

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)*

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

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:
obgyn@greenjournal.org.

Date: Apr 16, 2020
To: "Baha M. Sibai" baha.m.sibai@uth.tmc.edu
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-564

RE: Manuscript Number ONG-20-564

Was the Meis trial a false positive: re-examination of the evidence

Dear Dr. Sibai:

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).

Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by May 16, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Thank you for the opportunity to review your work. Authors reviewed Meis and PROLONG trials head to head and made an argument that withdrawal of Makena from the market would be detrimental to US patient population. Thank you for working so diligently on improving lives of women at risk for PTB.

Comments

1. Topic of much importance to the practicing OBGYNs and to the journal audience. Aside from ACOG and SMFM advisories on the topic, not a lot of literature has been published yet as a "pro and con" debate.
2. In terms of content, article is focused on direct comparison and it goes into great detail on study design and results with are outlined consisely. I am wondering if it would be of use to add a few more sub-topics which might help set the stage for the argument itself:
 - a. History and current situation of Makena on US market. It might be that not all of the audience is aware of details and history around Makena introduction to the market, reasons behind change from IM to SQ formulation, lack of coverage by Medicaid, % of patient who end up using compounding pharmacies despite commercially available product, recent FDA advisory board recs, and timeline as to when FDA is going to make a decision about its removal. How does all this affect day to day lives of clinicians and patients in the "trenches" and what might look like in the future if withdrawn?
 - b. In the background, it seems that including ACOG statement and SMFM practice advisory from 10/25/2019 would be of help.
 - c. How are insurers reacting to those events? How about patients? NPR segment below is interesting to read from that standpoint

<https://khn.org/news/call-for-fda-to-withdraw-preterm-birth-drug-makena-divides-doctors-and-insurers/>

- d. Are there other studies of 17OH-P such as the one below that attempted to study it post-Meis publication that are of better quality than others?

Nelson DB, McIntire DD, McDonald J, Gard J, Turrichi P, Leveno KJ. 17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. Am J Obstet Gynecol. 2017;216(6):600.e601-600.e609.

3. Given that PTB is multifactorial entity, would it be possible to elaborate what the next steps should be to study 17OHp within that risk-stratification approach?
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address. Would it be possible to elaborate?

Reviewer #2: This is a needed review of these two important trials, the results of each have caused substantial confusion among patients, physicians and policy makers. Thanks to the authors for the comprehensive review.

The abstract is clear and concise.

The introduction provides a good summary of the history of these trials with excellent details.

In the conclusion, the authors provide a solid comparison of the similarities and differences between the two trials. The authors point out substantial and legitimate concerns about these differences and what may have accounted for the outcome differences.

The argument presented and supported that the PROLONG trial is more likely underpowered than the Meis trial is false positive is compelling and should be made available to physicians who now have to counsel patients on what may be the best options for managing their pregnancy with a history of spontaneous preterm birth. The tables are easy to read and appropriate for the manuscript.

Reviewer #3:

Summary:

The purpose of this commentary is to compare the different results from Meis 2003 and PROLONG 2019. These Clinical Trials had similar protocols and eligibility criteria. The hypothesis on both studies was to Test the effectiveness of 17 OHPC as compare with placebo in the prevention of recurrent preterm delivery.

Abstract

Sets the principal argument clearly. The PROLONG, a confirmatory trial, with an inadequate sample size was not able to access the difference in the PTB rates between the placebo and the 17OHPC groups.

I have Minor comments and questions:

In line 91 the authors explain the adjusted analysis for prior PTBs in the placebo group. Other variables like race, smoking or substance abuse don't need to get adjusted?

In line 51 the authors discuss the O Brein- Fleming Boundary in the study design. Does this approach has some limitations?

EDITOR'S COMMENTS:

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Numbers below refer to line numbers.

31: Please spell out all abbreviations on first use. This has to be done separately in the abstract and the manuscript, unfortunatley. You have a lot of abbreviations throughout to deal with. (GA, SPTB,MFMU, NICHHD, etc etc)

36: could you mention why the PROLONG trial was done (Required by FDA)

50: was the 2nd interim analysis prespecified?

116: We do not allow authors to claim clinical significance if there is not statistical significance. You could say that this was a secondary outcome, the study was not powered to assess this outcome, but it is was at least reassuring.

143: please add that the results were non significant

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. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

- A. OPT-IN: Yes, please publish my point-by-point response letter.
- B. OPT-OUT: No, please do not publish my point-by-point response letter.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

3. Please cite lines 130-133 [When comparing demographics...outside the US] and 145-147 [The key safety...from the Meis study].

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

6. 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.

7. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

- * All financial support of the study must be acknowledged.
- * Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
- * All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
- * If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

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: Current Commentary articles, 250 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 standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%).

12. 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.

13. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifauth.htm>.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

14. If you choose to revise your manuscript, please submit your revision through Editorial Manager at <http://ong.editorialmanager.com>. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:

- * A confirmation that you have read the Instructions for Authors (<http://edmgr.ovid.com/ong/accounts/authors.pdf>), and
- * A point-by-point response to each of the received comments in this letter.

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

Again, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by May 16, 2020, we will assume you wish to withdraw the manuscript from further consideration..

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: <https://www.editorialmanager.com/ong/login.asp?a=r>). Please contact the publication office if you have any questions.

April 24, 2020

Dear Editors,

Thank you for your review of our manuscript. We appreciate the questions and comments raised and have included the original reviewer/editor response with our response (in italics), following each comment.

While incorporating the comments, we have identified a few areas where we propose deleting text in order to stay within the word count limitations; even with these cuts, we recognize that this submission is slightly over the allotted word count (~3,050 words) to include the reviewer requested additions. Please advise if this is acceptable.

Best,

A handwritten signature in black ink, appearing to read "Baha Sibai", is written over a horizontal blue line.

Baha Sibai, MD

Reviewer #1: Thank you for the opportunity to review your work. Authors reviewed Meis and PROLONG trials head to head and made an argument that withdrawal of Makena from the market would be detrimental to US patient population. Thank you for working so diligently on improving lives of women at risk for PTD.

We appreciate this comment very much.

1. Topic of much importance to the practicing OBGYNs and to the journal audience. Aside from ACOG and SMFM advisories on the topic, not a lot of literature has been published yet as a "pro and con" debate.

Thank you; we agree.

2. In terms of content, article is focused on direct comparison and it goes into great detail on study design and results which are outlined concisely. I am wondering if it would be of use to add a few more sub-topics which might help set the stage for the argument itself:

a. History and current situation of Makena on US market. It might be that not all of the audience is aware of details and history around Makena introduction to the market, reasons behind change from IM to SQ formulation, lack of coverage by Medicaid, % of patient who end up using compounding pharmacies despite commercially available product, recent FDA advisory board recs, and timeline as to when FDA is going to make a decision about its removal. How does all this affect day to day lives of clinicians and patients in the "trenches" and what might look like in the future if withdrawn?

We recognize there is considerably more information that could be included that is of interest to the practicing obstetrician. Some additional information has been added to the introduction and conclusion regarding the history of Makena, including the approval of generic equivalents and the SQ formulation, as we recognize this is germane to the topic/reader.

We believe that information regarding utilization of compounded drug and payer coverage is relevant, but out of scope for the purpose of this Current Commentary, which is intended to address the criticisms of the Meis trial and provide context for the PROLONG trial.

Regarding FDA recommendations, the key vote (whether FDA should pursue withdrawal) is described in the introduction of the original submission. FDA has not outlined a timeline for when they will take any action. Additional information regarding how this complex issue could affect day to day lives of clinicians and patients if Makena and generic equivalents are withdrawn, as well as some of the additional topics, could be addressed by us in a separate paper with a different scope, if the Green Journal is interested.

We are definitely interested in expanding on these issues, however given the word limits and the focus of this commentary on the inappropriate criticisms leveled at the Meis trial, we feel that this may be better addressed in a separate publication.

b. In the background, it seems that including ACOG statement and SMFM practice advisory from 10/25/2019 would be of help.

Thank you for this recommendation; information has been added (see tracked changes).

c. How are insurers reacting to those events? How about patients? NPR segment below is interesting to read from that standpoint

https://urldefense.proofpoint.com/v2/url?u=https-3A_khn.org_news_call-2Dfor-2Dfda-2Dto-2Dwithdraw-2Dpreterm-2Dbirth-2Ddrug-2Dmakena-2Ddivides-2Ddoctors-2Dand-2Dinsurers_&d=DwIGaQ&c=bKRySV-ouEg_AT-w2QWsTdd9X_KYh9Eq2fdmQDVZgw&r=QyL0y4qIM9SctVY7MWY2ICIBn4CT-IKxdGv0B1_cYo&m=09ez2jVWcbPxynRf0DqpGo_t5cZ5cl9oJqoZhQtPK0I&s=nbr4VQwKslqrEGMssgj1TnPcHiEbUxS5zY_OCcz3jn4&e=

We agree that this is an interesting, pragmatic question to ask, but believe it is out of scope for the current paper submitted. As above, we would be interested in addressing this in a separate manuscript. Given that the Green journal published a Current Commentary in a recent issue from a “Medicaid Evidenced-Based Decisions Project”, we presume this topic of payer coverage is of interest to the Green journal and we would be pleased to address this topic in a separate paper, if the editors are interested.

d. Are there other studies of 17OH-P such as the one below that attempted to study it post-Meis publication that are of better quality than others?

Nelson DB, McIntire DD, McDonald J, Gard J, Turrichi P, Leveno KJ. 17-alpha Hydroxyprogesterone caproate did not reduce the rate of recurrent preterm birth in a prospective cohort study. Am J Obstet Gynecol. 2017;216(6):600.e601-600.e609.

This study and an additional observational study have been added to the conclusion (see track changes).

3. Given that PTB is multifactorial entity, would it be possible to elaborate what the next steps should be to study 17OHp within that risk-stratification approach?

We have added additional information the conclusion (see track changes)

4. Lines 131-132. Race and surrogates of SES status. This seems to be most one of the most important topics to address. Would it be possible to elaborate?

We have added additional information (see track changes).

Reviewer #2: This is a needed review of these two important trials, the results of each have caused substantial confusion among patients, physicians and policy makers. Thanks to the authors for the comprehensive review.

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The tables are easy to read and appropriate for the manuscript.

Thank you for your review and comments; we appreciate them very much.

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Abstract

Sets the principal argument clearly. The PROLONG, a confirmatory trial, with an inadequate sample size was not able to access the difference in the PTB rates between the placebo and the 17OHPC groups.

I have Minor comments and questions:

In line 91 the authors explain the adjusted analysis for prior PTBs in the placebo group. Other variables like race, smoking or substance abuse don't need to get adjusted?

In the Meis study, demographic and baseline characteristics were well balanced between treatment groups (Table 1 of NEJM manuscript) with the exception of the number of previous preterm deliveries. Given that the number of previous preterm deliveries was the only baseline covariate that was imbalanced between treatment groups, no other variables were included in the adjusted analysis. No update has been made in the manuscript.

In line 51 the authors discuss the O'Brien-Fleming Boundary in the study design. Does this approach has some limitations?

With the O'Brien-Fleming spending function, the statistical penalty (ie, how much alpha is used) is low with early looks at the data and increases with later looks at the data such that alpha levels are close to those from a fixed design. Thus, the early results have to be extremely compelling in order to trigger early termination of the study. This conservative nature of the O'Brien-Fleming spending function at the early looks is sometimes considered a limitation. In addition, use of the O'Brien-Fleming boundary alone requires the time points of the interim analyses to be pre-specified. The Meis trial utilized the Lan-DeMets procedure along with an O'Brien Fleming spending function and the manuscript has been updated with this detail. The Lan-DeMets procedure overcomes the issue of pre-specifying the time

points for the interim analyses. In addition, in the Meis trial, the O'Brien-Fleming boundary was chosen in part because of this inherent conservatism in stopping the trial early.

EDITOR'S COMMENTS:

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All abbreviations in both the abstract and body have been defined in the first use (see track changes).

36: could you mention why the PROLONG trial was done (Required by FDA)

The introduction now explicitly states that the PROLONG trial was conducted as required by the FDA.

50: was the 2nd interim analysis prespecified?

The protocol specified that the DSMB would meet at least yearly to review interim analyses of efficacy, thus the second interim analysis was pre-specified. The timing of the analysis (ie when 70% of patients had delivery data available) was not specified as use of the Lan-DeMets method, which was specified in the protocol, does not require the total number or the exact time of the interim analyses to be specified. The manuscript was updated to indicate that the Lan-DeMets procedure was used with the O'Brien-Fleming spending function.

116: We do not allow authors to claim clinical significance if there is not statistical significance. You could say that this was a secondary outcome, the study was not powered to assess this outcome, but it is was at least reassuring.

This verbiage has been updated to reflect that the neonatal composite index from the Meis trial was "reassuring" as opposed to clinically significant (see track changes).

143: please add that the results were non significant

The direction and magnitude of the relative risk for PTB <32 weeks and the neonatal composite index in the US subgroup has been updated to specify that it did not reach statistical significance (see track changes).

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A. OPT-IN: Yes, please publish my point-by-point response letter

We opt-in to have the point-by-point response letter published.

B. OPT-OUT: No, please do not publish my point-by-point response letter.

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Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

This has been done.

3. Please cite lines 130-133 [When comparing demographics...outside the US] and 145-147 [The key safety...from the Meis study].

The reference citations have been added appropriately for these lines.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://urldefense.proofpoint.com/v2/url?u=https-3A__www.acog.org_About-2DACOG_ACOG-2DDepartments_Patient-2DSafety-2Dand-2DQuality-2DImprovement_reVITALize&d=DwIGaQ&c=bKRySV-ouEg_AT-w2QWsTdd9X__KYh9Eq2fdmQDVZgw&r=QyL0y4qIM9ScrtVY7MWY2ICIBn4CT-IKxdGv0B1_cYo&m=09ez2jVWcbPxynRf0DqpGo_t5cZ5cI9oJqoZhQtPK0I&s=S2pT6ProPxuHbAPyGUzv7LwnaswtyqrSrIJCh5RfXvs&e= . If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

The reVITALize definitions have been reviewed and the definition of spontaneous preterm birth is identical to that used in the manuscript. We note that gestational age is conventionally used by including weeks and days; for all endpoints identified in each trial, the GA listed indicates 0 days (i.e., an endpoint of 37 weeks is 37 weeks/0 days)