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: Jan 02, 2020
To: "Veronica Gomez-Lobo"
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-2102

RE: Manuscript Number ONG-19-2102

Prenatal Dilemma: When Fetal Sex Results of Non-Invasive Prenatal Testing and Ultrasound Differ

Dear Dr. Gomez-Lobo:

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 Jan 23, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors performed a retrospective analysis of a cohort of low risk results for aneuploidy but discrepancy of fetal sex between SNP based NIPT and clinical/ultrasound results.

Why was a control group with follow up not selected for comparison?

14 of 83 of the apparently discordant results were due to human or methodological error. What is the rate of methodological error for the entire cohort?

What was the lab error or specific limitation of the SNP based method in the 3 cases?

It is speculation in the discussion to suggest other labs may not have the same quality assurance or less tracking of cases or inferior methodology.

Chorionic villus sampling often is able to suggest confined placental mosaicism. Also when CVS chromosomes are normal, it suggests normal fetal chromosomes.

Reviewer #2: This is an uncommon occurrence but data on the outcomes is useful. However, the authors cannot report the rate of discordant sex as they do not have follow up data on the vast majority of the cases. That being said, the outcomes of the 83 cases on which they do have at least some outcome data are useful, although the limitations in ascertainment need to be emphasized.

1. Is there any process for collecting outcome data on apparently normal cases?
2. Do you have any information on how often providers report back when sex discordance is identified?
3. Lines 125-34: You report a prevalence based on a denominator of over 1mil cases. However, the large majority do not fulfill your inclusion criteria. While the data on outcomes of those cases with reported discordance are useful, I do not think the data on prevalence of discordance are accurate and these should not be included unless you have a complete cohort with outcomes. I suspect the FP rate of discordance is far higher than 1/14,298 and this needs to be clear. Not sure this prevalence should be reported at all. This should really just be a report on the 83 cases in which you have information. I'd recommend removing the sentences in the discussion lines 284-86: "Although likely an underestimate, the data
Reviewer #3: Dhamankar and colleagues report findings from an industry sponsored retrospective study of cases of gender discordance between NIPT testing and ultrasound/clinical findings. The authors derive their study from a cohort of 1,301,117 NIPT test results, among which 91 cases of fetal sex discordance was noted. Causes for the gender discordance were evaluated. The leading causes for discordant NIPT results noted were human error and disorders of sexual development. The manuscript is well written and addresses an important and emerging area of perinatal medicine. A point-by-point critique of the paper follows:

1) In the Abstract of the paper the authors conclude that they propose a protocol for evaluation of cases where there is discordance between NIPT results and fetal gender. While there appears to have been a process in the laboratory, there does not appear to be a protocol that is useful to the clinician managing these cases. This would be a very helpful addition to the paper and could be included as an additional figure in the paper to help guide the clinician and reader when these situations are encountered clinically.

2) In the Results section of the paper on lines 197-199, the author report the most common human/methodologic error was sample mislabeling (n=14) and Table 1 is referenced. This does not appear in the references Table 1. This should be more clearly listed in the table.

3) Table 1: The rows under the 2-5 columns are not aligned with the initial column, making the table challenging to interpret. What does "error" mean? What does "limitation" mean? What is IVF Sample transcription? It would be helpful to provide more explanatory labels to the rows or include definition in the table footer.

4) The Discussion of the paper is 4 1/2 pages long and somewhat excessive. The Discussion could be shortened to be more concise.

STATISTICAL EDITOR COMMENTS:

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

lines 50-60, 191-197 and elsewhere in text and Tables: There were 91 discordant cases, so citing %s with that denominator should be rounded to nearest integer %.

lines 56-57: Which test was correct in the n = 7 with "apparently normal outcomes"?

Should describe overall frequency (91/1,301,117) as 7.0 per 100,000 with CIs 5.6 - 8.6 per 100,000. Or, if preferred, as 1:14,300 with CIs 1:11,600 to 1:17,800.

Table 1: How was phlebotomy sample swap established as etiology? How was US mis-assignment established? Were the original US reviewed and found to be incorrectly interpreted?

Table 3: Worth emphasizing the frequency of Turner syndrome and variants as contributing cause of DSD
Supplemental Table 2: A frequent issue seems to be cases of hypospadius leading to incorrect US ascertainment of sex, so that seems worthy of discussion.

Supplemental Table 3: None of these apparently normal outcomes had post-natal genetic testing and only 1 had repeat SNP-NIPT. Therefore to describe these as apparently normal seems jumping to conclusion. Better to describe as incomplete.

General: There is sufficient ambiguity (missing or insufficient data) that precise estimates of %s of etiologies would be imprecise and fraught with error. Should simply describe what is identified and what was incomplete or unknown.

EDITOR 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 41: please provide the source of the data set used.

Line 45: The journal style does not support the use of the virgule except in mathematical expressions. Please remove here and elsewhere.

I agree with reviewer 2 that you should be very cautious about reporting an incidence or frequency like this in the manuscript. It’s a bit misleading since you do not have outcome data on all of the fetuses (Sex assignment at birth). In the methods section, please consider adding a statement emphasizing this point and that this is a descriptive study of the cases reported to you. In the manuscript text of course it’s fine to report the rate of reporting of discordance (labeled as such) and in discussion emphasize that this is likely an underestimation of the true rate of discordance given your incomplete knowledge of results in the 1million + samples.

Lines 50-54: Since the DSD category is the greatest by percentage AND as this is what you emphasize in the conclusion, I recommend that you list it first here, followed by the human error category.

Lines 58-65 It seems prudent in your conclusion to emphasize more overtly the need for collaboration between the laboratory that performed the test and the patient’s clinician.

Lines 78-81: Is this information relevant to the current study? It seems that providing information about the accuracy of sex-chromosome number, rather than T21 prediction, is the important piece of information for this paper. Could that be substituted?

Line 85: Should read “Fetal sex predication CAN be reported”…..as some women get this testing in the 2nd trimester, when US can evaluate for fetal sex.

Line 89: Is this for SNP based testing? Also, as the reader will have no way of judging the extent of your knowledge, and since this is essentially a primacy claim (you are the first to report or this is the biggest study, etc), please provide the database(s)searched (Embase, PUBmed, Google Scholar) and the search terms used in order to substantiate this statement.

Line 133: Why did you exclude egg donor or surrogates?
Line 139: State the lab name and location.

Line 163: What is PGT-A?

Line 194: See notes in abstract section.

Line 201: What were the outcomes for these 4 women with confirmed NIPT results? I think it is important to emphasize the outcomes when clinicians and patients do the steps your lab recommends (repeat NIPT testing, placental testing, etc) as if these steps alter outcomes in terms of work up then this should be emphasized.

Line 205-206: I don’t know what you mean “or limitations of the SNP-based NIPT method”. This would need to be described in the methods section as one of the categories and the meaning defined.

Line 281: on line 82, with this same reference, you state it’s >80% of providers and here you indicate it is >80% of families. While they are likely to be the same (Providers ask if women want this information) what does the reference use as the “asker”. Also, would you consider substituting “women” for “families” if the reference indicates that the >80% is of patients and not providers? The patient undergoing the test is the woman, not the family.

Line 358: Please explain what a “molecular barcode” is.

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. 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. Obstetrics & Gynecology follows the Good Publication Practice (GPP3)* guideline for manuscripts that report results that are supported or sponsored by pharmaceutical, medical device, diagnostics and biotechnology companies. The GPP3 is designed to help individuals and organization maintain ethical and transparent publication practices.

   (1) Adherence to the GPP3 guideline should be noted in the cover letter.

   (2) For publication purposes, the portions of particular importance to industry-sponsored research are below. In your cover letter, please indicate whether the following statements are true or false, and provide an explanation if necessary:
      (2a) All authors had access to relevant aggregated study data and other information (for example, the study protocol) required to understand and report research findings.
      (2b) All authors take responsibility for the way in which research findings are presented and published, were fully involved at all stages of publication and presentation development and are willing to take public responsibility for all aspects of the work.
      (2c) The author list accurately reflects all substantial intellectual contributions to the research, data analyses, and publication or presentation development. Relevant contributions from persons who did not qualify as authors are disclosed in the acknowledgments.
      (2d) The role of the sponsor in the design, execution, analysis, reporting, and funding (if applicable) of the research has been fully disclosed in all publications and presentations of the findings. Any involvement by persons or organizations with an interest (financial or nonfinancial) in the findings has also been disclosed.
      (2e) All authors have disclosed any relationships or potential competing interests relating to the research and its publication or presentation.

   (3) The abstract should contain an additional heading, "Funding Source," and should provide an abbreviated listing of the funder(s).

   (4) In the manuscript, a new heading—"Role of the Funding Source"—should be inserted before the Methods and contain a
Detailed description of the sponsor's role as well as the following language:

"The authors had access to relevant aggregated study data and other information (such as study protocol, analytic plan and report, validated data table, and clinical study report) required to understand and report research findings. The authors take responsibility for the presentation and publication of the research findings, have been fully involved at all stages of publication and presentation development, and are willing to take public responsibility for all aspects of the work. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately. The role of the sponsor in the design, execution, analysis, reporting, and funding is fully disclosed. The authors' personal interests, financial or non-financial, relating to this research and its publication have been disclosed." Authors should only include the above statement if all of it is true, and they should attest to this in the cover letter (see #2, above).


4. Please submit a completed STROBE checklist.

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

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology 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.

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. 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.

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

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* 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).

9. 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 that states 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."
You cannot use a virgule to replace "and" or "or" in a sentence.

10. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

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

11. 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.

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13. 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").

14. 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.

15. Figure 1: Please upload as a figure file on Editorial Manager.

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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 21 days from the date of this letter. If we have not heard from you by Jan 23, 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

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