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.*

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Nov 15, 2019
To: "Candace O'Quinn" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-19-1947

RE: Manuscript Number ONG-19-1947

Antenatal diagnosis of marginal and velamentous placental cord insertion: a 4-year cohort

Dear Dr. O'Quinn:

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 Dec 06, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This might be a relevant topic since no major guidelines exist (as mentioned in Line 120) on the management after vasa praevia is ruled out, as in this study.

A few queries that came up after perusal of the article are as follows:

1. Line 134/275-76 says vasa previa and placenta previa were excluded. Placenta previa may be excluded but there is a high association of vasa previa with velamentous cord insertion (VCI). Hence we might be missing a major proportion of cases of VCI.This might also contribute to the lower incidence of VCI as compared to other studies(as mentioned in Lines 276-78)

2. Many studies (including Ref 6, Suzuki et al)have demonstrated increased incidence of VCI in pregnancies conceived by assisted reproduction (ART). Table 1 here shows similar incidence in velamentous and central cord insertions and a comparative higher incidence in marginal insertions. Any explanations to justify this finding?

3. Line 267-68/table 2 :The relative risk of perinatal deaths is 8.15 which seems to be high as compared to the systematic review by Vahanian et al (Ref 19) where the relative risk is 2.15. Is it because the current study has lower number of cases of VCI and might not be adequately powered?

4. Lines 290-91: the authors conclude that the addition of a 3rd trimester scan may help in identification of at-risk fetuses earlier. Several studies (including Ref 22 by Padula et al,2016) mention a higher detection of abnormal cord insertions at 20-23 weeks(98.3%) as compared to later gestations(88.9% at 30-34 weeks and 72.2% at 35-38 weeks). Hence it would be a better option to consider screening in first and 2nd trimester and confirmation (rather than detection) in 3rd trimester scan.

Reviewer #2: Review of Manuscript ONG-19-1740 "Antenatal diagnosis of marginal and velamentous placental cord insertion: a 4-year cohort"

O'Quinn and colleagues have constructed a four-year cohort of pregnant patients from Canada that is based on ultrasound assessment following the adoption of noting umbilical cord insertion. I have the following questions and comments.

1. Title - No comments.

2. Précis - Acceptable and consistent with reported findings.

3. Abstract - In the abstract and introduction the authors note that the primary objectives include SGA, perinatal mortality and cesarean delivery. In the methods, they note the primary outcomes of IUGR, perinatal mortality and cesarean delivery. Please be consistent. Please spell out "percentile."

4. Introduction - In line 110 it is mentioned that pathology series are used to describe the findings in question rather than U/S. Are series available which report such a finding?

5. Methods - As noted previously terms SGA and IGR used interchangeably although I would encourage one and one alone. Use of central cord insertion seems as reference seems appropriate. Cesarean is also spelled different ways so again be consistent.

6. Results - Please add the total number of included patients in the first paragraph so the reader does not have to go to the figure to get this information. Line 202 - I guess you mean one or more?

7. Discussion - I think you can remove the word "both" from line 232 and state the association as noted. The authors note that the U/S findings were not confirmed pathologically and/or at the time of delivery. You surmised earlier that pathologic assessment was likely for abnormalities - line 111 (? Selection bias), yet there was not routine pathologic assessment of these placentas so does that mean that the delivering provider did not think there was an abnormality(ies)? The discussion seemed somewhat bland just noting the various associations in the data. The authors do a reasonable job of noting why their study may or may not be consistent with previously published papers. You note in line 270 it is difficult to provide recommendations based on the small number of cases yet in the concluding paragraph you do this.

8. Tables - Consider what tables could be supplementary. For table 1 since smoking is any during the pregnancy may be able to change the label for this row. Also what is meant in Table 1 by placental site < / > 2cm.

9. Figures - I am not sure what the figure legend means.

Reviewer #3: This is a large cohort study where the authors explore the relationship between antenatally diagnosed placenta cord insertion site and its correlation with fetal growth restriction, perinatal mortality and cesarean delivery. Strengths of the study include the relative large size of the cohort (35,000 singleton mid-trimester ultrasound studies between 18-21 weeks gestation) conducted at a single institution and the ability to successfully link those studies with a perinatal data base for the entire region in over 97% of the cases.

I have the following questions for the authors:

1. During the study period, were there regional/ national norms that guided management of pregnancies complicated by velamentous and marginal cord insertion sites? If so, it would be important to discuss how those interventions might have influenced the study results

2. It would be helpful for the readers to understand why the 5th percentile was chosen to define SGA by the authors as primary outcome. This discussion would greatly enhance the ability to interpret the study results and potential implications for clinical practice, and has significant implications for the study's conclusions (see below).

3. In the conclusion paragraph the authors state that BOTH marginal and velamentous cord insertion are associated with the adverse fetal outcomes, however their results only depict adverse outcomes for velamentous cord insertion. This difference has huge impact in the amount of ultrasounds (and resources) that would need to be allocated for the management of a relative common finding (marginal cord insertion) in the mid trimester.

4. This study did not evaluate and provides no insight as to when or how many ultrasounds should be performed in the third trimester. The recommendation by the authors of "a 34-week assessment of fetal growth may be reasonable" is not supported by their current study.

STATISTICAL EDITOR'S COMMENTS:

1. lines 138-139: Were their any pregnancies which were excluded due to missing data re: U/S at 18-21 weeks?

2. lines 161-165, 171-175: Missing from this calculation is the relative number of referent to velamentous and marginal insertion cases. Also, need to stipulate which outcome is primary. That is, velamentous and marginal categories (or their aggregate) as the exposure variable and IUGR, perinatal death or CS as the outcome of interest, or a composite. If multiple exposures and multiple outcomes, then would need to change the inference level to more restrictive than $p < 0.05$. Why was the power/sample size calculation specific for SGA < 5th %-tile only?

3. Also, how did the U/S diagnosis at 18-21 weeks of placental insertion compare with the findings at delivery?

4. Table 2: The number of adverse outcomes among those with velamentous insertions was small: pre-term delivery spontaneous (6), indicated (8), SGA <5th %-tile (12), < 10th %-tile (21), perinatal death (2). All of these are too few to allow for adjustment with 3 covariates. The RRs shown in Table 2 are flawed in that there are multiple baseline differences that have not been adjusted for.

5. Tables 3, 4: The aORs for velamentous cohort are likely over fitted to the data for SGA. Should attempt to match the velamentous cohort with a subset of the reference group, matching on smoking status, GDM and HTN and any other relevant characteristics to corroborate the association. Also, the aORs and their CIs should be rounded to nearest 0.01 level of precision.

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.

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. In order for an administrative database study to be considered for publication in Obstetrics & Gynecology, the database used must be shown to be reliable and validated. In your response, please tell us who entered the data and how the accuracy of the database was validated. This same information should be included in the Materials and Methods section of the manuscript.

4. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: 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.

6. 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).

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:

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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).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

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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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 Dec 06, 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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December 19, 2019

Re: Antenatal diagnosis of marginal and velamentous placental cord insertion: a 4-year cohort

The Editors

Obstetrics & Gynecology

409 12th Street SW, Washington, DC 20024-2118

Dear Editors:

On behalf of my co-authors, I am pleased to submit our revised manuscript, "Antenatal diagnosis of marginal and velamentous placental cord insertion: a 4-year cohort," for consideration for publication as original research solely in *Obstetrics & Gynecology.*

As part of this project, each author participated actively in developing the project, conducting analyses, drafting sections of the manuscript, editing, and approving the final, submitted version. None of the authors has a financial or other conflict of interest. Ms. Susan Crawford gave permission to be included in the acknowledgements.

This study was approved by our institutional review board (University of Calgary REB14-2037). The manuscript has not been previously published or submitted to another journal for publication. The results of this study were presented at John

Jarrell Research Day (Department of Obstetrics and Gynecology Research Day) University of Calgary, Calgary, AB, Canada on May 11, 2018.

Our manuscript uses a large cohort to examine the role of antenatal diagnosis of placental cord insertion on fetal growth. In addition, it looks at marginal and velamentous cord insertions separately rather than combined together as peripheral cord insertions. Both databases used in this study collect data in a standardized fashion. The Astraia database is an ultrasound reporting system where data is entered directly by sonographers and physicians to complete patient reports. The Alberta Perinatal Health program collects delivery data using a standardized form for all deliveries in the province of Alberta, Canada. The data collected by the patient care nurse or midwife for each delivery.

The instructions for authors documents has been reviewed. Our responses to the reviewer's comments are noted in the following paragraphs. We OPT-IN to have our point- by-point responses published in the review letter. Our study uses the ACOG obstetric definitions. In completing the revisions an additional study published this year was discovered and included in our discussion.

REVIEWER COMMENTS:

Reviewer #1: This might be a relevant topic since no major guidelines exist (as mentioned in Line 120) on the management after vasa praevia is ruled out, as in this study.

A few queries that came up after perusal of the article are as follows:

1. Line 134/275-76 says vasa previa and placenta previa were excluded.

Placenta previa may be excluded but there is a high association of vasa previa with velamentous cord insertion (VCI). Hence we might be missing a major proportion of cases of VCI.This might also contribute to the lower incidence of VCI as compared to other studies (as mentioned in Lines 276-78).

Thank you. We agree that excluding the vasa previa cases likely reduced the incidence of velamentous cord insertion. Given the association of vasa previa with preterm delivery and caesarean section these cases were purposely excluded.

2. Many studies (including Ref 6, Suzuki et al)have demonstrated increased incidence of VCI in pregnancies conceived by assisted reproduction (ART). Table 1 here shows similar incidence in velamentous and central cord insertions and a comparative higher incidence in marginal insertions. Any explanations to justify this finding?

This may be due to the fact that we excluded placenta previa and vasa previa, whereas other papers i.e Ref 6, Suzuki et al. included the placenta previa and vasa previa cases.

3. Line 267-68/table 2 :The relative risk of perinatal deaths is 8.15 which seems to be high as compared to the systematic review by Vahanian et al (Ref 19)

where the relative risk is 2.15. Is it because the current study has lower number of cases of VCI and might not be adequately powered?

Yes. Given the low numbers of perinatal death while an association was identified strong conclusions cannot be drawn from this data. (See lines 311-315).

4. Lines 290-91: the authors conclude that the addition of a 3rd trimester scan may help in identification of at-risk fetuses earlier. Several studies (including Ref 22 by Padula et al,2016) mention a higher detection of abnormal cord insertions at 20-23 weeks(98.3%) as compared to later gestations(88.9% at 30-34 weeks and 72.2% at 35-38 weeks). Hence it would be a better option to consider screening in first and 2nd trimester and confirmation (rather than detection) in 3rd trimester scan.

Thank you. The purpose of the suggested 3rd trimester ultrasound is to assess fetuses at risk of growth restriction (small for gestational age) rather than the cord insertion. We recommend the cord insertion be visualized at the time of the anatomic survey (19-20 weeks gestation) rather than the third trimester. (Please see line 326-340).

Reviewer #2: Review of Manuscript ONG-19-1740 "Antenatal diagnosis of marginal and velamentous placental cord insertion: a 4-year cohort"

O'Quinn and colleagues have constructed a four-year cohort of pregnant patients from Canada that is based on ultrasound assessment following the adoption of noting umbilical cord insertion. I have the following questions and comments.

1. Title - No comments.

2. Précis - Acceptable and consistent with reported findings.

3. Abstract - In the abstract and introduction the authors note that the primary objectives include SGA, perinatal mortality and cesarean delivery. In the methods, they note the primary outcomes of IUGR, perinatal mortality and cesarean delivery. Please be consistent. Please spell out "percentile."

Thank you this has been corrected.

4. Introduction - In line 110 it is mentioned that pathology series are used to describe the findings in question rather than U/S. Are series available which report such a finding?

Yes. The appropriate references have been added. (Line 114)

5. Methods - As noted previously terms SGA and IGR used interchangeably although I would encourage one and one alone. Use of central cord insertion seems as reference seems appropriate. Cesarean is also spelled different ways so again be consistent.

Thank you. This has been corrected for consistency.

6. Results - Please add the total number of included patients in the first paragraph so the reader does not have to go to the figure to get this information. Line 202 - I guess you mean one or more?

The total number of included patients has been added to line 210. Regarding line 202 we did intend to say one or more sonographic examinations. This has now been corrected (now line 224).

7. Discussion - I think you can remove the word "both" from line 232 and state the association as noted. The authors note that the U/S findings were not confirmed pathologically and/or at the time of delivery. You surmised earlier that pathologic assessment was likely for abnormalities - line 111 (? Selection bias), yet there was not routine pathologic assessment of these placentas so does that mean that the delivering provider did not think there was an abnormality(ies)? The discussion seemed somewhat bland just noting the various associations in the data. The authors do a reasonable job of noting why their study may or may not be consistent with previously published papers. You note in line 270 it is difficult to provide recommendations based on the small number of cases yet in the concluding paragraph you do this.

The word "both" has been removed as you suggested. At our centre the placenta is routinely inspected though a complete pathological examination with documentation is not done. We did not feel that accurate and complete documentation of placenta pathology would be available from our centre. Regarding line 270 this refers to the small number of perinatal deaths in the study. As stated, we do not believe there is strength to draw conclusions for this outcome but do feel the present study demonstrates a strong association with growth restriction as the number of cases was much more robust, which is why the conclusion was written in such a fashion.

8. Tables - Consider what tables could be supplementary. For table 1 since smoking is any during the pregnancy may be able to change the label for this row. Also what is meant in Table 1 by placental site < / > 2cm.

We have adjusted the table label to smoking and provided and explanation in the methods. The placental site </> 2 cm refers to the distance from the internal os. This has been added in the table to clarify for the reader. The multivariate analysis has now been made supplementary material.

9. Figures - I am not sure what the figure legend means.

I have removed the figure legend as on review it appears to be redundant. The explanation of the excluded cases is included in line 212-214.

Reviewer #3: This is a large cohort study where the authors explore the relationship between antenatally diagnosed placenta cord insertion site and its correlation with fetal growth restriction, perinatal mortality and cesarean delivery. Strengths of the study include the relative large size of the cohort (35,000 singleton mid-trimester ultrasound studies between 18-21 weeks gestation) conducted at a single institution and the ability to successfully link those studies with a perinatal data base for the entire region in over 97% of the cases.

I have the following questions for the authors:

1. During the study period, were there regional/ national norms that guided management of pregnancies complicated by velamentous and marginal cord insertion sites? If so, it would be important to discuss how those interventions might have influenced the study results

Thank you. This information has been entered (see line 126-130).

2. It would be helpful for the readers to understand why the 5th percentile was chosen to define SGA by the authors as primary outcome. This discussion would greatly enhance the ability to interpret the study results and potential implications

for clinical practice, and has significant implications for the study's conclusions (see below).

The 5th percentile was chosen as the primary outcome for significant SGA as the study team felt this was a much more significant and important SGA cut off compared with the 10th percentile. (This has been added to lines 174-176).

3. In the conclusion paragraph the authors state that BOTH marginal and velamentous cord insertion are associated with the adverse fetal outcomes, however their results only depict adverse outcomes for velamentous cord insertion. This difference has huge impact in the amount of ultrasounds (and resources) that would need to be allocated for the management of a relative common finding (marginal cord insertion) in the mid trimester.

Both marginal and velamentous cord insertion were found to be associated with fetal growth restriction though the association for marginal cord insertion was no significant at the 5th percentile it was significant at the 10th percentile. (Lines 235-238). We appreciate that the association of marginal cord insertion with SGA at the 10th %ile was not a primary outcome. We felt that some obstetrical providers may feel the association at the 10th percentile is significant.

4. This study did not evaluate and provides no insight as to when or how many ultrasounds should be performed in the third trimester. The recommendation by

the authors of "a 34-week assessment of fetal growth may be reasonable" is not supported by their current study.

Thank you. The suggestion regarding the timing of a 3rd trimester study has been removed and the conclusions modified. (See line 343-247)

STATISTICAL EDITOR'S COMMENTS:

1. lines 138-139: Were their any pregnancies which were excluded due to missing data re: U/S at 18-21 weeks?

Our sample was collected through only (100%) completed cases. Any cases that did not have the normal values (checkboxes) completed (with the exception of placental cord insertion site and placental insertion site) were not pulled from the database search as it is possible the unclicked normal value possibly indicated an abnormality was present rather than missing information. Our database could not separate this in the search. Partially completed cases or cases completed over multiple visits were not included in the study. Unfortunately we are unable to quantify the number of cases.

2. lines 161-165, 171-175: Missing from this calculation is the relative number of referent to velamentous and marginal insertion cases. Also, need to stipulate which outcome is primary. That is, velamentous and marginal categories (or their aggregate) as the exposure variable and IUGR, perinatal death or CS as the outcome of interest, or a composite. If multiple exposures and multiple

outcomes, then would need to change the inference level to more restrictive than $p < 0.05$. Why was the power/sample size calculation specific for SGA < 5th %-tile only?

Thank you. Marginal and velamentous cord insertion groups were examined separately as the primary outcome. No cases would have contained a marginal and velamentous cord insertion. A note has been added to line 179. The outcomes were separate rather than a composite outcome. No composite outcome was calculated. We assumed 1% of cases would have a velamentous cord insertion (which is less common than marginal cord insertion). The 5th percentile was chosen as the primary outcome for significant SGA as the study team felt this was a much more significant and important SGA cut off compared with the 10th percentile. (This has been added to lines 174).

3. Also, how did the U/S diagnosis at 18-21 weeks of placental insertion compare with the findings at delivery?

Unfortunately, we are unable to correlate the antenatal diagnosis with the post natal diagnosis given the retrospective nature of the study. (Lines 325-340)

4. Table 2: The number of adverse outcomes among those with velamentous insertions was small: pre-term delivery spontaneous (6), indicated (8), SGA <5th %-tile (12), < 10th %-tile (21), perinatal death (2). All of these are too few to

allow for adjustment with 3 covariates. The RRs shown in Table 2 are flawed in that there are multiple baseline differences that have not been adjusted for.

I appreciate your comment. We have adjusted our tables to clearly indicate this is an unadjusted relative risk. Our adjusted analysis were exploratory. We have explained this in lines 262-276.

5. Tables 3, 4: The aORs for velamentous cohort are likely over fitted to the data for SGA. Should attempt to match the velamentous cohort with a subset of the reference group, matching on smoking status, GDM and HTN and any other relevant characteristics to corroborate the association. Also, the aORs and their CIs should be rounded to nearest 0.01 level of precision.

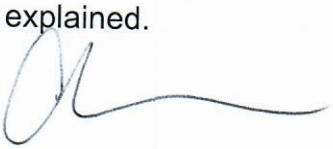
The aOR and Ci's have been adjusted accordingly for precision. As mentioned above our adjusted analysis were exploratory. We have tried to explained this lines 262-276. We will also now provide these tables as supplementary data rather than include them with the main manuscript.

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

"Figure 1: Please add n values to the first two boxes."

This has been completed.

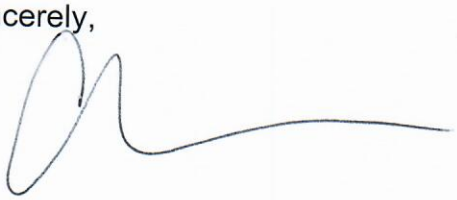
"The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Signed by: 

Thank you for your suggestions regarding revisions. We hope that you will find the revisions adequate.

If you have any questions about the manuscript, I will be serving as the corresponding author. Thank you for your consideration.

Sincerely,



Candace O'Quinn, MD, FRCSC