

OBSTETRICS & GYNECOLOGY



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- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

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

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

Date: Oct 24, 2019
To: "Ibrahim A. Hammad" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1884

RE: Manuscript Number ONG-19-1884

Umbilical Cord Abnormalities and Stillbirth

Dear Dr. Hammad:

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 Nov 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Hammad and colleagues present findings from a nested case-control study of umbilical cord abnormalities as a potential cause for stillbirth. The authors utilized data from the NICHD Stillbirth Collaborative Research Network. Cause of death analysis was classified using the INCODE system. In their cohort of 496 women with stillbirth, 19% were associated with umbilical cord abnormalities as defined by the authors. No clear clinically useful risk factors were identified in their analysis. Overall the paper is well written. A point-by-point critique of the manuscript follows:

- 1) In the Precis and conclusion section of the Abstract, the authors alternatively state "nearly 20%" and 19% of stillbirth cases are associated with umbilical cord abnormalities. This is somewhat confusion. It would improve readability of the revised paper to consistently state the actual incidence of stillbirth related to umbilical cord abnormalities for consistency.
- 2) In the Abstract and Results section of the paper the authors state that "19.0%" of all stillbirths were associated with umbilical cord abnormalities. In the Discussion of the paper on line 198, the authors state that "...over 19.2% of all stillbirths... ..were associated with umbilical cord abnormalities". This statement does not appear to be supported by the data presented in the results section of the paper. The authors should carefully review the manuscript with their revision to ensure that the actual incidence of stillbirth related to umbilical cord abnormalities be consistently stated throughout the manuscript.
- 3) In the Abstract a definition is provided for each of the cord abnormalities except for "compromised fetal microcirculation". As this is probably abnormality that readers would least understand, it would be useful to include the parameters, similar to the other cord abnormalities, included in this cord abnormality component.
- 4) On page 9 of the manuscript, lines 180-190, the authors present data related to the Umbilical Cord Index (UCI). Data is presented for high and low UCI but no data is presented on the intermediate group. It would be helpful to include the data for all 3 of the UCI groups in the revised manuscript.
- 5) The authors have a unique opportunity in their dataset to provide a more robust assessment of UCI (n=1331). It would be of great interest to evaluate UCI on a continuum rather than a categorically to explore whether there is a more optimal threshold for UCI that could be used clinically to risk stratify pregnancies for this antenatal metric.
- 6) Table 4 - UCI is not defined in the table. Given the similarity to UCA, it would be important to include the definition of UCI in the title or footer when used. This would improve readability of the Table.

Reviewer #2: I congratulate the authors on carrying out what was clearly a very careful and thorough study. They say at line 118 that "The protocol included an in-hospital interview, medical record abstraction, placental and umbilical cord gross and histopathology examination, and biospecimen collection for cases and controls. For stillbirths, a standardized postmortem examination was also performed". This represents a very substantial piece of work.

However I have concerns about the primary hypothesis, or rather the lack of it, underlying their study. They say at line 96 "our purpose was to thoroughly characterize stillbirths associated with umbilical cord abnormalities in the Stillbirth Collaborative Research Network (SCRN) study and to explore maternal and clinical factors associated with these stillbirths". This approach has sometimes been disparagingly referred to as "a fishing expedition". There is no suggestion from the authors as to what they hypothesised they might expect to find. This inevitably leads to statistical difficulties. They have studied a very large number of characteristics and yet despite this they say at line 157 that "No corrections for multiple comparisons were made". They do not explain why they have chosen this approach when it would be usual to use the Bonferroni correction or something similar.

However more fundamentally, I think it is a problem that they have put a wide number of disparate causes of stillbirth into a single category simply on the basis that there was some involvement of the umbilical cord. The major category was cord entrapment (48%) and on first principles I would associate this with cord compression related to fetal growth restriction and oligohydramnios, because when the fetus is well grown and the cord is pulsatile, being slippery it tends to push itself out of the way, which is aided when there is plenty of fluid around the baby. However, there is no mention of birthweight in the paper. When cord entrapment occurs in association with a well grown fetus, in my experience for it to be sufficient to cause stillbirth it tends to be associated with prolonged labour, however I note that the duration of labour has not been recorded. In contrast, "compromised fetal microcirculation" which occurred in 29% of stillbirths was diagnosed when there was "histopathology evidence of vascular obstruction". This is not a category which I am familiar with but on first principles I would have linked it with chronic hypertension and pre-eclampsia. I note that the group as a whole were not associated with these conditions so I remain at a loss to understand what the significance of this vascular obstruction might have been, or indeed what caused it.

The main point is that I cannot see on first principles why one would expect cord entrapment and compromised fetal microcirculation to have any aetiological factors in common. Cord prolapse, which occurred in 5%, is associated as the authors suggest with prelabour preterm rupture of the membranes, again a very different scenario to cord entrapment or placental vascular obstruction. The authors say at line 261 that "our ability to sub-analyze UCA stillbirths by type was limited by sample size, despite having one of the largest cohorts of UCA stillbirths to date" but that does not in my opinion justify combining disparate groups with little in common into one category that lacks any logical coherence.

My view therefore is that (A) despite the lack of statistical power the authors should have subdivided the umbilical cord cases according to aetiology (which would have given small numbers for evaluation, but the small numbers is not in my opinion a justification for combining diagnostic groups which have little in common other than an anatomical structure) and then (B) examined specific hypotheses relating to their aetiology.

Reviewer #3: The authors report on a subset of data from a large prospective stillbirth study in which they analyze association of umbilical cord anomalies with stillbirth.

While no conclusive information guiding clinical practice can be deducted at this time from the reported findings, the reported data add to our knowledge base and point out umbilical cord anomalies as a possible important cause for stillbirth.

The finding that hypocoiled cord is associated with stillbirth, whereas hypercoiled cord may not be, desires further evaluation and may be important for clinical management.

STATISTICAL EDITOR COMMENTS:

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

Table 1: Due to sample sizes, should round %s to nearest integer, not cite to nearest 0.1%.

Tables 2,3: Should format mean(SD), not mean(SE). Need units for maternal age.

Table 3: Many of the comparisons involve small counts and should have used Fisher's test, not Chi-square. Also, many of those with small counts were NS, but also had low power to generalize the conclusion of NS (eg, alcohol use, TSH < 0.1, etc).

Table 4: Should format mean(SD), not mean(SE). Need units for maternal age. Due to sample sizes, should round %s to nearest integer, not cite to nearest 0.1%. Many of the comparisons involve small counts and should have used Fisher's test, not Chi-square. Also, many of those with small counts were NS, but also had low power to generalize the conclusion of NS (eg, tobacco use, etc). Notably, the comparison of thyroid disorder ($p = .047$ becomes $p = 0.12$), comparison of chronic HTN ($p = .002$ becomes $p = 0.07$)

Fig 1: Why was there no analysis of cord anatomy among the live births to contrast with cord abnormalities among the stillbirth cohort? Should also include among limitations that the UCI subset excluded ~ 31% of the original total and thus may represent a biased subset. Should compare the original cohort vs the UCI cohort (could be supplemental) to evaluate whether there were any demographic/clinical differences which could have affected the conclusions from the UCI subset.

Fig 2: I presume the stats test was by use of Chi-square, but should state the test used.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- This sentence is unclear--you are talking about stillbirth, so "fetal injury" seems out of place. I think your quote is referring to the definition of cord accidents, which can cause fetal injury or still birth, but your sentence is about stillbirth. Please edit.

- Is this the rate of stillbirths associated with cord abnormalities or the rate of cord abnormalities associated with stillbirths? I think the former.

- PRESENTATION OF STATS INFORMATION - P Values vs Effect Size and Confidence Intervals

While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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. This is true for the abstract as well as the manuscript. Please provide absolute values for variables, in addition to assessment of statistical significance. We ask that you provide crude OR's followed by adjusted OR's for all variables.

- this should be an aOR shouldn't it?

- Please avoid causal language throughout your manuscript. Your study can identify and quantify associations, but not causation. Language should be changed in the precis, abstract, and manuscript, if causal language is used in those sites. In this case "that are associated with live births in a majority of cases"...

- Please use reVITALize terminology. In this case, prelabor rupture of membranes is now the accepted term.

2. 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.

3. 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.

4. This appears to have been presented at SMFM. Please disclose this on the title page.

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

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

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

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 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. 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%).

12. Line 262: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

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. Figures

Figure 1: In exclusion box where n=652, are the items totaling 167 not mutually exclusive?

Figure 2: Okay. The current figure file may be resubmitted as-is.

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

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

16. 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 Nov 14, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

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

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

Dear editor-in-chief, *Obstetrics and Gynecology*

We are honored and grateful for the opportunity to have our manuscript revised and considered for publication. We have attempted to improve the paper by addressing the reviewers comments as follows. We would be happy to further revise the paper at the discretion of the editors and reviewers.

Thank you for your consideration.

Our responses to all reviewer/editor comments are in the following format:

A. Point made by the reviewer/editor.

B. Reply to the reviewer/editor (by the authors) - you may agree or disagree with the comment - if you disagree, it is necessary to explain the reasons and provide evidence in the form of references, if necessary, in support of your point.

C. Provide the specific page and line on which any changes were made (if applicable).

Reviewer #1

Reviewer #1 Point #1

- A. In the Precis and conclusion section of the Abstract, the authors alternatively state "nearly 20%," and 19% of stillbirth cases are associated with umbilical cord abnormalities. This is somewhat confusion. It would improve readability of the revised paper to consistently state the actual incidence of stillbirth related to umbilical cord abnormalities for consistency.
- B. **Thank you for pointing that out. We agree with your suggestion and have made changes to reflect that. We've changed the text to 19% and added a 95% confidence interval.**
- C. **Page 4, and 5 lines 53 and 70**

Reviewer #1 Point #2

- A. In the Abstract and Results section of the paper the authors state that "19.0%" of all stillbirths were associated with umbilical cord abnormalities. In the Discussion of the paper on line 198, the authors state that "...over 19.2% of all stillbirths...were associated with umbilical cord abnormalities". This statement does not appear to be supported by the data presented in the results section of the paper. The authors should carefully review the manuscript with their revision to ensure that the actual incidence of stillbirth related to umbilical cord abnormalities be consistently stated throughout the manuscript.
- B. **We agree with the reviewer, and we have made changes to reflect that. It now states "19%" and we added a 95% confidence interval in the results section.**
- C. **Page 5, 8, and 10 lines 53, 166, and 203**

Reviewer #1 Point #3

- A. In the Abstract a definition is provided for each of the cord abnormalities except for "compromised fetal microcirculation". As this is probably abnormality that readers would least understand, it would be useful to include the parameters, similar to the other cord abnormalities, included in this cord abnormality component.
- B. **We thank the reviewer for their recommendation and have made the change by adding a definition to compromised fetal microcirculation into the abstract.**
- C. **Page 5, lines 64-67.**

Reviewer #1 Point #4

- A. On page 9 of the manuscript, lines 180-190, the authors present data related to the Umbilical Cord Index (UCI). Data is presented for high and low UCI but no data is presented on the intermediate group. It would be helpful to include the data for all 3 of the UCI groups in the revised manuscript.
- B. **We've added data for the intermediate group as recommended by the reviewer.**
- C. **Page 9, lines 186-189.**

Reviewer #1 Point #5

- A. The authors have a unique opportunity in their dataset to provide a more robust assessment of UCI (n=1331). It would be of great interest to evaluate UCI on a continuum rather than a categorically to

explore whether there is a more optimal threshold for UCI that could be used clinically to risk stratify pregnancies for this antenatal metric.

- B. We thank the reviewer for their suggestion. We've evaluated UCI on a continuum and added these results.**
- C. Page 10, lines 204-208.**

Reviewer #1 Point #6

- A. Table 4 - UCI is not defined in the table. Given the similarity to UCA, it would be important to include the definition of UCI in the title or footer when used. This would improve readability of the Table.
- B. Thank you for bringing this to our attention. We have added a definition of the acronym in the title and table and made the requested changes in the manuscript.**
- C. Page 11, 19 and line 154, and table 4**

Reviewer #2

Reviewer #2 Point #1

- A. However I have concerns about the primary hypothesis, or rather the lack of it, underlying their study. They say at line 96 "our purpose was to thoroughly characterize stillbirths associated with umbilical cord abnormalities in the Stillbirth Collaborative Research Network (SCRN) study and to explore maternal and clinical factors associated with these stillbirths". This approach has sometimes been disparagingly referred to as "a fishing expedition". There is no suggestion from the authors as to what they hypothesized they might expect to find. This inevitably leads to statistical difficulties. They have studied a very large number of characteristics and yet despite this they say at line 157 that "No corrections for multiple comparisons were made". They do not explain why they have chosen this approach when it would be usual to use the Bonferroni correction or something similar.

However more fundamentally, I think it is a problem that they have put a wide number of disparate causes of stillbirth into a single category simply on the basis that there was some involvement of the umbilical cord. The major category was cord entrapment (48%) and on first principles I would associate this with cord compression related to fetal growth restriction and oligohydramnios, because when the fetus is well grown and the cord is pulsatile, being slippery it tends to push itself out of the way, which is aided when there is plenty of fluid around the baby. However, there is no mention of birthweight in the paper. When cord entrapment occurs in association with a well grown fetus, in my experience for it to be sufficient to cause stillbirth it tends to be associated with prolonged labour, however I note that the duration of labour has not been recorded. In contrast, "compromised fetal microcirculation" which occurred in 29% of stillbirths was diagnosed when there was "histopathology evidence of vascular obstruction". This is not a category which I am familiar with but on first principles I would have linked it with chronic hypertension and pre-eclampsia. I note that the group as a whole were not associated with these conditions so I remain at a loss to understand what the significance of this vascular obstruction might have been, or indeed what caused it.

The main point is that I cannot see on first principles why one would expect cord entrapment and compromised fetal microcirculation to have any aetiological factors in common. Cord prolapse, which occurred in 5%, is associated as the authors suggest with prelabour preterm rupture of the membranes, again a very different scenario to cord entrapment or placental vascular obstruction. The authors say at line 261 that "our ability to sub-analyze UCA stillbirths by type was limited by sample size, despite having one of the largest cohorts of UCA stillbirths to date" but that does not in my opinion justify combining disparate groups with little in common into one category that lacks any logical coherence.

My view therefore is that (A) despite the lack of statistical power the authors should have subdivided the umbilical cord cases according to aetiology (which would have given small numbers for evaluation, but the small numbers is not in my opinion a justification for combining diagnostic groups which have little in common other than an anatomical structure) and then (B) examined specific hypotheses relating to their aetiology.

- B. We thank the reviewer for their comments and agree with several points. First, we openly and clearly state that this is a *descriptive study* intended to describe and characterize stillbirths associated with umbilical cord abnormalities. This contrasts with many studies, which aim to test a straightforward hypothesis. We believe this approach is justified for several reasons. Importantly, virtually all umbilical cord abnormalities may be found in both live births and stillbirths. Accordingly, it is difficult, if not impossible, to state with certainty that any of these abnormalities are true "causes" of stillbirth. We also agree that individual abnormalities likely confer different risks for stillbirth via varied pathophysiologic

pathways. It is precisely for these reasons that we have been cautious not to make unsubstantiated claims about our findings or to overstate our statistical comparisons. For example, we use the expression “associated with” rather than “cause” throughout the paper. For these reasons, we do not believe it is appropriate to perform a correction for multiple comparisons, although we would be happy to do so if the editors or reviewers feel strongly about the need for it. With that being said, it would not change any meaningful conclusions. We also agree that subsets of abnormalities are of interest and we present the data so that readers can assess them individually. However, the subgroups are too small to permit meaningful statistical analysis as stated in the paper. We hope that our data will spur more work on larger numbers of stillbirths associated with individual cord abnormalities to allow for such analysis.

In addition to the above, there are very few data available regarding umbilical cord abnormalities and stillbirth. Thus, even this descriptive study helps to address a considerable knowledge gap regarding cord abnormalities and stillbirth. These stillbirths are very attractive as a target because they often occur late in gestation in otherwise healthy infants. However, they have been remarkably “understudied.” The first step in being able to conduct meaningful research about stillbirths associated with cord abnormalities is to describe and characterize the condition, as is done in this paper.

The pathophysiology of compromised fetal microcirculation is thought to be due to umbilical cord compression. Of course, this is not absolutely certain, and as with most placental histopathology, there is overlap in conditions and pathways. We elaborate on this issue in the revised paper.

C. Page 12, lines 226-227.

Reviewer #3

Reviewer #3 Point #1

- A. The authors report on a subset of data from a large prospective stillbirth study in which they analyze association of umbilical cord anomalies with stillbirth.

While no conclusive information guiding clinical practice can be deducted at this time from the reported findings, the reported data add to our knowledge base and point out umbilical cord anomalies as a possible important cause for stillbirth.

The finding that hypocoiled cord is associated with stillbirth, whereas hypercoiled cord may not be, desires further evaluation and may be important for clinical management.

- B. We thank the reviewer for their comments**

STATISTICAL EDITOR COMMENTS:

Statistical editor Point #1

- A. Table 1: Due to sample sizes, should round %s to nearest integer, not cite to nearest 0.1%.
- B. **We thank the editor for their suggestion and have made the changes as recommended in the tables and text. We've now report percentages as integers.**
- C. **All reported results and all tables.**

Statistical editor Point #2

- A. Tables 2,3: Should format mean(SD), not mean(SE). Need units for maternal age.
- B. **We've made the changes in the tables as recommended. The tables now report SD, and age units have been added. (note: SD is not automatically generated in the survey procedures, and was calculated separately – but validated vs. unweighted results).**
- C. **All reported results and all tables.**

Statistical editor Point #3

- A. Table 3: Many of the comparisons involve small counts and should have used Fisher's test, not Chi-square. Also, many of those with small counts were NS, but also had low power to generalize the conclusion of NS (eg, alcohol use, TSH < 0.1, etc).
- B. **We thank the editor for their comments. Our answer is included in our response to the following point (#4).**

Statistical editor Point #4

- A. Table 4: Should format mean(SD), not mean(SE). Need units for maternal age. Due to sample sizes, should round %s to nearest integer, not cite to nearest 0.1%. Many of the comparisons involve small counts and should have used Fisher's test, not Chi-square. Also, many of those with small counts were NS, but also had low power to generalize the conclusion of NS (eg, tobacco use, etc). Notably, the comparison of thyroid disorder ($p = .047$ becomes $p = 0.12$), comparison of chronic HTN ($p = .002$ becomes $p = 0.07$)
- B. **We've made the changes as requested and the tables and text have been updated to report percentages as integers. SD and age units have been added. In addition, the sampling weights used in the analyses of these data preclude use of Fisher's exact test (using surveyfreq to include sampling weights in SAS software). Exact confidence intervals are an option in the survey procedures, but not exact chi-square tests. We Previously reported results from rao scott chi square; we now report p-values from wald chi-square.**
- C. **All reported results and all tables.**

Statistical editor Point #5

- A. Fig 1: Why was there no analysis of cord anatomy among the live births to contrast with cord abnormalities among the stillbirth cohort? Should also include among limitations that the UCI subset excluded ~ 31% of the original total and thus may represent a biased subset. Should compare the original cohort vs the UCI cohort (could be supplemental) to evaluate whether there were any demographic/clinical differences which could have affected the conclusions from the UCI subset.

- B. We thank the editor for their comments, we've added a comparison of demographics and clinical characteristics of deliveries for which Umbilical Cord Index (UCI) was missing vs. available. Since the results do not change the final outcome of the paper, we would like to add the analysis as supplemental. The subset of deliveries excluded from (UCI) comparisons comprised 21% of stillbirths and 24% of livebirths. We compared deliveries excluded from the UCI analysis to those included in the UCI analysis and report demographic and clinical differences.

Demographically (Table A1)

- Among stillbirths, significantly more women who were excluded had an obese BMI (38 vs 27%, $p=0.049$) compared to women who were included.
- Among livebirths, women differed significantly by race ($p=0.002$) with excluded women less frequently of white race (41 vs 50%) and more frequently of black race (15 vs 9%) and Hispanic ethnicity (36 vs 33%) vs women who were included; similar in percentage of other race and ethnicity (both 8%).

Clinically (Table A2)

- Among stillbirths, pregnancies that were excluded had shorter average cord length (15.5 vs 16.8 cm, $p<0.001$), more frequently used ART (10 vs 3%, $p=0.024$, less frequently had low birth weight (10 vs 25%, $p=0.002$), and estimated stillbirth occurred at an earlier gestational age (25.7 vs 28.6, $p<0.001$) compared to included deliveries.
- Among livebirths: excluded deliveries less frequently had prenatal care (96 vs 98%, $p=0.049$), Thyroid disorder (3 vs 5%, $p=0.024$), and tobacco use during pregnancy (5 vs 8%, $p=0.024$) compared to included deliveries.

- C. Supplemental table A1 and A2

Statistical editor Point #6

- A. Fig 2: I presume the stats test was by use of Chi-square, but should state the test used.
- B. For the comparison of categorical variables, we used wald chi-square, and for continuous variables, we used two-sample t-test. We've added this to our figure.

EDITOR COMMENTS:

Editor Point #1

Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- A. This sentence is unclear--you are talking about stillbirth, so "fetal injury" seems out of place. I think your quote is referring to the definition of cord accidents, which can cause fetal injury or still birth, but your sentence is about stillbirth. Please edit.
- B. Thank you for noticing the mistake. We've re-edited the text as recommended.**
- C. Page 6, line 93**

- A. Is this the rate of stillbirths associated with cord abnormalities or the rate of cord abnormalities associated with stillbirths? I think the former.
- B. The rates shown are the reported cord abnormalities associated with stillbirth.**

- PRESENTATION OF STATS INFORMATION - P Values vs Effect Size and Confidence Intervals

- A. While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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. This is true for the abstract as well as the manuscript. Please provide absolute values for variables, in addition to assessment of statistical significance. We ask that you provide crude OR's followed by adjusted OR's for all variables.
 - B. We thank the editor for their comment, we've added a confidence interval to the percentage of stillbirths attributed to UCA in the abstract as well as in the results. We've also replaced the p-value describing the unadjusted relationship between low UCI and stillbirth with an unadjusted odds ratio and 95% confidence interval; this is followed by an adjusted odds ratio which was previously included.**
 - C. Page 5, 8, lines 72, 169**
- A. Please avoid causal language throughout your manuscript. Your study can identify and quantify associations, but not causation. Language should be changed in the precis, abstract, and manuscript, if causal language is used in those sites. In this case "that are associated with live births in a majority of cases"...
 - B. We thank the editor for their comment, we've reviewed the manuscript made sure no causation language has been use.**
- A. Please us reVITALize terminology. In this case, prelabor rupture of membranes is now the accepted term.

- B. Thank you for your suggestion, we've reviewed our manuscript to ensure that we're using reVITALize terminology.
- C. Page 10, line 225

Editor Point #2

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.**

Editor Point #3

- A. 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.
- B. **We've checked with our coauthors and confirmed the disclosures.**

Editor Point #4

- A. This appears to have been presented at SMFM. Please disclose this on the title page.
- B. **We've made the changes as requested.**
- C. **Page 3, lines 53-55.**

Editor Point #5

- A. 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.
- B. **Thank you for your suggestion, we've reviewed our manuscript to ensure that we're using reVITALize terminology.**

Editor Point #6

- A. 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.

B. We confirmed that the manuscript is adherent to the recommended restrictions.

Editor Point #7

- A. 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).
- B. We've confirmed that all financial support, preparation assistance, contributing persons have been acknowledged. We've also stated the scientific meeting in which the paper was presented.**

Editor Point #8

- A. 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.
- B. We thank the editor for their comments. We've reviewed the abstract and confirmed that the presented data is reflective of the manuscript. We've also adhered to the structure and word limits guidelines.**

Editor Point #9

- A. 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.
- B. We've revised our abstract and manuscript and made the recommended changes with regards to the abbreviations and acronyms.**

Editor Point #10

- A. 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.
- B. **We've made the changes in the body of the text has been to remove the forward slash.**

Editor Point #11

- A. 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%).
- B. **The tables and text have been updated to the suggested format (percentages do not have any decimal places per the statistical reviewer).**
- C. **All tables**

Editor Point #12

- A. Line 262: We discourage claims of first reports since they are often difficult to prove. How do you know this is the first report? If this is based on a systematic search of the literature, that search should be described in the text (search engine, search terms, date range of search, and languages encompassed by the search). If on the other hand, it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.
- B. **We thank the editor for their comment and made the changes as recommended.**
- C. **Page 12, line 280**

Editor Point #13

- A. 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.
- B. **We've reviewed the journal's table checklist and made sure that our tables conform to the journal style.**

Editor Point #14

- A. Figures
Figure 1: In exclusion box where n=652, are the items totaling 167 not mutually exclusive?
Figure 2: Okay. The current figure file may be resubmitted as-is
- B. **Figure 1: That is correct, the 5 and the 163 are not mutually exclusive.**
Figure 2: Thank you
- C. **All figures**

Editor Point #15

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

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

B. Thank you

Editor Point #16

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.