OBSTETRICS & GYNECOLOGY

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

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

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

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

Date: Apr 29, 2022
To: "Loic Sentilhes" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-665

RE: Manuscript Number ONG-22-665

Trial of labor or elective cesarean delivery for low-lying placenta? A propensity score analysis.

Dear Dr. Sentilhes:

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.

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 May 20, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: In this manuscript, the authors present an analysis of outcomes for women who have low-lying placentas. The analysis appears well done and demonstrates that planned vaginal delivery is a viable option for IOL<20mm. A few comments and questions follow.

1. Tables- why didn't the authors include all the cesarean indications for completeness of reporting?

2. Abstract- conclusions state new findings in several places. For instance, the results in the abstract do not discuss differences in the IOD groups of 1-10 and 11-20mm but conclusions are drawn. Either eliminate these subgroups from conclusions or include in the Results.

3. Abstract line 33 should read "after 35 weeks" to be consistent with the methods.

4. Why did the authors search by codes that were excluded (placenta accrete and previa)?

5. Were there any Center differences that were explored for the potential differences in the study site management and characteristics?

Reviewer #2: In this original manuscript, the authors compare a trial of labor vs elective cesarean in cases of low-lying placenta. They use propensity score analysis to balance the patients in the study and find that there is no difference in perinatal complication outcomes between the two groups. The major flaws of this manuscript are the lack of clear definitions of the population (and selection), exposure definitions, and most importantly, the primary and secondary outcomes. The authors do not consider that intrapartum bleeding is important and this is not discussed anywhere in the

manuscript as an indication for emergent cesarean and its associated complications (i.e. GETA). This coupled with the extremely small sample size which is likely underpowered are the major limitations of this study.

Abstract:
Introduction and methods are well-written. Please see comments on the methods and results below for individual points.

Conclusions: The authors report that trial of labor may be suggested for those with 11-20mm low-lying placenta, and that <11mm reduces the likelihood of vaginal birth. These results are not presented in the results section of the abstract and the conclusion here is not supported.

Introduction:
- The authors combine placenta previa and low-lying placenta in their introduction - regarding delivery guidelines and incidence. As this paper focuses only on low-lying placenta, I would consider revising the introduction to only describe low-lying placenta as placenta previa is outside the scope of this manuscript and detracts from the question.

- Line 72: the authors report compare the outcome... "what outcome?"

- The objective using IOD in the introduction is not discussed in the abstract

Methods:
- The way the authors describe their population ascertainment is curious. The report using previa, accreta, low-lying to classify the population. They then report that files were reviewed. It is unclear if they only included low-lying placenta and excluded PAS or previa. In addition, did they exclude those suspected of PAS but not? or conversely PAS that were not antenatally identified?

- In addition, the report that placentas were classified as low-lying with an IOD < 20mm. Was each patient chart reviewed to include only low-lying placentas and then each chart reviewed for inclusion? Or was this based on some other report? In addition, when was this last TVUS performed? Low-lying placentas may resolve and so the time frame of these 3rd trimester exams is of paramount importance.

- as written now, it seems the only review of the files for accuracy was mode of delivery?

- The authors do not report if they assessed antepartum hemorrhage or intrapartum hemorrhages - this is a major limitation as the planned mode of delivery may change due to significant bleeding which would not be captured in this outcome, but be integral to evaluation of maternal outcomes

- Primary outcome: the authors report the primary outcome of PPH > 1L; however, for patients who underwent vaginal delivery, PPH is defined in a different manner and should be utilized to assess for hemorrhage

- The lack of ascertained of antepartum or intrapartum bleeding and any transfusion (that may result from intrapartum complications) is a lost opportunity and should be included for this study to be of value especially as the issue with low-lying placenta is mostly intrapartum bleeding (necessitating mode of delivery choices) as opposed to postpartum bleeding; estimated blood loss, while subjective would also be an outcome to evaluate, as would need for emergency cesarean

- The exposure is oddly defined: trial of labor should include anyone that labored, regardless of ultimate mode of delivery. Items such as non-reassuring outcome, intrapartum bleeding should be outcomes; elective cesarean should just be defined as need for planned cesarean per medical records; trial of labor should be planned labor per medical records. Both should be irrespective of ultimate mode of delivery - although these outcomes are integral.

- Lines 125-126: The authors report that confounders for propensity adjustment were based on literature and other hypotheses. What about other baseline differences between the groups which is the usual way this is performed.

- The authors should justify why a sensitivity analysis expands teh population to all deliveries (i.e. 22 weeks to term instead of near term). This is 1) a larger population than the primary study and 2) no deliveries at preterm GA are elective. I would omit this analysis.

Results:
- Can the authors speculate as to why their rates of low-lying placenta are significantly lower than the general rates (0.5% vs 0.13%)

- The sample size is very small for this analysis and likely lacks adequate power for rare outcomes as is evidenced in the stratified analysis

- The key findings of this data suggests an extremely high emergency CS rate for women (25%) who undergo trial of labor with IOD <11mm because of intrapartum bleeding. This again reinforces the comments about about choice of outcome. While PP hemorrhage may not be different, clearly intrapartum hemorrhage is and this is what we seek to avoid with a planned cesarean vs offering trial of labor. As such, I would recommend the authors revisit their chosen outcome as to exactly what they seek to answer.

- The propensity matching appears balanced however, I am unsure whether Table 1 is pre-propensity balancing (as there are multipe p< 0.05) or after. If it is before matching, the actual matched characteristics should be displayed in table 1. The goal of propensity scores is to demonstrate the matching (which should only be off for BMI). Lines 174-178 should be the descriptors of table 1. And moved higher up within the results.

- The analytic approach is sound; however, the outcome is the major concern in this manuscript

- Lines 183-186: none of the results report or even mention the higher emergency cs rate for bleeding in the laboring group. This is a major oversight and should be included. Emerency CS is known for being more complicated than elective ones and this could lead to other severe maternal morbidities including general anesthesia, etc. As such, this needs to be explored.

Comment:
- The results in the first paragraph are not supported and are a overreach from the results for the reasons defined above

- Lines 228-231: This group is also included by the current authors

- However, the authors discuss only PP bleeding. Isnt bleeding throughout the labor process important? I would argue that intrapartum bleeding is at least at important in this group if not more important than only PP bleeding

- Lines 236-237: EBl for PPH is defined as different based on mode of delivery

- I would exclude the sensitivity analysis using all deliveries > 22 weeks

- A strong limitation would be that not all TVUS were done at the same interval before delivery

Reviewer #3: The submitted manuscript is a retrospective multi-center study on trial of labor after 3rd trimester confirmation of a low-lying placenta. Overall, the study is well written and reaches appropriate conclusions. Despite its retrospective nature, the study's object is best answered in this fashion.

Comments:

-The data presented is from 2007-2012, why is this data a decade old? In this case, limitations should be expanded as much as changed in 10 years especially in the labor and imaging.

-A collector bag was used for calculation of blood loss, I assume this was for vaginal deliveries, how was this applied to cesarean deliveries? If a trial of labor was converted to cesarean, were these blood losses summative or only measured at delivery?

-Why were women with a history of >2 cesarean deliveries included in the study if trial of labor was not an option for these patients?

-In table 1, the total patient population = 171 yet in table 3, this only adds up to 163, why is this?

-Table 1 shows 2/3 of the planned cesarean deliveries were for IOD 1-10mm, this should me discussed as a potential limitation as it may have been driven by labor complication fears.

STATISTICAL EDITOR COMMENTS:

Table 1: Many of the characteristics have low counts and there is insufficient stats power to generalize the NS p-values. For the column of TOL, the N= 70, so all proportions should be rounded to nearest integer %, not cited to 0.1% precision. The previous C-section, esp since > in the elective C-section cohort may have biased the outcomes re: mode of delivery.

Table 2: Same issue with TOL column and precision of %s and with low power to generalize most NS comparisons, due to low counts.

Table 3: Previous issues re: precision and low power are compounded in this subset analysis.

Fig 2: The common problem to all the models is the relatively small sample size relative to the number of potential confounders.

Appendix A: The adjustment for odds of Severe PPH, which occurred in 16 +23 =39 cases, compared to 6 adjustor variables, is an unfavorable ratio and likely resulted in over fitting. On the other hand, as can be seen from the wide CIs, there is low power to discern a significant association.

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. 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."

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric 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.

6. 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.

Original Research: 3,000 words

7. For your title, please note the following style points and make edits as needed:
* Do not structure the title as a declarative statement or a question.
* Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles.
* Abbreviations, jargon, trade names, formulas, and obsolete terminology should not be used.
* Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," "A Systematic Review," or "A Cost-Effectiveness Analysis" as appropriate, in the subtitle. If your manuscript is not one of these four types, do not specify the type of manuscript in the title.

8. 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.

9. 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.

Original Research: 300 words

10. 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.

11. 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.

12. 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.

13. 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.

14. 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. Each supplemental file in your manuscript should be named an "Appendix," numbered, and ordered in the way they are first cited in the text. Do not order and number supplemental tables, figures, and text separately. References cited in appendixes should be added to a separate References list in the appendixes file.

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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 May 20, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason D. Wright, MD
Editor-in-Chief

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

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May 19th, 2022

Ref. Manuscript Number ONG-22-665: " Trial of labor or elective cesarean delivery for low lying placenta? A propensity score analysis "

Dear Dr. Wright,

We thank you for your e-mail dated April 29, 2022, and the useful comments by the three reviewers, the Statistical Editor, and the Editorial team. The manuscript has now been completely revised in accordance with these comments. As recommended, we have responded point-by-point to the comments of each reviewer, the statistical editor, and the editor and return a copy of the revision, in which the changes have been highlighted with the “track changes” feature.

The mode of delivery for women with a third trimester asymptomatic low-lying placenta remains a matter of debate.

Only a few studies have described the perinatal outcomes of women diagnosed with a low-lying placenta at term, and none provided data on both their antenatal symptoms and the indication for either the elective cesarean delivery or the trial of labor. Furthermore, most used study protocols that did not take the intended treatment into account and are likely to introduce selection biases. In this context, a randomized controlled trial might resolve this question but difficulties in recruiting and ethical concerns undoubtedly make such a study impossible.

The aim of our study was to evaluate and compare the outcome of women with a low-lying placenta according to their planned mode of delivery and stratified by the distance from the internal os (IOD) at the last ultrasound examination before delivery while using propensity score analyses to ensure the comparability of the study groups and minimize the indication bias.

Among 128,233 births during the study period, 171 (0.13%) women were diagnosed with a low-lying placenta at more than 35 weeks of gestation, including 70 (40.9%) in the TOL group and 101 (59.1%) in the elective CD group (note that women with placenta previa were excluded). Almost 40% of women with a low-lying placenta at or near term who attempted labor had a successful vaginal birth without an increased risk of maternal or perinatal complications compared with those who had an elective cesarean. In particular, trial of labor did not result in a higher postpartum hemorrhage rate after controlling for the indication bias by a propensity score analysis. An IOD of 11-20 mm at the last transvaginal ultrasound scan before delivery substantially increased the chance of successful vaginal birth compared to women with an IOD of 1-10 mm.

We would like emphasize that, compared with the existing literature, our study presents several methodological advantages, as the previous reviewers highlighted. The first is our comparison according to planned mode of delivery rather than of women with vaginal versus cesarean deliveries; the latter comparison is obviously biased in favor of the vaginal delivery group. Second, we used propensity score analyses, as encouraged in the literature and by your journal, to ensure the comparability of the study groups and minimize the impact of uncontrolled confounders and in particular indication biases related to mode of delivery. To our knowledge, based on a thorough search of Medline with appropriate queries, our study is the first to address these two major limitations found in previous studies.

Although we are aware of the limitations of our paper and have acknowledged them in the Discussion, we believe that our results are sufficiently important to be delivered to the readers of the Green Journal, specifically, that the choice of planned mode of delivery in cases of low-lying placenta should primarily consider the success rate of vaginal delivery, rather than the postpartum hemorrhage rate, which does not appear to differ according to the intended mode of delivery.

We are confident that this study constitutes new evidence useful to your readers that will enable them to inform and share the decision-making about management with women with a low-lying placenta.

The authors hereby confirm 1) that all authors have made a substantial contribution to the information or material submitted for publication; 2) that all have read and approved the final manuscript; 3) that they have no direct or indirect commercial financial incentive associated with publishing the article; 4) that there was no source of extra-institutional funding, particularly that provided by commercial sources; 5) that the manuscript or portions thereof are not under consideration by another journal or electronic publication and have not been previously published; 6) that this study was approved by an appropriate Research Ethics Committee and informed consent was obtained from all study participants.

Each author fulfils the authorship criteria of the ICMJE Recommendations. The authors also agree to the inclusion of their names in the list of authors on the manuscript in the order shown on the title page.

We confirm that we have carefully read the Instructions for Authors.

Thank you for considering our article for publication in *Obstetrics & Gynecology.*

Sincerely yours,

Pr. Loïc Sentilhes, MD, PhD, FRCOG
Corresponding author,
For and on behalf of all authors.

RE: Manuscript Number ONG-22-665: “Trial of labor or elective cesarean delivery for low-lying placenta? A propensity score analysis.”

Point by point responses to the reviewers’ comments

We would like to thank the three reviewers, the Statistical Editor, and the Editorial Office for their comments, which have helped us to improve the quality of this paper.

Reviewer #1:

In this manuscript, the authors present an analysis of outcomes for women who have low-lying placentas. The analysis appears well done and demonstrates that planned vaginal delivery is a viable option for IOL<20mm. A few comments and questions follow.

We are grateful to the reviewer for this comment.

1. Tables- why didn't the authors include all the cesarean indications for completeness of reporting?

We chose to focus on low-lying placenta as the indication for cesarean birth, given that it is the primary topic of the paper and to avoid overloading our tables. The other indications are dominated by abnormal fetal heart rate without hemorrhage and protracted labor.

Nonetheless, to make these clear, we have added the following sentence as a footnote to Tables 2 and 3:
“Other indications for cesarean deliveries were abnormal fetal heart rate without hemorrhage during labor and protracted labor.”

2. Abstract- conclusions state new findings in several places. For instance, the results in the abstract do not discuss differences in the IOD groups of 1-10 and 11-20mm but conclusions are drawn. Either eliminate these subgroups from conclusions or include in the Results.

We thank the reviewer for this comment and we apologize for this error.
To specify this point, we have modified the following sentence in the
Abstract, section Results, page 3, lines 65-66:
“The vaginal delivery rate in the trial-of-labor group was respectively 50.0% (19/38) and 18.5% (5/27) in the 11-20 mm and 1-10 mm subgroups.”

3. Abstract line 33 should read "after 35 weeks" to be consistent with the methods.

We apologize for this error and have now corrected it.

4. Why did the authors search by codes that were excluded (placenta accrete and previa)?

We chose to use a broad ICD search criterion to avoid missing any low-lying placentas due to misclassification.

5. Were there any Center differences that were explored for the potential differences in the study site management and characteristics?

To avoid overloading our manuscript and our tables, we chose not to detail the data of each participating center, but we performed analyses to identify a potential center effect and found none. In addition, each participating tertiary maternity hospital had the same management policy for low-lying placenta, in particular, for the choice of the planned mode of delivery. As we specified in the Discussion section, lines 305-307, page 15, no perinatal center had an elective cesarean policy before 35 weeks' gestation.

Thus, since we did not identify a center effect in our analyses (shown below), and since only one reviewer raised this point, we have not modified the manuscript.

However, if the Editors think it useful, we propose the following options:
1/ we will add a sentence to the Results Section of our manuscript stating that there is no center effect (data not shown).
2/ or we will add a sentence in the Results Section of our manuscript stating that there is no center effect, and we will add the analyses below to the Supplemental Files:

Characteristics of women included	**Trial of Labor group n = 70**	**Elective Cesarean Delivery group n = 101**	***P***
Center			.3
Angers	10 (14)	16 (15.8)	
Brest	9 (13)	17 (16.8)	
Caen	14 (20)	18 (17.8)	
Nantes	6 (9)	9 (8.9)	
Rennes	19 (27)	11 (10.9)	
Tours	22 (31)	20 (19.8)	

	Severe Postpartum Hemorrhage ≥ 1000 mL		
	Crude OR (95% CI)	Adj. OR (95% CI)	*P* *
Planned mode of delivery			
Elective cesarean delivery	Ref	Ref	
Trial of labor	0.99 (0.48-2.05)	1.19 (0.52-2.71)	.7
Center	**1.05 (0.86-1.28)**	**1.09 (0.88-1.35)**	**.5**
Angers	Ref	Ref	
Brest	1.47 (0.40-4.75)	2.07 (0.48-5.81)	
Caen	1.12 (0.31-4.07)	1.64 (0.39-4.85)	
Nantes	0.62 (0.10-3.65)	0.79 (0.12-4.65)	
Rennes	1.01 (0.27-3.77)	1.32 (0.30-4.54)	
Tours	1.60 (0.49-5.24)	2.07 (0.58-6.11)	
Maternal age >30 (years)	1.46 (0.70-3.06)	1.59 (0.70-3.58)	.3
BMI before pregnancy ≥ 30 (kg/m²)	2.04 (0.56-7.39)	-	-
Nulliparity	0.55 (0.23-1.29)	0.85 (0.33-2.20)	.7
Previous cesarean delivery	3.27 (1.24-8.61)	2.55 (0.86-5.50)	.01
Tobacco use during pregnancy	1.52 (0.66-3.49)	-	-
First episode of antepartum hemorrhage <29 weeks	0.43 (0.09-2.00)	-	-
Recurrent episodes of antepartum hemorrhage (≥ 3)	1.14 (0.56-2.32)	-	-
Anterior placental location	0.56 (0.26-1.22)	-	-
Internal os distance, 0-10 mm	1.37 (0.65-2.89)	1.49 (0.66-3.37)	.3

Reviewer #2:

In this original manuscript, the authors compare a trial of labor vs elective cesarean in cases of low-lying placenta. They use propensity score analysis to balance the patients in the study and find that there is no difference in perinatal complication outcomes between the two groups. The major flaws of this manuscript are the lack of clear definitions of the population (and selection), exposure definitions, and most importantly, the primary and secondary outcomes. The authors do not consider that intrapartum bleeding is important and this is not discussed anywhere in the manuscript as an indication for emergent cesarean and its associated complications (i.e. GETA). This coupled with the extremely small sample size which is likely underpowered are the major limitations of this study.

Abstract:

Introduction and methods are well-written. Please see comments on the methods and results below for individual points.

We are grateful to the reviewer for this comment.

Conclusions: The authors report that trial of labor may be suggested for those with 11-20mm low-lying placenta, and that <11mm reduces the likelihood of vaginal birth. These

results are not presented in the results section of the abstract and the conclusion here is not supported.

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“The vaginal delivery rate in the trial-of-labor group was respectively 50.0% (19/38) and 18.5% (5/27) in the 11-20 mm and 1-10 mm subgroups.”

Introduction:
- The authors combine placenta previa and low-lying placenta in their introduction - regarding delivery guidelines and incidence. As this paper focuses only on low-lying placenta, I would consider revising the introduction to only describe low-lying placenta as placenta previa is outside the scope of this manuscript and detracts from the question.

We thank the reviewer for this comment, with which we agree.
We have substantially modified the Introduction section to focus the reader on our topic.

- Line 72: the authors report compare the outcome... "what outcome?"

To specify this point, we have modified the following sentence in the Introduction Section, lines 112-115, page 6:
“Our study aimed to evaluate and compare maternal and neonatal morbidity of women with a low-lying placenta by their planned mode of delivery and stratified by the IOD at the last predelivery ultrasound examination, while using propensity score analysis to ensure the study groups' comparability and minimize the indication bias.”

- The objective using IOD in the introduction is not discussed in the abstract

We thank the reviewer for this comment.
To correct this point, we have modified the following sentence in the Abstract Section, line 52-54, page 3:
“OBJECTIVE: To compare outcomes of women with low-lying placenta by planned mode of delivery and **internal os distance (IOD**) with propensity score analysis to ensure comparability and minimize indication bias.”

Methods:
- The way the authors describe their population ascertainment is curious. The report using previa, accreta, low-lying to classify the population. They then report that files were reviewed. It is unclear if they only included low-lying placenta and excluded PAS or previa. In addition, did they exclude those suspected of PAS but not? or conversely PAS that were not antenatally identified?

We chose to use broad ICD search criteria to avoid missing any low-lying placentas due to misclassification. Each file with women with a low-lying placenta was then reviewed to ensure she also met all the other inclusion criteria.

To clarify the selection of our population, we have modified the following sentences of the Method section, lines 119-137, page 7:
“Each hospital searched its database for all consecutive case files with one of the following International Classification of Diseases, 10th edition (ICD-10) codes: ICD-10 O44 and O43.2. These codes correspond to placenta previa and low-lying placenta, with or without hemorrhage, and to placenta accreta spectrum (PAS). Two independent investigators (PJ and VR) first reviewed each paper file to select only those with a low-lying placenta to avoid misclassification. Women were not eligible for the study if their medical files were incomplete, contained a classification error, or if the delivery took place outside a participating center. Each medical chart at each center was then reviewed to include only women who met all the inclusion criteria and no exclusion criteria: women with singleton or multiple pregnancies who were diagnosed with a low-lying placenta (IOD < 20 mm at the last predelivery transvaginal ultrasound) and gave birth at or after 35 weeks' gestation. Exclusion criteria included placenta previa, antenatally suspected PAS, and termination of pregnancy. The inclusion and diagnostic criteria were the same for all six centers.
Simultaneously, the chart review collected maternal baseline clinical characteristics, course of labor, mode of delivery, postpartum hemorrhage, and maternal and neonatal outcomes. We also sought to retrieve variables that might have influenced the choice of planned mode of delivery."

Concerning the exclusion of PAS, we apologize for our lack of precision in describing the selection of our population.
As previously described, we now specify that all women with antenatally suspected PAS were excluded from the study.
We chose not to exclude the PAS discovered in postpartum and confirmed by pathological analysis since our analysis mimics an intention-to-treat design: when PAS is not suspected before delivery, the physician does not know it exists when determining the mode of delivery (trial of labor or elective cesarean delivery) and only discovers it at delivery or postpartum. Because we chose to analyze data with an intention-to-treat approach (trial of labor versus planned elective cesarean delivery rather than vaginal versus cesarean delivery), we further chose not to exclude women with unsuspected PAS before delivery.

However, no PAS was discovered during delivery or at pathological examination. Only one woman had a hysterectomy due to severe PPH, and PAS was not found on the hysterectomy specimen.

- In addition, the report that placentas were classified as low-lying with an IOD < 20mm. Was each patient chart reviewed to include only low-lying placentas and then each chart reviewed for inclusion? Or was this based on some other report? In addition, when was this last TVUS performed? Low-lying placentas may resolve and so the time frame of these 3rd trimester exams is of paramount importance.

We confirm that each patient chart was reviewed to include only a low-lying placenta with an IOD < 20 mm, measured by the last transvaginal ultrasound before delivery.
To avoid any confusion and provide more details about the methodology, we now describe the selection of our population in greater detail in the Method section:
“Two independent investigators (PJ and VR) first reviewed each paper file to select only those with a low-lying placenta to avoid misclassification. Women were not eligible for the study if their medical files were incomplete, contained a classification error, or if the delivery took place outside a participating center. Each medical chart at each center was then reviewed

to include only women who met all the inclusion criteria and no exclusion criteria: women with singleton or multiple pregnancies who were diagnosed with a low-lying placenta (IOD < 20 mm at the last predelivery transvaginal ultrasound) and gave birth at or after 35 weeks' gestation. Exclusion criteria included placenta previa, antenatally suspected PAS, and termination of pregnancy. The inclusion and diagnostic criteria were the same for all six centers.
Simultaneously, the chart review collected maternal baseline clinical characteristics, course of labor, mode of delivery, postpartum hemorrhage, and maternal and neonatal outcomes. We also sought to retrieve variables that might have influenced the choice of planned mode of delivery."

We confirm that all women had an ultrasound scan at the third trimester of pregnancy to determine the IOD, and as mentioned in our methodology, we collected the IOD determined at the last ultrasound, i.e., as close as possible to delivery.
In fact, standard care in France for all pregnancies is to perform three mandatory ultrasounds during the pregnancy, notably with a final one at 32-34 weeks of gestation. French legislation requires that the location of the placenta be mentioned on the report of this examination. Moreover, women with low-lying placenta usually undergo an additional third-trimester around 36 weeks of gestation.

To clarify this point, we have now added the following sentence in the Method Section, lines 138-141, page 7 "In France, besides the last mandatory ultrasound, at 32 weeks, the report of which must specify placental location, another ultrasound is recommended for both placenta previa and low-lying placenta at 36 weeks to determine the IOD and therefore the planned mode of delivery."

Table 1 already included the intervals between delivery and the last ultrasound scan: 75% of women underwent an ultrasound scan in the 15 days preceding the delivery. The median was 4 days for the trial-of-labor group and 10.5 days for the elective cesarean group.

- as written now, it seems the only review of the files for accuracy was mode of delivery?

We apologize for our lack of precision in describing the collection and control of our data. We chose to focus on ensuring that our exposure was well collected, as this is a crucial point.
However, to specify that each characteristic and outcome was reviewed, we have now modified the following sentences:
- Line 134 , page 7: "Simultaneously, the chart review collected maternal baseline clinical characteristics, course of labor, mode of delivery, postpartum hemorrhage, and maternal and neonatal outcomes."
- Line 157, page 8: "Exposure was the planned mode of delivery. Each medical chart was independently reviewed by two independent investigators (PJ and VR) to ensure the accuracy of the planned mode of delivery and other data (described above)."

- The authors do not report if they assessed antepartum hemorrhage or intrapartum hemorrhages - this is a major limitation as the planned mode of delivery may change due to significant bleeding which would not be captured in this outcome, but be integral to evaluation of maternal outcomes

We apologize for our lack of precision in defining our outcomes, and we thank the reviewer for enabling us to clarify this important point.

Antepartum hemorrhage was defined by a blood loss during the pregnancy not requiring an immediate birth. In our study, this corresponds to a complication of the low-lying placenta and was the leading cause of hospitalization during pregnancy. We also took this variable into account as a covariate for the calculation of our propensity score because we believe that it constitutes a factor that might influence both the choice of management and the primary outcome (1).

Intrapartum hemorrhage is defined by a blood loss requiring emergency cesarean delivery (1) (2) (3). In our study, we considered severe primary postpartum hemorrhage defined as blood loss above 1,000 mL as the primary outcome. This definition follows the recommendations in the latest US guidelines regarding PPH, which defined PPH as "cumulative blood loss greater than or equal to 1,000 mL … within 24 hours after the birth process (includes intrapartum loss)" (4).

(1) Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org, Gyamfi-Bannerman C. Society for Maternal-Fetal Medicine (SMFM) Consult Series #44: Management of bleeding in the late preterm period. Am J Obstet Gynecol. 2018;218(1):B2-B8.
(2) Sentilhes L, Vayssière C, Deneux-Tharaux C, Aya AG, Bayoumeu F, Bonnet M-P, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol. 2016;198:12-21.
(3) Ornaghi S, Colciago E, Vaglio Tessitore I, et al. Mode of birth in women with low-lying placenta: protocol for a prospective multicentre 1:3 matched case-control study in Italy (the MODEL-PLACENTA study). BMJ Open. 2021;11(12):e052510.
(4) American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 183, October 2017: postpartum hemorrhage. Obstet Gynecol. 2017;130(4):e168-e186. doi:10.1097/AOG.0000000000002351.

To make the article easy to read, we preferred to use the standard term of PPH as the primary outcome.

However, to clarify this crucial point, we have now added the following sentences to the Method section, line 144, page 8:
"The main endpoint was severe primary postpartum hemorrhage, defined as blood loss more than 1,000 mL within 24 hours after delivery,[21,22] measured with a collector bag in vaginal births and with graduated drapes, suction canister or by weighing in cesarean deliveries.[11,23-25] This cumulative endpoint summing all blood loss measurements also included intrapartum blood loss.[11,22] Intrapartum hemorrhage was defined as blood loss requiring emergency cesarean delivery.[5,11,26]"

We also added the following footnotes to Table 1 to specify the definition of antepartum hemorrhage:
"Antepartum hemorrhage was defined by a blood loss during the pregnancy not requiring immediate birth.[4,5]"

- Primary outcome: the authors report the primary outcome of PPH > 1L; however, for patients who underwent vaginal delivery, PPH is defined in a different manner and should be utilized to assess for hemorrhage

In accordance with the latest US guidelines regarding PPH, we used the new definition of PPH (defined as a cumulative blood loss of greater than or equal to 1,000 mL regardless of route of delivery) (4).

Moreover, like these most recent American guidelines, cited above, the most recent United Kingdom guidelines for PPH management (5), and the most recent updates of the World Health Organization (WHO) (6) and French College of Obstetricians and Gynecologists (CNGOF) guidelines (2) do not apply different cutoff points for blood loss for vaginal and cesarean deliveries because no solid evidence justifies this difference. In particular, it is hard to see how the same volume of blood loss could have different consequences for maternal morbidity according to mode of delivery.

(2) Sentilhes L, Vayssière C, Deneux-Tharaux C, Aya AG, Bayoumeu F, Bonnet M-P, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol. 2016;198:12-21.

(4) American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 183, October 2017: postpartum hemorrhage. Obstet Gynecol. 2017;130(4):e168-e186. doi:10.1097/AOG.0000000000002351.

(5) Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No. 52. BJOG. 2017;124(5):e106-e149. doi:10.1111/1471-0528.14178

(6) WHO recommendations for the prevention of postpartum haemorrhage. World Health Organisation, Geneva (Switzerland), 2012. [cited 2016 May 1]. Available from: http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf

- The lack of ascertained of antepartum or intrapartum bleeding and any transfusion (that may result from intrapartum complications) is a lost opportunity and should be included for this study to be of value especially as the issue with low-lying placenta is mostly intrapartum bleeding (necessitating mode of delivery choices) as opposed to postpartum bleeding; estimated blood loss, while subjective would also be an outcome to evaluate, as would need for emergency cesarean

We thank the reviewer for this comment and have clarified the primary endpoint by stating that it includes intrapartum blood loss, measured cumulatively and summed, as described above.

- The exposure is oddly defined: trial of labor should include anyone that labored, regardless of ultimate mode of delivery. Items such as non-reassuring outcome, intrapartum bleeding should be outcomes; elective cesarean should just be defined as need for planned cesarean per medical records; trial of labor should be planned labor per medical records. Both should be irrespective of ultimate mode of delivery - although these outcomes are integral.

We thank the reviewer for this comment and agree that this point should be more detailed and clarified for the readers. We also agree that elective cesarean should just be defined as need

for planned cesarean per medical records, as well as trial of labor should be planned labor per medical records.

To make these clearer, we have reformulated the following Method section, line 157-167, pages 8-9:
"Exposure was the planned mode of delivery. Each medical chart was independently reviewed by two independent investigators (PJ and VR) to ensure the accuracy of the planned mode of delivery and other data (described above). Trial of labor was defined as a planned trial of labor confirmed by medical records, regardless of ultimate mode of delivery — a successful vaginal delivery or an emergency cesarean performed before or during labor for severe intrapartum bleeding, abnormal fetal heart rate, or failure to progress. An elective cesarean delivery was defined as a planned cesarean, recorded in the medical records, performed before labor regardless of the indication, or during labor for women starting labor before the planned cesarean delivery date in the medical file. Women with a history of 2 or more cesareans had elective cesareans, in accordance with French guidelines.[31] "

- Lines 125-126: The authors report that confounders for propensity adjustment were based on literature and other hypotheses. What about other baseline differences between the groups, which is the usual way this is performed.

The sentence on lines 175-176 "Variables included in the multivariable analysis were chosen based on the literature and other hypothesized potential confounders" concerns only the multivariable analysis.

To build our propensity score analysis, we chose variables that might influence both management choice and primary outcome. Baseline differences were therefore included, as already described in Method section, line 182-187, page 9:
"The propensity score was defined as each woman's probability of attempting labor, based on her individual characteristics, and was estimated with a multivariable logistic regression model including the following covariates: maternal age, body mass index (BMI) before pregnancy, nulliparity, previous cesarean delivery, recurrent episodes of antepartum hemorrhage, anterior placental location, and distance between the cervical os and the placenta."

- The authors should justify why a sensitivity analysis expands the population to all deliveries (i.e. 22 weeks to term instead of near term). This is 1) a larger population than the primary study and 2) no deliveries at preterm GA are elective. I would omit this analysis.

We added this sensitivity analysis because we speculated that some reviewers or readers would be interested in the results from the total population. However, we agree with the reviewer that this analysis should be omitted.
Therefore, we have removed the sentences related to this sensitivity analysis in the Method, Results and Discussion sections and from the results in Appendix C.

Results:
- Can the authors speculate as to why their rates of low-lying placenta are significantly lower than the general rates (0.5% vs 0.13%)

The general rate mentioned of 0.5% concerns the prevalence of both low-lying and previa placentas combined (7) (8). This suffices to explain why our prevalence of low-lying placentas is lower than this cumulative prevalence. Nonetheless, we have not found any study assessing the incidence of low-lying placenta alone at or near term.

To specify this point, we have modified the following sentence in the Introduction, line 89, page 5:
"The combined prevalence of both placenta previa (defined as the placenta lying directly over the internal os) and low-lying placenta in the literature varies widely and is estimated at around 0.5% of pregnancies at term.[3,7]"

To comment on the selection of our population and to emphasize that despite a retrospective design, our rigorous collection of all cases of low-lying and previa placentas according to an established protocol has reduced the selection bias, we previously mentioned in the Discussion section, (now at line 311 page 16):
"The primary limitation of our cohort study lies in its retrospective design. Nonetheless, all data for every case were collected according to a defined protocol. While eligible cases might have been missed, the combined prevalence of low-lying and placenta previa observed in our study (0.56%) is consistent with rates reported in the literature.[3,7]"

(7) Silver RM. Abnormal Placentation: Placenta Previa, Vasa Previa, and Placenta Accreta. Obstet Gynecol. 2015;126:654–68.

(8) Jauniaux E, Grønbeck L, Bunce C, Langhoff-Roos J, Collins SL. Epidemiology of placenta previa accreta: a systematic review and meta-analysis. BMJ Open. 2019;9(11):e031193. doi:10.1136/bmjopen-2019-031193.

- The sample size is very small for this analysis and likely lacks adequate power for rare outcomes as is evidenced in the stratified analysis

We agree with the reviewer and have from the start highlighted this limitation in the Discussion section, (now line 319-323), page 16:

"Third, the infrequency of severe maternal morbidity such as second-line therapies to control postpartum hemorrhage (pelvic arterial embolization or surgical therapies), admission to the ICU, thromboembolic events, and maternal death limited our statistical power to detect potentially clinically meaningful differences between planned modes of delivery."

We also agree with this comment concerning the lack of power being exacerbated by the stratified analysis. However, we have underlined that this Table 3 is mainly descriptive rather than comparative. The *P*-values are given as an indication.

We would nonetheless like to underline that our study has the largest sample size for this topic (comparison of mode of delivery among women with low-lying placenta): we included 171 women. The other published studies, which have a less robust methodology (because they compared vaginal versus cesarean delivery, rather than planned cesarean versus planned

vaginal delivery) included a mean of 50 women with low-lying placenta (9); the largest included 98 women (10).

(9) Jansen C, Mooij Y, Blomaard C, Derks J, Leeuwen E, Limpens J, et al. Vaginal delivery in women with a low-lying placenta: a systematic review and meta-analysis. BJOG. 2019;126:1118-26.

(10) Wortman AC, Twickler DM, McIntire DD, Dashe JS. Bleeding complications in pregnancies with low-lying placenta. J Matern Fetal Neonatal Med. 2016;29:1367-71.

- The key findings of this data suggests an extremely high emergency CS rate for women (25%) who undergo trial of labor with IOD <11mm because of intrapartum bleeding. This again reinforces the comments about choice of outcome. While PP hemorrhage may not be different, clearly intrapartum hemorrhage is and this is what we seek to avoid with a planned cesarean vs offering trial of labor. As such, I would recommend the authors revisit their chosen outcome as to exactly what they seek to answer.

We have already addressed this misunderstanding of the definition of our outcome by improving the manuscript's, as the reviewer suggested above.
We thank the reviewer for for enabling us to clarify this important point.

As we have described above, intrapartum hemorrhage is defined by a blood loss requiring emergency cesarean delivery. (1) (2) (3). In our study, we considered the primary outcome to be severe primary postpartum hemorrhage defined as blood loss above 1,000 mL. We have clarified the primary endpoint by stating that it includes intrapartum blood loss, measured cumulatively and summed, as described above, as recommended in the latest American guidelines regarding PPH, which defined PPH as “cumulative blood loss greater than or equal to 1,000 mL … within 24 hours after the birth process (includes intrapartum loss)” (4).

(1) Society for Maternal-Fetal Medicine (SMFM). Electronic address: pubs@smfm.org, Gyamfi-Bannerman C. Society for Maternal-Fetal Medicine (SMFM) Consult Series #44: Management of bleeding in the late preterm period. Am J Obstet Gynecol. 2018;218(1):B2-B8.
(2) Sentilhes L, Vayssière C, Deneux-Tharaux C, Aya AG, Bayoumeu F, Bonnet M-P, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol. 2016;198:12-21.
(3) Ornaghi S, Colciago E, Vaglio Tessitore I, et al. Mode of birth in women with low-lying placenta: protocol for a prospective multicentre 1:3 matched case-control study in Italy (the MODEL-PLACENTA study). BMJ Open. 2021;11(12):e052510.
(4) American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 183, October 2017: postpartum hemorrhage. Obstet Gynecol. 2017;130(4):e168-e186. doi:10.1097/AOG.0000000000002351.

To make the article easy to read, we preferred to use the standard term PPH as the primary outcome.

However, to specify this crucial point, we have added the following sentences to the Method section, line 144-49, page 8:
"The main endpoint was severe primary postpartum hemorrhage, defined as blood loss more than 1,000 mL within 24 hours after delivery,[21,22] measured with a collector bag in vaginal births and with graduated drapes, suction canister or by weighing in cesarean deliveries.[11,23-25] This cumulative endpoint summing all blood loss measurements also included intrapartum blood loss.[11,22] Intrapartum hemorrhage was defined as blood loss requiring emergency cesarean delivery.[5,11,26] "

- The propensity matching appears balanced however, I am unsure whether Table 1 is pre-propensity balancing (as there are multiple p< 0.05) or after. If it is before matching, the actual matched characteristics should be displayed in table 1. The goal of propensity scores is to demonstrate the matching (which should only be off for BMI). Lines 174-178 should be the descriptors of table 1. And moved higher up within the results.

The data presented in Table 1 are pre-propensity balancing.
We chose to present these data in this way because they reflect our sample before any weighting by propensity score and thus illustrate their robustness and representativeness. Moreover, this allows us to illustrate to the reader the need to minimize the indication bias with the propensity score approach since we observe, as the reviewer emphasizes, that some baseline characteristics are unbalanced between the two groups.

Finally, to enable the reader to judge the correct balance of the characteristics after weighting, we have provided in Supplemental material (Appendix 2), the standardized absolute differences before (corresponding to the total population) and after propensity score weighting (corresponding to the propensity score-weighted population). Absolute standardized difference is a measure of effect size between two groups that is independent of sample size.

Thus, to avoid overloading our manuscript and our tables, we do not consider it necessary to provide the quantitative description of the data after weighting, since the main information to evaluate the quality of our propensity score is given by the figure in Appendix 2.

However, if the Editor considers it useful, we are willing to provide the Table detailing the population characteristics after weighting.

- The analytic approach is sound; however, the outcome is the major concern in this manuscript

We have already addressed this misunderstanding of the definition of our outcome by improving the manuscript's clarity, as the reviewer suggested (see above). We hope that this clarification will satisfy the reviewer.

- Lines 183-186: none of the results report or even mention the higher emergency cs rate for bleeding in the laboring group. This is a major oversight and should be included. Emergency CS is known for being more complicated than elective ones and this could

lead to other severe maternal morbidities including general anesthesia, etc. As such, this needs to be explored.

We agree with the reviewer that this point must be highlighted.

To highlight the higher emergency cesarean delivery rate for bleeding in the trial of labor group, we have modified the following sentence in Results section, line 228, page 12:
"Table 3 compares the perinatal outcomes by IOD. Women with planned trial of labor had a vaginal delivery rate of 50.0% (19/38) in the 11-20 mm subgroup and 18.5% (5/27) in the 1-10 mm subgroup, and the rates of emergency cesarean delivery for bleeding before or during labor were respectively 27.0% (10/37) and 50.0% (13/26). Neither maternal nor perinatal outcomes differed significantly between the groups."

To highlight the maternal morbidity induced by emergency cesarean delivery, we have also added the rates of general endotracheal anesthesia in Tables 2 and 3.

Comment:
- **The results in the first paragraph are not supported and are a overreach from the results for the reasons defined above**

We have now addressed this misunderstanding of the definition of our outcome by improving the clarity if our manuscript, as suggested by the reviewer (see above).

- **Lines 228-231: This group is also included by the current authors**

We disagree with the reviewer. Contrary to the reference cited in lines 228-231, women in our study who had an emergency cesarean delivery during labor due to intrapartum hemorrhage after a trial of labor were analyzed in the trial-of-labor group, rather than in the group of the effective mode of delivery, i.e. cesarean group.

This is a crucial point that differentiates our study from the majority of existing literature and is an important strength of our study, since we take the intended mode of delivery into account.

- **However, the authors discuss only PP bleeding. Isnt bleeding throughout the labor process important? I would argue that intrapartum bleeding is at least at important in this group if not more important than only PP bleeding**

We have already addressed this misunderstanding of the definition of our outcome by improving our manuscript's clarity, as the reviewer suggested (see above). Intrapartum bleeding was cumulative with the postpartum bleeding and was therefore taken into account in our primary outcome.

- **Lines 236-237: EBl for PPH is defined as different based on mode of delivery**

Like the latest American guidelines regarding PPH (4), the most recent United Kingdom guidelines for PPH management (5), and the most recent updates of the World Health Organization (WHO) (6) and French College of Obstetricians and Gynecologists (CNGOF) guidelines (2), do not apply different cutoff points for blood loss for vaginal and cesarean deliveries because no solid evidence justifies this difference. In particular, it is hard to see

how the same volume of blood loss could have different consequences for maternal morbidity according to mode of delivery.

(2) Sentilhes L, Vayssière C, Deneux-Tharaux C, Aya AG, Bayoumeu F, Bonnet M-P, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF). Eur J Obstet Gynecol Reprod Biol. 2016;198:12-21.

(4) American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 183, October 2017: postpartum hemorrhage. Obstet Gynecol. 2017;130(4):e168-e186. doi:10.1097/AOG.0000000000002351.

(5) Prevention and Management of Postpartum Haemorrhage: Green-top Guideline No. 52. BJOG. 2017;124(5):e106-e149. doi:10.1111/1471-0528.14178

(6) WHO recommendations for the prevention of postpartum haemorrhage. World Health Organisation, Geneva (Switzerland), 2012. [cited 2016 May 1]. Available from: http://apps.who.int/iris/bitstream/10665/75411/1/9789241548502_eng.pdf

- **I would exclude the sensitivity analysis using all deliveries > 22 weeks**

We added this sensitivity analysis because we speculated that some reviewers or readers would be interested in the results from the total population. However, we agree with the reviewer that this analysis should be omitted.
Therefore, we have removed the sentences related to this sensitivity analysis in the Method, Results and Discussion sections and from the results in Appendix C.

- **A strong limitation would be that not all TVUS were done at the same interval before delivery**

We agree with the reviewer about this comment. This is an observational study, therefore the practices were not controlled. However, this represents daily clinical routine. The objective of this study was to investigate maternal and neonatal morbidity according to the planned mode of delivery, with the decision about this mode of delivery reflecting the routine and the evidence in the medical record available at the time of the decision making.

However, standard care in France for all pregnancies is to perform three mandatory ultrasounds during the pregnancy, notably with a final one at 32-34 weeks of gestation. French legislation requires that the location of the placenta be mentioned on the report of this examination. Moreover, women with a low-lying placenta usually undergo an additional third-trimester around 36 weeks gestation.

Table 1 previously included the intervals between delivery and the last ultrasound scan: 75% of women underwent an ultrasound scan in the 15 days preceding the delivery. The median was 4 days for the trial-of-labor group and 10.5 days for the elective cesarean group.

Reviewer #3:

The submitted manuscript is a retrospective multi-center study on trial of labor after 3rd trimester confirmation of a low-lying placenta. Overall, the study is well written and reaches appropriate conclusions. Despite its retrospective nature, the study's object is best answered in this fashion.

We are grateful to the reviewer for this comment.

Comments:

-The data presented is from 2007-2012, why is this data a decade old? In this case, limitations should be expanded as much as changed in 10 years especially in the labor and imaging.

We agree with the reviewer. To highlight this limitation, we have now added the following sentence in the Discussion section, line 332, page 16-17:
"Lastly, since our data are a decade old, we cannot exclude the possibility that practices of antenatal imaging and labor management have changed in relevant ways."

-A collector bag was used for calculation of blood loss, I assume this was for vaginal deliveries, how was this applied to cesarean deliveries? If a trial of labor was converted to cesarean, were these blood losses summative or only measured at delivery?

In accordance with the latest American guidelines regarding PPH, we used the new definition of PPH (defined as cumulative blood loss greater than or equal to 1,000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth process (includes intrapartum loss) regardless of route of delivery) (4). Thus, if a trial of labor was converted to emergency cesarean delivery, the intrapartum blood losses were summed.
Lastly, in cases of cesarean delivery, we also apply the latest American guidelines concerning the quantification of blood loss during cesarean births (11), by measuring the amount of blood loss in graduated drapes, suction canister or weighing (see TRAAP2 (12)).

(4) American College of Obstetricians and Gynecologists. ACOG Practice Bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists Number 183, October 2017: postpartum hemorrhage. Obstet Gynecol. 2017;130(4):e168-e186. doi:10.1097/AOG.0000000000002351.

(11) Quantitative blood loss in obstetric hemorrhage. ACOG Committee Opinion No. 794. American College of Obstetricians and Gynecologists. Obstet Gynecol 2019;134:e150–6.

(12) Sentilhes L, Sénat MV, Le Lous M, Winer N, Rozenberg P, Kayem G, et al. Tranexamic Acid for the Prevention of Blood Loss after Cesarean Delivery. N Engl J Med. 2021;384(17):1623-1634. doi:10.1056/NEJMoa2028788

To highlight this point, we have modified the following sentence in the Method section, line 144-48, page 8:
"The main endpoint was severe primary postpartum hemorrhage, defined as blood loss more than 1,000 mL within 24 hours after delivery,[21,22] measured with a collector bag in vaginal births and with graduated drapes, suction canister or by weighing in cesarean deliveries.[11,23-25] This cumulative endpoint summing all blood loss measurements also included intrapartum blood loss.[11,22]"

-Why were women with a history of >2 cesarean deliveries included in the study if trial of labor was not an option for these patients?

Only 4 women had a history of 2 cesarean deliveries. We chose not to exclude these 4 women to avoid a possible selection bias in favor of the trial of labor group as maternal morbidity may increase with the number of cesareans. However, we performed a sensitivity analysis by removing these women, and found that it did not change the results.

-In table 1, the total patient population = 171 yet in table 3, this only adds up to 163, why is this?

As we have specified in the footnotes of the Table 3, there were 5 and 3 missing data items for the planned trial of labor and elective cesarean groups, respectively, because in these cases, the internal os distance was reported as <20 mm but not otherwise specified.
This explains the modified total of 163 women in Table 3, who were stratified on the IOD.

-Table 1 shows 2/3 of the planned cesarean deliveries were for IOD 1-10 mm, this should be discussed as a potential limitation as it may have been driven by labor complication fears.

The presence of differences in baseline characteristics between the two groups (trial of labor and elective cesarean delivery) was expected since these characteristics guided the decision-making regarding the planned of delivery. This justified our approach of using a propensity score analysis to minimize the indication bias. In particular, we have taken into account this variable (IOD 1-10 mm versus 11-20 mm) to estimate the propensity score, as described in the Method section.

STATISTICAL EDITOR:

Table 1: Many of the characteristics have low counts and there is insufficient stats power to generalize the NS p-values. For the column of TOL, the N= 70, so all proportions should be rounded to nearest integer %, not cited to 0.1% precision. The previous C-section, esp since > in the elective C-section cohort may have biased the outcomes re: mode of delivery.

We have followed the Editorial Office instructions included at the end of these reviewer comments: “Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.”
However, if the Editors think it useful, we are willing to change the TOL results and all others with denominator less than 100 as recommended by the Statistical Editor.

The higher rate of previous cesarean delivery in the elective cesarean group was expected. In general, the presence of differences in baseline characteristics between the two groups (trial of labor and elective cesarean delivery) was expected since these characteristics guided the decision-making regarding the planned of delivery. This justified our approach by propensity score analysis to minimize the indication bias. We have taken this variable (previous cesarean delivery or not) into account to estimate the propensity score, as described in Method section.
We chose not to exclude women with previous cesarean deliveries as these are frequent situations in clinical practice, which enables our results to be extrapolated a larger population of women than only nulliparous women as in some previous studies and to avoid to bias the results in favor of the TOL group.

Table 2: Same issue with TOL column and precision of %s and with low power to generalize most NS comparisons, due to low counts.

We have followed the Editorial Office instructions included at the end of these reviewer comments: “Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.”
However, if the Editors think it useful, we are willing to change the TOL results and all others with denominator less than 100 as recommended by the Statistical Editor.

Table 3: Previous issues re: precision and low power are compounded in this subset analysis.

We agree with the Statistical Editor about the lack of power.
We did, however, highlight this limitation in the Discussion section, page 16, lines 319:
“Third, the infrequency of severe maternal morbidity such as second-line therapies to control postpartum hemorrhage (pelvic arterial embolization or surgical therapies), admission to the ICU, thromboembolic events, and maternal death limited our statistical power to detect potentially clinically meaningful differences between planned modes of delivery.”

We also agree with the comment about the lack of power being exacerbated by the stratified analysis. However, we underline that Table 3 is mainly descriptive rather than comparative. We believe that it provides interesting information for the readers (as underlined by the three previous reviewers) and may assist obstetricians in choosing between trial of labor or elective cesarean delivery according to the internal os distance.
The *P*-values are given as an indication.

Fig 2: The common problem to all the models is the relatively small sample size relative to the number of potential confounders.

Appendix A: The adjustment for odds of Severe PPH, which occurred in 16 +23 =39 cases, compared to 6 adjustor variables, is an unfavorable ratio and likely resulted in over fitting. On the other hand, as can be seen from the wide CIs, there is low power to discern a significant association.

We propose to answer both previous comments about Figure 2 and Appendix A in the same answer.

We agree with the Statistical Editor and we must acknowledge a lack of power to generalize the nonsignificant finding concerning our primary outcome. We nonetheless believe that this information is a substantial contribution to the existing literature about the management of third-trimester asymptomatic low-lying placenta and thus important for readers of this journal to have.
Many obstetricians and other professionals counsel elective cesareans because they feel or believe that it is safer, with a lower risk of postpartum hemorrhage than a trial of labor because a severe postpartum hemorrhage may occur during labor. But our results show that the rates of both PPH and severe PPH are very similar between the trial-of-labor and elective cesarean groups; and thus the choice of the mode of delivery should be based instead on the

expected success rate of vaginal delivery. This is one of the main results of our study using a propensity score analysis and including one of the largest cohorts yet studied.

Furthermore, our post-hoc analysis determined that with a sample size of 171 patients and 23% of deliveries with adverse maternal outcome (severe postpartum hemorrhage) in the unexposed group (elective cesarean group), the study would have had a power of 80% and an alpha risk of 0.05, able to detect an OR > 2.5 in the univariate logistic regression. It would also have been able to detect an OR > 2.5 in univariate logistic regression for the risk of postpartum hemorrhage above 500 mL.
Accordingly, this result appears sufficiently relevant to inform readers that, contrary to preexisting beliefs, the choice of an elective cesarean rather than a trial of trial should be based primarily on the woman's probability of a successful vaginal delivery with a trial of labor, rather than the risk of postpartum hemorrhage, severe or not.

We have already specified this limitations in the Discussion section, line 320-332, page 16:
“Third, the infrequency of severe maternal morbidity, such as second-line therapies to control postpartum hemorrhage (pelvic arterial embolization or surgical therapies), admission to the ICU, thromboembolic events, and maternal death limited our statistical power to detect potentially clinically meaningful differences between planned modes of delivery. In addition, considering the small difference in postpartum hemorrhage rates between the trial-of-labor and elective cesarean groups (respectively 22.9% versus 23.0%), we acknowledge that our study is underpowered to confirm an absence of difference in maternal adverse outcomes. Nonetheless, a post hoc analysis determined that with a sample size of 171 patients and 23% of deliveries complicated by severe postpartum hemorrhage in the unexposed (elective cesarean) group, the study would have had a power of 80% and an alpha risk of 0.05, able to detect an OR > 2.5 in the univariate logistic regression. It would also have been able to detect an OR > 2.5 in the univariate logistic regression for the risk of postpartum hemorrhage greater than 500 mL.”

Lastly, concerning the number of confounders in our multivariable analysis, we have respected the ratio of 6-7 events per adjustment variable.
However, if the Editor considers it useful, we are willing to provide a modified Appendix 1, with the removal of an adjustment variable (shown below). The results are unchanged.

	Severe Postpartum Hemorrhage ≥ 1000 mL		
	Crude OR (95% CI)	Adj. OR (95% CI)	*P* *
Planned mode of delivery			
Elective cesarean delivery	Ref	Ref	
Trial of labor	0.99 (0.48-2.05)	1.24 (0.55-2.81)	.6
Maternal age >30 (years)	1.46 (0.70-3.06)	1.51 (0.68-3.37)	.3
BMI before pregnancy ≥ 30 (kg/m²)	2.04 (0.56-7.39)	-	-
Nulliparity	0.55 (0.23-1.29)	0.81 (0.32-2.07)	.6
Previous cesarean delivery	3.27 (1.24-8.61)	2.57 (0.87-5.85)	.09
Tobacco use during pregnancy	1.52 (0.66-3.49)	-	-
First episode of antepartum hemorrhage <29 weeks	0.43 (0.09-2.00)	-	-

Recurrent episodes of antepartum hemorrhage (≥ 3)	1.14 (0.56-2.32)	-	-
Anterior placental location	0.56 (0.26-1.22)	-	-
Internal os distance, 0-10 mm	1.37 (0.65-2.89)	1.42 (0.64-3.18)	.4

OR, odds ratio; CI, confidence interval; BMI, body mass index.

* Adjusted logistic regression analyses. Adjustment for maternal age, nulliparity, previous cesarean delivery, and cervix-to-placenta distance. The number of adjustment variables included is limited due to the low number of events (n=39).

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

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