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)*

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Date: Sep 11, 2019
To: "Dominique Heinke" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1537

RE: Manuscript Number ONG-19-1537

Risk of Stillbirth for Fetuses with Specific Birth Defects

Dear Dr. Heinke:

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 Oct 02, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors are to be congratulated for this population based court to determine the risk of stillbirth for isolated birth defects based on NBDPS data over from 1997 to 2011. Some findings were expected and others were surprising including increased stillbirth risk for isolated cleft lip with palate. The authors were also able to estimate the potential contribution of elective terminations to the various risks which could bias results especially for severe neurologic abnormalities.

I would like the authors to expand on why they excluded isolated heart defects. In the era of high quality ultrasound machines, at least half of major cardiac malformations, such as hypoplastic left heart, are easily identified antenatally. This, too, is of major interest to clinicians. I feel this is a drawback of the paper.

The paper is well written and conclusions are appropriate for the data.

Reviewer #2: This is a retrospective population-based cohort study from a multi state surveillance program National Birth Defects Prevention Study looking at the risk of stillbirth associated with specific birth defects in pregnancies > 20 weeks. Fetuses with known chromosomal or single gene disorders were excluded.

Abstract:

1. The manuscript should have numbered lines for editing purposes.

2. In the results section what is transverse?

3. The results for the specific defects should be consistent with the way the overall still birth rate is reported per 1000. It is not clear in this section.

4. Although higher than the the national average the CI were quite large. What specific changes to counseling and management are proposed? NST or BPP along with interval growth scans?

Introduction:

5.The first paragraph is a good overview of the topic along with an explanation for the objectives and why the author is breaking down the risk by specific birth defect.

6. Describe the what was done for enhanced monitoring for the gastroschisis studies in references 10-14.

Methods:

7. The study population here states there were 10 states in the program but the abstract says 9. Please clarify if data was excluded from the total or if this was a misprint.

8. If genetics studies were not required what specifically was meant by strongly suspected? The possibility of coexisting genetic disorders may bias the results. Is there a sub-analysis on those with confirmed normal diagnostic genetic testing?

9. Analysis did not include New Jersey which I assume accounts for the 9 states. By including data from states which did not include termination this may affect the quantified bias analysis. How many of the total patients were from these states?

10. Specify which isolated heart defects were excluded? Echos are getting better and these are reported more often with little data to guide risk and or surveillance.

Results:

11. The reported rates of still-birth for lethal conditions in the neonatal period is probably not clinically useful or related to the conclusion of using this information for counseling or surveillance. Calculating an overall rate with and without lethal conditions would be helpful. Including all of these in the first section and acknowledging this was important.

12 Figures 2 and 3 are hard to read by including the bounds for possible termination. The first two graphs do not show arrows or circles. I do see a repeat figure for each. Were both sets of figures meant to be included in the manuscript?

Discussion:

13. Framing the discussion in the context of a 35 year old risk of 10 per 1000 is a good idea and gives the reader an idea of what type of surveillance and utility there may be. Ie NST/BPP.

14. The limitations of this study were acknowledged including unconfirmed genetic disorders. Specifically disorders with known associations like omphalocele. Although the use of quantified bias analysis for termination to assess upper and lower bound rates of still birth was worthy, I am not sure about the validity of the assumptions and how much this adds to the study.

Reviewer #3: Heinke, et al present data regarding the risk of stillbirth for various congenital defects. The manuscript is well written but could benefit for editing for length throughout. I have several specific comments:

1. In the first line of Abstract, Methods, the strong implication is that stillbirths were tested for genetic conditions and those that tested positive were eliminated. In fact, the authors merely selectively eliminated those defects with a strong suspicion for a chromosomal etiology. This is a major point that needs to be clarified in the abstract and manuscript as it impacts the interpretation and utility of the findings in significant ways. In fact, many of the defects that were left in have strong associations with chromosomal defects (viz, duodenal atresia and trisomy 21).

2. I like the "quantified bias analysis" approach. I think it is overstated, however, in the last line of the results. The boundaries around spina bifida for example are pretty tight.

3. The second line of the introduction to me implies causality (don't know if this was authors' intention) - consider association instead of contributor.

4. Although it probably seems very obvious to the authors, they should state in plain English how they calculated the stillbirth risk!

5. In the discussion on why fetal anomalies might be associated with IUFD, undiagnosed chromosomal defects (especially those that impact placental function) is a possibility.

STATISTICAL EDITOR'S COMMENTS:

Although this represents a large data set and extends the estimates of stillbirth risk by considering that terminations potentially may have resulted in stillbirth, limitations remain. Not all the diagnoses listed would be obvious on post-mortem (eg, duodenal atresia/stenosis, esophageal atresia, diaphragmatic hernia). The analysis assumes complete ascertainment by post-mortem exam of all stillborn and all terminations in each of the States over a 14 year period. Thus,

especially for rarer diagnoses, these estimates may be faulty.

Figs: The use of (‰) for stillbirth rates may not be understood by many readers. Suggest instead citing as per 1,000.

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. 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.

4. 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.

5. 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).

6. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

7. 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.

8. 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.

9. 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.

10. 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%").

11. 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.

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

"Figure 1: Please upload a figure file to Editorial Manager."

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

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Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

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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.

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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 21 days from the date of this letter. If we have not heard from you by Oct 02, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

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

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time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.

October 2, 2019

RE: Resubmission of manuscript *Risk of Stillbirth for Fetuses with Specific Birth Defects,* ONG-19-1537

The Editors
Obstetrics & Gynecology
409 12th Street, SW
Washington, DC 20024

Dear Editors:

Thank you for the opportunity to revise our manuscript *Risk of Stillbirth for Fetuses with Specific Birth Defects.* We appreciate the thoughtful review and constructive suggestions. We believe our manuscript has been improved through the suggested edits.

Following this letter are the editor and reviewer comments with our responses in blue text including where and how the manuscript was modified. Changes in the manuscript are marked by track changes. All changes have been made in collaboration with all coauthors who have given their approval of the manuscript in its final form.

Sincerely,

Dr. Dominique Heinke, ScD

REVIEWER COMMENTS:

REVIEWER #1

The authors are to be congratulated for this population based court to determine the risk of stillbirth for isolated birth defects based on NBDPS data over from 1997 to 2011. Some findings were expected and others were surprising including increased stillbirth risk for isolated cleft lip with palate. The authors were also able to estimate the potential contribution of elective terminations to the various risks which could bias results especially for severe neurologic abnormalities.

I would like the authors to expand on why they excluded isolated heart defects. In the era of high quality ultrasound machines, at least half of major cardiac malformations, such as hypoplastic left heart, are easily identified antenatally. This, too, is of major interest to clinicians. I feel this is a drawback of the paper.

The paper is well written and conclusions are appropriate for the data.

We would like to thank Reviewer #1 for their kind and thoughtful comments.

We agree with the Reviewer that inclusion of major cardiac malformations would be ideal. Two limitations led to our decision. First, during the time of the study, the prenatal detection of cardiac malformations was not as complete as it is now. Although it improved over the course of the study, greater improvements occurred after the conclusion of the study, particularly with guidance issued in 2013 (AIUM practice guideline – J Ultrasound Med 2013). Our second limitation is that identified heart defect cases where the mother did not participate in the interview portion of the study have not yet received clinical genetics and pediatric cardiology review to confirm diagnosis – means that we do not currently have sufficient cases to analyze and analyses of only the interviewed cases could be biased by factors associated with participation.

We have added to the following text to the methods to further explain our exclusion: “We further excluded isolated heart defects based on the low sensitivity of prenatal diagnosis during the study period **and incomplete cardiology review for a subset of heart defect cases with high detection (e.g., hypoplastic left heart syndrome).”** (bolded words added)

REVIEWER #2

This is a retrospective population-based cohort study from a multi state surveillance program National Birth Defects Prevention Study looking at the risk of stillbirth associated with specific birth defects in pregnancies > 20 weeks. Fetuses with known chromosomal or single gene disorders were excluded.

Abstract:

1. The manuscript should have numbered lines for editing purposes.

We apologize for this oversight. Consecutive line numbers have been added.

2. In the results section what is transverse?

We apologize for this oversight. This should say “transverse limb deficiencies”. The text has been updated to reflect this.

3. The results for the specific defects should be consistent with the way the overall still birth rate is reported per 1000. It is not clear in this section.

We have updated this section to clarify that risks are reported per 1000 fetuses.

4. Although higher than the the national average the CI were quite large. What specific changes to counseling and management are proposed? NST or BPP along with interval growth scans?

We agree that the CIs are quite large for many defects. However, the lower bound of the CIs exclude the national average for all but 6 isolated birth defects. In addition, the large CIs could be considered in counseling and management to better inform both practitioners and families regarding the range of uncertainty.

Introduction:

5.The first paragraph is a good overview of the topic along with an explanation for the objectives and why the author is breaking down the risk by specific birth defect.

We thank the Reviewer for this kind comment.

6. Describe the what was done for enhanced monitoring for the gastroschisis studies in references 10-14.

A description of the protocol used by the study reporting the 58% reduction in gastroschisis fetal death (reference 14) has been added to the introduction as follows.

"...for example, a recent study of an enhanced monitoring program for prenatally-diagnosed gastroschisis **of regular growth ultrasound scans at 28, 32, and 36 weeks' gestation (with additional scans for concerns about fetal growth) and twice weekly Cardiotocograph monitoring from 34 weeks' to planned delivery at 38 weeks'**..."

Methods:

7. The study population here states there were 10 states in the program but the abstract says 9. Please clarify if data was excluded from the total or if this was a misprint.

The NBDPS includes 10 states, but we included only 9 in our analysis. As noted below, this is because we excluded New Jersey.

We have added the following text to the Analysis section where we describe the exclusion of New Jersey **"...resulting in analyses among 9 states"**.

8. If genetics studies were not required what specifically was meant by strongly suspected? The possibility of coexisting genetic disorders may bias the results. Is there a sub-analysis on those with confirmed normal diagnostic genetic testing?

We have added the following to the methods section to clarify the process of excluding those with strongly suspected disorders and the reason we do not require confirmed normal genetic testing:

"For those without confirmatory testing, if review by board-certified geneticists identified features (e.g., a pattern of major or minor anomalies, strong family history of disorder with known genetic basis) which

strongly suggested that the presence of a chromosomal or genetic disorder, these cases were excluded."

In the discussion we have added: "We did not require confirmed chromosomal testing as the poor success of available methods (i.e., karyotype) among stillbirths would disproportionately exclude these cases, leading to an underestimate of stillbirth risk."

9. Analysis did not include New Jersey which I assume accounts for the 9 states. By including data from states which did not include termination this may affect the quantified bias analysis. How many of the total patients were from these states?

As noted above, the Reviewer is correct that the exclusion of New Jersey accounts for the 9 states.

There were 2,399 cases with a gestational age ≥20 weeks from sites that collected stillbirths but not terminations. Of these, 2330 were live born, 61 stillborn, and 8 terminations (NB: one state began collecting terminations in the final year of the study but because these were not consistently collected, they would be excluded if these sites are excluded).

To evaluate the potential effect, we ran the analyses excluding sites not collecting terminations and compared the upper risk bounds under that analysis to those presented here. The impact on the results of the bias analyses was minimal.

10. Specify which isolated heart defects were excluded? Echos are getting better and these are reported more often with little data to guide risk and or surveillance.

All isolated heart defects eligible for the NBDPS were excluded from our analysis. The full list of eligible birth defects is included in the supplemental materials.

We agree with the Reviewer that inclusion of major cardiac malformations would be ideal as noted in our response to Reviewer 1. Although fetal echocardiography has led to improved prenatal diagnosis over time, during the time of the study (1997-2011) the prenatal detection of cardiac malformations was not as high as it is now. Although it improved over the course of the study, major improvements occurred after the study period, such as with guidance on fetal heart imaging issued in 2013 (AIUM practice guideline – J Ultrasound Med 2013).

Results:

11. The reported rates of still-birth for lethal conditions in the neonatal period is probably not clinically useful or related to the conclusion of using this information for counseling or surveillance. Calculating an overall rate with and without lethal conditions would be helpful. Including all of these in the first section and acknowledging this was important.

We respectfully disagree with the Reviewer that the inclusion of lethal conditions is not clinically useful or related to counseling and surveillance. While the information provided cannot improve the ultimate outcome for lethal conditions, counseling parents receiving the prenatal diagnosis of a lethal condition is an important part of clinical care and many such families wish to know the chances of their infant being born alive; we believe our data are relevant to the needs of these families and perinatal palliative care providers.

We have noted this by adding the following to the discussion: "Nonetheless, our results provide some reassurance for parents and providers since most fetuses with the examined birth defects survive to live

birth **and provide import information on the likelihood of survival to live birth for counseling parents of fetuses with a perinatal lethal defect**."

Additionally, we would like to thank the reviewer for the suggestion to calculate estimates after excluding lethal conditions. We have added the results of this analysis as a supplemental table, which is described in the results as follows:

"After restricting to cases with nonfatal defects most stillbirth risk estimates and risk bounds did not change from those among all cases (eTable 2). However, the following stillbirth risk estimates (per 1000) were reduced: omphalocele (115 to 105), sacral agenesis (13 to 7), and transverse and longitudinal limb deficiencies (41 to 36 and 25 to 21, respectively). Additionally, the risk bounds narrowed for these defects and others."

12 Figures 2 and 3 are hard to read by including the bounds for possible termination. The first two graphs do not show arrows or circles. I do see a repeat figure for each. Were both sets of figures meant to be included in the manuscript?

We apologize for the duplication of figures. Following the instructions to authors, we included the figures in the manuscript, but when they were uploaded and converted to a PDF some of the elements (e.g., the symbols for risk bounds) were lost. Therefore, we also included a separate version with the complete figure.

Discussion:

13. Framing the discussion in the context of a 35 year old risk of 10 per 1000 is a good idea and gives the reader an idea of what type of surveillance and utility there may be. Ie NST/BPP.

We thank the reviewer for this kind comment and are pleased that the framing helped to convey the utility of this study.

14. The limitations of this study were acknowledged including unconfirmed genetic disorders. Specifically disorders with known associations like omphalocele. Although the use of quantified bias analysis for termination to assess upper and lower bound rates of still birth was worthy, I am not sure about the validity of the assumptions and how much this adds to the study.

We recognize that the language used to describe the risk bounds may have created some confusion – the text of the methods has been updated as follows to clarify:

"Note that both extremes are unrealistic and just meant to provide bounds of the stillbirth risk in the absence of any terminations: **i.e., the first (lower limit) had none of the terminations been stillbirths and the second (upper limit) had all been stillborn."**

The bias analysis is conducted without any assumptions as to the risk of stillbirth for that would have occurred in the absence of termination – i.e., the bounds provide the absolute maximum and minimum risk that could be observed.

This is noted in the text as follows: "We quantified the possible impact of termination of birth defect cases by estimating the lower and upper bounds of the possible birth defect-specific risk given our observed data **without additional assumptions**."

One utility of these bounds is that they allow for more accurate comparisons of stillbirth risk for fetuses with birth defects across areas with different termination rates, e.g., comparing risks in the US to Ireland where termination was illegal until recently. Additionally, they allowed us to identify defects where our estimates are potentially biased by high termination rates.

REVIEWER #3

Heinke, et al present data regarding the risk of stillbirth for various congenital defects. The manuscript is well written but could benefit for editing for length throughout. I have several specific comments:

1. In the first line of Abstract, Methods, the strong implication is that stillbirths were tested for genetic conditions and those that tested positive were eliminated. In fact, the authors merely selectively eliminated those defects with a strong suspicion for a chromosomal etiology. This is a major point that needs to be clarified in the abstract and manuscript as it impacts the interpretation and utility of the findings in significant ways. In fact, many of the defects that were left in have strong associations with chromosomal defects (viz, duodenal atresia and trisomy 21).

Please see the updates to the text noted in the response to Reviewer 1 (point 8).

In the discussion we have tried to clearly state the limitations of this approach, as follows:
"Because genetic testing was not universal and testing methods during this time period were limited, some included cases may have unidentified genetic or chromosomal conditions. This limitation may particularly impact estimates for omphalocele as this defect is associated with various chromosomal disorders. [40] However, strongly-suspected genetic or chromosomal cases were excluded following geneticist review and eligibility criteria changed throughout the course of the study as new associations with single gene disorders were discovered **which should limit the potential influence of these disorders**. [20]"

We have updated the abstract to state: "without **known or strongly suspected** chromosomal or single-gene disorders". (bolded words added)

2. I like the "quantified bias analysis" approach. I think it is overstated, however, in the last line of the results. The boundaries around spina bifida for example are pretty tight.

We are pleased that the reviewer found our bias analysis to be beneficial to the manuscript.

As the last line of the results refers to anencephaly, we assume the reviewer is referring to the last line of the prior paragraph which states "Quantified bias estimates suggest that risk of stillbirth for isolated spina bifida (24 per 1000 [33/1347 cases; RB: 22-108; 95% CI: 17-34]), holoprosencephaly (30 per 1000 [5/167 cases; RB: 27-120; 95% CI: 10-68]) may be up to 4 times higher than observed risks after accounting for the potential impact of terminations."

The risk bounds reported for spina bifida are 22-108; we suspect the reviewer may have been confused by the 95% confidence interval for the estimated risk, which is much smaller (17-34).

3. The second line of the introduction to me implies causality (don't know if this was authors' intention) - consider association instead of contributor.

Although – as we note in the discussion – not all birth defects will be causally related to stillbirth, some are unquestionably a cause of stillbirth, such as anencephaly and bilateral renal agenesis. Therefore, we believe that our statement that birth defects are a major contributor to the stillbirth rate in the US is accurate.

4. Although it probably seems very obvious to the authors, they should state in plain English how they calculated the stillbirth risk!

In the third paragraph following "Analyses" within the methods section, we state the following: "We calculated absolute birth defect-specific risk as the number of stillbirths divided by the total number of live births and stillbirths with that defect."

At the end of the methods we note "Risk estimates, bounds, and 95% CIs are reported as stillbirths per 1000 birth defect cases."

Additionally, we describe the method for calculating all values in the footnotes of the figures and supplemental tables.

5. In the discussion on why fetal anomalies might be associated with IUFD, undiagnosed chromosomal defects (especially those that impact placental function) is a possibility.

We thank the reviewer for this excellent suggestion. The text in this section has been updated to state: "Additional examples are maternal pre-pregnancy diabetes and **undiagnosed genetic or chromosomal disorders** which are strongly associated with both birth defects and stillbirth."

STATISTICAL EDITOR'S COMMENTS

Although this represents a large data set and extends the estimates of stillbirth risk by considering that terminations potentially may have resulted in stillbirth, limitations remain. Not all the diagnoses listed would be obvious on post-mortem (eg, duodenal atresia/stenosis, esophageal atresia, diaphragmatic hernia). The analysis assumes complete ascertainment by post-mortem exam of all stillborn and all terminations in each of the States over a 14 year period. Thus, especially for rarer diagnoses, these estimates may be faulty.

We agree with the statistical editor that not all included birth defects would be obvious without a full postmortem examination. However, we included these defects in the analysis as they have good prenatal diagnosis based on ultrasound and/or prenatal signs (e.g., polyhydramniosis for duodenal atresia/stenosis and esophageal atresia). We excluded from analyses those defects which have poor prenatal diagnosis due to low sensitivity of ultrasound and absence of prenatal signs, and which would be particularly difficult to detect on a limited postmortem evaluation (e.g., anorectal atresia, biliary atresia, hypospadias).

We have noted this limitation in the discussion: "Identification of birth defects among stillborn and terminated fetuses may be incomplete, particularly in the absence of autopsy. Consequently, if co-occurring birth defects remained undiagnosed, our results may underestimate risks for birth defects with decreased prenatal identification in addition to overestimating risks for isolated cases."

Figs: The use of (‰) for stillbirth rates may not be understood by many readers. Suggest instead citing as per 1,000.

We appreciate this suggestion and have updated the figures as requested.

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.

We would like to take option A to have our point-by-point response published.

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. 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=lDF7oMaPKXpkYvev9V-fVahWL0QWnGCCAfCDz1Bns_w&r=1-7-yfkObCZEEPyegDF0q85BrdJB4vvFwwwsOowqBnY&m=aPqC1ZEcBZtZFiNIDIqRXTvVXsjGi5KsR0cDxwGFoYM&s=k7-m9TN1zaU1OpXyriuBYTnkJ0xtT9bdkufx8nRYs-o&e=. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

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Our manuscript fits within the stated page (22 pages excluding references) and word limits (3266 words).

5. 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.
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* 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).

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We have added this to the title page.

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We have edited the abstract to ensure consistency with the reporting in the manuscript and have added a word count for the abstract (294 words).

8. Only standard abbreviations and acronyms are allowed. A selected list is available online at https://urldefense.proofpoint.com/v2/url?u=http-3A__edmgr.ovid.com_ong_accounts_abbreviations.pdf&d=DwIGaQ&c=lDF7oMaPKXpkYvev9V-fVahWL0QWnGCCAfCDz1Bns_w&r=1-7-yfkObCZEEPyegDF0q85BrdJB4vvFwwwsOowqBnY&m=aPqC1ZEcBZtZFiNIDIqRXTvVXsjGi5KsR0cDxwGFoYM&s=5_agIi97wBVqr2T0QNiyeKKso39Wz3HDDDfbBwWIJzU&e=. 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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The manuscript has been edited to remove the virgule symbol in sentences.

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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%").

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