreviation might be confused for “chronic renal failure”.

9. 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.

Authors' response: Thank you, the manuscript has been reviewed for the use of the virgule symbol and does not include this symbol in sentences with words, except for when we express data or a measurement, for example “uterine contractions (8 contractions/hour)” (page 7, line 147).

10. 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.

Authors' response: The journal's Table Checklist has been reviewed and the authors assure that the tables now conform to journal style. Please see the track changes in the revised manuscript.

11. The Journal's Production Editor had the following to say about the figures in your manuscript:

"Figure 2: Is this figure available at a higher resolution?"

Authors' response: Thank you, Figure 2 has been added in a higher resolution (please see file "Figure 2 PPROMEXIL-III Kaplan Meier time to delivery_revised.pdf").

Daniel Mosier

From: Liselotte van Kempen [REDACTED]
Sent: Wednesday, October 10, 2018 3:52 AM
To: Daniel Mosier
Cc: E. Pajkrt
Subject: Re: Manuscript Revisions: ONG-18-1508R1
Attachments: 18-1508R1 ms (10-9-18v4)_LvK.docx

Dear Daniel Mosier,

Many thanks for pointing out this inconsistency in the manuscript. It is indeed correct that we dichotomized the single deepest pocket to less than 20 mm and 20 mm or greater. We have checked and corrected this inconsistency throughout the manuscript (please see line 391 and line 489 of the attached manuscript: 18-1508R1 ms (10-9-18v4)_LvK.docx).

Sincerely,

Liselotte van Kempen

Op di 9 okt. 2018 om 22:16 schreef Daniel Mosier <dmosier@greenjournal.org>:

Dr. van Kempen,

Thank you very much for responding in a timely manner. The editor on your manuscript has reviewed your latest revision, and has a follow-up question:

1. LINE 277: You have missed my point. It seems like you dichotomized to less than 20 mm and 20 mm or greater but the symbol you use here does not reflect this dichotomy. Please standardize throughout manuscript.

When revising, please use the attached version of the manuscript. Leave the track changes on, and do not use the "Accept all Changes" function prior to re-submission.

Please let us know if you have any other questions or concerns.

Sincerely,

-Daniel Mosier

Daniel Mosier

Editorial Assistant

Obstetrics & Gynecology

Tel: 202-314-2342

From: Liselotte van Kempen [REDACTED]
Sent: Friday, October 5, 2018 2:50 PM
To: Daniel Mosier <dmosier@greenjournal.org>
Cc: E. Pajkrt [REDACTED]
Subject: Re: Manuscript Revisions: ONG-18-1508R1

Dear Daniel Mosier,

Thank you very much for your E-mail regarding our revised manuscript number ONG-18-1508R1.

Please see our point-to-point responses to the queries in green below. Also, please find attached the manuscript in which the adjustments corresponding to our responses have been incorporated.

Please let me know if you have any (remaining) questions.

On behalf of all authors,

Sincerely,

Liselotte van Kempen

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.
Authors' response: Thank you very much. We agree with these changes.

2. LINE 1: "Midtrimester" has been changed to "second trimester" throughout per journal style.

Authors' response: The authors agree with this adjustment.

3. LINE 5: Please correct the author byline so the names appear in this way: first name, middle initial, last name, degrees (no more than two degrees per author)

Authors' response: The author byline has been corrected. Please see line 5-11 of the attached manuscript (18-1508R1 ms (10-2-18v2)_LvK.docx).

4. LINE 7: Please ask Martina Porvath to respond to her authorship confirmation email. We emailed her at [REDACTED]. The email contains a link that needs to be clicked on. The sender of the email is EM@greenjournal.org.

Authors' response: Thank you. Martina Porath has been contacted and has assured us she has now confirmed her authorship.

5. LINE 90: Please be sure the trial registration date is in the body text (somewhere other than the abstract).

Authors' response: Thank you very much. Line 210-211 has been added to the Material and Methods section accordingly.

6. LINE 119: After reading the discussion, it seems like there is only one prior truly randomized trial? Please clarify

Authors' response: It is indeed correct that there is only one prior truly randomized trial. We have adjusted line 176 of the attached manuscript to clarify this. The sentence now reads: "...while the only randomized controlled trial to date found no difference in perinatal mortality and neonatal morbidity."

7. LINE 121: Please say why you did another study-were the the prior 5 small, biased, flawed?

Authors' response: The prior trials that showed a reduction in perinatal mortality after amnioinfusion were all observational trials and thus potentially biased. The only prior randomized controlled trial, which was small (56 participants) and published after the PPROMEXIL-III study had started, showed no difference in perinatal outcome between women managed with amnioinfusion compared to no intervention. Because the results from these previous studies are contradictive we decided to perform another randomized trial to either confirm or contradict these previous findings.

8. LINE 180: "Bi-weekly" is every two weeks. Do you mean "twice weekly"?

Authors' response: Indeed, by "Bi-weekly" we mean "twice weekly". We have changed the manuscript accordingly, please see line 272.

9. LINE 264: Please be sure the trial registratoin date is in the body text (somewhere other than the abstract).

Authors' response: Thank you very much. Line 210-211 has been added to the Material and Methods section accordingly.

10. LINE 268: You mean "became septic before amnioinfusion was performed"?

Authors' response: Yes, indeed we mean that this woman became septic before the first amnioinfusion. We have adjusted line 377-378 accordingly.

11. LINE 273: Really you mean "greater than or equal to" yes?

Authors' response: We mean that in 3/28 (11%) women of the no intervention group the

single deepest pocket spontaneously increased to greater than 20 mm and remained like this for greater than or equal to 48 hours.

12. **LINE 286:** What does "post hoc analysis" mean in this context?

Authors' response: Post hoc analysis in this context means that these parameters were not defined as secondary outcomes in the PPROMEXIL-III protocol and were selected after the protocol had been published.

13. **LINE 295:** Preceded or followed?

Authors' response: We mean preceded.

14. **TABLE 1:** Please report weeks to only one place beyond the decimal point

Authors' response: Thank you. This has been changed, please see the revised version of Table 1 in the attached manuscript.

15. **TABLE 2:** Please move this to supplemental digital content. Please rename it "Appendix 1" and renumber all subsequent tables and citations.

Authors' response: This table has been moved to supplemental digital content and has additionally been renamed and renumbered.

16. **TABLE 3:** Please remove this Table and represent by Kaplan-Meier curves

Authors' response: Thank you very much. Table 3 has been removed and represented by Kaplan-Meier curves.

17. **TABLE 6:** Please move this to supplemental digital content as well (rename it to Appendix 2").

Authors' response: This table has been moved to supplemental digital content and has additionally been renamed.

Op vr 5 okt. 2018 om 14:21 schreef Pajkrt, E. <e.pajkrt@amc.uva.nl>:

Verstuurd vanaf mijn iPhone

Begin doorgestuurd bericht:

Van: Daniel Mosier <dmosier@greenjournal.org>

Datum: 2 oktober 2018 om 21:37:38 CEST

Aan: [REDACTED]

Onderwerp: Manuscript Revisions: ONG-18-1508R1

Dear Dr. Pajkrt,

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 1: "Midtrimester" has been changed to "second trimester" throughout per journal style.
3. LINE 5: Please correct the author byline so the names appear in this way: first name, middle initial, last name, degrees (no more than two degrees per author)
4. LINE 7: Please ask Martina Porvath to respond to her authorship confirmation email. We emailed her at [REDACTED]. The email contains a link that needs to be clicked on. The sender of the email is EM@greenjournal.org.
5. LINE 90: Please be sure the trial registration date is in the body text (somewhere other than the abstract).
6. LINE 119: After reading the discussion, it seems like there is only one prior truly randomized trial? Please clarify
7. LINE 121: Please say why you did another study-were the the prior 5 small, biased, flawed?
8. LINE 180: "Bi-weekly" is every two weeks. Do you mean "twice weekly"?
9. LINE 264: Please be sure the trial registratoin date is in the body text (somewhere other than the abstract).
10. LINE 268: You mean "became septic before amnioinfusion was performed"?
11. LINE 273: Really you mean "greater than or equal to" yes?
12. LINE 286: What does "post hoc analysis" mean in this context?
13. LINE 295: Preceded or followed?
14. TABLE 1: Please report weeks to only one place beyond the decimal point
15. TABLE 2: Please move this to supplemental digital content. Please rename it "Appendix 1" and renumber all subsequent tables and citations.
16. TABLE 3: Please remove this Table and represent by Kaplan-Meier curves
17. TABLE 6: Please move this to supplemental digital content as well (rename it to Appendix 2").

Each of these points are marked in the attached manuscript. Please respond point-by-point to these queries in a return email, and make the requested changes to the manuscript. When revising, please leave the track changes on, and do not use the "Accept all Changes" function in Microsoft Word.

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 **Thursday, October 4th**.

Sincerely,

-Daniel Mosier

Daniel Mosier

Editorial Assistant

Obstetrics & Gynecology

The American College of Obstetricians and Gynecologists

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Web: <http://www.greenjournal.org>



From: [REDACTED]
To: [Stephanie Casway](#)
Subject: RE: O&G Figure Revision: 18-1508
Date: Wednesday, October 10, 2018 6:46:55 AM
Attachments: [image001.png](#)

Dear Stephanie,

We have checked the figures and found no mistakes.

Kind regards

Eva



Prof. dr. Eva Pajkrt | [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Van: Stephanie Casway <SCasway@greenjournal.org>

Verzonden: dinsdag 9 oktober 2018 16:35

Aan: Pajkrt, E. [REDACTED]

Onderwerp: O&G Figure Revision: 18-1508

Good Morning Dr. Pajkrt,

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 Thursday, 10/11. Thank you for your help.

Best wishes,

Stephanie Casway, MA
Production Editor

Obstetrics & Gynecology

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