Date: Nov 30, 2018
To: "Ahizechukwu Chigoziem Eke" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-2011

RE: Manuscript Number ONG-18-2011

17-alpha-hydroxyprogesterone caproate and the risk of glucose intolerance in pregnancy: a systematic review and meta-analysis.

Dear Dr. Eke:

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 21, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

This is an interesting manuscript with a purpose to "comprehensively synthesize the literature on the risk of glucose intolerance in women with singleton pregnancies treated with 17-OHPC compared to controls." This was a systematic review and meta-analysis.

1. What specific definitions of glucose intolerance and gestational diabetes mellitus were used to assess eligibility of the studies by the two reviewers who read the full-text of each manuscript? Were all studies required to use the same definition of Gestational diabetes and glucose intolerance? Please list the specific criteria to diagnose glucose intolerance and gestational Diabetes which were acceptable for inclusion in this study. Was the mean plasma glucose determined by the same method in all the studies included in this meta-analysis?

2. Could the authors supply a funnel plot? Was there any evidence of publication bias?

3. Line 254 "intrauterine fetal demise before 28 weeks leading preterm birth." Please re-write this sentence.

4. Line 255-256: "recurrent preterm delivery before 28 weeks in the current pregnancy," Please clarify.

5. Could the authors please discuss any advantages or limitations to including randomized and non-randomized studies in the meta-analysis? Why did they include a secondary analysis of two randomized controlled trials?

REVIEWER #2:

I enjoyed reading your interesting manuscript. I have a few comments that I hope may assist in strengthening it.

1. LN 115: I found this sentence a bit confusing, and had to reread it several times. I would suggest substituting "related to" for "of" as I believe it would make the sentence easier to understand.

2. Lns 289 - 294: You refer to "risk of abnormal glucose tolerance not diagnostic of gestational diabetes". This is not a commonly used term. Initially, I thought you might be referring to abnormal 50 g GCT results followed by normal 100 g GTT results. However, after reading your reference, I believe that you mean the difference in the prevalence of GDM diagnosed utilizing the Carpenter Coustan criteria for interpreting the 3 hr. 100 gm GTT in comparison to that diagnosed by

the stricter National Diabetes Data Group criteria. However, this is not entirely clear, and I believe that this outcome needs to be more carefully defined

3. Table 2: It appears that all of the prior authors included in your analysis utilized a 2 - step, 50 g GCT, 100 g GTT testing scheme. I might be useful for the reader to also know which of several possible criteria were used to interpret the tests.

4. Finally, none of studies included in your analysis utilized ISPDGS criteria for the diagnosis of GDM. While the use of this technique is controversial, it is currently recommended by the WHO and ADA and has been adopted by several centers in the USA. It might be helpful to point out to the reader that there is no information regarding the effect of 17 - OHPC use on the diagnosis of GDM utilizing the ISPDGS methodology.

REVIEWER #3:

In this paper, Ele et al performed a meta-analysis on the reported association between progesterone treatment and the risk of gestational diabetes or glucose intolerance in pregnancy. They found there was a significantly higher incidence of GDM in exposed women versus unexposed controls.

I think this topic is of interest to readers of this journal given the frequent use of progesterone and the importance of understanding the risks and benefits of its use.

I found the paper to be well-written with sound methods and a reasonable conclusion based on their findings.

STATISTICAL EDITOR'S COMMENTS:

1. lines 58-62: Should cite some measure of absolute risks, both in Abstract and in text, to put the risk in context.

2. Table 1: Unclear what is meant by the row entries for "Ethnicity" with values expressed as N±SD.

3. lines 298-300, 307-309 and fig 4: There is no "trend", the difference was NS. Were these fasting or random glucose concentrations?

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. 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. Variance needs to be added to the entire sources and study selections sections. These are taken nearly verbatim from the author's 2018 meta-analysis in Acta. Lines 264-284 are also taken nearly verbatim from this paper. This should be rewritten. Same issue with lines 357-362. This is excessive self-plagiarism.

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: Review articles should not exceed 25 typed, double-spaced pages (6,250 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. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

8. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

9. 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: Reviews, 300 words. Please provide a word count.

10. 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.

11. 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.

12. Our readers are clinicians and a detailed review of the literature is not necessary. Please shorten the Discussion and focus on how your results affect or change actual patient care. Do not repeat the Results in the Discussion section.

13. 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.

14. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly. If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at http://www.acog.org/Resources-And-Publications.

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

"Figure 2: Please upload as high res image files (EPS, TIFF, JPEG). Text inside each figure should be crisp when zoomed in."

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.

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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 21, 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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In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.

COVER LETTER

Nancy C. Chescheir, *MD FACOG,*
Editor in Chief,
Obstetrics & Gynecology,
409 12th Street, SW,
Washington, DC 20024-2188.

December 5th, 2018.

CONTRIBUTIONS OF AUTHORS AND CONFLICTS OF INTERESTS.

It is our pleasure to re-submit this systematic review and meta-analysis titled ***'17-hydroxyprogesterone caproate and the risk of glucose intolerance in pregnancy: A systematic review & meta-analysis'*** for publication in Obstetrics & Gynecology. In the July 2009 issue of the Green Journal (*Obstet Gynecol 2009; 114(1):45-9*), Waters et al. reported on the effect of 17α-hydroxyprogesterone caproate on glucose intolerance during pregnancy. They demonstrated that women receiving weekly intramuscular 17alpha-hydroxyprogesterone caproate had more frequent abnormal glucose testing and gestational diabetes compared with unexposed controls. These results are consistent with published data regarding the effect of progesterone on insulin resistance in some studies, but other studies suggest little to no risk of gestational diabetes. Therefore, the aim of this systematic review and meta-analysis was to comprehensively synthesize the literature on the risk of glucose intolerance in women with singleton pregnancies treated with 17-OHPC compared to controls. **We have addressed all the reviewer questions, and have attached an author response to our submission.**

Dr Ahizechukwu Eke, Dr Jeanne Sheffield and **Dr Ernest Graham** conceived and designed the study. **Dr Eke, Dr Sheffield** and **Dr Graham** did the literature search. **Dr Eke, Dr Graham** and **Dr Sheffield** assisted in writing and revising the manuscript. All THREE authors reviewed the text and agreed on the final version.

This manuscript has been solely submitted to Obstetrics & Gynecology, and is not under peer review with any other journal. There are no conflict of interests. The authors alone are responsible for the contents of this manuscript. All authors met the author requirements for this journal and the author agreement forms have been signed. The word count in the abstract is **297**, while the word count is **4834** (main text plus references**). The PROSPERO registration number for this systematic review and meta-analysis is CRD42016041694.**

We look forward to acceptance of this manuscript for publication in Obstetrics & Gynecology.

Very Respectfully,

Ahizechukwu Eke, MD, MPH (Harvard), FACOG,
[redacted]

aeke2@jhu.edu

RE: Manuscript Number ONG-18-2011.

Thank you for re-considering our manuscript for publication in Obstetrics and Gynecology. We revised the manuscript, responding to all reviewer comments:

1. We have now limited our introduction to 250 words (Lines 100-122)
2. We also limited our discussion to 750 words, including information relevant to clinicians
3. We addressed all reviewer comments (Lines 314-381).

Thank you again for considering this manuscript for publication in Obstetrics and Gynecology.

REVIEWER #1:

1. What specific definitions of glucose intolerance and gestational diabetes mellitus were used to assess eligibility of the studies by the two reviewers who read the full-text of each manuscript? Thank you so much for reviewing our manuscript. The specific definitions of glucose intolerance and gestational diabetes used to assess inclusion in all 6 studies in this meta-analysis include:

A). Glucose intolerance - Abnormal 1 hour 50-gram glucose screen was defined as a venous plasma glucose level of at least 135 mg/dL 1 hour after a non-fasting 50g oral glucose load; and B). Gestational diabetes mellitus was defined as a 1-hour 50 gram glucose screen of at least 200 mg/dL OR if two or more abnormal results were identified on a confirmatory 3-hour 100 gram oral glucose tolerance test. - (Lines 148-154)

Were all studies required to use the same definition of Gestational diabetes and glucose intolerance? - Yes, all the studies used similar criteria for diagnosis of abnormal 1 hour glucose and gestational diabetes.

Please list the specific criteria to diagnose glucose intolerance and gestational Diabetes which were acceptable for inclusion in this study – The specific criteria to diagnose glucose intolerance and gestational diabetes include: Abnormal 1 hour 50-gram screen was defined as a venous plasma glucose level of at least 135 mg/dL 1 hour after a non-fasting 50g oral glucose load; and Gestational diabetes mellitus was defined as a 1-hour 50 gram glucose screen of at least 200 mg/dL OR if two or more abnormal results were identified on a confirmatory 3-hour 100 gram oral glucose tolerance test. - (Lines 148-154)

Was the mean plasma glucose determined by the same method in all the studies included in this meta-analysis? – Yes, this was uniform in all three studies that reported mean plasma glucose levels (Waters 2009; Wolfe 2011; and Rouholamin 2015). Thank you.

2. Could the authors supply a funnel plot? Thank you so much for reviewing our paper, and for your comments. We have now provided funnel plots for gestational diabetes (primary outcome) and abnormal 1 hour 50-gram glucose screen; mean plasma glucose concentrations (secondary outcomes).- (Figures 5 and 6)

Was there any evidence of publication bias? - The asymmetric nature of the funnel plots would suggest possible publication bias. However, assessment of publication bias in this review is particularly difficult given that the number of studies were less than 10 (in this case, 6 studies). Funnel plots are thought to be

unreliable methods of investigating potential bias if the number of studies is less than 10. - (Lines 297-306)

3. Line 254 "intrauterine fetal demise before 28 weeks leading preterm birth." Please re-write this sentence – This has been revised. The sentence now reads: …"history of intrauterine fetal demise before 28 weeks of gestation"... Thank you! - (Line 248)

4. Line 255-256: "recurrent preterm delivery before 28 weeks in the current pregnancy," Please clarify. This has been corrected. The sentence has been restructured to read: "recurrent preterm delivery before 28 weeks". Thank you! - (Lines 249-250)

5. Could the authors please discuss any advantages or limitations to including randomized and non-randomized studies in the meta-analysis? – Thank you for this question. Combination of different study types into a meta-analysis is not new in the medical literature. Small studies (irrespective of design) can be problematic because of small sample sizes and possible inadequacies in design, thereby increasing the risk of chance findings. Meta-analysis of these small studies overcomes the small sample sizes of individual studies to detect the effects of interest, analyze end points that require larger sample sizes (in this case, development of gestational diabetes mellitus and abnormal 1-hour glucose tolerance testing), increase precision in estimating effects, and evaluate effects in subsets of patients. The ideal is meta-analysis of high-quality, large, randomized trials. However, in the absence of such randomized controlled trials, we have to make the best of the information available and of all the information available. That is the justification, as here, for including information from both randomized trials and observational studies. Furthermore, Sensitivity analysis was evaluated on the primary outcome (gestational diabetes mellitus) excluding all cohort studies. Even after exclusion of the cohort studies, the summary estimate of effect was still non-significant. (RR 1.21, 95% CI 0.63–2.36).

Why did they include a secondary analysis of two randomized controlled trials? – Thank you for this question. We included the secondary analysis of 2 randomized controlled trials because secondary analysis of RCTs are considered observational studies. Secondary analysis of randomized controlled trials, no matter how well analysed, they are subject to the same issues encountered in cohort studies - selection bias, implications of collider stratification bias, potential for unmeasured confounding, and importance of ensuring that a planned secondary data analysis is sufficiently statistically powered. This is why they are considered observational studies.

REVIEWER #2:

I enjoyed reading your interesting manuscript. I have a few comments that I hope may assist in strengthening it.

1. LN 115: I found this sentence a bit confusing, and had to reread it several times. I would suggest substituting "related to" for "of" as I believe it would make the sentence easier to understand – Thank you for your comment. We have now substituted “of” with “related to”. Thank you. - (Line 109)

2. Lns 289 - 294: You refer to "risk of abnormal glucose tolerance not diagnostic of gestational diabetes". This is not a commonly used term. Initially, I thought you might be referring to abnormal 50 g GCT results followed by normal 100 g GTT results. However, after reading your reference, I believe that you mean the difference in the prevalence of GDM diagnosed utilizing the Carpenter Coustan criteria for interpreting the 3 hr. 100 gm GTT in comparison to that diagnosed by the stricter National Diabetes Data Group criteria. However, this is not entirely clear, and I believe that this outcome needs to be more carefully defined - Thank you for your comment. Here is an explanation to clarify things: - The primary outcome of interest of this systematic review is the proportion of women who developed gestational diabetes mellitus, defined as a 1-hour 50 gram glucose screen of at least 200 mg per dL OR if two or more abnormal results were identified on a confirmatory 3-hour 100 gram oral glucose tolerance test. The secondary outcomes of interest include: (1) abnormal 1 hour 50 gram glucose screen and (2) mean venous plasma glucose concentrations. Abnormal 1-hour 50 gram glucose screen was defined as a non-fasting venous plasma glucose concentration of at least 135 mg per dL but less than 200 mg per dL. - (Lines 148-154)

We have corrected “risk of abnormal glucose tolerance not diagnostic of gestational diabetes” to “abnormal 1 hour non-fasting venous plasma glucose concentration of at least 135 mg per dL but less than 200 mg per dL”. Thanks. - (Lines 148-154)

3. Table 2: It appears that all of the prior authors included in your analysis utilized a 2 - step, 50 g GCT, 100 g GTT testing scheme. I might be useful for the reader to also know which of several possible criteria were used to interpret the tests - Thanks for your comments. Yes, the included studies reported using the ACOG criteria for diagnosis of gestational diabetes (2 - step, 50 g GCT, 100 g GTT testing scheme). This was the only criteria we used to evaluate studies for inclusion into our meta-analysis. However, we agree that it is important to know that other diagnostic criteria exist, for example: diagnosis of gestational diabetes mellitus using the National Diabetes Group 2 step method, and the one step diagnosis with 75 g 2 hours oral glucose tolerance test using the International Association of Diabetes and Pregnancy study group (IADPSG) criteria. - (Lines 148-154)

4. Finally, none of studies included in your analysis utilized ISPDGS criteria for the diagnosis of GDM. While the use of this technique is controversial, it is currently recommended by the WHO and ADA and has been adopted by several centers in the USA. It might be helpful to point out to the reader that there is no information regarding the effect of 17 - OHPC use on the diagnosis of GDM utilizing the ISPDGS methodology - Yes, none of the studies included the ISPDGS criteria for diagnosis of gestational diabetes. While the use of this technique is controversial, it is currently recommended by the WHO and ADA and has been adopted by some centers in the USA. Also, as you rightly stated, there is no information regarding the effect of 17-OHPC use on the diagnosis of GDM utilizing the ISPDGS methodology. Thank you.

REVIEWER #3:

In this paper, Eke et al performed a meta-analysis on the reported association between progesterone treatment and the risk of gestational diabetes or glucose intolerance in pregnancy. They found there was a significantly higher incidence of GDM in exposed women versus unexposed controls.

I think this topic is of interest to readers of this journal given the frequent use of progesterone and the importance of understanding the risks and benefits of its use – Thank you!

I found the paper to be well-written with sound methods and a reasonable conclusion based on their findings – Thank you!

STATISTICAL EDITOR'S COMMENTS:

1. Lines 58-62: Should cite some measure of absolute risks, both in Abstract and in text, to put the risk in context – Thank you so much for reviewing our paper, and for your comments. We have now used a measure of absolute risk (number needed to treat – NNT), and applied it to the text. This was how we calculated the NNT for the gestational diabetes mellitus and abnormal glucose tolerance cases:

A). For gestational diabetes
Number of cases of gestational diabetes in 17-OHPC group - 168
Number of cases of gestational diabetes in control group - 216
Total number of people in the 17-OHPC group - 1535
Total number of people in the control group - 3515
AR (absolute risk) in 17-OHPC group = 168/1538 = 0.11
AR (absolute risk) in control group = 216/3515 = 0.06
ARR (absolute risk reduction) = 0.11 – 0.06 = 0.05 (5%)
NNT (number needed to treat) = 1 / 0.05 = 20 - (Lines 61-62; 294-298)

Interpretation:
One additional woman is expected to develop gestational diabetes for every 20 women receiving 17-OHPC compared to unexposed controls (NNT=20) - (Lines 61-62; 294-298)

B). For abnormal 1 hour 50-gram glucose screen
Number of cases of abnormal 1-hour 50 gram glucose screen in 17-OHPC group - 60
Number of cases of abnormal 1-hour 50 gram glucose screen in control group - 79
Total number of people in the 17-OHPC group - 258
Total number of people in the control group - 553
AR (absolute risk) in 17-OHPC group = 60/258 = 0.23
AR (absolute risk) in control group = 79/553 = 0.14
ARR (absolute risk reduction) = 0.23– 0.14 = 0.09 (9%)
NNT (number needed to treat) = 1 / 0.09 = 11 (Lines 61-62; 294-298)

Interpretation:

One additional woman is expected to develop abnormal glucose tolerance for every 11 women receiving 17-OHPC compared to unexposed controls (NNT=11). - (Lines 61-62; 294-298)

2. Table 1: Unclear what is meant by the row entries for "Ethnicity" with values expressed as N±SD – Thank you for your comment. We have now clarified what "Ethnicity" means. We extracted information on African-Americans, Whites, and other races as listed in the included studies, comparing the 17-OHPC group to unexposed controls. In studies where they are not reported, we used 'NR' to mean 'not reported'. - (Table 1)

3. Lines 298-300, 307-309 and fig 4: There is no "trend", the difference was NS. Were these fasting or random glucose concentrations? – Thank you for your comments. These have been corrected, stating they were not statistically significant. They were random glucose concentrations. Thanks. - (Lines 292-293)

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. 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. Variance needs to be added to the entire sources and study selections sections. These are taken nearly verbatim from the author's 2018 meta-analysis in Acta. Lines 264-284 are also taken nearly verbatim from this paper. This should be rewritten. Same issue with lines 357-362. This is excessive self-plagiarism - Thank you for this comment. We have now revised lines 264-284 and 357-362. - (Lines 258-267)

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 - Thank you. We have reviewed all these definitions, familiarized ourselves with them, and have used them for consistency in this manuscript.

4. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 25 typed, double-spaced pages (6,250 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) – Thank you. We have adhered to these.

Please limit your Introduction to 250 words and your Discussion to 750 words – Thank you. We have now limited the introduction to 250 words and the discussion to 750 words. Thanks.

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 – We have adhered to this. Thank you.

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) – We have provided this information. Thank you.

7. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot - We have provided this information. Thank you.

8. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words, written in the present tense and stating the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents." - We have provided this information. Thank you.

9. 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 – There are no inconsistencies between our abstract and the manuscript. Thank you.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Reviews, 300 words. Please provide a word count – Our abstract word count is 300 words.

10. 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.

11. 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 – We have removed all (/) symbols from the manuscript. Thanks.

12. Our readers are clinicians and a detailed review of the literature is not necessary. Please shorten the Discussion and focus on how your results affect or change actual patient care. Do not repeat the Results in the Discussion section – We have shortened our discussion and shown how this may affect patient care. Thanks.

13. 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 - We have done this, and have formatted our tables to conform to the journal style. Thanks.

14. The American College of Obstetricians and Gynecologists' (College) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite College documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly. If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if a College document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All College documents (eg, Committee Opinions and Practice Bulletins) may be found via the Resources and Publications page at http://www.acog.org/Resources-And-Publications - Thanks.

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

"Figure 2: Please upload as high res image files (EPS, TIFF, JPEG). Text inside each figure should be crisp when zoomed in." – Thank you. We have provided the images in EPS, and have art saved them in digital format.

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) – Thank you. We have uploaded each file as a separate file in Editorial Manager. Thanks.

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 – This has been done. Thanks.

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 - This has been done. Thanks.

Daniel Mosier

From: Ahizechukwu Eke [redacted]
Sent: Wednesday, December 12, 2018 1:19 PM
To: Daniel Mosier
Cc: Ahizechukwu Eke
Subject: Manuscript Revisions: ONG-18-2011R1
Attachments: 18-2011R1 ms (12-11-18v2)_Eke Final Edits.docx; ATT00001.htm

Also, please let me know if you need anything else.

Thanks,

Ahizechukwu Eke, MD

Begin forwarded message:

> **From:** Ahizechukwu Eke [redacted]
> **Date:** December 11, 2018 at 8:22:48 PM EST
> **To:** Daniel Mosier <dmosier@greenjournal.org>, [redacted]
> **Subject: Re: Manuscript Revisions: ONG-18-2011R1**
>
> Hi Daniel,
>
> Please see attached. I agreed and accepted all the Editor's and Denise Shield's corrections. Dr Sheffield has responded to authorship. I filled in 'X', provided the reference, and cited the studies with numbers instead of years.
>
> Please let me know if you have any other questions.
>
> Thanks again.
>
> Best,
>
> **Ahizechukwu Eke, MD MPH**
> Postdoctoral Fellow, Maternal Fetal Medicine & Clinical Pharmacology,
> PhD Candidate, Clinical Investigation (JHSPH),
> Division of Maternal Fetal Medicine,
> Department of Gynecology & Obstetrics,

Johns Hopkins University School of Medicine,
[redacted]

From: Daniel Mosier <dmosier@greenjournal.org>
Sent: Tuesday, December 11, 2018 10:11:03 AM
To: [redacted] Ahizechukwu Eke
Subject: Manuscript Revisions: ONG-18-2011R1

Dear Dr. Eke,

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 4: Please ask Jeanne Sheffield to respond the authorship confirmation email we sent. We sent an email from em@greenjournal.org. The message contains a link that needs to be clicked on. We emailed Dr. Sheffield at [redacted] is this the correct address?
3. LINE 60: Please fill in X
4. LINE 155: Ref please
5. TABLE 1: Please cite these with their reference numbers instead of years

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, December 13th.**

Sincerely,

-Daniel Mosier

Daniel Mosier
Editorial Assistant
Obstetrics & Gynecology
The American College of Obstetricians and Gynecologists
409 12th Street, SW
Washington, DC 20024
Tel: 202-314-2342
Fax: 202-479-0830
E-mail: dmosier@greenjournal.org
Web: http://www.greenjournal.org

From: [redacted]
To:
Cc: Stephanie Casway
Subject: Re: O&G Figure Revision: 18-2011
Date: Wednesday, December 12, 2018 1:16:17 PM

Thanks Stephanie. I've reviewed and can't find any mistakes.

Please let me know if you need anything else from me.

Thanks,

Ahizechukwu Eke, MD

On Dec 11, 2018, at 3:46 PM, Ahizechukwu Eke [redacted] wrote:

> Thanks Steph. I'll get back to you tonight.
>
> Best,
>
> Ahize.
>
> ---
>
> **From:** Stephanie Casway <SCasway@greenjournal.org>
> **Sent:** Tuesday, December 11, 2018 1:37 PM
> **To:** [redacted]
> **Subject:** O&G Figure Revision: 18-2011
>
> Good Afternoon Dr. Eke,
>
> 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. Note that Figures 3-5 are not attached, as no edits were made.
>
> 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
409 12th St, SW
Washington, DC 20024
Ph: (202) 314-2339
Fax: (202) 479-0830
scasway@greenjournal.org