OBSTETRICS & GYNECOLOGY

NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

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

Date: Aug 13, 2020
To: "Lakshmi Panagiotakopoulos" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1818

RE: Manuscript Number ONG-20-1818

Evaluating stillbirths after maternal immunization in the Vaccine Safety Datalink

Dear Dr. Panagiotakopoulos:

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 Sep 12, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Timely, well conceived, well designed, well analyzed, and well presented.
Congratulations!

Reviewer #2: This is a case control study that seeks to determine whether receipt of the flu vaccine or the Tdap vaccine is associated with IUFD. This data is important in counseling women about risks/benefits.

abstract
(1) methods - it is not clear in your power calculation mentioned whether you are considering the odds of flu vax or Tdap to separately/independently be associated with IUFD, or together - in other words - are you looking at the relationship between flu and IUFD, and Tdap and IUFD, or are you looking at the relationship between flu and/or Tdap and IUFD ?

(2) methods - matching - what did you match on ? can you briefly mention in the abstract?

intro
--well written

methods
(1) lines 110-114, exclusion criteria. would you consider eliminating any pregnancies in which other vaccines were administered, to truly isolate the effect of administration or non administration of flu and tdap specifically on the outcome ? also, while I agree that multifetal pregnancies are at increased risk for IUFD, there are other risk factors, like prior IUFD for instance - can you justify why to exclude some risk factors for IUFD but control for others as your confounders ?

(2) lines 138-148 - why include all vaccines in this paper, and not focus solely on flu/Tdap, which are the most important in pregnancy ? or if the goal/primary exposure of interest is all vaccination opportunities in pregnancy, then perhaps the focus in the precis and abstract on flu/Tdap could be made more general to be "maternal immunization"

(3) can you specify exactly how you know the date of the vaccine administration? EMR review, or billing code for that prenatal visit ? Not clear to me, and later in the discussion we learn more about how you got the specific info about the primary exposure. Would include more details here.

(4) sample size calculation - here, my reading of your power calc seems like you powered on all immunizations, but in the

abstract, it seems like your power calc was based on tdap/flu vaccination events

results
(1) table 1 - GA at vaccination - this data point is hard to follow, as a pregnant women can get multiple vaccinations - so in that case, is this the first vaccination event?

(2) table 1 - can you include the frequency of each vaccination administered in both groups of women?

(3) table 2 - tdap vaccination rates - can you calculate in only the group of women in the recommended GA range for Tdap ? even though you can get Tdap at any GA unless in an epidemic time (some states may have been in epidemic time your time frame) most women get in the third trimester, rather than at all times of the pregnancy, so women with an IUFD 20-28w weren't really "eligible" to have the exposure.

discussion
(1) I would consider removing the contraindicated vaccines and non-routinely administered vaccines from this paper - not that many of them and makes it a little confusing to follow, whether the focus is flu, Tdap, flu and/or Tdap, all vaccines?

(2) another limitation for generalizability is that this is a continuously enrolled population of patients, with continuous enrollment even prior to pregnancy. although your rates of stillbirth and GA trends are consistent with national average, there may still be something different about this population than other populations that influences both their uptake of vaccines and their stillbirth rate.

Reviewer #3: The authors have performed a detailed case control analysis to look for an association between receipt of vaccines in pregnancy or periconception period and still birth. They used a 1:4 case to control ratio. The authors report the study was set within a cohort study of 2007-2015. This entire time period was used to establish the background still birth rate, (to look for any linear trends). To this reviewer, the actual time of the study was 2012-2015, and it is confusing to the reader to figure out why the years of 2007-2011 are included as the first line lead for the study time period. This reviewer had to read that part through several times. It would be more appropriate to this reviewer to state the study was from 2012-2015 and then say background stillbirth rates were analyzed from 2007-2015 to assure no change over time.

The authors state the study period is limited from 2012-2015 given the change in Tdap recommendations - although the change from post partum administration of Tdap to 3rd trimester of pregnancy was voted on by ACIP in October of 2012 but published in the MMWR in Feb 2013 - so please clarify why 2012 was included for the Tdap component.

One of the most difficult aspects of a study like this is determining gestational age. The authors state the gestational age hierarchy in lines 123-127. As one of the peak still birth times was 22 weeks, and stillbirth definition used is 20 weeks, and this is well within the error margin of dating, please provide (even as a supplement) how often the dating was assigned by various methods of your hierarchy.

Please do not use PEA as an abbreviation. It is not a standard abbreviation and is difficult to remember throughout the manuscript and is a distraction.

How was chorioamnionitis defined? (line 204)

Matching method seems logical and appropriate. Clear statement of how antepartum and intrapartum was identified

In discussion 276-278 state data includes covariates from different sources. Can you please speak more about this and the potential impact this has for the reliability of your data?

The authors clearly list the a priori confounders they consider. Black race is used as an a priori confounder. If the authors adjusted for the medical co morbidities was black race still a factor? Given that this is likely not a biologic racial difference, but more a reflection of other sociodemographic and/or medical risk factors, or history of prior still birth, it would be appropriate to assess whether, when adjusting for these other factors, race was still a factor.

The authors state all patients were insured- and it looks like almost all the data bases were Kaiser enrollees. Are there any other socio economic indicators or pieces of data that can be used (average income of zipcodes for instance, or other factors) that would allow for more nuanced analysis of "race".

This reviewer questions the publication of yet another article using race a priori.

pregnancy complications defined as hospitalizations during pregnancy are listed clearly and seem appropriate.

Periconception period: vaccines 30 days prior to LMP till 14 days after LMP is clear and appropriate—but only if the gestational age is well known and accurate. Could the authors comment on how many of the women who were cases and who were controls for the periconception period had reached the highest level of certainty in the dating hierarchy that was

used?

Please provide information on the timing of the Tdap immunization relative to the stillbirth for the cases. Given that Tdap is not recommended until 27 weeks or after, and a peak of still birth cases was at 22 weeks - please clarify the timing to Tdap relative to the still birth.

The authors clearly state their power calculations but do not provide adequate information about how they chose 1.5 OR to guide the sample size. That is a 50% increase in stillbirth- which, frankly, is a pretty high elevation that is not reached by many of the known stillbirth risk factors. Also, given all the prior studies that the authors quote that were protective or had a OR close to 1.0, picking an OR of 1.5 seems high.

This reviewer agrees with authors that reviewing the still birth charts was a strength of the study. Can the authors give some indication of how often this review changed the adjudication?

The authors have a high rate of finding pathology or abnormal test for the still birth cases. Given that the literature quotes 25-60% of stillbirths are without a definable etiology, can the authors discuss why they think they had 77% with pathology available with an abnormal results?

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

lines 273, Table 1: As stated by the Authors, there were multiple baseline characteristics that differentiated between the stillbirth vs live birth cohorts. The probability of receiving vaccines during pregnancy could have been influenced by several of them, including maternal age, maternal comorbidities, parity, race and unmeasured covariates, in terms of socio-economic status, education level, insurer etc.

Tables 2, 3: In addition to attempting to adjust for the various baseline differences, since the initial cohort of livebirths was so large, should have corroborated the findings by a better matching of stillbirth vs live birth cohorts.

EDITOR'S COMMENTS

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues and other relevant topics. Adherence to these requirements with your revision will avoid delays during the revision process by avoiding re-revisions on your part in order to comply with formatting.

Numbers below refer to line numbers.

48. I agree w/ the reviewer who asked for clarity about the dates of inclusion, using earlier dates for baseline still birth rate and later dates for “study” dates. Please tell us something about the VSD—who contributes to this data set? By the way VSD is not an acceptable abbreviation and will need to be spelled out. See instructions for authors about abbreviation use. Same true for PEA.

66. What is the parent organization of the ACIP?

76. Do you mean ….”have not found increase risks of pregnancy, fetal or infant ADVERSE outcomes”?

77. You can delete the sentence “Among the many outcomes….” And just state the sentence starting with “Although studies….” On line 78.

82-83. I don’t understand this sentence. Sounds like 2 objectives..”to study the stillbirth rate”..and “risk of stillbirth”. How are these different? This needs to be expanded somewhat. Also, please avoid single sentence paragraphs.

In the methods section, please describe how you did the matching. This is particularly important in revision given the concerns raised about the matching process by the stats editor.

89-92 has unclear punctuation so this is hard to read. Perhaps better “Seven sites [Kaiser Permanente Washington (Seattle, WA), HealthPartners Institute (Minneapolis, MN),….] would be clearer.

130. Not clear what this means. “high correlation between live birth outcome and pregnancy start and end dates”. Start and end dates seem like some assessment of gestational age at delivery. Since stillbirths more common earlier in pregnancy, are you just saying that the correlation noted was with more likely to have a stillbirth at earlier gestational ages? Or are you saying the livebirths more correlated w/ a start date in, lets say, November?

128-137. Here is the matching description. As noted by reviewers, on revision, the matching needs to be more robust. Could you match by race, for instance? Or parity? Or presence of comorbidities which you have? Matching just on site, month and year of LMP isn’t very robust.

144. If the index date is “the outcome date of the matched stillbirth” (lin3 136) how does this date avoid including vaccines given in post partum period? Should the delivery date of each pregnancy be used to assure this? Also, if you had 4 controls for each case, which “index date” did you use?

154. One reviewer, with whom I agree, is asking for a more nuanced approach to race here.
In addition, The AMA style manual, which the Journal uses, asks that “authors to provide an explanation of who classified individuals’ race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes).”
In addition, the nonspecific “other” as it is sometimes used for comparison in data analysis may also be a “convenience” grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. Also, White and Black, as racial categories, are now capitalized.

178. I agree w/ reviewer who felt that “coverage” may be interpreted to mean insurance coverage. Please edit.

179. I also agree with the reviewer who is concerned about your power assessment using a 50% difference in stillbirth rate seems extremely high. Could you please also report a power analysis if you assumed a less extreme difference? Post hoc, given your 795 cases, what difference in stillbirth rate did you have power to detect?

202. The journal style does not support the use of the virgule (/) except in mathematical expressions. Please remove here and elsewhere.

237. Here is where you could report the post hoc power analysis.

Salient aspects of Figure 1 are well described in the text. This can be move to supplemental digital content.

Table 1 is confusing with respect to EGA at timing of vaccination. Is this just for the flu vaccine? TDaP is given late in pregnancy. Please comment. We don’t uses tables formatted with 2 parts like this. Given that so much of the second half of the table is blank, is there a way to provide this data in the text or online supplemental digital content?

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

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

4. For studies that report on the topic of race, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes).

Use "Black" and "White" (capitalized) when used to refer to racial categories.

The category of "Other" is a grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

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 has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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 print appendixes) but exclude references.

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 limit for Original Research articles is 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. ACOG is moving toward discontinuing the use of "provider." Please replace "provider" throughout your paper with either a specific term that defines the group to which are referring (for example, "physicians," "nurses," etc.), or use "health care professional" if a specific term is not applicable.

12. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

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%").

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' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG 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 (exceptions could include manuscripts that address items of historical interest). 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 an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found at the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top).

15. Figures 1-2: Please upload as figure files on Editorial Manager.

16. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

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* 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 Sep 12, 2020, we will assume you wish to withdraw the manuscript from further consideration..

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2019 IMPACT FACTOR: 5.524
2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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