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: Sep 24, 2021
To: "Diane Korb" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-1730

RE: Manuscript Number ONG-21-1730

Survival without severe neonatal morbidity in very preterm twins according to planned mode of delivery

Dear Dr. Korb:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 15, 2021, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

I reviewed your article on survival without severe neonatal morbidity in very preterm twins according to plan mode of delivery with great interest. This is a secondary analysis of a larger French national prospective population based cohort that was conducted from 2014-2015. Your findings suggest that there is no difference in morbidity and mortality based on mode of delivery. I have several concerns about your study design
1. I am concerned about your sample size since in your power calculations a 7-10% difference would have been missed (this seems low and maybe based on the low levels of poor outcomes). However, 7-10% is an extremely clinically significant difference when dealing with such a major complication. Interestingly, your original paper noted a decrease in morbidity in those individuals that had a vaginal delivery less than 37 weeks. Please comment
2. Although I appreciate the propensity score approach, one must realize there are limitations of this method. The largest bias is that introduced by the physicians preference, is impossible to control. Furthermore, initial exam (dilation, station, effacement) and labor progress was also not controlled. Thus the only true way answer this question is by randomized control trial.
3. It is hard to ignore the striking difference between the groups as listed on table 1 and 2. Pregnancy complications were significantly higher in those that underwent a cesarean delivery, and significantly lower in those that had pre term labor. Thus, simple pre term labor I would assume would lead the clinician to allow spontaneous vaginal delivery, as opposed to those with complications. Once again how this was weighted in your propensity score needs to be considered.
4. Gestational Age >30 weeks was significantly greater in the vaginal delivery group (prior to controlling for multiple measurements, p=0.33). The significance of gestational age on morbidity and mortality cannot be over emphasized. Although this is one of the co variants that you controlled , I doubt it was appropriately weighted in your propensity score.
5. Some general comments on propensity scoring (PS) and IPTW. Most common threats to external validity for appropriate PS matching is the failure to include appropriate confounding variables, for this study it is physician preference for delivery method and state of active labor (exam). Could this be adjusted by looking at a physicians past behavior? In addition, the propensity score balance I feel needs to be adjusted by more appropriate balance weighting for gestational age. The significant loss of power when performing propensity scoring may be magnified by this smaller sample size .
6. This conclusion has been noted in previous studies as you, have mention in reference 7 and 14. In your discussion, it may be helpful to explain how your study is different? Your study is also retrospective not prospective or randomize, thus how does it add to this question. In addition your sample size is questionable especially when you consider the propensity scoring method used to compare results.
In addition:
Ln 74: This line is crucial in determining the bias of your study. Please comment

LN 79: Do think you controlled for this substantial difference in returning warts simply by looking at what region the delivery occurred? Would not be more relevant to look at number of deliveries that were performed in each of those individual institutions as a marker of likelihood to perform vaginal or cesarean delivery (NICU, # of deliveries, MFM specialist, etc) I doubt the simple region would be enough to account for this difference in your propensity score
LN 89: Was the immediate completion of the detail would base questionnaires, unique to this time., to this study or is this what occurs normally at the included hospitals.
LN 93: Did the research nurses collect this data from charts or from interviews with patients?
Ln 95: Since this data is over 6 years old has there been any follow-up on the the children that were delivered during the study period.
Ln 156: I am confused as to the total number of patients in this study. Was it 742 or 702 as was outlined in appendix 3. Thus would propensity matching as expected your patient's for analysis was cut in half.
LN 160: I am confused how you can say that the women in table 1 characteristics appeared similar, when there was significant difference in pregnancy complications and pre term labor including pprom? Please comment?
LN 234: I disagree, a multiple site/country randomized control trial would be the only way to answer this question.

Reviewer #2:

Interesting study with practical application. The information will be very useful to providers managing twin pregnancies and pursue vaginal delivery if safe. I have the following comments.

1. Was vaginal delivery allowed if the first twin was breech and the second vertex. If so, what about the risk of interlocking heads, a rare but serious complication.

2. Was vaginal delivery allowed if discordancy was greater than 20% and if the second was breech twin. If so, what was the outcome of these pregnancies and were there any head entrapments.

3. Were there any head entrapments in the planned vaginal cohort?

4. Contraindications to vaginal delivery are described but little detail is given about the individual obstetrician decision to go vaginal or cesarean in the absence of such contraindications.

5. Morbidity is thought to be higher in the combined twin delivery. There are only 12 of these, but further description of outcomes in this group may be helpful.

Reviewer #3:

The manuscript on "Survival without severe neonatal morbidity in very preterm twins according to planned mode of delivery" is an interesting read. The study shows that there was no statistically significant difference in the Survival to discharge without severe neonatal morbidity between a planned cesarean or planned vaginal delivery. While there are studies that have explored the impact of planned delivery route in very preterm twins between 24-30 weeks or even afterwards, the role of planned route of delivery between the specific time range of 26-31 weeks has been understudied in the literature. This are my submissions.
These are my submissions:
1. Abstract
- The abstract is clear and easily understood.
- Introduction
- The introduction is also clear and succinct. .
2. Methods
While the methodology section is rich and exhaustive, I believe having them as subsections will improve interest and readability.
3. Results
- Result section is clear and succinct.

4. Discussion
- The authors did not follow the Journal's guidelines as the discussion (and the Methodology section) was written without subsections which could have led to a very beautiful narrative.
5. References
The fact that the authors restricted themselves to only 14 references and yet had a very exhaustive manuscript is commendable.
6. Tables
- The tables are clear and easily understood.

STATISTICS EDITOR COMMENTS:

Table 1: Need units for age, BMI. Would a sensitivity analysis with exclusion of the ~ 10% not receiving antenatal corticosteroids have materially changed the analysis for the primary outcome?

Table 3: The number of planned vaginal deliveries = 41, so all %s should be rounded to nearest integer %, not cited to 0.1% precision.

Tables 4, Appendix 3 and Methods: These calculations are based on the assumption that each of the n = 384 and n = 464 are independent events, within their respective cohorts. However, since they represent twin pairs, there is some correlation of outcomes within a given twin pair. That reduces the effective sample sizes and makes the inferences less strong. Need to account for the intra-class correlation of outcomes within a twin pair. The conclusions from inferences does not change materially, but the p-values should be corrected. Should also make clearer that the first outcome cited is the primary and all others are secondary ones.

Appendix 2: For completeness and to compare results with Table 4, should include not only proportions, but RR with CIs.

General: It would be informative for the reader if detectable alternative relative risks were estimated, based on the sample sizes, the usual 80% power, $p < 0.05$ and the stated survival proportions for the control groups. For Appendix 2, this requires no correction for the sample sizes, but for the main primary outcome (Table 4), the previously described adjustment of sample sizes would have to be used.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology have increased transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:

A. OPT-IN: Yes, please publish my point-by-point response letter.
B. OPT-OUT: No, please do not publish my point-by-point response letter.

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

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

4. Our journal requires that all evidence-based research submissions be accompanied by a transparency declaration statement from the manuscript's lead author. The statement is as follows: "The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained." *The manuscript's guarantor.

If you are the lead author, please include this statement in your cover letter. If the lead author is a different person, please ask him/her to submit the signed transparency declaration to you. This document may be uploaded with your submission in Editorial Manager.

5. If your study is based on data obtained from the National Center for Health Statistics, please review the Data Use Agreement (DUA) for Vital Statistics Data Files that you or one of your coauthors signed. If your manuscript is accepted for publication and it is subsequently found to have violated any of the terms of the DUA, the journal will retract your article. The National Center for Health Statistics may also terminate your access to any future vital statistics data.

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 for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), observational studies using ICD-10 data (ie, RECORD), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. 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 http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, RECORD, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

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. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 5,500 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

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

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

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

In addition, the abstract length should follow journal guidelines. The word limit for Original Research articles is 300 words; Reviews is 300 words; Case Reports is 125 words; Current Commentary articles is 250 words; Executive Summaries, Consensus Statements, and Guidelines are 250 words; Clinical Practice and Quality is 300 words; Procedures and Instruments is 200 words. Please provide a word count.

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. 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.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

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

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the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

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

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* A point-by-point response to each of the received comments in this letter. Do not omit your responses to the Editorial Office or Editors' comments.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each

author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 15, 2021, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,
Dwight J. Rouse, MD
Associate Editor, Obstetrics

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

[redacted]

Paris, October 12th 2021

Dear Editor,

Thank you for your response on September 24th 2021, concerning our manuscript ONG-21-1730 entitled “Survival without severe neonatal morbidity in very preterm twins according to planned mode of delivery” informing us you would be willing to give further consideration to a revised version.

The authors are very grateful to the Reviewers and Editors for their constructive help. We think the paper has been much improved. Our revised version has taken into account all the following points raised by the Reviewers and Editors.

All the authors have read and approved the revised version of the paper.

We hope our manuscript now meets the standards of *Obstetrics and Gynecology*.

Yours sincerely,

Diane Korb

All line numbers refer to the revised version of the manuscript without the highlighted changes.

Response to the Reviewers

REVIEWER #1:

I reviewed your article on survival without severe neonatal morbidity in very preterm twins according to plan mode of delivery with great interest. This is a secondary analysis of a larger French national prospective population based cohort that was conducted from 2014-2015. Your findings suggest that there is no difference in morbidity and mortality based on mode of delivery. I have several concerns about your study design

1. I am concerned about your sample size since in your power calculations a 7-10% difference would have been missed (this seems low and maybe based on the low levels of poor outcomes). However, 7-10% is an extremely clinically significant difference when dealing with such a major complication. Interestingly, your original paper noted a decrease in morbidity in those individuals that had a vaginal delivery less than 37 weeks. Please comment

As mentioned in the discussion, with a survival without severe neonatal morbidity rate of 80.8% in the planned vaginal delivery group as observed in this study, we calculated at posteriori that we had a statistical power of 80% to show an increase of 7% in this risk in the planned cesarean delivery group (we found a rate of 80.2% in this study). We agree with the reviewer that an increase from 80% to 87% is clinically significant. We added a sentence in the discussion section stating that we could not formally exclude increases in neonatal survival associated with planned cesarean smaller than 7%, page 11, line 280.

In comparison with the original paper (1), we have not included the same population (≥32 GW *versus* very preterm birth -<32GW). In addition, for the analysis of the impact of the planned mode of delivery for very preterm twins, we decided to analyze as main outcome the survival without severe neonatal morbidity and not the severe neonatal morbidity and mortality. Indeed, for a population of very preterm neonates before 32 gestational weeks, an outcome of severe neonatal morbidity and mortality would be less relevant.

1. Schmitz T, Prunet C, Azria E, Bohec C, Bongain A, Chabanier P, et al. Association Between Planned Cesarean Delivery and Neonatal Mortality and Morbidity in Twin Pregnancies. Obstet Gynecol. juin 2017;129(6):986-95.

2. Although I appreciate the propensity score approach, one must realize there are limitations of this method. The largest bias is that introduced by the physicians preference, is impossible to control. Furthermore, initial exam (dilation, station, effacement) and labor progress was also not controlled. Thus the only true way answer this question is by randomized control trial.

The originality of this study in comparison with previous studies is its prospective population-based design. The choice of the planned mode of delivery was collected prospectively limiting bias due to misclassification present in retrospective studies and providing valid information.

Physician preference is difficult to consider with JUMODA data but it is poorly informative in the French obstetrical context. In France, each maternity unit has local protocol in accordance with the national guidelines for managing some particular obstetrical situations like twin deliveries. Within each maternity unit, decision concerning the choice of the mode of delivery for each woman with twin pregnancy is discussed in daily staff meeting by the obstetrical team and is based on these protocols. The decision is discussed with the patient and is written in the medical file. In delivery room, physician's practice is guided and in accordance with this collegial decision and it is not an individual preference and decision. So, in your point of view, it was be more relevant to control potential bias by introducing in propensity score variables characterizing maternity unit (number of twin births by

years, university center). This is the reason why we modified the text that was confusing, we agree, in the Methods section page 4, lines 75-76, and replaced physician by obstetrical team.
A randomized trial providing comparable groups for the two planned modes of delivery and circumventing indication bias would be the appropriate study design to determine the safest mode of delivery for very preterm twins. However, the likelihood to complete such a trial is very low, given the large number of pregnancies required to demonstrate a significant difference between groups. The feasibility of such a trial appears very doubtful, as shown by the failure of at least two previous randomized trials aimed at comparing neonatal outcomes according to the planned mode of delivery for preterm breech and preterm vertex singletons were interrupted because of the inability of the investigators to recruit women (1-3). We added these 2 references in the discussion section page 10, line 248. Consequently, the choice of the best mode of planned delivery for very preterm twins will continue to rely on the results of observational studies.

1. Zlatnik FJ. The Iowa premature breech trial. Am J Perinatol. janv 1993;10(1):60-3.
2. Penn ZJ, Steer PJ, Grant A. A multicentre randomised controlled trial comparing elective and selective caesarean section for the delivery of the preterm breech infant. BJOG Int J Obstet Gynaecol. déc 2014;121 Suppl 7:48-53.
3. Lumley J, Lester A, Renou P, Wood C. A failed RCT to determine the best method of delivery for very low birth weight infants. Control Clin Trials. juin 1985;6(2):120-7

3. It is hard to ignore the striking difference between the groups as listed on table 1 and 2. Pregnancy complications were significantly higher in those that underwent a cesarean delivery, and significantly lower in those that had pre term labor. Thus, simple pre term labor I would assume would lead the clinician to allow spontaneous vaginal delivery, as opposed to those with complications. Once again how this was weighted in your propensity score needs to be considered.
To take into account this potential bias, in the regression logistic model used to create propensity score we included pregnancy complications: preterm labor and premature rupture of membranes. We checked comparability of two groups after inverse ponderation on propensity score for pregnancy complications, by comparison of standardized differences between two groups for these two variables, and they are less than 10% as shown in the appendix 1. In addition, we performed a sensitivity analysis limited to spontaneous preterm births to study population that is more homogeneous. Sensitivity analyses showed similar results.

4. Gestational Age >30 weeks was significantly greater in the vaginal delivery group (prior to controlling for multiple measurements, p=0.33). The significance of gestational age on morbidity and mortality cannot be over emphasized. Although this is one of the co variants that you controlled , I doubt it was appropriately weighted in your propensity score.
Gestational age at delivery had an important impact on neonatal morbidity and mortality in a study about prematurity. The difference for gestational age at delivery was not significantly different between the two groups of comparison. Despite this, this variable was included for the creation of the propensity score. We checked comparability of two groups after inverse ponderation on propensity score for gestational age, by comparison of standardized differences between two groups for this variable, and they were less than 10% as shown in the appendix 1.

5. Some general comments on propensity scoring (PS) and IPTW. Most common threats to external validity for appropriate PS matching is the failure to include appropriate confounding variables, for this study it is physician preference for delivery method and state of active labor (exam). Could this be adjusted by looking at a physicians past behavior? In addition, the propensity score balance I feel needs to be adjusted by more appropriate balance weighting for

gestational age. The significant loss of power when performing propensity scoring may be magnified by this smaller sample size.

We used the propensity score approach based on IPTW and not on matching because it would have been responsible for a too important reduction of our sample size.

Among the variables chosen to construct the propensity score, we included maternity unit characteristics: number of twin births by years, university center. This choice is explain in our response to the point 2 raised by the Reviewer.

6. This conclusion has been noted in previous studies as you, have mention in reference 7 and 14. In your discussion, it may be helpful to explain how your study is different? Your study is also retrospective not prospective or randomize, thus how does it add to this question. In addition your sample size is questionable especially when you consider the propensity scoring method used to compare results.

As mentioned in the Discussion section, on line 211, our results are in accordance with two studies reporting no difference in severe neonatal morbidity by planned mode of delivery (1,2). These studies, however, had some methodological limitations, including:

- small sample sizes
- retrospective design or retrospective classification of the planned mode of delivery, while in the JUMODA cohort, due to its prospective population-based design, data on planned mode of delivery was collected prospectively limiting bias due to a misclassification and providing valid information.

In addition, the indication bias inherent in this design was taken into account by an appropriate statistical method.

Therefore, our study adds the question by the prospective classification of the planned mode of delivery and its larger sample size.

1. Sentilhes L, Lorthe E, Marchand-Martin L, Marret S, Ancel P-Y, Delorme P, et al. Planned Mode of Delivery of Preterm Twins and Neonatal and 2-Year Outcomes. Obstet Gynecol. janv 2019;133(1):71-80.

2. Sentilhes L, Oppenheimer A, Bouhours A-C, Normand E, Haddad B, Descamps P, et al. Neonatal outcome of very preterm twins: policy of planned vaginal or cesarean delivery. Am J Obstet Gynecol. juill 2015;213(1):73.e1-73.e7

In addition:

Ln 74: This line is crucial in determining the bias of your study. Please comment

We modified the sentence and replaced physician by obstetrical team. We realized the confusion induced by the original sentence. Indeed, in France, each maternity unit has local protocol in accordance with the national guidelines for managing some particular obstetrical situations like twin deliveries. Within each maternity unit, decision concerning the choice of the mode of delivery for each woman with twin pregnancy is discussed in daily staff meeting by the obstetrical team and is based on these protocols. The decision is discussed with the patient and is written in the medical file. In delivery room, physician's practice is guided and in accordance with this collegial decision and it is not an individual appreciation, preference or decision.

LN 79: Do think you controlled for this substantial difference in returning warts simply by looking at what region the delivery occurred? Would not be more relevant to look at number of deliveries that were performed in each of those individual institutions as a marker of likelihood to perform vaginal or cesarean delivery (NICU, # of deliveries, MFM specialist, etc) I doubt the simple region would be enough to account for this difference in your propensity score

We modified the sentence by adding that we discussed about caesarean section "for fetal indication," and by removing that-"it depended on the practitioner's judgment of prognosis" because it induced confusion between on the one hand the maternal management with the choice of the planned mode of delivery and on the other hand, the decision concerning the management of extremely premature births occurring at the limit of viability. Indeed, during the study period, there was no consensus in France about the attitudes or practices for perinatal or neonatal management of extremely preterm deliveries below 26 weeks that could vary between maternity units.
The sentence now appears as follow, page 4, line 79: "For this planned secondary analysis of the JUMODA cohort, we included twin pregnancies from 26+0 weeks of gestation, because during the study period, active antenatal care, including the willingness to perform a cesarean section for fetal indication between 24 and 26 weeks of gestation, was not general practice in France and differed quite substantially from one maternity ward to another."

LN 89: Was the immediate completion of the detail would base questionnaires, unique to this time, to this study or is this what occurs normally at the included hospitals.
The analysis of the impact of the planned mode of delivery on neonatal outcomes was the main objective of the JUMODA cohort, so this information was collected prospectively, and was unique to the study time. Immediately after delivery, obstetricians completed a detailed web-based questionnaire of the JUMODA study about the planned mode of delivery, indications for planned cesarean delivery or induction of labor, and details about the delivery management and classified it as a planned cesarean or planned vaginal delivery.

LN 93: Did the research nurses collect this data from charts or from interviews with patients?
Research nurses collected data about maternal characteristics, medical history, pregnancy complications, and neonatal health on the medical files.

Ln 95: Since this data is over 6 years old has there been any follow-up on the the children that were delivered during the study period.
Unfortunately, the follow-up of the children was not scheduled at the conception of JUMODA.

Ln 156: I am confused as to the total number of patients in this study. Was it 742 or 702 as was outlined in appendix 3. Thus would propensity matching as expected your patient's for analysis was cut in half.
In main analysis, we included 424 twin deliveries (848 neonates overall). As we performed a propensity score approach with IPTW and not with a matching, there is no modification of the sample size (Table 4). In the sensitivity analysis limited to spontaneous preterm births we included 351 twin deliveries (702 neonates overall) (Appendix 3).

LN 160: I am confused how you can say that the women in table 1 characteristics appeared similar, when there was significant difference in pregnancy complications and pre term labor including pprom? Please comment?
As mentioned in the results section, maternal characteristics were similar between the two groups concerning maternal age, BMI, region of birth, parity and smoking. But some differences were observed for pregnancy characteristics: pregnancy complications, preterm labor, PPROM (table 1). To avoid confusion we added the word demographic between maternal and characteristics. Therefore, it is now written: "Maternal demographic characteristics were similar…", page 7, line 167.

LN 234: I disagree, a multiple site/country randomized control trial would be the only way to answer this question.
We already responded to this comment in point 2 raised by the Reviewer.

REVIEWER #2:
Interesting study with practical application. The information will be very useful to providers managing twin pregnancies and pursue vaginal delivery if safe. I have the following comments.
1. Was vaginal delivery allowed if the first twin was breech and the second vertex. If so, what about the risk of interlocking heads, a rare but serious complication.
There was no strict indication for planned caesarean delivery when the first twin was in breech presentation and the second in cephalic presentation. The choice of the planned mode of delivery depended on maternity unit's protocols.
When the first twin was in breech presentation with a planned vaginal delivery, they were 7/32 second twin in cephalic presentation, among them: one caesarean was performed for both twins and one caesarean for the second twin, and none for interlocking heads.
Interlocking heads is a very rare event. In a previous JUMODA analysis including first twin in breech presentation after 32 gestational weeks, among 298 planned vaginal deliveries, only one case of interlocking twins occurred in the planned vaginal delivery group at 37 weeks of gestation, indicating emergency caesarean delivery. The first twin had severe neonatal morbidity because of an Apgar score of less than 4 at 5 minutes. The 5-minute Apgar score of the second twin was 9. Both twins were discharged home on day 7 (7).

2. Was vaginal delivery allowed if discordancy was greater than 20% and if the second was breech twin. If so, what was the outcome of these pregnancies and were there any head entrapments.
There was no strict indication for planned caesarean delivery if discordancy was greater than 20% and second twin in breech presentation. The choice of the planned mode of delivery depended on maternity unit's protocols.
In the planned vaginal group they were only 4 pregnancies with a discordancy greater than 20% and second twin in breech presentation. In these situations they were 2/4 caesarean deliveries for both twins, and no caesarean for the second twin. There was no head entrapments.

3. Were there any head entrapments in the planned vaginal cohort?
In the planned vaginal delivery group, no head entrapment occured.

4. Contraindications to vaginal delivery are described but little detail is given about the individual obstetrician decision to go vaginal or cesarean in the absence of such contraindications.
We already responded to this comment in point Ln 74 raised by Reviewer 1.**5. Morbidity is thought to be higher in the combined twin delivery. There are only 12 of these, but further description of outcomes in this group may be helpful**.
Among the 12 cesareans for the second twin, we observed 8 neonatal morbidity and mortality events for the second twins (including one neonatal death). Indications of cesarean for the second twin when complicated by neonatal morbidity and mortality (n=8) were: cervical retraction (4), bradycardia (1),

failure of maneuvers (1), arm prolapse (1), placental abruption (1). We let the Editor decide if this information deserves to be added in the text.

REVIEWER #3:

The manuscript on "Survival without severe neonatal morbidity in very preterm twins according to planned mode of delivery" is an interesting read. The study shows that there was no statistically significant difference in the Survival to discharge without severe neonatal morbidity between a planned cesarean or planned vaginal delivery. While there are studies that have explored the impact of planned delivery route in very preterm twins between 24-30 weeks or even afterwards, the role of planned route of delivery between the specific time range of 26-31 weeks has been understudied in the literature. This are my submissions.

These are my submissions:

1. **Abstract**

- **The abstract is clear and easily understood.**
- **Introduction**
- **The introduction is also clear and succinct.**

We thank the Reviewer for his/her comments.

2. **Methods**

While the methodology section is rich and exhaustive, I believe having them as subsections will improve interest and readability.

We added subsections in method section.

3. **Results**

- **Result section is clear and succinct.**

We thank the Reviewer for his/her comment.

4. **Discussion**

- **The authors did not follow the Journal's guidelines as the discussion (and the Methodology section) was written without subsections which could have led to a very beautiful narrative**.

We added subsections in method section.

5. **References**

The fact that the authors restricted themselves to only 14 references and yet had a very exhaustive manuscript is commendable.

We thank the Reviewer for his/her comment.

6. **Tables**

- **The tables are clear and easily understood**.

We thank the Reviewer for his/her comment.

STATISTICS EDITOR COMMENTS:

Table 1: Need units for age, BMI. Would a sensitivity analysis with exclusion of the ~ 10% not receiving antenatal corticosteroids have materially changed the analysis for the primary outcome?

Units for age and BMI have been added as requested in Table 1.
We did not performed a sensitivity analysis with exclusion of the ~ 10% not receiving antenatal corticosteroids because the potential bias linked to this practice is low after 26 gestational weeks due to the management of very preterm birth that does not influence the choice of the mode of delivery. In addition, exclusion of the neonate not receiving antenatal corticosteroids could favour the planned vaginal delivery group since most of the neonates unexposed to antenatal corticosteroids would be those born after spontaneous preterm delivery.

Table 3: The number of planned vaginal deliveries = 41, so all %s should be rounded to nearest integer %, not cited to 0.1% precision.
We modified the Table 3.

Tables 4, Appendix 3 and Methods: These calculations are based on the assumption that each of the n = 384 and n = 464 are independent events, within their respective cohorts. However, since they represent twin pairs, there is some correlation of outcomes within a given twin pair. That reduces the effective sample sizes and makes the inferences less strong. Need to account for the intra-class correlation of outcomes within a twin pair. The conclusions from inferences does not change materially, but the p-values should be corrected. Should also make clearer that the first outcome cited is the primary and all others are secondary ones.
We agree that it needs to account for the intra-class correlation of outcomes within a twin pair. It is for that reason, as explained in the Methods section, lines 121-123, generalized estimating equations were applied to take the correlation between the first and second twin from the same pregnancy into account. We added in footnote of table 4 that this correlation was considered.
We modified Table 4 and Appendix 3 as suggested.

Appendix 2: For completeness and to compare results with Table 4, should include not only proportions, but RR with CIs.
RR with CIs have been added as requested in Appendix 2.

General: It would be informative for the reader if detectable alternative relative risks were estimated, based on the sample sizes, the usual 80% power, $p < 0.05$ and the stated survival proportions for the control groups. For Appendix 2, this requires no correction for the sample sizes, but for the main primary outcome (Table 4), the previously described adjustment of sample sizes would have to be used.
With a survival without severe neonatal morbidity rate of 80.8% in the planned vaginal delivery group as observed in this study, our analysis had a statistical power of 80% to show a significant RR equal to 1.08 (1.10-2.37) associated with an increase of 7% in this risk in the planned cesarean delivery group (we found a rate of 80.2% RR=1.02 (0.93-1.11) in this study).

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This sentence was included in the cover letter and in the answers of reviewers.

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We included the STROBE list.

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.
We used the reVITALize definitions.

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