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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.
RE: Manuscript Number ONG-21-1695

Obstetric complications in women with congenital uterine anomalies, according to the 2013 ESHRE / ESGE classification: a systematic review and meta-analysis

Dear Dr. Panagiotopoulos:

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).

Please be sure to address the Editor comments (see "EDITOR COMMENTS" below) in your point-by-point response.

Your paper will be maintained in active status for 14 days from the date of this letter. If we have not heard from you by Oct 01, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: ONG 21-1695

In the meta-analysis under review, we examine the results of a comprehensive assessment of the adverse perinatal outcomes associated with congenital uterine anomalies. The authors compiled 48 studies and found that these anomalies were associated with an increased risk of PTL, fetal malpresentation, FGR, abruption, placenta previa and cesarean delivery.

A few comments on the manuscript are as follows:

ABSTRACT
1. No major issues identified.

INTRODUCTION
2. Presents the pertinent literature in a summarized, well organized fashion.

METHODS
3. Although this analysis most likely qualifies for exempt status from any IRB, was this request formally filed?
4. Line 91 - why the EMBASE database excluded?
5. Line 124-127 how was data from studies that just reported "uterine anomalies" categorized? Or were they simply dropped?
6. Line 128 - what was the primary outcome of the meta-analysis?

RESULTS
7. Tables 1 and 2 should be reorganized. Adding more columns to table 1 (p value, I2, and total number of participants in the studies included) would make the table cleaner and easier to read. Same goes for table 2.

DISCUSSION
8. Line 235-236 what search terms were used to assure that this in fact was "the first study"?
Reviewer #2:

The authors present a systematic review and meta-analysis describing the association between obstetric complications in women with congenital uterine anomalies, as defined by the 2013 ESHRE/ESGE classification system for uterine malformations. The authors report on 48 studies included in a review which demonstrated an increase in risk among women with congenital uterine anomalies (CUA) for: preterm labor, cervical insufficiency, preterm rupture of membranes, fetal malpresentation, intrauterine growth restriction, placental abruption, placenta previa, retained placenta, and cesarean delivery. While these data have all been demonstrated previously the authors also classify the uterine anomalies separately and found increased risk of preterm labor, malpresentation, cesarean delivery and placental abruption in the three main classes of uterine anomalies (ESHRE/ESGE classification system). The authors describe the systematic review and meta-analysis as more comprehensive reporting of these outcomes with first ever use of novel ESHRE classification for such a review.

While these data are important to describe my major criticism surrounds the use of the ESHRE/ESGE classification system for reporting uterine anomalies. In the United States, the ASRM classification system is more commonly used. Because it contains more discrete strata, it may be viewed as a more thorough classification system of uterine anomalies. If this work is accepted for publication a greater discussion should be included of the differences between the ESHRE and ASRM/AFS classification systems and consideration should be given to a pictorial representation of the major strata in the ESHRE system.

Specific feedback:

Abstract: Results describe OR for adverse outcomes CUA vs no-CUA groups. This is has been demonstrated in multiple prior publications. Recommend focusing on the independent association of each class of uterine anomalies with adverse outcomes and where they differ.

Introduction: As above, would include a more lengthy description of differences between ESHRE and ASRM classification systems.

Methods: If possible would group adverse obstetric outcomes into categories that are maternal/fetal/placental. Are individuals with history of septate uterus who have undergone surgery included in studies selected for this systematic review--or are these all uteri that have not been operated upon?

Results: Focus more on sub analysis of differences in outcomes between three main classes of uterine anomalies. Table 1: readable, no changes recommended

Table 2: consider pectoral representation of 3 classes of uterine anomalies. Is it possible to compare OR across groups?

Table 3: is it possible to know how many studies for each subclass? The text sets that table 3 presents "frequency of each obstetric complication" while the title on the Table is "pooled estimated proportions." are these the same thing? If it is a frequency of each outcome that is being presented would it also be possible to include frequency in the control population (pooled)?

Discussion: Would spend more time distinguishing this study from the prior systematic reviews (citation 3,4,67, 68). If the distinguishing feature is the use of ESHRE classification system I am wondering about utility to the Green Journal readership if this is not a commonly used system in the United States.

Why do the authors speculate there may be a relationship between preeclampsia and CUA? Is there biologic plausibility? Would also spend more time discussing possible sources of bias--where there was evidence and where there was not.

Reviewer #3:

The authors present a systematic review that aims to identify the risks of obstetric complications in women with congenital uterine anomalies. The review then further attempts to classify the risks within each main anomaly classification. This is a somewhat novel approach as previous systematic reviews have focused on overall reproductive outcomes in this particular patient population. The authors specifically wanted to know about rates of preterm labor, premature rupture of membranes, fetal malpresentation, cervical insufficiency, intrauterine fetal growth restriction, preeclampsia, placental abruption, abnormal placentation, birthweight and Cesarean delivery. The authors followed standard procedures for identifying potential articles for their review. The authors elected to exclude articles that involved small numbers of patients including case reports and case series with less than 10 patients. The authors also excluded class U1 (dysmorphic) and class U5 (aplastic) uteruses, instead focusing on U2 (septate), U3 (bicoporeal) and U4 (hemi-uterus) which is reasonable at U1 and U5 type uteruses are not expected to be able to carry a normal pregnancy. The authors then use the
more familiar American Fertility Society classification terms to help readers understand what types of uteri fall in to each category (U2-U4). A starring system was used to rank the quality of all comparative studies (20 studies total). The authors conclude that the systematic review show a significant positive association between obstetric complications and congenital uterine anomalies.

Line 154-how were small studies defined for this calculation? Where did you draw the line and why did you pick this particular number?

Supplemental table S1-the case series from Ghi (ref 27) has 8 patients although you say that you have excluded all small case series with less than 10 patients. Why was this study included? If this study is included then you should use a different number (such as <5 patients) and include any other case series with 5-9 patients or you should remove this study and recalculate the statistics.

Line 181-Women with anomalies delivered neonates that were on average 353.72 grams less than women without anomalies. Does this control for the increased risk of preterm delivery? Women who deliver preterm will have small babies than those women who deliver at term. If there is not a way to stratify infant weight based on weeks gestation at delivery this may be a misleading piece of data and may be better removed from the manuscript.

Line 204-"This suggests an inability" may be too strongly worded was we know that women with anomalous uterus can carry pregnancies to term and delivery normal size infants. Would consider changing this wording to something like "This suggests a decreased ability" or something similar.

Line 208-Can you explain why the reduced endometrial volume may lead to high rates of fetal malpresentation?

Paragraph line 226-230-Would also like to see the authors comment that the increased risk of Cesarean delivery may be related to other developmental anomalies that the patient may have. We know that patients with anorectal malformations including cloacas have an increased incidence of mullerian anomalies. Currently we recommend that these women delivery via Cesarean because of their complex reconstructions. It would be helpful to include other anatomical anomalies in this laundry list of reasons why someone with a uterine anomaly may delivery via Cesarean.

This manuscript is helpful for clinicians caring for women with mullerian anomalies throughout the lifespan. Starting at a young age, parents of children diagnosed with mullerian anomalies will ask about future reproductive potential. This manuscript adds to the existing literature to help discuss potential risks that a pregnancy in an anomalous uterus may face. While the number of included studies is small, this is consistent with what can be found in the literature. This manuscript can serve as a call to action for clinicians caring for these patients to design and perform prospective cohort studies to further our knowledge of this topic.

STATISTICS EDITOR COMMENTS:

Tables 1, 2 and Abstract and in main text: The p-values should be removed. Since CIs are given, the p-values are redundant.

lines 182-184: Since the p = 0.06, there was no "trend", it was simply NS.

General: Could simplify the Results section by not repeating each of the ORs that are in Tables. That would make the text more easily read.

Tables 1, 2: In cases where the number of studies pooled = 2, there is insufficient data to reliably estimate I². Should simply omit the I² for those cases.

Fig S2.1.1, and all those with estimates for proportions : Need to include columns with actual counts in each study and respective weight given to each study.

Fig S2.1.4, S2.1.12, S2.1.17, S2.1.20, S2.2.22, S2.3.16, S2.3.21, S2.4.11: These are essentially recapitulations of one study, rather than pooled analyses. Need to acknowledge in limitations section.
EDITOR COMMENTS:

1. Thank you for submitting this work to Obstetrics and Gynecology. If you opt to submit a revision, please include the Forest plots for the anomalies overall for each outcome in the main manuscript (not supplemental material). Forest plots for different classes can be kept in supplemental.
2. In the tables that state the number of studies, please also provide the total n for the studies when pooled.
3. The abstract mentions 3 main classes of anomalies, please tell the reader what those classes are in the abstract.
4. Replace "cesarean section" with "cesarean birth" throughout.
5. Replace "IUGR" with fetal growth restriction throughout.
6. Revise the precis to reflect what can be stated from this analysis specifically- delete the assumption that these pregnancy complications cause cesarean births.
7. Please clarify if the outcome is preterm labor or preterm birth. Preterm labor is difficult to define and would likely not be comparable across studies. Preterm birth would be an outcome of value. If it truly is preterm labor, how was this defined?
8. Make sure that absolute values are included in addition to odds ratios as the absolute numbers will be important for use in patient counseling. Also do this in the abstract.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
   * Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).
   * Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.
   * Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
   * Name the IRB or Ethics Committee institution in the Methods section (if applicable).
   * Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

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 data.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 6,250 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, 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).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

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 limit for Reviews is 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. Your manuscript contains a priority claim. 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 it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

12. 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.

13. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

14. Figure 1: Please upload as a figure file on 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).

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.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.
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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 as a Microsoft Word document. 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),
* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

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 01, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Torri D. Metz, MD
Associate Editor, Obstetrics

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd 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 Dr Metz,

Re: Obstetric complications in women with congenital uterine anomalies, according to the 2013 ESHRE / ESGE classification: a systematic review and meta-analysis

We would like to thank you for taking the time to review our manuscript and for considering it for publication in your esteemed journal. We have now carefully studied your comments and revised our manuscript accordingly. In addition, we confirm that we have read the Instructions for Authors and ensured that our manuscript adheres to the guidelines. We believe that the present revision solves the issues that were mentioned and communicates a clear message to readers. Every reviewers’ comment was addressed and the lines mentioned in this document refer to the document with tracked changes.

REVIEWER COMMENTS:

Reviewer #1: ONG 21-1695

*In the meta-analysis under review, we examine the results of a comprehensive assessment of the adverse perinatal outcomes associated with congenital uterine anomalies. The authors compiled 48 studies and found that these anomalies were associated with an increased risk of PTL, fetal malpresentation, FGR, abruption, placenta previa and cesarean delivery.*

A few comments on the manuscript are as follows:

**ABSTRACT**

1. No major issues identified.

**INTRODUCTION**

2. Presents the pertinent literature in a summarized, well organized fashion.

Reply: Thank you for your comments

**METHODS**

3. Although this analysis most likely qualifies for exempt status from any IRB, was this request formally filed?
Reply: We did not request ethical approval for this study, as it did not include patient recruitment.

4. Line 91 - why the EMBASE database excluded?

Reply: We opted for Scopus instead, as it is a larger database than EMBASE. Furthermore, according to the author’s guidelines, a minimum of two databases were required, including MEDLINE and Clinical Trials.gov.

We believe that, through searching reference lists of included articles, we are unlikely to have missed relevant data written in English.

5. Line 124-127 how was data from studies that just reported "uterine anomalies" categorized? Or were they simply dropped?

Reply: Studies that reported on congenital uterine anomalies or Mullerian anomalies as a single study group were included only in the analysis regarding congenital uterine anomalies, as there was limited or no information for each specific type of uterine anomaly. This may cause heterogeneity and was one of the limitations reported in the discussion section.

We excluded any studies that reported on acquired uterine anomalies, such as leiomyomas.

6. Line 128 - what was the primary outcome of the meta-analysis?

Reply: We have now clarified in our text that outcomes sought were obstetric outcomes, namely preterm birth, PROM, fetal malpresentation, cervical insufficiency, FGR, hypertensive disorders of pregnancy, placental abruption, abnormal adhesion of placenta, neonatal birthweight and cesarean birth.

RESULTS

7. Tables 1 and 2 should be reorganized. Adding more columns to table 1 (p value, I2, and total number of participants in the studies included) would make the table cleaner and easier to read. Same goes for table 2.

Reply: Tables 1 and 2 have been reorganized. Total number of patients was added. There was conflicting advice regarding the inclusion of p values, as the statistics editor suggested that we removed them.

We hope, nevertheless, that through editing the tables, they are now easier to read.

DISCUSSION

8. Line 235-236 what search terms were used to assure that this in fact was "the first study"?

Reply: We thank you for your comment. This is a point that was also raised by the editorial office, and we have decided to remove the statement altogether.

However, we should point out that during our systematic search we noted previous relevant systematic reviews on the field in order to assess the originality of our idea. These previous reviews
have been cited in the discussion section where relevant, but none of them had estimated frequencies of each obstetric complication or used the rather new ESHRE/ESGE classification.

Reviewer #2:

The authors present a systematic review and meta-analysis describing the association between obstetric complications in women with congenital uterine anomalies, as defined by the 2013 ESHRE/ESGE classification system for uterine malformations. The authors report on 48 studies included in a review which demonstrated an increase in risk among women with congenital uterine anomalies (CUA) for: preterm labor, cervical insufficiency, preterm rupture of membranes, fetal malpresentation, intrauterine growth restriction, placental abruption, placenta previa, retained placenta, and cesarean delivery. While these data have all been demonstrated previously the authors also classify the uterine anomalies separately and found increased risk of preterm labor, malpresentation, cesarean delivery and placental abruption in the three main classes of uterine anomalies (ESHRE/ESGE classification system). The authors describe the systematic review and meta-analysis as more comprehensive reporting of these outcomes with first ever use of novel ESHRE classification for such a review.

While these data are important to describe, my major criticism surrounds the use of the ESHRE/ESGE classification system for reporting uterine anomalies. In the United States, the ASRM classification system is more commonly used. Because it contains more discrete strata, it may be viewed as a more thorough classification system of uterine anomalies. If this work is accepted for publication a greater discussion should be included of the differences between the ESHRE and ASRM/AFS classification systems and consideration should be given to a pictorial representation of the major strata in the ESHRE system.

Reply: We thank you for your comment. Regarding using pictorial representation, although this would be helpful to readers, we would prefer not to include it, as it would burden our paper with yet an extra figure. We hope that readers can easily access the ESHRE/ESGE system through the relevant publication, which is cited in our paper and is available freely.

With regards to the ESHRE/ESGE classification, this was introduced as a more comprehensive tool for global use. Looking through the official Journal of the ASRM, the ESHRE/ESGE classification is often quoted. Therefore, we believe it is relevant to all readerships.

Specific feedback:

Abstract: Results describe OR for adverse outcomes CUA vs no-CUA groups. This has been demonstrated in multiple prior publications. Recommend focusing on the independent association of each class of uterine anomalies with adverse outcomes and where they differ.

Reply: We thank you for this suggestion. Although this would be useful information, we are limited by the word count of the abstract.

Introduction: As above, would include a more lengthy description of differences between ESHRE and ASRM classification systems.
Reply: Thank you for this suggestion, we have now introduced a more detailed description of the ESHRE/ESGE classification and included differences with the AFS/ASRM classification. [lines 105-111]

Methods: If possible would group adverse obstetric outcomes into categories that are maternal/fetal/placental.

Reply: Although we understand how this might be helpful, we decided against using such a categorization, on the basis that adverse obstetric outcomes often encompass maternal, fetal and placental complications. We hope this reasoning is acceptable, particularly as this was not a strong recommendation by the reviewer.

Are individuals with history of septate uterus who have undergone surgery included in studies selected for this systematic review--or are these all uteri that have not been operated upon?

Reply: We have only included uteri that have not been operated upon. We thank you for your comment; this was not clear in the methods section. Therefore, we have added this information in the study selection section of methods. [lines 131-132]

Results: Focus more on sub analysis of differences in outcomes between three main classes of uterine anomalies.

Reply: Although we could indeed include more detail on the three main classes, this would make the result section more verbose. We feel that this information is easily extracted from the relevant tables.

Table 1: readable, no changes recommended

Table 2: consider pectoral representation of 3 classes of uterine anomalies. Is it possible to compare OR across groups?

Reply: ORs have been included in the table. They are in the same row for each complication, which allows for easy comparison.

Table 3: is it possible to know how many studies for each subclass? The text sets that table 3 presents "frequency of each obstetric complication" while the title on the Table is "pooled estimated proportions." are these the same thing? If it is a frequency of each outcome that is being presented would it also be possible to include frequency in the control population (pooled)?

Reply: Thank you for pointing this out. The information for the number of studies and participants in each subclass is included in the supplemental forest plots. If it is acceptable with you, we would prefer not to incorporate these numbers in Table 3, as we feel it would make the table less easy to read.

With regards to the terms, frequency and pooled estimated proportions can be used interchangeably.

In the analysis of estimated proportions, we have included data from both comparative and non-comparative studies.
Discussion: Would spend more time distinguishing this study from the prior systematic reviews (citation 3,4,67, 68). If the distinguishing feature is the use of ESHRE classification system. I am wondering about utility to the Green Journal readership if this is not a commonly used system in the United States.

Reply: Looking through the discussion, we feel that there is adequate comparison with other systematic reviews in the area and the contrasts and similarities have been cited accordingly. Distinguishing features of our manuscript go beyond the usage of the ESHRE/ESGE classification, which should be useful to the wide readership of the Green Journal, both within and beyond the United States.

We present as novelties the increased risk for placental retention, placenta previa and cesarean birth. The latter has been further highlighted in the text. Moreover, we have estimated specific frequencies for each obstetric complication, information which should be of clinical significance when counseling patients with Mullerian anomalies.

Why do the authors speculate there may be a relationship between preeclampsia and CUA? Is there biologic plausibility?

Reply: Thank you for your comment. We have rephrased this comment as this summary effect was not statistically significant. We added in the discussion that when müllerian anomalies are combined with unilateral renal agenesis, this may be a predisposing factor to preeclampsia, according to a study by Heinonen et al. in 2004. [lines 269-272]

Would also spend more time discussing possible sources of bias--where there was evidence and where there was not.

Reply: Thank you for your suggestion. We have now added a comment about the publication bias, which was generally undetected. In the cases where suspected bias was found, further analysis with “trim and fill” showed no significant alteration in the direction or size of the effect. We discuss also the relatively low number of studies, small number of participants and the retrospective nature of most studies.

Reviewer #3:

The authors present a systematic review that aims to identify the risks of obstetric complications in women with congenital uterine anomalies. The review then further attempts to classify the risks within each main anomaly classification. This is a somewhat novel approach as previous systematic reviews have focused on overall reproductive outcomes in this particular patient population. The authors specifically wanted to know about rates of preterm labor, premature rupture of membranes, fetal malpresentation, cervical insufficiency, intrauterine fetal growth restriction, preeclampsia, placental abruption, abnormal placentation, birthweight and Cesarean delivery. The authors followed standard procedures for identifying potential articles for their review. The authors elected to exclude articles that involved small numbers of patients including
case reports and case series with less than 10 patients. The authors also excluded class U1 (dysmorphic) and class U5 (aplastic) uteruses, instead focusing on U2 (septate), U3 (bicoporeal) and U4 (hemi-uterus) which is reasonable at U1 and U5 type uteruses are not expected to be able to carry a normal pregnancy. The authors then use the more familiar American Fertility Society classification terms to help readers understand what types of uteri fall in to each category (U2-U4). A starring system was used to rank the quality of all comparative studies (20 studies total). The authors conclude that the systematic review show a significant positive association between obstetric complications and congenital uterine anomalies.

Line 154-how were small studies defined for this calculation? Where did you draw the line and why did you pick this particular number?

Reply: We arbitrarily opted to limit case series to those with more than 10 patients. The number may appear small, but due to the rarity of uterine anomalies, we did not want to lose important data by using a higher inclusion threshold.

Supplemental table S1-the case series from Ghi (ref 27) has 8 patients although you say that you have excluded all small case series with less than 10 patients. Why was this study included? If this study is included, then you should use a different number (such as <5 patients) and include any other case series with 5-9 patients or you should remove this study and recalculate the statistics.

Reply: During the screening process, the case series from Ghi et al. was included because there were 24 women in this study. During data extraction, we only included the 8 women who gave live birth, as the remaining 16 had a miscarriage.

Line 181-Women with anomalies delivered neonates that were on average 353.72 grams less than women without anomalies. Does this control for the increased risk of preterm delivery? Women who deliver preterm will have small babies than those women who deliver at term. If there is not a way to stratify infant weight based on weeks gestation at delivery this may be a misleading piece of data and may be better removed from the manuscript.

Reply: Thank you for your comment. We have carefully thought of this. We are unable to clearly identify whether lower birthweight is solely secondary to fetal growth restriction. Unfortunately, there is no way to stratify birthweight based on gestational age in the three studies included. We would prefer to retain the information on birthweight, but we agree that the limitations need to be stressed in the discussion section.

We have commented on this accordingly. [lines 262-265]

Line 204-"This suggests an inability" may be too strongly worded was we know that women with anomalous uterus can carry pregnancies to term and delivery normal size infants. Would consider changing this wording to something like "This suggests a decreased ability" or something similar.

Reply: Thank you for your suggestion. We have corrected ‘inability’ to ‘decreased ability’.
Line 208-Can you explain why the reduced endometrial volume may lead to high rates of fetal malpresentation?

Reply: Thank you for your comment; we have rephrased this information. We assume that the primary cause of fetal malpresentation is the anatomical distortion of the uterus. However, reduced endometrial volume may also play a role, in the same way that breech presentation is less likely to revert to cephalic beyond 39 weeks’ gestation – possibly due to less relative room being available.

Paragraph line 226-230-Would also like to see the authors comment that the increased risk of Cesarean delivery may be related to other developmental anomalies that the patient may have. We know that patients with anorectal malformations including cloacas have an increased incidence of Mullerian anomalies. Currently we recommend that these women delivery via Cesarean because of their complex reconstructions. It would be helpful to include other anatomical anomalies in this laundry list of reasons why someone with a uterine anomaly may delivery via Cesarean.

Reply: We agree with this thoughtful remark and have included information regarding women with complex urogenital malformations and their need to deliver by cesarean section. A citation regarding this was also added.

This manuscript is helpful for clinicians caring for women with Mullerian anomalies throughout the lifespan. Starting at a young age, parents of children diagnosed with Mullerian anomalies will ask about future reproductive potential. This manuscript adds to the existing literature to help discuss potential risks that a pregnancy in an anomalous uterus may face. While the number of included studies is small, this is consistent with what can be found in the literature. This manuscript can serve as a call to action for clinicians caring for these patients to design and perform prospective cohort studies to further our knowledge of this topic.

Reply: We are flattered by the positive remarks of reviewer 3. We also thank them for taking the time to go through the text in such detail.

STATISTICS EDITOR COMMENTS:

Tables 1, 2 and Abstract and in main text: The p-values should be removed. Since CIs are given, the p-values are redundant.

Reply: We thank you. We have removed p values accordingly.

lines 182-184: Since the p = 0.06, there was no "trend", it was simply NS.

Reply: Thank you for your comment. We have revised it accordingly. The line now reads as follows: “On the other hand, the summary effect about the risk of preeclampsia was not statistically significant”
General: Could simplify the Results section by not repeating each of the ORs that are in Tables. That would make the text more easily read.

Reply: Thank you for your suggestion. We removed ORs from the text.

Tables 1, 2: In cases where the number of studies pooled = 2, there is insufficient data to reliably estimate I². Should simply omit the I² for those cases.

Reply: We removed those I², as suggested.

Fig S2.1.1, and all those with estimates for proportions: Need to include columns with actual counts in each study and respective weight given to each study.

Reply: Thank you for your input. We added tables containing actual counts and weights following each figure.

Fig S2.1.4, S2.1.12, S2.1.17, S2.1.20, S2.2.22, S2.3.16, S2.3.21, S2.4.11: These are essentially recapitulations of one study, rather than pooled analyses. Need to acknowledge in limitations section.

Reply: We thank you for pointing this out. This was indeed a problem, given the limited number of studies in some analyses. We further acknowledged this in the discussion section. [lines 305-307]

EDITOR COMMENTS:

1. Thank you for submitting this work to Obstetrics and Gynecology. If you opt to submit a revision, please include the Forest plots for the anomalies overall for each outcome in the main manuscript (not supplemental material). Forest plots for different classes can be kept in supplemental.

Reply: We would like to thank you for your time reviewing our manuscript. We added these forest plots in the revised main manuscript. In addition, we also kept them in the supplemental material to maintain symmetry and completion in the file.

2. In the tables that state the number of studies, please also provide the total n for the studies when pooled.

Reply: We agree and have updated the tables to include this

3. The abstract mentions 3 main classes of anomalies, please tell the reader what those classes are in the abstract.

Reply: Thank you for this observation. We have clarified that the 3 main classes are U2-Septate, U3-Bicorporeal, U4-Hemi-uterus.

4. Replace "cesarean section" with "cesarean birth" throughout.
5. Replace "IUGR" with fetal growth restriction throughout.

6. Revise the precis to reflect what can be stated from this analysis specifically - delete the assumption that these pregnancy complications cause cesarean births.

7. Please clarify if the outcome is preterm labor or preterm birth. Preterm labor is difficult to define and would likely not be comparable across studies. Preterm birth would be an outcome of value. If it truly is preterm labor, how was this defined?

8. Make sure that absolute values are included in addition to odds ratios as the absolute numbers will be important for use in patient counseling. Also do this in the abstract.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased 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:


2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).

* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.

* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).

* Name the IRB or Ethics Committee institution in the Methods section (if applicable).

* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

**Reply:** Thank you. We added the title page and all relevant information that was previously omitted.

3. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA), which must be completed by all authors. When you uploaded your manuscript, each co-author received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please check with your coauthors to confirm that they received and completed this form, and that the disclosures listed in their eCTA are included on the manuscript's title page.

**Reply:** All authors have received and completed the form. The authors report no conflict of interest.

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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

**Reply:** We have studied and used the reVITALize definitions.

5. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 6,250 words. Stated word
limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

Reply: Our revised manuscript is within length range.

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).

* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

Reply: We noted these guidelines. No funding was received. The authors report no conflict of interest.

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 limit for Reviews is 300 words. Please provide a word count.

Reply: We have checked and revised the abstract, after the changes in main manuscript.
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.

Reply: All abbreviations and acronyms have been spelled out.

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.

Reply: The symbol has not been used in sentences with words.

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%")

Reply: Thank you for this comment. We have removed any p-values.

11. Your manuscript contains a priority claim. 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 it is not based on a systematic search but only on your level of awareness, it is not a claim we permit.

Reply: We thank you for this clarification. We have decided to remove the statement altogether.

12. 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.

Reply: We checked that the tables in our manuscript conform to journal guidelines.
13. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources"). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

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If the reference you are citing has been updated and replaced by a newer version, please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Reply: References are cited according to instructions, using superscript.

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Reply: We removed the figures from the revised manuscript and uploaded them as separate files.
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Sincerely,
On behalf of all authors,

Michail Panagiotopoulos, MD, MSc