OBSTETRICS & GYNECOLOGY

NOTICE: This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- 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: May 27, 2022
To: "Kurt T. Barnhart" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-776

RE: Manuscript Number ONG-22-776

Obstetrical outcomes of late presenting intrauterine pregnancies

Dear Dr. Barnhart:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration as a Research Letter.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jun 17, 2022, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

1. Thank you for submitting your work to Obstetrics and Gynecology.

IMPORTANT: If you opt to submit a revision, please change the format to a Research Letter and follow author instructions for that article type.

REVIEWER COMMENTS:

Reviewer #1: Comments to Author

Manuscript Number: ONG-22-776

Manuscript Title: Obstetrical outcomes of late presenting intrauterine pregnancies

Overview
1. This retrospective study attempts to determine any differences in pregnancy outcomes based on the hCG when an IUP is visualized on ultrasound. Evaluating all parameters, the only one that was statistically significant was birth weight. However, one must ask if it is clinically significant.

2. Also, the title should be revised. I thought this article was about pregnancies presenting late in their gestation, not early IUPs diagnosed with higher hCG levels.

3. Please address the comments below.

Introduction

4. Line 45. You should cite references 8 and 11 here.

Results
5. Line 116. Due to the high number of African Americans, one must question whether the findings will be applicable to a more diverse population.
6. Line 138. One must ask if 4 ounces is clinically significant.

Discussion
7. Line 172. Again, one must ask if 4 ounces is clinically significant.
8. Lines 180-184. Thus, no clinical significance in this finding.
9. Lines 195-196. One should indicate this is hypothetical, unless supported by literature. Please clarify and revise.
10. Lines 207-208. Thank you for acknowledging this issue.

References
11. Reference #1. Need a complete reference, e.g., the journal name and proper citation.
12. Reference #9. Please use proper journal abbreviation.
13. Reference #12. Please use the correct journal abbreviation.
14. One should include the Doubilet reference:
15. Doubilet PM, Benson CB. Further evidence against the reliability of the human chorionic gonadotropin discriminatory level. J Ultrasound Med 2011; 30:1637-42.

Reviewer #2:

Thank you for the opportunity to review this retrospective cohort describing the perinatal outcomes of patients with delayed presentation of intrauterine pregnancy landmarks on ultrasound later diagnosed with an ongoing IUP based on hCG cutoffs.

1. Suggest revising the manuscript title as it does not reflect the nature of the article (I initially thought that the paper was going to detail late 3rd trimester presentations).
2. Line 228 - the citation of reference 1 needs to be amended (journal name, year omitted).
3. Methods, Lines 66-67 - were patients with uterine anomalies excluded?
4. Results, Line 150 - the study time period of 2007 - 2019 encompasses some change in thought concerning iatrogenic preterm deliveries with enhanced neonatal care units. Did you look at whether there was any difference in the iatrogenic preterm delivery rate between the first half and second half of the study period?
5. Discussion, Line 196 - was placental pathology available on the cohort? This would be very interesting to evaluate especially in the neonates with birth weights <1500 grams and <2500 grams.
6. Discussion - suggest including an algorithm for the readership of stepwise management of women who present with delayed presentation of IUP landmarks.

Reviewer #3:

Authors performed a retrospective cohort study population of women initially presenting with a pregnancy of unknown location and eventually diagnosed with an intrauterine pregnancy at an urban university hospital system between January 2007 and December 2019. The authors further sought to investigate the relationship between delayed presentation of ultrasonographic landmarks of an intrauterine pregnancy (IUP) and perinatal outcomes

Recommend authors clearly define and consistently use a standard set of terminology to describe the study population. In the title, abstract and introduction, the terms "pregnancy of unknown location", "hCG above and below discriminatory zone", "delayed presentation", and "serum intrauterine landmarks", were being used interchangeably and thus the intent of the study was not clear. Similarly, authors may want to consider renaming title as I was not clear what the study was about from the title alone, for example "Perinatal Outcomes in Pregnancies of Unknown Location with hCG above the discriminatory zone".

Abstract:
30 Clearly define what is meant by "serum intrauterine landmarks above the discriminatory zone."

66-68 Why were patients who had "multiple gestations or were conceived using assisted reproductive technologies" excluded from this study? Were patients who had "induced abortions" equivalent to elective abortions, and if not, why were they excluded?

Introduction: The authors do a good job of developing a sound introduction, defining why this research question is important to study.
Materials and Methods:
63 It was not clear from the abstract, precis or title that the population being studied were presenting with obstetrical complaints.

Study design is appropriate to study associations between delayed presentation of ultrasonographic landmarks of an intrauterine pregnancy (IUP) and perinatal outcomes.

Regarding one of the premises of the study the delayed IUP with hCG above discriminator zone may represent abnormal placentation, did the authors consider other adverse outcomes associated with abnormal placentation such as c-scar pregnancy, placenta accreta spectrum, or oligohydramnios?

Did the authors exclude pregnancies complicated with fetal aneupoloidy, congenital anomalies, medical comorbidities, or history of prior sPTB or cervical insufficiency that increase risk for preterm delivery or fetal growth restriction and which could act as confounding variables?

Describe how authors intended to deal with missing data.

Initial statistical analysis appears to be appropriate. How did the authors choose the baseline demographic variables they adjusted for? Why was primiparity not adjusted for? For this study, I encourage authors to give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included.

STROBE checklist not provided.

Results
106-111 Recommend flowchart

Discussion
209 In order to conclude this as a strength, recommend describing power calculation in methods.

STATISTICS EDITOR COMMENTS:

Lines 26-28: The Authors do not stipulate an inference threshold, but I assume it to be 0.05, in which case there is no "trend", the differences in iatrogenic PTb were NS.

Table 1: Need units for BMI. Need to enumerate any missing data.

Table 2: Should clearly separate the primary from all secondary outcomes. Although the difference in success rates was small and NS, what difference could be discerned from these data and what difference would be clinically significant? Using these data, a control group success rate of 73.3%, a two-sided alpha = 0.05 and 80% power, the discernible difference would be < 61% or > 84%. By that standard, the study is underpowered. Need to put the results in context. Would also be informative to put the success rates in context by providing CIs for each proportion. The math is much worse for comparison of spontaneous abortion rates of IUD rates, in terms of power to generalize the NS findings.

Table 3, lines 91-95: Need to include footnote to Table citing the adjustors used. Regarding the difference in BW, lines 102-103, the difference, although statistically significant after adjustment, represents a small effect. The RRs, besides being uniformly NS, were often underpowered due to small counts of adverse outcomes.

Fig 1 legend: Need to state that unadjusted and adjusted p-values. The distributions appear skewed. If they do not conform to normal distributions, then should use a non-parametric test, rather than a test which assumes normality.

Fig 2, inspection of lines 147-148: Although the mean BWs show a monotonic decrease, the SDs are quite different, essentially by an order of magnitude. Again, were these normally distributed? Should use a nonparametric ANOVA test.

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

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:
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
* 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's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories.

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "Patients with obesity" instead of "obese patients," "Women with disabilities" instead of "disabled women," "women with HIV" instead of "HIV-positive women," "women who are blind" instead of "blind women."

6. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines:

CHEERS: economic evaluations of health interventions
CHERRIES: studies reporting results of Internet e-surveys
CONSERVE: reporting trial protocols and completed trials modified due to the COVID-19 pandemic and other extenuating

circumstances
CONSORT: randomized controlled trials
MOOSE: meta-analyses and systematic reviews of observational studies
PRISMA: meta-analyses and systematic reviews of randomized controlled trials
PRISMA for harms: PRISMA for harms
RECORD: observational studies using ICD-10 data
STARD: studies of diagnostic accuracy
STROBE: observational studies
SQUIRE 2.0: quality improvement in health care studies

Include the appropriate checklist for your manuscript type upon submission, if applicable, and indicate in your cover letter which guideline you have followed. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at www.equator-network.org/.

7. 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.

8. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Research Letters: 600 words (do not include more than two figures and/or tables [2 items total])

9. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

* 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 or indicate whether the meeting was held virtually).
* 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]."
* Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

10. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Research Letter: 125 words

11. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com /ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

12. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

13. In your abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001").

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

14. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available at http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

15. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. 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 formal reference list. Please cite them on the line in parentheses.

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. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

15. Figures 1-2: Please upload as figure files on Editorial Manager.

16. 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 https://wkauthorservices.editage.com/open-access/hybrid.html.

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

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

If you submit a revision, we will assume that it has been developed in consultation with your coauthors and that each author has given approval to the final form of the revision.

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jun 17, 2022, 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

_____

Attn:

Obstetrics & Gynecology

409 12th Street SW

Washington, DC 20024-2188

To the Editorial Staff of Obstetrics & Gynecology,

Thank you for taking the time to review our manuscript, “Obstetrical outcomes of late presenting intrauterine pregnancies,” and for your feedback. We have revised the manuscript according to the reviewer comments we received and would like you to reconsider the submission with these revisions in place.

Thank you again for your review. We are happy to answer any questions about the manuscript throughout your review.

Sincerely,

Olanrewaju Dawodu, MD

Jessica Wu, BS

Robert Gallop, PhD

Kurt T. Barnhart, MD, MSCE

EDITOR COMMENTS:

1. Thank you for submitting your work to Obstetrics and Gynecology.

IMPORTANT: If you opt to submit a revision, please change the format to a Research Letter and follow author instructions for that article type.
Thank you for your comment. The format of the submission has been changed from Original Research to Research Letter.

REVIEWER COMMENTS:

Reviewer #1: Comments to Author

Manuscript Number: ONG-22-776

Manuscript Title: Obstetrical outcomes of late presenting intrauterine pregnancies

Overview
1. This retrospective study attempts to determine any differences in pregnancy outcomes based on the hCG when an IUP is visualized on ultrasound. Evaluating all parameters, the only one that was statistically significant was birth weight. However, one must ask if it is clinically significant.
Thank you for your comment. We agree with this and have included that conclusion in the revision.

2. Also, the title should be revised. I thought this article was about pregnancies presenting late in their gestation, not early IUPs diagnosed with higher hCG levels.
Thank you for your comment. We agree with this revision and the title has been changed to, "Perinatal outcomes of pregnancies of unknown location with hCG above the discriminatory zone."

3. Please address the comments below.

Introduction
4. Line 45. You should cite references 8 and 11 here.
Thank you for your comment—this correction has been made, and the order of references was adjusted appropriately.

Results
5. Line 116. Due to the high number of African Americans, one must question whether the findings will be applicable to a more diverse population.
Thank you for your comment. We agree with this point and have addressed it as an addition to our limitations section (in Discussion, line 605).

6. Line 138. One must ask if 4 ounces is clinically significant.
Thank you for your comment. We agree with this point and have addressed this important caveat of the result in the Discussion section (line 599).

Discussion
7. Line 172. Again, one must ask if 4 ounces is clinically significant.
Thank you for your comment—please see above (comment #6).
8. Lines 180-184. Thus, no clinical significance in this finding.
Thank you for your comment—we agree, no changes were made.
9. Lines 195-196. One should indicate this is hypothetical, unless supported by literature. Please clarify and revise.
Thank you for your comment. We agree with this need for clarification and have revised this statement in our Discussion section.
10. Lines 207-208. Thank you for acknowledging this issue.
Thank you for your comment—no changes necessary.

References
11. Reference #1. Need a complete reference, e.g., the journal name and proper citation.
Thank you for your comment. We agree with this change, and the reference has been corrected.
12. Reference #9. Please use proper journal abbreviation.
Thank you for your comment. We agree with this change, and the reference has been corrected.
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Thank you for your comment. We agree with this change, and the reference has been corrected.
14. One should include the Doubilet reference:
Doubilet PM, Benson CB. Further evidence against the reliability of the human chorionic gonadotropin discriminatory level. J Ultrasound Med 2011; 30:1637-42.
Thank you for your comment. We appreciate the suggestion of this additional reference; however, it was already included in our reference list (reference #11 in original manuscript, now #4 with adjusted reference order), and no changes were made.

Reviewer #2:

Thank you for the opportunity to review this retrospective cohort describing the perinatal outcomes of patients with delayed presentation of intrauterine pregnancy landmarks on ultrasound later diagnosed with an ongoing IUP based on hCG cutoffs.

1. Suggest revising the manuscript title as it does not reflect the nature of the article (I initially thought that the paper was going to detail late 3rd trimester presentations).
Thank you for your comment. The title has been revised to, “Perinatal outcomes of pregnancies of unknown location with hCG above the discriminatory zone.”
2. Line 228 - the citation of reference 1 needs to be amended (journal name, year omitted).
Thank you for your comment. We agree with this change, and the reference has been corrected.
3. Methods, Lines 66-67 - were patients with uterine anomalies excluded?
Thank you for your comment. Patients with uterine anomalies were not excluded, and data on the presence of uterine anomalies were not collected.
4. Results, Line 150 - the study time period of 2007 - 2019 encompasses some change in thought concerning iatrogenic preterm deliveries with enhanced neonatal care units. Did you look at whether there was any difference in the iatrogenic preterm delivery rate between the first half and second half of the study period?
Thank you for your comment. We agree that this is a relevant point to consider, but we did not specifically look at this difference in analyzing our data.
5. Discussion, Line 196 - was placental pathology available on the cohort? This would be very interesting to evaluate especially in the neonates with birth weights <1500 grams and <2500 grams.
Thank you for your comment. We agree that data on placental pathology would be valuable to analyze, but these data were not collected for our cohort.
6. Discussion - suggest including an algorithm for the readership of stepwise management of women who present with delayed presentation of IUP landmarks.
Thank you for your comment. We agree that this would be a very valuable clinical addition to our manuscript and appreciate the suggestion; however, we are not able to make this change within the length restrictions of a Research Letter format.

Reviewer #3:

Authors performed a retrospective cohort study population of women initially presenting with a pregnancy of unknown location and eventually diagnosed with an intrauterine pregnancy at an urban university hospital system between January 2007 and December 2019. The authors further sought to investigate the relationship between delayed presentation of ultrasonographic landmarks of an intrauterine pregnancy (IUP) and perinatal outcomes

Recommend authors clearly define and consistently use a standard set of terminology to describe the study population. In the title, abstract and introduction, the terms "pregnancy of unknown location", "hCG above and below discriminatory zone", "delayed presentation", and "serum intrauterine landmarks", were being used interchangeably and thus the intent of the study was not clear. Similarly, authors may want to consider renaming title as I was not clear what the study was about from the title alone, for example "Perinatal Outcomes in Pregnancies of Unknown Location with hCG above the discriminatory zone".
Thank you for your comment. We agree on the importance of standardizing terminology and in improving clarity from our manuscript title.
In our revisions, we consistently use “delayed presentation of IUP” in our Methods and Discussion sections to signify IUPs diagnosed at hCG above the discriminatory zone, which is defined in the Methods.
The title of the manuscript has been changed in accordance with your suggestion to read, “Perinatal outcomes of pregnancies of unknown location with hCG above the discriminatory zone.”

Abstract:
30 Clearly define what is meant by "serum intrauterine landmarks above the discriminatory zone."
Thank you for your comment. We defined intrauterine landmarks as presence of a gestational sac with yolk sac and/or embryo with or without cardiac activity. we are not able to make this change within the length restrictions of a Research Letter format..

66-68 Why were patients who had "multiple gestations or were conceived using assisted reproductive technologies" excluded from this study? Were patients who had "induced abortions" equivalent to elective abortions, and if not, why were they excluded?
Thank you for these comments. Patients with multiple gestations or those conceived using assisted reproductive technologies may have increased perinatal risk so were excluded as they may confound the association we sought to look into.
Induced abortions is equivalent to elective abortions in our study. They were excluded because our goal was to evaluate perinatal outcomes.

Introduction: The authors do a good job of developing a sound introduction, defining why this research question is important to study.
Thank you for your comment—no changes necessary.

Materials and Methods:
63 It was not clear from the abstract, precis or title that the population being studied were presenting with obstetrical complaints.
Thank you for your comment. We agree that this is an important feature of our study sample. Since we did not intentionally select for patients with early obstetrical complaints when identifying our study sample, this was not indicated in our manuscript title; however, since patients who were diagnosed with PULs frequently received ultrasounds because of obstetrical complaints, we acknowledged this bias of our study in our Discussion section.

Study design is appropriate to study associations between delayed presentation of ultrasonographic landmarks of an intrauterine pregnancy (IUP) and perinatal outcomes.
Thank you for your comment– no changes necessary.

Regarding one of the premises of the study the delayed IUP with hCG above discriminator zone may represent abnormal placentation, did the authors consider other adverse outcomes associated with abnormal placentation such as c-scar pregnancy, placenta accreta spectrum, or oligohydramnios?
Thank you for your comment. We agree on this point and did collect data on abnormal placentation. However we found no difference between groups so did not include this in our paper. We did not collect data on fluid status.

Did the authors exclude pregnancies complicated with fetal aneupoloidy, congenital anomalies, medical comorbidities, or history of prior sPTB or cervical insufficiency that increase risk for preterm delivery or fetal growth restriction and which could act as confounding variables?
Thank you for your comment. While we did include medical comorbidities and prior preterm birth, we did not collect data on the suggested variables.

Describe how authors intended to deal with missing data.
Thank you for your comment. Unlike a standard randomized clinical trial where intervention effects may be dependent on attrition patterns, these data consist of a retrospective cohort looking at PULs diagnosed at our sospital between 2007-2019. Any missing data is assumed to be missing at random, with our analysis consisting of anyone with an outcome measure with N=487 (or N=439 for live births).

Initial statistical analysis appears to be appropriate. How did the authors choose the baseline demographic variables they adjusted for? Why was primiparity not adjusted for? For this study, I encourage authors to give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included.
Thank you for your comment. We adjusted for age, gestational age, and number of term births because these were the variables found to be confounders during our statistical analysis. Other variables were tested but were excluded due to either missing data or collinearity.

STROBE checklist not provided.

Thank you for your comment. We followed the STROBE statement criteria for observational studies.

Results
106-111 Recommend flowchart
Thank you for your comment. We agree with the value of this but are unable to include a flowchart due to the limitations of the Research Letter.

Discussion
209 In order to conclude this as a strength, recommend describing power calculation in methods.
Thank you for your comment. *A priori* statistical power indicated that with our sample sizes, we are sufficiently powered to detect a difference of 13% or 14% in prevalence for a sample size of 487 (and 439 live births) with at least 80% power for an unadjusted analysis. Similarly, we are sufficiently powered to detect a standardized mean difference of .26 or .27 for a sample size of 487 and 439 with at least 80% power for an unadjusted analysis. We were unable to include this in the revised paper due to word count limitations.

STATISTICS EDITOR COMMENTS:

Lines 26-28: The Authors do not stipulate an inference threshold, but I assume it to be 0.05, in which case there is no "trend", the differences in iatrogenic PTb were NS.
Thank you for your comment. We agree with this and have made the appropriate edits, indicating that this finding is not significant.

Table 1: Need units for BMI. Need to enumerate any missing data.
Thank you for your comment. We agree with the need to include this information, but due to the limitations of a Research Letter, this table was removed from the submission.

Table 2: Should clearly separate the primary from all secondary outcomes. Although the difference in success rates was small and NS, what difference could be discerned from these data and what difference would be clinically significant? Using these data, a control group success rate of 73.3%, a two-sided alpha = 0.05 and 80% power, the discernible difference would be < 61% or > 84%. By that standard, the study is underpowered. Need to put the results in context. Would also be informative to put the success rates in context by providing CIs for each proportion. The math is much worse for comparison of spontaneous abortion rates of IUD rates, in terms of power to generalize the NS findings.
Thank you for your comment. We apologize for the lack of clarity in our sample size and the ability to be sufficiently powered to detect effects. The *a priori* power analysis shows power to detect effects in an unadjusted model. After data collection, we adjusted all contrasts for patient age and number of previous full term births. Through the *a priori* power calculations above, we are powered to detect a significant difference of 0.27 with 80% power in an unadjusted analysis. In an adjusted analysis with our observed sample size of live births (N=439), where the covariates explain 40% of the variance of the outcome, we have over 80% power to detect a standardized difference of 0.21. How much of the variance each covariate accounts for varies outcome to outcome, therefore making the detectable effect vary depending on the strength of the association for each outcome.

Table 3, lines 91-95: Need to include footnote to Table citing the adjustors used. Regarding the difference in BW, lines 102-103, the difference, although statistically significant after adjustment, represents a small effect. The RRs, besides being uniformly NS, were often underpowered due to small counts of adverse outcomes.
Thank you for your comment. We have amended our footnotes to include the adjusters used. We agree that the difference in BW is a small effect, and this is commented on in our Discussion section. We also agree that the RRs were often underpowered, an unfortunate effect of analyzing rare adverse outcomes, but they did not represent any significant differences in those outcomes and thus were not commented on.

Fig 1 legend: Need to state that unadjusted and adjusted p-values. The distributions appear skewed. If they do not conform to normal distributions, then should use a non-parametric test, rather than a test which assumes normality.

Thank you for your comment. The figure legend has been amended to reflect that the p-value is an adjusted value.
We agree that the respective models depend on the assumption the model-based residuals are approximately normal. Skewed and bimodal distributed data can cause the residuals to violate the model-based assumptions. Formal Box-Cox test was implemented with the PROC TRANSREG procedure in SAS/STAT 15.1, which provides both the optimal power transformation, which in this case was 1.25, as well as a convenient power transformation 1.00. The optimal transformation says raising the outcome to the 1.25 will yield approximately normal residuals; therefore, meeting the respective parametric models assumptions. The convenient lambda indicates there is not a significant reduction of fit using the power transformation of 1.00, which corresponds to no transformation needed. Implementing the optimal power transformation yields an adjusted p-value of 0.042 and an unadjusted p-value of .073. We did investigate non-parametric techniques using the Van der Waerden non-parametric test which yielded similar results of an adjusted p-value of 0.036 and an unadjusted p-value of .073. The discussion of this analysis was not able to be included in our manuscript text due to limitations of the Research Letter, but a line addressing this comment was added to the Figure 1 legend.

Fig 2, inspection of lines 147-148: Although the mean BWs show a monotonic decrease, the SDs are quite different, essentially by an order of magnitude. Again, were these normally distributed? Should use a nonparametric ANOVA test.
Thank you for your comment. Due to the limitations of a Research Letter, this figure was removed from the submission.

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Funding information was previously disclosed on the initial title page that was submitted. The IRB institution information has been added to the Methods section. Other points here are not applicable to our study.

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