Date: Sep 27, 2018
To: "Erika Franklin Werner" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1703

RE: Manuscript Number ONG-18-1703

Association between gestational diabetes mellitus and neonatal respiratory morbidity

Dear Dr. Werner:

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 Oct 18, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

Abstract:

1. Line 52 In addition to respiratory morbidity another big focus of maternal blood sugar control is neonatal glycemic control after delivery. This may not be the outcome of interest in this sub analysis but it is an important outcome of interest.

2. Line 70 What is meant by outcomes did not vary by treatment group? Was this steroid administration?

Introduction:

This is a good historic overview of the problem.

3. Line 82 The description of L/S ratios and delayed lung maturation is interesting. Given the composite primary respiratory outcome in this study there is always the potential for neonatal intervention bias on the basis of non blinded maternal status of GDM. Another important point to address is the dose response effect. In this study pregestational diabetes was excluded.

4. Within GDMA1 to GDMA2 there is a continuum in regards to glycemic impact on everything from anomalies to respiratory morbidity. If this can be discussed further, especially given the trends in changing management to oral hypoglycemics, it would be helpful. The modern study looking at this issue in reference 4 Impact of Maternal Diabetes Mellitus on Mortality and Morbidity of Preterm Infants. Pediatrics 2011; 128: 848-855, compared pre gestational to GDM patients. In this study there was a higher rate of steroids given to the pre gestational diabetics compared to GDMA still leaving the dose response question open to debate. The reported conflicting data from France showing there was an increased risks may need to be further justified. The reference of the larger study in 6 found the GDM [OR adjusted on mother's age and gestational age, 1.2(1.1-1.3)] (personal data not yet published). Was this subsequently published?

Methods:

5. Line 108-109 The lack of information on diagnostic criteria, treatment and control of GDM are a significant limitation to this study. This was addressed later in the discussion.

6. Line 113-116 The primary composite outcome is confusing as written. Still birth and neonatal death were not the drivers

of the respiratory composite. Why were these rare events in the near term included to begin with? Was the original study powered for these outcomes? These outcomes are also included in the secondary outcomes. It seems as though it needs to be one or the other. Also state as to whether the neonatal care givers were blinded to both steroid administration and GDM status. The subjective use of supplemental O2 in the composite may be prone to bias if this was not blinded.

7. The time period of recruitment is important to explicitly state related to the secondary outcome of hyperbilirubinemia. The Committee Opinion on Delay Cord Clamping Number 684, January 2017 went into effect not distinguishing term from preterm with noted increased risk of hyperbilirubinemia associated with delayed clamping in diabetics. This may confound the results.

8. Line 135-140 The a priori power calculation is confusing. It was done for the initial study but this is a secondary analysis of the data and the power appears to post hoc. The researchers did not have a choice to change the subjects or increase the power, it was predetermined.

Results:

9. Line 153 The phrase "were not more likely" is awkward as a double negative. Perhaps restating that the primary outcomes were NS different between GDM and controls.

10. Line 156 Was there any information on delayed cord clamping? This could be a confounder in the GDM group.

11. Line 161 Define treatment arm. I assume this is betamethasone. It gets confusing going between the original RCT and this 2nd analysis. Also although there was no difference between GDM and no GDM for primary and secondary outcomes was there an analysis for within group effects? Ie subanalysis of the original study for outcomes in just the diabetic population who received steroids and those that did not. I could not find this in the original article.

Discussion:

12. Line 168-170 Discuss the original results from the RCT here as well. The main driver for composite in the primary outcomes was CPAP and high flow nasal canula for > 2hrs. Also there was a higher rate of neonatal hypoglycemia in the original RCT. 24.0% vs. 15.0%; relative risk, 1.60; 95% CI, 1.37 to 1.87; P<0.001. Given the objective of this study looking at concerns for glycemic control and neonatal RDS this is important to address and would be readily available data.

13. Line 184-189 The conclusion regarding treating GDM the same as non diabetics patients in the late preterm management should be expanded. Specifically discuss the drivers of the composite outcome, number needed to treat and r/b in regards to hyperbilirubinemia and hypoglycemia.

REVIEWER #2:

General Comment-
Thank you sincerely for your dedication to the advancement of our field and the wellbeing of patients. This was a secondary analysis of a placebo-controlled RCT of women at risk for late preterm delivery. Congratulations on your successful study.

Specific Comments (by section and line number)-

1. Abstract- Well organized, in STROBE format, concise

2. Abstract Results- Please specify that the demographic differences were what was controlled for in the adjusted RR if the character count permits.

3. Introduction- Well written and concise.

4. Methods- Clear explanation of study methodology with a few notes:

5. Methods line 111- How did this study handle patients who were suspected to have pregestational diabetes without prior testing or late to prenatal care?

6. Methods line 129- Were continuous variables tested for normalcy before analyses?

7. Methods line 140- Was the power analysis completed for univariable or multivariable analysis? If this power analysis is for univariable, please change to multivariable. Overall, this magnitude of effect size is clinically relevant if accurate.

8. Results- Well organized and straightforward.

9. Discussion- Interesting discussion. The major limitation of this study was clearly explained. Due to the fact that this study was not designed to study diabetes, there is no way to compare whether or not the patients with GDM are on

medications, type of medications, or dosages of medications. This dose/response relationship is a critical criteria to demonstrate causation. Although this was a negative study, the exposure group is heterogeneous and may mask a relationship.

10. Discussion Line 177-180- Please provide a reference here or state that this has been observed by the authors.

11. Tables and Figures- Clear and easily interpretable.

REVIEWER #3:

This is a secondary analysis of a randomized placebo-controlled trial which seeks to assess neonatal respiratory morbidly in pregnancies with and without gestational diabetes mellitus at imminent risk of late preterm delivery. The study concludes that among pregnancies at high risk for late preterm birth, maternal GDM is not associated with increased neonatal respiratory morbidity.

1. Line 92. Excellent clinical question given the discordance of suspected neonatal morbidity reported in the literature.

2. Line 107. Pregestational diabetes was excluded from the original ALPS study. Can you please comment on the subset of patients in the current secondary analysis cohort who screened positive for gestational diabetes mellitus early (<20 weeks) in pregnancy by risk factors, whom potentially have suspected pregestational diabetes?

STATISTICAL EDITOR'S COMMENTS:

1. lines 129-130: I assume the overall threshold for inference was also p < .05. In Table 1, I believe the p-value for smoking is actually slightly > .05, should clarify how it relates to threshold.

2. lines 147-149, Table 1: The study groups differed in indication for trial entry overall, but also in proportion with preterm labor and proportion with gestational hypertension or preeclampsia. Why were those factors not included in the adjustment model of Table 2?

3. lines 158-159: The difference in rates appears to be < .05. Should include n(%) for the comparison and cite whether the difference crosses the .05 threshold. What were the results if the primary outcome was evaluated separately for CD vs non CD patients?

4. Since about 50% of each cohort received betamethasone, what were the analysis results the cohorts with/without betamethasone were evaluated?

5. lines 160-162: Was there sufficient statistical power to test for interaction for all comparisons?

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. Each author on this manuscript must submit a completed copy of our revised author agreement form (updated in the January 2018 issue). Please note:

a) Any material included in your submission that is not original or that you are not able to transfer copyright for must be listed under I.B on the first page of the author agreement form.

b) All authors must disclose any financial involvement that could represent potential conflicts of interest in an attachment

to the author agreement form.

c) All authors must indicate their contributions to the submission by checking the applicable boxes on the author agreement form.

d) The role of authorship in Obstetrics & Gynecology is reserved for those individuals who meet the criteria recommended by the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org):

* Substantial contributions to the conception or design of the work;
OR
the acquisition, analysis, or interpretation of data for the work;
AND
* Drafting the work or revising it critically for important intellectual content;
AND
* Final approval of the version to be published;
AND
* Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The author agreement form is available online at http://edmgr.ovid.com/ong/accounts/agreementform.pdf. Signed forms should be scanned and uploaded into Editorial Manager with your other manuscript files. Any forms collected after your revision is submitted may be e-mailed to obgyn@greenjournal.org.

4. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), and quality improvement in health care (ie, SQUIRE 2.0). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, or SQUIRE 2.0 guidelines, as appropriate.

5. 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.

6. 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.

7. 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).

8. 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.

9. 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.

10. 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.

11. 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.

***

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 Oct 18, 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

October 11, 2018

Dear Editorial Staff,

Thank you for reviewing our manuscript entitled "Association between gestational diabetes mellitus and neonatal respiratory morbidity". We appreciated your reviewers' feedback and have made the changes suggested. The comments that required edits are listed below. We removed the positive feedback comments that did not require edits for brevity.

Thank you again for considering our manuscript. We look forward to your hearing from you in the near future.

Sincerely,

Erika Werner, M.D., M.S.
[redacted]

REVIEWER #1:

Abstract:

1. Line 52 In addition to respiratory morbidity another big focus of maternal blood sugar control is neonatal glycemic control after delivery. This may not be the outcome of interest in this sub analysis but it is an important outcome of interest.

Change made. Appreciate suggestion.

2. Line 70 What is meant by outcomes did not vary by treatment group? Was this steroid administration?

We removed this sentence from the abstract and more completely explained it in the results.

Introduction:

3. Line 82 The description of L/S ratios and delayed lung maturation is interesting. Given the composite primary respiratory outcome in this study there is always the potential for neonatal intervention bias on the basis of non blinded maternal status of GDM. Another important point to address is the dose response effect. In this study pregestational diabetes was excluded.

Thank you. Clarification that pregestational diabetes was excluded was added to the discussion as a limitation.

4. Within GDMA1 to GDMA2 there is a continuum in regards to glycemic impact on everything from anomalies to respiratory morbidity. If this can be discussed further, especially given the trends in changing management to oral hypoglycemics, it would be helpful. The modern study looking at this issue in reference 4 Impact of Maternal Diabetes Mellitus on Mortality and Morbidity of Preterm Infants. Pediatrics 2011; 128: 848-855, compared pre gestational to GDM patients. In this study there was a higher rate of steroids given to the pre gestational diabetics compared to GDMA still leaving the dose response question open to debate. The reported conflicting data from France showing there was an increased risks may need to be further justified. The reference of the larger study in 6 found the GDM [OR adjusted on mother's age and gestational age, 1.2(1.1-1.3)] (personal data not yet published). Was this subsequently published?

We have no found any subsequent publication related to reference 6. We have added a brief discussion of the continuous effects of dysglycemia (GDMA1 to GDMA2) to the discussion.

Methods:

5. Line 108-109 The lack of information on diagnostic criteria, treatment and control of GDM are a significant limitation to this study. This was addressed later in the discussion.

Thank you. It is absolutely a limitation of this study and we added some to the discussion.

6. Line 113-116 The primary composite outcome is confusing as written. Still birth and neonatal death were not the drivers of the respiratory composite. Why were these rare events in the near term included to begin with? Was the original study powered for these outcomes? These outcomes are also included in the secondary outcomes. It seems as though it needs to be one or the other. Also state as to whether the neonatal care givers were blinded to both steroid administration and GDM status. The subjective use of supplemental O2 in the composite may be prone to bias if this was not blinded.

The primary outcome is based on the original study and it was powered for this outcome. With regard to blinding, this was a great suggestion to include. We have added text that the care givers were not blinded to GDM. We have also added this as a limitation.

7. The time period of recruitment is important to explicitly state related to the secondary outcome of hyperbilirubinemia. The Committee Opinion on Delay Cord Clamping Number 684, January 2017 went into effect not distinguishing term from preterm with noted increased risk of hyperbilirubinemia associated with delayed clamping in diabetics. This may confound the results.

Excellent suggestion. Thank you. Recruitment occurred prior to this change. We have added enrollment dates to the first line of the results.

8. Line 135-140 The a priori power calculation is confusing. It was done for the initial study but this is a secondary analysis of the data and the power appears to post hoc. The researchers did not have a choice to change the subjects or increase the power, it was predetermined.

We apologize for the confusion. The power calculation was a priori to the secondary analysis. We changed the wording to read "A power calculation, after the primary study, but prior to performing this secondary analysis, was performed"

Results:
9. Line 153 The phrase "were not more likely" is awkward as a double negative. Perhaps restating that the primary outcomes were NS different between GDM and controls.
Thank you. Wording was changed.

10. Line 156 Was there any information on delayed cord clamping? This could be a confounder in the GDM group.
This study was performed prior to delayed cord clamping trial. We added the dates to clarify this point.

11. Line 161 Define treatment arm. I assume this is betamethasone. It gets confusing going between the original RCT and this 2nd analysis. Also although there was no difference between GDM and no GDM for primary and secondary outcomes was there an analysis for within group effects? Ie subanalysis of the original study for outcomes in just the diabetic population who received steroids and those that did not. I could not find this in the original article.
We clarified that treatment arm was betamethasone or placebo. There was no difference even in the sub-analysis.

Discussion:
12. Line 168-170 Discuss the original results from the RCT here as well. The main driver for composite in the primary outcomes was CPAP and high flow nasal canula for > 2hrs. Also there was a higher rate of neonatal hypoglycemia in the original RCT. 24.0% vs. 15.0%; relative risk, 1.60; 95% CI, 1.37 to 1.87; P<0.001. Given the objective of this study looking at concerns for glycemic control and neonatal RDS this is important to address and would be readily available data.
We very much appreciate this point and added a summary of the ALPS finding to the beginning of the discussion. The neonatal hypoglycemia data is being re-evaluated by the MFMU and will be presented shortly we hope.

13. Line 184-189 The conclusion regarding treating GDM the same as non diabetics patients in the late preterm management should be expanded. Specifically discuss the drivers of the composite outcome, number needed to treat and r/b in regards to hyperbilirubinemia and hypoglycemia.
Thank you. We described the original NNT, but again could not comment on the hypoglycemia issue as that is being re-evaluated.

REVIEWER #2:

2. Abstract Results- Please specify that the demographic differences were what was controlled for in the adjusted RR if the character count permits.
Changes made. Thank you!

5. Methods line 111- How did this study handle patients who were suspected to have pregestational diabetes without prior testing or late to prenatal care?

It was based on clinician definition in the medical record at the time of admission. We added lack of detail about timing of GDM diagnosis to the discussion.

6. Methods line 129- Were continuous variables tested for normalcy before analyses?
Age was the only continuous variable and it was normally distributed.

7. Methods line 140- Was the power analysis completed for univariable or multivariable analysis? If this power analysis is for univariable, please change to multivariable. Overall, this magnitude of effect size is clinically relevant if accurate.
Thank you for this suggestion. We clarified the approach by changing the wording surrounding the power analysis.

9. Discussion- Interesting discussion. The major limitation of this study was clearly explained. Due to the fact that this study was not designed to study diabetes, there is no way to compare whether or not the patients with GDM are on medications, type of medications, or dosages of medications. This dose/response relationship is a critical criteria to demonstrate causation. Although this was a negative study, the exposure group is heterogeneous and may mask a relationship.
Thank you. We expanded the discussion moderately to further highlight this.

REVIEWER #3:

2. Line 107. Pregestational diabetes was excluded from the original ALPS study. Can you please comment on the subset of patients in the current secondary analysis cohort who screened positive for gestational diabetes mellitus early (<20 weeks) in pregnancy by risk factors, whom potentially have suspected pregestational diabetes?
This data is not available. We have added this as a limitation.

STATISTICAL EDITOR'S COMMENTS:

1. lines 129-130: I assume the overall threshold for inference was also $p < .05$. In Table 1, I believe the p-value for smoking is actually slightly > .05, should clarify how it relates to threshold.
The overall threshold for inference was indeed p (0.05. The p-value for smoking was 0.0501 and thus not significant.

2. lines 147-149, Table 1: The study groups differed in indication for trial entry overall, but also in proportion with preterm labor and proportion with gestational hypertension or preeclampsia. Why were those factors not included in the adjustment model of Table 2?

We did include control for <u>pre-randomization</u> hypertensive disorders. We have made this more clear in the results. Indication for trial entry, and specifically, preterm labor and gestational hypertension as indications for trial entry, would temporally follow GDM, and

thus would be possible mediators rather than confounders (i.e., these are possible consequences of GDM status rather than causes of GDM status).

However, as a precaution, we ran two new sets of models – 1) with adjustment for indication at entry, and 2) adjusted by indicators for those two specific indications to the model for comparison. We have included a summary statement about these results but would prefer not to include these tables as we feel they are mediators.

Table : Neonatal complications	**Adjusted relative risk[a] (95% CI)**	**Adjusted relative risk[b] (95% CI)**	**Adjusted relative risk[c] (95% CI)**
Respiratory support in first 72 hours	0.84 (0.61-1.17)	0.81 (0.59, 1.13)	0.83 (0.60, 1.14)
Severe respiratory complications	0.91 (0.63-1.31)	0.88 (0.61, 1.27)	0.89 (0.61, 1.29)
Neonatal intensive care unit admission of ≥3 days	1.03 (0.88-1.21)	1.02 (0.88, 1.20)	1.02 (0.88, 1.19)
Hyperbilirubinemia (>15mg/dl)	1.39 (1.03-1.88)	1.35 (1.002, 1.82)	1.37 (1.01, 1.84)

Data are n (%) unless otherwise specified.
[a] Adjusted for age, parity, and hypertension (pre-randomization)
[b] Adjusted for age, parity, hypertension (pre-randomization), and indication for trial entry
[c] Adjusted for age, parity, hypertension (pre-randomization), indication for trial entry of preterm labor, and indication for trial entry of preeclampsia/gestational hypertension

3. lines 158-159: The difference in rates appears to be < .05. Should include n(%) for the comparison and cite whether the difference crosses the .05 threshold. What were the results if the primary outcome was evaluated separately for CD vs non CD patients?

Among women without GDM, 771 (30.5%) delivered by c-section. Among women with GDM, 114 (37.3%) delivered by c-section. The p-value was recalculated and I had made an error. We initially calculated it to be 0.046 but on recalculation is was 0.019. We changed this is the text. We did not observe evidence of a difference in the association between GDM and the primary outcome according to delivery type (p=0.11).

4. Since about 50% of each cohort received betamethasone, what were the analysis results the cohorts with/without betamethasone were evaluated?
Among those that did not receive betamethasone RR=0.83; 95% CI: 0.54, 1.28. Among those that did receive betamethasone RR=0.84; 95% CI: 0.51, 1.38. The p-value for interaction was 0.97.

5. lines 160-162: Was there sufficient statistical power to test for interaction for all comparisons?
We had power for the primary analysis but likely did not have power to identify some modifiers. We added a sentence to the limitations to reflect this, "we may not have been powered to detect differences in all confounders (e.g. racial/ethnic differences)."

Daniel Mosier

From: Werner, Erika [redacted]
Sent: Tuesday, October 30, 2018 7:43 PM
To: Daniel Mosier
Subject: Re: Manuscript Revisions: ONG-18-1703R1
Attachments: Author_Agreement_Peaceman.pdf

Last one. Thanks for being patient.

Erika

Erika F. Werner, MD, MS
Division Director and Fellowship Director
Maternal Fetal Medicine, Women & Infants Hospital
Associate Professor, Obstetrics and Gynecology
Alpert Medical School of Brown University
Associate Professor, Epidemiology
Brown University School of Public Health
[redacted]

On Tue, Oct 30, 2018 at 6:07 PM Werner, Erika [redacted] wrote:

> I am attaching an updated version from Drs. Jain and Norton and a new author's agreement from Dr. Tita. I am just waiting on Dr. Peaceman. I will send it to you as soon as I receive it (hopefully tomorrow).
>
> Thanks!
>
> Erika

Erika F. Werner, MD, MS
Division Director and Fellowship Director
Maternal Fetal Medicine, Women & Infants Hospital
Associate Professor, Obstetrics and Gynecology
Alpert Medical School of Brown University
Associate Professor, Epidemiology
Brown University School of Public Health
[redacted]

> On Mon, Oct 29, 2018 at 9:08 AM Daniel Mosier <dmosier@greenjournal.org> wrote:

Daniel Mosier

From: Erika Werner [redacted]
Sent: Monday, October 29, 2018 1:59 PM
To: Daniel Mosier
Subject: Re: Manuscript Revisions: ONG-18-1703R1
Attachments: Author_Agreement_Norton.pdf; Author_Agreement_Sorokin.pdf; Author_Agreement_Iams.pdf; Author Agreement Caritis.pdf; Author Agreement Form_Jain_10.29.18.pdf; STROBE_checklist.docx; 18-1703R1 ms (10-26-18v2)_EW.docx

Thank you for your help with this manuscript. I would like to opt in to the revisions being available for review. With regard to the other questions:

1+4: I agree with all the edits made and changed the sentence requiring reworking. The updated version is attached.
2. I have attached all missing authorship agreements with the exception of Tita and Peaceman. I will get those to you by tomorrow.
3. I have attached the Strobe checklist.

Thank you so much!
Erika

Erika F. Werner, MD, MS
Division Director and Fellowship Director
Maternal Fetal Medicine, Women & Infants Hospital
Associate Professor, Obstetrics and Gynecology
Alpert Medical School of Brown University
Associate Professor, Epidemiology
Brown University School of Public Health

[redacted]

On Mon, Oct 29, 2018 at 9:08 AM Daniel Mosier <dmosier@greenjournal.org> wrote:

> Dr. Werner,
>
> Apologies for the multiple emails, but the Journal's Manuscript Editor has an additional query for you and your co-authors:
>
> "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

Dr. Werner,

Apologies for the multiple emails, but the Journal's Manuscript Editor has an additional query for you and your co-authors:

"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:

- OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
- OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries."

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: Daniel Mosier
Sent: Friday, October 26, 2018 11:07 AM
To: [redacted]
Subject: Manuscript Revisions: ONG-18-1703R1

Dear. Dr. Werner,

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 2: Please provide completed author agreement forms for the following authors using the latest version of our author agreement form, which can be found at http://edmgr.ovid.com/ong/accounts/agreementform.pdf. Note that both the "Authorship" and "Disclosure of Potential Conflicts of Interest" sections need to be completed, along with providing a signature. Please read the form carefully.

- Alan T.N. Tita
- Lucky Jain
- Jay D. Iams
- Alan M. Peaceman
- Mary E. Norton
- Steve N. Caritis
- Yoram Sorokin

3. LINE 31: Please provide a completed STROBE checklist. The checklist is available at http://ong.editorialmanager.com.

4. LINE 90: Please revise this sentence so that it does not include the word 'studies' and 'GDM' 3 times each.

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 **Tuesday, October 30th.**

Sincerely,

-Daniel Mosier

Daniel Mosier

Editorial Assistant

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