

OBSTETRICS & GYNECOLOGY



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obgyn@greenjournal.org.

Date: Jan 31, 2020
To: "Laura Jean Viens" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-4

RE: Manuscript Number ONG-20-4

The Role of Prenatal Ultrasound and Amniocentesis in the Diagnosis of Congenital Zika Syndrome: A Systematic Review

Dear Dr. Viens:

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 14 days from the date of this letter. If we have not heard from you by Feb 14, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a systematic review of the relevant literature pertaining to prenatal and postnatal diagnosis of congenital Zika infection. The population of interest was women diagnosed with Zika infection during pregnancy. The objectives of the review were to evaluate the relationships between both prenatal ultrasound findings and amniotic fluid Zika virus nucleic acid results and postnatal diagnosis of congenital Zika syndrome (abbreviated as CZS). The investigators estimated that positive prenatal ultrasound findings predicted postnatal CZS in nearly 80% of cases, and the absence of specified abnormalities was associated with the absence of postnatal CZS approximately 80% of the time. Amniocentesis sampling for the presence of Zika virus RNA was estimated to predict postnatal CZS in two-thirds of cases; whereas the absence of Zika virus RNA in amniotic fluid samples ruled out postnatal CZS in only one-third of cases.

The manuscript is well written and easy to follow. The objectives were clearly stated; however, neither hypotheses nor research questions were specified.

What criteria were used to select pregnant women for inclusion into the analysis. Was inclusion based on any clinical suspicion or were specific diagnostic criteria required? The authors did a good job defining the methods for study selection, but they should define the human subjects more clearly, both in the Abstract and in the Methods section.

Why did the authors refrain from calculating likelihood ratios, sensitivity, and specificity statistics for ultrasound and amniotic fluid Zika virus testing?

Why did the authors omit 95% confidence intervals around their point estimates of positive and negative predictive values for prenatal ultrasound and amniotic fluid Zika virus RNA?

From line 174, what is appropriate clinical care for an infant with CZS, and what are the potential consequences of its delay?

From line 175-181, how was the timing of maternal Zika exposure and maternal Zika infection distinguished? How was the timing of maternal infection established?

Reviewer #2:

Abstract

Objective - to examine relationship between prenatal diagnostic ultrasound and amniotic fluid Zika and postnatal congenital zika syndrome abnormalities

Data sources - systematic searches - 27 databases

Methods - Study Selection - 84 articles - 402 mother/infant dyads, 385 included ultrasound and 56 with amnio (39 with both)

Tabulation/ Integration/ Results - 195 fetuses - congenital zika syndrome (CZS) on u/s and postnatal abnormalities then in 153 (78%)

microcephaly (76%) and brain abnormalities (78%) confirmed postnatally

190 with CZS on u/s - 17% had CZS abnormalities postnatally

structural abnormalities identified postnatally equally in those with and without Zika RNA in amniotic fluid - (68% and 67%)

6 pregnancies - Zika virus RNA in amniotic fluid but not in subsequent amniocentesis

Conclusions - prenatal ultrasound frequently detects structural findings from Zika

not all are detected and some Zika infections are transient

prenatal detection varies - detection Zika RNA in Amniotic fluid did not predict risk of CZS and clearance of Zika RNA is possible

Diagnostic testing - shared decision making and more info is needed

Intro - CZS - serial ultrasound for those with evidence of Zika infection and amnio to test for Zika RNA

systematic review - 1) relationship between prenatal ultrasound findings and postnatal outcome after congenital zika exposure

2) relationship between amniotic fluid for Zika and postnatal outcomes after congenital Zika virus exposure

Datasources -databases listed

Study selection - 84 articles - 77 case reports and 7 cohort studies - 402 dyads

Tabulation/Integration/ Results - study design, exposure, ultrasound, amnio, outcomes

maternal zika - 80% symptomatic, 67% NAT confirmed

402 dyads - 354 live births, 44 terminations, 4 losses

zika testing on 134 infants - 14 with NAT+ and 28 with serology +

Ultrasound - at least 1 ultrasound for 355; u/s identified prenatal CZS in 195 (51%), of those with normal prenatal findings, 17% had abnormal postnatal findings

of those with abnormal prenatal u/s, 65% had postnatal evaluation and 78% had abnormality confirmed

of those not confirmed, 50% had other CZS abnormalities and more than 2/3 of ultrasound findings were confirmed postnatally

Ultrasound timing and frequency - of 186 with findings confirmed postnatally, only 29 had prenatal serial ultrasounds time for infectio to 1st abnormality 7-23 weeks so not detected by 18-20 weeks in 1/2 of pregnancies

Amniocentesis - 56 with Zika NAT in AF - of those with Zika RNA +, 68% had postnatal abnormalities and those with Zika negative NAT - 67% had postnatal CZS

Amnio timing/frequency - 10 had serial amnios and 6 cleared Zika RNA

Discussion - CZS abnormalities in 78% of pregnancies with prenatal findings and postnatal brain imaging

ultrasound is valuable and CNS abnormalities are more likely to be confirmed

1/5 CZS not confirmed postnatally

17% with normal ultrasound had CZS at pregnancy completion

u/s can't always detect abnormalities and can vary based on timing of infection, timing of ultrasound, severity, and technical expertise

time lapse between infection and CZS on ultrasound could be up to 18 weeks from exposure so serial ultrasound is important

CZS abnormalities were found in similar proportion in women with positive and negative Zika NAT so amnio doesn't clarify things and Zika RNA can be cleared

limitations - publication bias - case reports

absence of u/s findings doesn't preclude CZS and Zika RNA is not predictive

Comments -

1. This is a good review of a topic which has limited information

2. It is a great summary of the findings available for this relatively new infection

3. It is important to have this information to counsel women with exposure on the importance of serial ultrasound, postnatal ultrasound, and that a negative amnio is not necessarily reassuring though this is likely influenced by publication bias with discussion of the significant cases, it does address concerns in symptomatic women

4. It would be helpful if there could be some information provided on women with asymptomatic exposure also, was there any information as to whether women were symptomatic themselves or possibly had sexually transmitted exposure?

Reviewer #3: The goal of this study was to determine the value of prenatal ultrasound and amniocentesis in predicting neonatal outcome with documented maternal Zika infections. This was accomplished by an exhaustive review of current literature describing the results of series and case reports.

Ultimately, 84 articles yielded 385 fetus/infant dyads in the review of prenatal ultrasound, 56 in the review of amniocentesis (39 in both).

78% of 195 fetuses with congenital zika syndrome (CZS) findings on prenatal ultrasound were noted to have neonatal CZS findings.

17% of 190 fetuses without CZS findings on prenatal ultrasound were noted to have neonatal CZS findings.

68% of 56 fetuses with positive nucleic acid testing (NAT) were noted to have neonatal CZS findings.

67% of 15 fetuses with negative NAT were noted to have neonatal CZS findings.

The authors conclude that prenatal ultrasound can detect structural findings with CZS, though negative findings do not preclude development of CZS secondary to multiple variables.

The authors conclude that detection of Zika RNA in amniotic fluid did not predict the risk for CZS abnormalities.

Comments

Exhaustive, well done literature review that describes many of the pitfalls associated with prenatal diagnosis of CZS including timing of infection, timing of ultrasound, number of ultrasounds, latency between positive nucleic acid testing and ultrasound examination, and maternal clearance of zika DNA from amniotic fluid.

Limitations of the study are outlined well including heterogeneity of study subjects, varying definitions of microcephaly, lack of testing for other viruses, and lack of laboratory testing for some subjects.

The authors conclusions are valid, although an argument may be made that detection of Zika RNA in amniotic fluid did predict risk for CZS abnormalities (28/41) (68%) with 23 having Zika positive NAT from infant or fetal tissue.

Although the authors caution against "generalizing" the results of this review, their study provides a valuable resource for physicians who encounter suspected Zika infection in pregnancy in terms of patient counseling and care.

STATISTICAL EDITOR COMMENTS:

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

Table 1: It would be useful to give more context by including CIs for all the proportion estimates.

Table 2: Although most fetuses in this series had prenatal US exams, among those with abnormal prenatal findings, not all findings were confirmed and for some categories, many were not examined post-natally. This is in part due to the heterogeneity of from where the cases arose.

Fig 2: It would be useful to elaborate on how many were live births vs terminations in each group.

Fig 3: Although this is important information, since these were not a random sample of all suspected CZS cases, these might represent a biased sample and it would be difficult to generalize the findings. To some extent, that is already stated indirectly from the wide CIs, but those are based on the relatively modest sample sizes, regardless of any possible bias. From these limited data, it seems that the probability of confirmed CZS abnormalities is not related to amniotic fluid NAT being (+) or (-), but the samples are limited and the results may be biased.

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 things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

Line 49: Indicate CDC and ACOG abbreviations here, and then use the abbreviations on line and any other times these organizations are referenced.

Line 71: isn't Endnote a brand name, and as such, it should be capitalized. Same true on line 93 for Excel.

Line 82: The journal style does not support the use of the virgule (/) except in mathematical expressions. Please remove here and elsewhere.

Line 116: Please clarify by including numerator and denominators here. Is the "76%" of your total (385) or 76% of the ones that had a prenatal diagnosis of microcephaly had a post natal dx of same?

Line 126. Typo

Line 187: I suspect you are prevented for also including the potential benefit of pregnancy termination if legally an option. If you are not prevented from doing so, could you please include that as a potential advantage of prenatal diagnosis. Additional potential benefits of prenatal diagnosis of CSZ is information gathering by the family for preparation for care of a child with special needs.

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:

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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. 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. 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: 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 print appendixes) but exclude references.

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

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- * 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.
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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.

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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.

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15. Figures 1-3 may be resubmitted with the revision.

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- * 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 14 days from the date of this letter. If we have not heard from you by Feb 14, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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