

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)*
- Email correspondence between the editorial office and the authors*

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Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office:

obgyn@greenjournal.org.

Date: Sep 13, 2018
To: "Loïc Sentilhes" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-1599

RE: Manuscript Number ONG-18-1599

Planned mode of delivery for preterm twins and neonatal and two-year outcomes: the EPIPAGE 2 population-based study.

Dear Dr. Sentilhes:

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Oct 04, 2018, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

REVIEWER #1:

1. General comments. This study is one of many analyses from EPIPAGE-2, a population-based cohort study of all preterm births between 22 and 34 weeks conducted at 546 maternity units across France in 2011. The manuscript is very well-written, and it addresses the topic of mode of delivery of preterm twins comprehensively and thoughtfully. The majority of my comments are relatively minor. Two larger issues might be addressed more fully however.

a. Would explore how you knew whether vaginal or cesarean delivery were planned. It appears that the authors determined the plan based on the mode of delivery and the stated indication for cesarean. For example, if indication for delivery was abnormal fetal heart rate or failure to progress, it was assumed that vaginal delivery had been planned (lines 110-112). My concern is that if one would normally perform cesarean delivery for preterm twins but a woman comes to the hospital with recurrent fetal heart rate decelerations, perhaps the indication for cesarean delivery might be coded as abnormal fetal heart rate (though the plan would have been for cesarean even if the heart rate had been normal). This is further relevant because of the way in which the authors write that their study is superior to others- please address and include in the discussion.

b. The authors convincingly demonstrate that the severe outcomes studied did not vary with mode of delivery. It would be helpful to know other outcomes, realizing that other outcome differences may reasonably affect a decision to proceed with cesarean delivery. Examples include intubation or need for oxygen in the first 24 hrs of life, hospital stay or duration of ICU admission, musculoskeletal injury (birth trauma, bruising), hyperbilirubinemia, and need for transfusion. If data are not available, this should be addressed in the discussion.

2. Precis (condensation). This may be misinterpreted to suggest that the study was about first twins only. Might revise.

3. Abstract. This is an excellent summary of the study findings.

a. Might clarify what is meant by planned vaginal and cesarean delivery (criteria for determining what was planned).

b. Inclusion and exclusion criteria are not mentioned. Would include the total number of twin pregnancies (932, not 383) and why the majority were excluded.

c. In the abstract conclusion, might include something about cephalic presentation of the first twin.

4. Introduction.

Based on the number of references cited in the first 2 paragraphs, the authors may want to use the discussion to emphasize what their study adds and whether they feel that recommendations should be changed.

Also, line 63 reads as though the authors have studied preterm cephalic first twins (rather than outcomes of both twins).

5. Methods. This section is very thorough and is clearly presented, but the subheadings are not necessary.

- a. Were twins included in any prior publications from the EPIPAGE-2 study?
- b. Line 147. Might define fetal growth restriction, realizing that it is defined differently in different countries.

6. Results.

- a. Lines 198-200. Might go through the figure in a little more detail. That 59% of preterm twins were excluded from analysis should probably be stated. Study findings may not apply to the majority of preterm twins that clinicians encounter. Might also specify the exclusion categories and relevant percentages. Might include this as a limitation.
- b. Lines 205-206. Might clarify that for the 20% of twin pregnancies with planned vaginal delivery in which cesarean delivery was required, both twins were delivered by cesarean in the majority of cases (that in only 3% was cesarean required for the second twin). This is reported in Table 1, but readers may not appreciate from the text that 1 in 5 didn't require emergent cesarean for the second twin.
- c. In the text, might include a sentence or two describing outcomes for the 52 sets of twins in which vaginal delivery was planned but cesarean was ultimately performed for both babies. I appreciate that the authors performed an intent-to-treat analysis, but any outcomes differences between these 52 pregnancies and the other cohorts would be important to know.
- d. As the authors have birthweight data, can they analyze results according to birthweight difference between twins (discordance)?
- e. In table 1, the gestational age percentages do not appear to be correct. Might comment on the fact that planned cesarean appears to be more common at earlier gestational age and vaginal delivery at later gestational ages (> 30 weeks). This is not unexpected but might be addressed.

REVIEWER #2:

With great interest I read this population-based cohort study.

1) Abstract:

There was no discrepancy between the abstract and the manuscript.

2) Introduction:

It was well written and informative.

3) Methods:

I agree with the authors that this is the best design to answer the study question, as performing a clinical trial will be unethical and unfeasible.

The method section was well written and thorough.

4)Results:

There was no discrepancy between the tables and the manuscript. good interpretation of the tables. However, in line 156 the author stated that they used chi square and they did not mention fisher exact test. May be it was missed by the writer of the manuscript. As we know it is incorrect to use chi square to compare variables with numbers < 25. based on the manuscript , they used chi square with the small numbers (<25) in table 1 and 2 and this means that the P-value of these variables is wrong.

5) Discussion and conclusion:

I enjoyed reading the discussion section it answered almost all the questions that I had. excellent explanation of the study limitations and strengths.

REVIEWER #3:

The study is a sub-analysis of the EPIPAGE-2. The analysis examines the outcomes of the twins, when the first twins were cephalic, comparing vaginal versus cesarean deliveries.

1. The condensation statement seems to imply that the study is only about the outcomes of the first twin.
2. Are the authors recommending that the present guidelines of the National College of French Gynecologists and Obstetricians be changed based on the study results?
3. In the database, do the authors have information about the experience level of the obstetricians who recommended vaginal delivery versus cesarean delivery?
4. Also, did the likelihood of vaginal delivery increase in larger perinatal centers?

STATISTICAL EDITOR'S COMMENTS:

1. Tables 1, 2: Need to cite the sample size for each cohort, not just the total. It appears from the (%) cited that the counts among the PCD cohort had more missing values. If so, then the comparisons may be biased. For example, for deafness, with total $n = 299$ out of $276+107$, the PCD count of 1 with deafness corresponds to a % of 3.1. That implies a total among the PCD of only 32, when the entire PCD cohort was $n = 107$. Contrast that with the count for cerebral palsy also of 1, but now representing 0.6% of the total.
2. Tables 2, 3: The problem with comparing survival at discharge, proportion without severe morbidity among survivors at discharge or survival at 2 yrs corrected age without severe or moderate disabilities is that the frequencies of adverse events is low. This yields insufficient power to generalize the NS findings. For example, assuming the total sample sizes given here, and evaluating the most discrepant differences (2nd twin, survival at discharge without severe morbidity, with proportions of 85.4 vs 91.4%) the power is only $\sim .40$, to discern a difference. For the proportions that are closer, of course the power is worse. Put another way, to discern the differences cited for those outcomes, the samples required would range from $\sim 3x$ to $\sim 40x$ those in this study.
3. Table 4: This analysis does help to mitigate the baseline differences between the cohorts, but does not address the small sample sizes, or more specifically, the small counts of adverse outcomes for the two cohorts.

Associate Editor's Comments:

Please in response to Statistical Editor's concern, sprinkle some caveats about limited statistical power throughout the manuscript including in Abstract.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. 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.

3. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

4. 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), 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), and quality improvement in health care (ie, SQUIRE 2.0). 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, CHEERS, or SQUIRE 2.0 guidelines, as appropriate.

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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words); Case Reports should not exceed 8 typed, double-spaced pages (2,000 words); Review articles should not exceed 25 typed, double-spaced pages (6,250 words); Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words); Clinical Practice and Quality articles should not exceed 22 typed, double-spaced pages (5,500 words); Procedures and Instruments articles should not exceed 8 typed, double-spaced pages (2,000 words); Personal Perspectives essays should not exceed 12 typed, double-spaced pages (3,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendices).

Please limit your Introduction to 250 words and your Discussion to 750 words.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). 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 also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

8. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).

9. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

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 limits for different article types are as follows: Original Research articles, 300 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. 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.

If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at <http://ong.editorialmanager.com>. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

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

has given approval to the final form of the revision, and that the agreement form signed by each author and submitted with the initial version remains valid.

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 04, 2018, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

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September, 28th 2018

Ref. Original Research: ONG-18-1599 “Planned mode of delivery for preterm twins and neonatal and two-year outcomes: the EPIPAGE 2 population-based study.”

Dear Editor,

Thank you for your e-mail dated September 13th, 2018 and the useful comments by the three Reviewers, Statistical Reviewer 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 each reviewer and editor’s comments and return a copy of the revision, in which the changes we have made are highlighted.

The optimal intended mode of delivery of preterm twins remains debatable. Several large retrospective population-based studies have shown an association between vaginal delivery and neonatal mortality and morbidity, mainly for the second twin, suggesting that a planned cesarean delivery may be the optimal option for the preterm second twins. Conversely, small hospital retrospective studies, with limited statistical power did not show increased adverse perinatal outcomes for preterm twins after vaginal birth compared with cesarean; and meta-analyses of observational studies failed to demonstrate a significant reduction of neonatal morbidity with either mode of delivery underlining the poor quality of the evidence these studies provide and the need to provide details related to clinical decision in published data in that field.

The aim of our study was to investigate both neonatal and two years outcomes for preterm first cephalic twins by comparing planned vaginal versus planned cesarean deliveries based on the EPIPAGE 2 population-based cohort study.

After propensity score analysis, planned cesarean delivery as compared to planned vaginal delivery was not associated for first and second twins with improved survival at discharge, survival at discharge without severe morbidity or survival at 2 years without neurosensory impairment.

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 the source of extra-institutional funding, particularly that provided by commercial sources, is indicated; 5) that the manuscript or portions thereof are not under consideration by another journal or electronic publication and have not been previously published.

Loïc Sentilhes, Elsa Lorthé and Gilles Kayem drafted the report. All authors participated in revision and critical review of the report, and all have seen and approved the final version.

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. [REDACTED]

I affirm 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."

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

With best regards,
Yours sincerely,

Loïc Sentilhes, M.D., Ph.D,
Corresponding author,
For and on behalf of all authors.

ONG-18-1599: Planned mode of delivery for preterm twins and neonatal and two-year outcomes: the EPIPAGE 2 population-based study

Point by point responses to Reviewers' comments

We would like to thank all the reviewers and editors for their comments, which have helped us to improve the quality of our paper.

Reviewer #1

- 1. General comments. This study is one of many analyses from EPIPAGE-2, a population-based cohort study of all preterm births between 22 and 34 weeks conducted at 546 maternity units across France in 2011. The manuscript is very well-written, and it addresses the topic of mode of delivery of preterm twins comprehensively and thoughtfully.**

We thank the Reviewer for his comment.

- 2. The majority of my comments are relatively minor. Two larger issues might be addressed more fully however.**

a. Would explore how you knew whether vaginal or cesarean delivery were planned. It appears that the authors determined the plan based on the mode of delivery and the stated indication for cesarean. For example, if indication for delivery was abnormal fetal heart rate or failure to progress, it was assumed that vaginal delivery had been planned (lines 110-112). My concern is that if one would normally perform cesarean delivery for preterm twins but a woman comes to the hospital with recurrent fetal heart rate decelerations, perhaps the indication for cesarean delivery might be coded as abnormal fetal heart rate (though the plan would have been for cesarean even if the heart rate had been normal). This is further relevant because of the way in which the authors write that their study is superior to others- please address and include in the discussion.

We thank the Reviewer for his comment. As previously written lines 110-115: "Planned vaginal delivery (PVD) was defined with vaginal delivery or cesarean section performed during labor for abnormal fetal heart rate or failure to progress or for second twin only. Planned cesarean delivery (PCD) was considered if performed during labor for the indication 'systematically due to gestational age and/or twins' or before labor whatever the indication. Women with two or more cesarean sections for previous pregnancies were allocated to PCD whatever the actual route of delivery."

Consequently, if one would normally perform cesarean delivery for preterm twins but a woman comes to the hospital with recurrent fetal heart rate decelerations, the woman was allocated to the PCD group if the woman WAS NOT in labor resulting in non-misclassification. However, we agree with the Reviewer that one cannot exclude a misclassification while in this case a PVD could have been decided for this woman before the pre-labor occurrence of fetal heart decelerations. Nevertheless, in this latter condition, it is unlikely that this possible misclassification resulted in significant biases as the woman was not in labor and that the indication for cesarean delivery was not linked with a labor or a planned labor.

A the opposite, if one would normally perform cesarean delivery for preterm twins but a woman comes to the hospital with recurrent fetal heart rate decelerations, the woman was allocated to the PVD group if the woman WAS in labor AND had no more than one previous cesarean section resulting in misclassification and consequently worsening the neonatal prognosis in the PVD group. Nevertheless, we speculate that the probability - that this case happened - was low; more importantly this case is unlikely to modify our results showing that PCD is not associated with improved neonatal outcomes for preterm twins born after PL or PPROM.

However, we agree with the Reviewer that misclassification cannot be totally excluded because attributing a case to PVD or PCD was performed a posteriori. This has been previously acknowledged as a limitation of our study in the Discussion section, lines 281-282. In order to underline this limitation, we have now added to this section the following sentences: “In particular, we cannot exclude that a sub-group of vaginal deliveries should have been classified as PCD, for example, if labor progressed too quickly to perform a cesarean section and resulted in vaginal delivery. This classical misclassification can result in bias in either direction (11, 13-17). The exclusion of women admitted after the beginning of active labor did not modify our findings, so if any bias existed, it would be weak.”.

b. The authors convincingly demonstrate that the severe outcomes studied did not vary with mode of delivery. It would be helpful to know other outcomes, realizing that other outcome differences may reasonably affect a decision to proceed with cesarean delivery. Examples include intubation or need for oxygen in the first 24 hrs of life, hospital stay or duration of ICU admission, musculoskeletal injury (birth trauma, bruising), hyperbilirubinemia, and need for transfusion. If data are not available, this should be addressed in the discussion.

We have done so. As suggested by the Reviewer, we have now given the following outcomes during hospital stay for both first and second twins in Table 2 and 3: Endotracheal intubation in the labor ward, attempt of CPAP in the first 24 hours of life, thrombocytopenia before day 7, transfusion of blood products, phototherapy (instead of hyperbilirubinemia), median length of hospital stay (among survivors).

Thus, we have now added in the Material and Methods section the following sentence, page 10: “The following variables related to neonatal outcomes during hospital stay were also included in the analysis: endotracheal intubation in the labor ward, attempt of CPAP in the first 24 hours of life, thrombocytopenia before day 7, transfusion of blood products, phototherapy, median length of hospital stay (among survivors).”.

We apologize because the following outcome was not available in our database: musculoskeletal injury (birth trauma, bruising).

3. Precis (condensation). This may be misinterpreted to suggest that the study was about first twins only. Might revise.

As suggested by the Reviewer, the following sentence “Planned cesarean delivery with preterm labor or preterm prelabor rupture of membranes is not associated with improved neonatal outcomes for preterm cephalic first twins.” has been changed to “Planned cesarean

delivery with preterm labor or preterm prelabor rupture of membranes is not associated with improved neonatal outcomes for preterm twins”.

4. Abstract. This is an excellent summary of the study findings.

We thank the Reviewer for his comment.

a. Might clarify what is meant by planned vaginal and cesarean delivery (criteria for determining what was planned).

We have done so.

b. Inclusion and exclusion criteria are not mentioned. Would include the total number of twin pregnancies (932, not 383) and why the majority were excluded.

We have done so.

5. c. In the abstract conclusion, might include something about cephalic presentation of the first twin.

We have done so.

6. Introduction.

Based on the number of references cited in the first 2 paragraphs, the authors may want to use the discussion to emphasize what their study adds and whether they feel that recommendations should be changed.

As suggested by the Reviewer, the following sentence has been now added to the Discussion, section, page 14: “Considering the higher risks of maternal morbidity associated with cesarean compared to vaginal delivery performed at low gestational age (31), French guidelines might be revised to encourage PVD for obstetricians experienced with vaginal twin deliveries for preterm twins with the first twin in cephalic presentation.”.

Also, line 63 reads as though the authors have studied preterm cephalic first twins (rather than outcomes of both twins).

As suggested by the Reviewer, in previous line 63, the following sentence : “Therefore, we investigated both neonatal and two years outcomes for preterm cephalic first twins by comparing planned vaginal versus planned cesarean deliveries based on the EPIPAGE 2 cohort sample using propensity score to ensure comparability of the study groups.” has been changed to “Therefore, we investigated both neonatal and two years outcomes for preterm twins with the first twin in cephalic presentation by comparing planned vaginal versus planned cesarean deliveries based on the EPIPAGE 2 cohort sample using propensity score to ensure comparability of the study groups.”.

7. Methods. This section is very thorough and is clearly presented, but the subheadings are not necessary.

As suggested by the Reviewer, the subheadings have been now deleted.

a. Were twins included in any prior publications from the EPIPAGE-2 study?

Mainly 3 publications from the EPIPAGE-2 study have included both singletons and twins:

- Lorthe E, Torchin H, Delorme P, Ancel PY, Marchand-Martin L, Foix-L'Hélias L, Benhammou V, Gire C, d'Ercole C, Winer N, Sentilhes L, Subtil D, Goffinet F, Kayem G. Preterm premature rupture of membranes at 22-25 weeks' gestation:

perinatal and 2-year outcomes within a national population-based study (EPIPAGE-2). *Am J Obstet Gynecol.* 2018 Sep;219(3):298.e1-298.

- Pierrat V, Marchand-Martin L, Arnaud C, Kaminski M, Resche-Rigon M, Lebeaux C, Bodeau-Livinec F, Morgan AS, Goffinet F, Marret S, Ancel PY; EPIPAGE-2 writing group. Neurodevelopmental outcome at 2 years for preterm children born at 22 to 34 weeks' gestation in France in 2011: EPIPAGE-2 cohort study. *BMJ.* 2017 Aug 16;358:j3448.
- Ancel PY, Goffinet F; EPIPAGE-2 Writing Group, Kuhn P, Langer B, Matis J, Hernandorena X, Chabanier P, Joly-Pedespain L, Lecomte B, Vendittelli F, Dreyfus M, Guillois B, Burguet A, Sagot P, Sizun J, Beuchée A, Rouget F, Favreau A, Saliba E, Bednarek N, Morville P, Thiriez G, Marpeau L, Marret S, Kayem G, Durrmeyer X, Granier M, Baud O, Jarreau PH, Mitanchez D, Boileau P, Boulot P, Cambonie G, Daudé H, Bédu A, Mons F, Fresson J, Vieux R, Alberge C, Arnaud C, Vayssière C, Truffert P, Pierrat V, Subtil D, D'Ercole C, Gire C, Simeoni U, Bongain A, Sentilhes L, Rozé JC, Gondry J, Leke A, Deiber M, Claris O, Picaud JC, Ego A, Debillon T, Poulichet A, Coliné E, Favre A, Fléchelles O, Samperiz S, Ramful D, Branger B, Benhammou V, Foix-L'Hélias L, Marchand-Martin L, Kaminski M. Survival and morbidity of preterm children born at 22 through 34 weeks' gestation in France in 2011: results of the EPIPAGE-2 cohort study. *JAMA Pediatr.* 2015 Mar;169(3):230-8.

Only one prior publication from the EPIPAGE-2 study has focused specifically on twins:

- Palas D, Ehlinger V, Alberge C, Truffert P, Kayem G, Goffinet F, Ancel PY, Arnaud C, Vayssière C. Efficacy of antenatal corticosteroids in preterm twins: the EPIPAGE-2 cohort study. *BJOG.* 2018 Aug;125(9):1164-1170.

We do not feel that this information is sufficiently important and relevant to be reported in the Materials and Methods section. Nevertheless, if the Editors wish that we mention these previous publications from the EPIPAGE-2 study including preterm twins, we will then add a sentence about this to our manuscript.

b. Line 147. Might define fetal growth restriction, realizing that it is defined differently in different countries.

As suggested by the Reviewer, we have now added the following underlined sentence in the Materials and Methods section: “At a fetal or neonatal level, we investigated the diagnosis or suspicion of fetal growth restriction (FGR), defined by estimated fetal weight below the tenth percentile according to the care providers’ reference curves,”.

8. Results.

a. Lines 198-200. Might go through the figure in a little more detail. That 59% of preterm twins were excluded from analysis should probably be stated. Study findings may not apply to the majority of preterm twins that clinicians encounter. Might also specify the exclusion categories and relevant percentages. Might include this as a limitation.

We have done so. As suggested by the Reviewer, the following underlined sentence has been added in the Results section, page 12: “Among the 932 women with twin pregnancy included in the EPIPAGE 2 study, 549 women (59%) were excluded (mainly for breech or transverse presentation of the first twin [n=151], cause of delivery other than PL or PPROM [n=122], at least one twin died before labor and admission [n=87], gestational age at delivery < 24 weeks gestation [n=58]; see detailed and other reasons in Figure 1). Thus, 383 women (766 fetuses) met our inclusion criteria and were available for analysis.”.

Moreover, we have now added the following sentence in the Discussion section, page 16: “Finally, our results are not generalizable to all preterm twin pregnancies but only to those that met our inclusion criteria (i.e. 41% of preterm twin pregnancies in the present study).”.

b. Lines 205-206. Might clarify that for the 20% of twin pregnancies with planned vaginal delivery in which cesarean delivery was required, both twins were delivered by cesarean in the majority of cases (that in only 3% was cesarean required for the second twin). This is reported in Table 1, but readers may not appreciate from the text that 1 in 5 didn't require emergent cesarean for the second twin.

We have done so. As suggested by the Reviewer, the following underlined sentence has been added in the Results section, page 13: “In the PVD group, 207 (80.2%) women delivered both twins vaginally, and 68 (19.8%) had a cesarean delivery including 16 (2.9%) who had a cesarean delivery for the second twin after vaginal birth of the first twin.”?

c. In the text, might include a sentence or two describing outcomes for the 52 sets of twins in which vaginal delivery was planned but cesarean was ultimately performed for both babies. I appreciate that the authors performed an intent-to-treat analysis, but any outcomes differences between these 52 pregnancies and the other cohorts would be important to know.

We are not sure to have well understood the request or wish of the Reviewer. We apologize for that.

However, we provide below for the Reviewer a comparison for all the outcomes (see table):

- Between these 52 pregnancies for which a vaginal delivery was planned but cesarean was ultimately performed AND the other pregnancies for which a vaginal delivery was planned and vaginal delivery occurred for one or both twins
- Between these 52 pregnancies for which a vaginal delivery was planned but cesarean was ultimately performed AND the other pregnancies for which a cesarean delivery was planned.

As you can read, results were not globally statistically different for both comparisons.

	Planned route of delivery						pvalue (1) vs (2)	pvalue (2) vs (3)
	PVD		PVD		PCD (3)			
	Vaginal delivery for both twin or cesarean delivery for the second twin (1)		Cesarean delivery for both twin (2)					
	(n=223)		(n=52)		(n=107)			
	n/N	(%)*	n/N	(%)*	n/N	(%)*		
First twin								
Outcome at delivery								
Sex male	119/223	(51.6)	31/52	(67.6)	54/107	(53.6)	0.11	0.2
Birthweight in grams; median [IQR]	1505 [1095-1831]		1435 [1050-1730]		1302 [1008-1576]		0.15	0.16
Small-for-gestational age†	51/223	(25.7)	16/52	(39.6)	33/107	(35.6)	0.14	0.72
Apgar score at 5 min < 7	20/216	(3.2)	9/52	(6.8)	16/100	(11.5)	0.076	0.28
Umbilical artery pH < 7	0/126	(0)	0/40	(0)	1/65	(1.0)	-	-
Outcomes during hospital stay								
Intubation in delivery room	77/217	(13.4)	22/51	(18.3)	48/106	(25.3)	0.29	0.30
Attempted CPAP in the first 24 hours of life	173/213	(92.8)	43/51	(94.5)	77/106	(85.7)	0.55	0.028
Transfusion of blood product	66/221	(14.3)	18/52	(14.1)	38/107	(18.6)	0.98	0.42
Phototherapy	181/217	(75.6)	41/48	(70.9)	94/106	(73.5)	0.64	0.83
Hospital stay (among survivors at discharge) median days [IQR]	24 [17-39]		32 [19-50]		38 [28-53]		0.049	0.88
Survival at discharge								
Death in delivery room	1/223	(0.1)	0/52	(0)	0/107	(0)	-	-
Death in NICU	18/223	(2.5)	1/52	(0.7)	4/107	(1.7)	-	-
Survival at discharge	204/223	(97.4)	51/52	(99.3)	103/107	(98.3)	0.15	0.39
Severe morbidity among survivors at discharge								
IVH and/or cPVL	8/198	(2.3)	1/50	(0.7)	3/102	(1.2)	0.25	0.59
Severe BPD	9/200	(1.5)	0/49	(0)	11/102	(4.7)	-	-
NEC	1/201	(0.2)	2/50	(1.8)	2/101	(3.1)	0.027	0.63
ROP	3/202	(0.4)	1/51	(0.7)	0/102	(0)	0.69	-
Survival at discharge without severe morbidity‡	179/224	(90.7)	46/52	(95.8)	87/107	(88.8)	0.090	0.022
Outcome at 2 years corrected age§								
Cerebral palsy	8/171	(2.8)	0/40	(0)	1/93	(0.6)	-	-
Blindness	0/161	(0)	0/38	(0)	0/87	(0)	-	-
Deafness	1/170	(0.2)	0/39	(0)	1/90	(3.1)	-	-
Survival at 2 years corrected age without severe or moderate neuromotor or sensory disabilities¶	197/224	(95.5)	50/52	(98.5)	101/107	(95.4)	0.12	0.13

(Continued)

	Planned route of delivery						pvalue (1) vs (2)	pvalue (2) vs (3)
	PVD		PVD		PCD (3)			
	Vaginal delivery for both twin or cesarean delivery for the second twin (1) (n=223)		Cesarean delivery for both twin (2) (n=52)		(n=107)			
	n/N	(%)*	n/N	(%)*	n/N	(%)*		
Second twin								
Outcome at delivery								
Sex male	111/223	(47.7)	30/52	(54.8)	63/107	(63.9)	0.49	0.41
Birthweight in grams; median [IQR]	1510 [1099-1843]		1490 [1060-1780]		1299 [981-1651]		0.33	0.037
Small-for-gestational age†	43/222	(21.9)	12/52	(32.3)	38/107	(37.8)	0.25	0.63
Apgar score at 5 min < 7	26/211	(7.4)	6/50	(9.0)	10/103	(6.7)	0.76	0.68
Umbilical artery pH < 7	2/140	(3.0)	0/39	(0)	1/68	(0.9)	-	-
Outcomes during hospital stay								
Intubation in delivery room	89/217	(17.8)	25/50	(30.4)	49/103	(24.2)	0.080	0.48
Attempted CPAP in the first 24 hours of life	167/208	(91.1)	39/50	(91.5)	70/101	(84.0)	0.90	0.11
Transfusion of blood product	58/219	(12.2)	16/52	(12.6)	36/107	(19.7)	0.92	0.21
Phototherapy	172/213	(71.4)	39/52	(62.4)	85/106	(67.9)	0.36	0.63
Hospital stay (among survivors at discharge) median days [IQR]	25 [17-39]		31 [19-46]		40 [30-55]		0.13	0.065
Survival at discharge								
Death in delivery room	3/223	(0.4)	0/52	(0)	0/107	(0)	-	-
Death in NICU	21/223	(4.5)	2/52	(1.3)	7/107	(2.9)	-	-
Survival at discharge	199/223	(95.0)	50/52	(98.7)	100/107	(97.1)	0.065	0.33
Severe morbidity among survivors at discharge								
IVH and/or cPVL	13/197	(2.9)	4/50	(3.0)	6/101	(2.8)	0.96	0.90
Severe BPD	5/186	(0.7)	3/49	(2.3)	7/98	(2.9)	0.12	0.72
NEC	2/199	(0.3)	3/51	(2.7)	5/101	(6.6)	0.008	0.24
ROP	1/200	(0.1)	0/51	(0)	1/102	(0.4)	-	-
Survival at discharge without severe morbidity‡	178/224	(90.2)	41/52	(90.9)	83/107	(84.5)	0.61	0.010
Outcome at 2 years corrected age§								
Cerebral palsy	7/167	(1.7)	1/41	(1.3)	4/89	(4.6)	0.81	0.26
Blindness	1/161	(0.3)	0/39	(0)	0/86	(0)	-	-
Deafness	0/165	(0)	0/39	(0)	1/86	(3.2)	-	-

Survival at 2 years corrected age without severe or moderate neuromotor or sensory disabilities¶	190/224	(92.6)	49/52	(94.7)	95/107	(90.8)	0.47	0.21
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Abbreviations: PVD, Planned Vaginal Delivery; PCD, Planned Cesarean Delivery; IQR, Interquartile Range; NICU, neonatal intensive care unit; IVH, intraventricular haemorrhage; cPVL, cystic periventricular leukomalacia; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

* Percentages are weighted to account for differences in sampling process between gestational age groups.

† Small-for- gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine growth curves.³⁰

‡ Survival at discharge without severe IVH, cPVL, severe BPD, NEC or ROP, among livebirth. Results based on multiply imputed data.

§ Among responders at 2 years corrected age.

¶ Among live births. Severe or moderate neuromotor or sensory disabilities without neuromotor or sensory disabilities: children with cerebral palsy not walking at 2 years of age without aids, or with blindness or deafness.

Results based on multiply imputed data.

Main outcome, propensity score analysis :

	n/N	(%)	IPWT cohort* OR (95% CI)	P value
Live Birth				
Survival at discharge				
First twin				
PVD + Vaginal delivery for both twin or cesarean delivery for the second twin	204/223	(97.4)	ref	
PVD + Cesarean delivery for both twin	51/52	(99.3)	4.46 (0.58-34.57)	0.15
Planned cesarean delivery	103/107	(98.3)	ref	
PVD + Cesarean delivery for both twin	51/52	(99.3)	4.71 (0.43-51.69)	0.21
Second twin				
PVD + Vaginal delivery for both twin or cesarean delivery for the second twin	199/223	(95.0)	ref	
PVD + Cesarean delivery for both twin	50/52	(98.7)	3.67 (0.83-16.22)	0.086
Planned cesarean delivery	100/107	(97.1)	ref	
PVD + Cesarean delivery for both twin	50/52	(98.7)	3.77 (0.66-21.71)	0.14
Survival at discharge without severe morbidity†				
First twin				
PVD + Vaginal delivery for both twin or cesarean delivery for the second twin	179/224	(90.7)	ref	
PVD + Cesarean delivery for both twin	46/52	(95.8)	1.88 (0.69-5.14)	0.22
Planned cesarean delivery	87/107	(88.8)	ref	
PVD + Cesarean delivery for both twin	46/52	(95.8)	1.96 (0.61-6.27)	0.26
Second twin				
PVD + Vaginal delivery for both twin or cesarean delivery for the second twin	178/224	(90.2)	ref	
PVD + Cesarean delivery for both twin	41/52	(90.9)	1.21 (0.54-2.69)	0.65
Planned cesarean delivery	83/107	(84.5)	ref	
PVD + Cesarean delivery for both twin	41/52	(90.9)	1.52 (0.59-3.90)	0.38
Survival at 2 years corrected age without severe or moderate neuromotor or sensory disabilities‡				

First twin				
PVD + Vaginal delivery for both twin or cesarean delivery for the second twin	197/224	(95.5)	ref	
PVD + Cesarean delivery for both twin	50/52	(98.5)	2.57 (0.57-11.57)	0.22
Planned cesarean delivery	101/107	(95.4)	ref	
PVD + Cesarean delivery for both twin	50/52	(98.5)	2.02 (0.31-13.41)	0.46
Second twin				
PVD + Vaginal delivery for both twin or cesarean delivery for the second twin	190/224	(92.6)	ref	
PVD + Cesarean delivery for both twin	49/52	(94.7)	3.59 (0.93-13.79)	0.063
Planned cesarean delivery	95/107	(90.8)	ref	
PVD + Cesarean delivery for both twin	49/52	(94.7)	4.68 (1.04-21.06)	0.044

Abbreviations : PVD, Planned Vaginal Delivery; PCD, Planned Cesarean Delivery; IVH, intraventricular haemorrhage; cPVL, cystic periventricular leukomalacia; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

* Propensity score analysis, results are weighted by the inverse of propensity score, estimated via marginal model (GEE) to take into account correlation between twins and are based on multiple imputation.

† Survival at discharge without severe IVH, cPVL, severe BDP, NEC or ROP.

‡ Severe or moderate neuromotor or sensory disabilities without neuromotor or sensory disabilities : cerebral palsy who were not walking at 2 years of age without aids, blindness or deafness.

d. As the authors have birthweight data, can they analyze results according to birthweight difference between twins (discordance)?

As suggested by the Reviewer, we attempted to compare outcomes between pregnancies with and without a birthweight differences between twins (of more than 20% as well as of more than 25%). Unfortunately, the sample sizes of pregnancies with a birthweight differences between twins of more than 20% (n=45) and of more than 25% (n=22) were too small and we were not able to “run” our marginal model (generalized estimating equations (GEE)) or to perform a propensity-score analysis.

However, for the Reviewer, we provide below the descriptive analysis for our main outcomes for the first and second twins according the planned mode of delivery for the subgroup of pregnancies with a birthweight differences between twins of more than 20% and 25% (see table).

	Birthweight difference between twins > 20%			Birthweight difference between twins > 25%	
	n/N	%	pvalue	n/N	%
Live Birth (n=383)					
Survival at discharge					
First twin					
Planned vaginal delivery	29/31	(98.4)	0.29	13/15	(96.9)
Planned cesarean delivery	14/14	(100.0)		7/7	(100.0)
Second twin					
Planned vaginal delivery	28/31	(97.6)	0.99	14/15	(98.4)
Planned cesarean delivery	13/14	(97.5)		6/7	(96.2)
Survival at discharge without severe morbidity†					
First twin					
Planned vaginal delivery	25/31	(94.0)	0.019	12/15	(94.8)
Planned cesarean delivery	11/14	(76.9)		5/7	(67.9)
Second twin					
Planned vaginal delivery	25/31	(92.1)	0.52	12/15	(94.1)
Planned cesarean delivery	10/14	(89.2)		5/7	(91.0)
Survival at 2 years corrected age without severe or moderate neuromotor or sensory disabilities‡					
First twin					
Planned vaginal delivery	28/31	(98.2)	0.57	12/15	(96.7)
Planned cesarean delivery	13/14	(99.7)		6/7	(99.6)
Second twin					
Planned vaginal delivery	27/31	(97.2)	0.47	13/15	(98.2)
Planned cesarean delivery	11/14	(94.9)		5/7	(96.0)

Abbreviations : PVD, Planned Vaginal Delivery; PCD, Planned Cesarean Delivery; IVH, intraventricular haemorrhage; cPVL, cystic periventricular leukomalacia; BPD, bronchopulmonary dysplasia; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.

* Percentages are weighted to account for differences in sampling process between gestational age groups.

† Survival at discharge without severe IVH, cPVL, severe BDP, NEC or ROP.

‡ Severe or moderate neuromotor or sensory disabilities without neuromotor or sensory disabilities : cerebral palsy who were not walking at 2 years of age without aids, blindness or deafness.

e. In table 1, the gestational age percentages do not appear to be correct. Might comment on the fact that planned cesarean appears to be more common at earlier gestational age and vaginal delivery at later gestational ages (> 30 weeks). This is not unexpected but might be addressed.

We confirm that the percentages are correct. As previously mentioned in footnote, “*Percentages are weighted to account for differences in sampling process between gestational age groups.”.

Reviewer #2

With great interest I read this population-based cohort study.
We thank the Reviewer for his/her comment.

1) Abstract:

There was no discrepancy between the abstract and the manuscript.

2) Introduction:

It was well written and informative.

3) Methods:

I agree with the authors that this is the best design to answer the study question, as performing a clinical trial will be unethical and unfeasible.

The method section was well written and thorough.

4)Results:

There was no discrepancy between the tables and the manuscript. good interpretation of the tables. However, in line 156 the author stated that they used chi square and they did not mention fisher exact test. May be it was missed by the writer of the manuscript. As we know it is incorrect to use chi square to compare variables with numbers < 25. based on the manuscript , they used chi square with the small numbers (<25) in table 1 and 2 and this means that the P-value of these variables is wrong.

We thank the Reviewer for his/her comment. We agree with him/her. We apologize because we made an error in the Material and Methods section. We have previously written that we used chi square test for for categorical variables. In fact we used Rao-Scott chi-square for categorical variables to account for differences in sampling process between gestational age groups.

Therefore, we have now replaced in the Material and Methods section, page 11, the following sentence:” then compared between PVD and PCD groups by chi-square for categorical variables” by “then compared between PVD and PCD groups by Rao-Scott chi-square for categorical variables to account for differences in sampling process between gestational age groups. ”.

Rao-Scott chi-square can be used for numbers < 25.

5) Discussion and conclusion:

I enjoyed reading the discussion section it answered almost all the questions that I had. excellent explanation of the study limitations and strengths.

Thank you very much for your comments.

Reviewer #3

The study is a sub-analysis of the EPIPAGE-2. The analysis examines the outcomes of the twins, when the first twins were cephalic, comparing vaginal versus cesarean deliveries.

1. The condensation statement seems to imply that the study is only about the outcomes of the first twin.

As suggested by the Reviewer, the following sentence “Planned cesarean delivery with preterm labor or preterm prelabor rupture of membranes is not associated with improved neonatal outcomes for preterm cephalic first twins.” has been changed to “Planned cesarean delivery with preterm labor or preterm prelabor rupture of membranes is not associated with improved neonatal outcomes for preterm twins”.

2. Are the authors recommending that the present guidelines of the National College of French Gynecologists and Obstetricians be changed based on the study results?

As suggested by the Reviewer, the following sentence has been now added to the Discussion, section, page 14: “Considering the higher risks of maternal morbidity associated with cesarean compared to vaginal delivery performed at low gestational age (31), French guidelines might be revised to encourage PVD for obstetricians experienced with vaginal twin deliveries for preterm twins with the first twin in cephalic presentation.”.

3. In the database, do the authors have information about the experience level of the obstetricians who recommended vaginal delivery versus cesarean delivery?

We agree with the Reviewer that such information would have been very interesting. Unfortunately, we do not have information about the experience level of obstetricians regarding PVD for preterm twins.

4. Also, did the likelihood of vaginal delivery increase in larger perinatal centers?

We have compared the likelihood of PVD :

- Between Level III centers versus Level I and II centers.
- Within centers with annual number of births before 34 weeks (n=390):
 - 0-50
 - 51-100
 - 101-150
 - >150

For these comparisons, there was no significant difference.

Consequently, the likelihood of PVD did not differ according to the characteristic of centers.

STATISTICAL EDITOR’S COMMENTS:

1. Tables 1, 2: Need to cite the sample size for each cohort, not just the total.

We have done so. We have now provided for Tables 2 and 3 the results of the outcome “survival at discharge without severe morbidity” based on multiply imputed data to help the Readers. Thus, the denominator for the outcomes “survival at discharge”, “ survival at

discharge without severe morbidity” and “survival at two years of corrected age without neurosensory impairment” are identical.

It appears from the (%) cited that the counts among the PCD cohort had more missing values. If so, then the comparisons may be biased. For example, for deafness, with total n = 299 out of 276+107, the PCD count of 1 with deafness corresponds to a % of 3.1. That implies a total among the PCD of only 32, when the entire PCD cohort was n = 107. Contrast that with the count for cerebral palsy also of 1, but now representing 0.6% of the total.

We have checked and confirmed that there is no error related to percentages. As previously written in footnote, we would like to underline that percentages are weighted to account for differences in sampling process between gestational age groups.”.

2. Tables 2, 3: The problem with comparing survival at discharge, proportion without severe morbidity among survivors at discharge or survival at 2 yrs corrected age without severe or moderate disabilities is that the frequencies of adverse events is low. This yields insufficient power to generalize the NS findings. For example, assuming the total sample sizes given here, and evaluating the most discrepant differences (2nd twin, survival at discharge without severe morbidity, with proportions of 85.4 vs 91.4%) the power is only ~ .40, to discern a difference. For the proportions that are closer, of course the power is worse. Put another way, to discern the differences cited for those outcomes, the samples required would range from ~ 3x to ~ 40x those in this study.

We agree with the Statistical Editor. This limitation has been now underlined in the Discussion section. Thus, the following sentences have been now added pages 16-17: “Although our study included women (766 fetuses) from a large population-based cohort study, it had not adequate power to show differences in rare and severe adverse events related to delivery route, such as death at discharge, death or survival at discharge with severe morbidity, and death or survival at two years of corrected age with neurosensory impairment. Consequently, our results should be interpreted with caution for the non significant findings, particularly for the primary, secondary and third outcomes.”.

3. Table 4: This analysis does help to mitigate the baseline differences between the cohorts, but does not address the small sample sizes, or more specifically, the small counts of adverse outcomes for the two cohorts.

This has been now addressed in the Discussion section. Thus, the following sentences have been now added pages 16-17: “Although our study included women (766 fetuses) from a large population-based cohort study, it had not adequate power to show differences in rare and severe adverse events related to delivery route, such as death at discharge, death or survival at discharge with severe morbidity, and death or survival at two years of corrected age with neurosensory impairment. Consequently, our results should be interpreted with caution for the non significant findings, particularly for the primary, secondary and third outcomes.”.

Associate Editor's Comments:

Please in response to Statistical Editor's concern, sprinkle some caveats about limited statistical power throughout the manuscript including in Abstract.

We have done so. We have now added the following sentences pages 16-17: “Although our study included women (766 fetuses) from a large population-based cohort study, it had not adequate power to show differences in rare and severe adverse events related to delivery route, such as death at discharge, death or survival at discharge with severe morbidity, and death or survival at two years of corrected age with neurosensory impairment. Consequently, our results should be interpreted with caution for the non significant findings, particularly for the primary, secondary and third outcomes.”.

Moreover, as suggested, we have now added the following sentence at the end of the Result section of the Abstract: “The power of the study was inadequate to conclude to the absence of differences for these outcomes.”

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. 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:

1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.

2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

Option 1: YES

2. 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.

We have done so.

3. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your

cover letter by submitting the URL of the IRB web site outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

We have done so.

4. 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), 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), and quality improvement in health care (ie, SQUIRE 2.0). 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, CHEERS, or SQUIRE 2.0 guidelines, as appropriate.

We have done so.

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 will be transitioning as much as possible to use of the reVITALize definitions, and we encourage authors to familiarize themselves with them. The obstetric data definitions are available at <http://links.lww.com/AOG/A515>, and the gynecology data definitions are available at <http://links.lww.com/AOG/A935>.

We have used definitions that have been developed through the reVITALize initiative.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words); Case Reports should not exceed 8 typed, double-spaced pages (2,000 words); Review articles should not exceed 25 typed, double-spaced pages (6,250 words); Current Commentary articles should not exceed 12 typed, double-spaced pages (3,000 words); Clinical Practice and Quality articles should not exceed 22 typed, double-spaced pages (5,500 words); Procedures and Instruments articles should not exceed 8 typed, double-spaced pages (2,000 words); Personal Perspectives essays should not exceed 12 typed, double-spaced pages (3,000 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and appendixes).

We have done so.

Please limit your Introduction to 250 words and your Discussion to 750 words.

Our Introduction and Discussion are longer but the length of the entire manuscript complies with the space limitations. Moreover, Reviewers kindly underline the quality of our Introduction and Discussion. Moreover, the Discussion contains a little more than 750 words in order to respond correctly to the Reviewers' request. Thus, we have not modified the Introduction and Discussion and will hope that this will be accepted by the Editors.

7. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). 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 also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

We have done so.

8. Specific rules govern the use of acknowledgments in the journal. Please edit your acknowledgments or provide more information in accordance with 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 signature on the journal's author agreement 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).**

We have done so.

9. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

We have done so.

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.

We have checked the abstract very carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

The word count of the abstract is 397 word in order to comply to the Reviewer #1 requests and wishes. Nevertheless, if the Editors wish that we delete the sentences that have been added (except for the one related to the lack of power) in the revised manuscript, we will comply with the wishes of the Editors.

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.

We have done so.

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.

We have done so.

13. 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.

We have done so.

Daniel Mosier

From: SENTILHES Loïc [REDACTED]
Sent: Friday, October 5, 2018 12:05 AM
To: Daniel Mosier
Subject: Re: Manuscript Revisions: ONG-18-1599R1

Dear Daniel Mosier,
Thank you very much for your email.
I apologize for this discrepancy for the disclosure.

I forgot to disclosure FERRING for the current article and made a non intentional mistake.

I apologize for this error and I agree (of course) to add this disclosure in the current paper.

I thank the Editors very much for their attention and for avoiding me potential future troubles.

Best regards,

Loïc Sentilhes

Envoyé de mon iPhone

Le 5 oct. 2018 à 00:07, Daniel Mosier <dmosier@greenjournal.org> a écrit :

Dr. Sentilhes,

Thank you for submitting your revisions in a timely manner. The editors are currently evaluating your submission, and we will contact you if we have any additional questions.

Additionally, the Journal's Manuscript Editor noticed a discrepancy in your disclosures. In your article "Neonatal Morbidity After Management of Vaginal Noncephalic Second-Twin Delivery by Residents," you had the following disclosure: "Loïc Sentilhes carried out consultancy work and was a lecturer for Ferring Laboratories in the previous 3 years." This is not disclosed in the current paper. We will add this disclosure to the current paper.

Please let us know if you have any questions or concerns.

Sincerely,
-Daniel Mosier

Daniel Mosier
Editorial Assistant
Obstetrics & Gynecology
Tel: 202-314-2342

From: SENTILHES Loïc [REDACTED]
Sent: Tuesday, October 2, 2018 6:33 PM
To: Daniel Mosier <dmosier@greenjournal.org>
Subject: RE: Manuscript Revisions: ONG-18-1599R1

Dear Daniel Mosier,

Thank you very much for your email and for your help regarding our manuscript.

My responses are below in your previous email.

Please find also enclosed the manuscript with responses to your queries and proposed additional deletions.

Best regards,

Loïc Sentilhes

De : Loïc Sentilhes [REDACTED]
Envoyé : mardi 2 octobre 2018 22:54
À : SENTILHES Loïc
Objet : Fwd: Manuscript Revisions: ONG-18-1599R1

Envoyé de mon iPhone

Début du message transféré :

Expéditeur: Daniel Mosier <dmosier@greenjournal.org>
Date: 2 octobre 2018 à 22:08:56 UTC+2
Destinataire: [REDACTED]
Objet: Manuscript Revisions: ONG-18-1599R1

Dear Dr. Sentilhes,

Thank you for submitting your revised manuscript. It has been reviewed by the editor, and there are a few issues that must be addressed before we can consider your manuscript further:

1. Please note the minor edits and deletions throughout. Please let us know if you disagree with any of these changes.

I agree with the minor edits and deletions throughout

2. LINE 5: Please ask the following authors to respond to their authorship confirmation email. We emailed them at the email addresses listed below. The email contains a link that needs to be clicked on. The sender of the email is EM@greenjournal.org.

Mathilde Quere
[REDACTED]

I have sent an email to them. They will respond sooner

3. LINE 6: Please provide a completed author agreement forms for Mathilde Quere using the latest version of our author agreement form, which can be found at

<http://edmgr.ovid.com/ong/accounts/agreementform.pdf>. Note that both the "Authorship" and "Disclosure of Potential Conflicts of Interest" sections need to be completed, along with providing a signature. Please read the form carefully.

I have sent an email to her. She will respond sooner

4. LINE 46: Is the year correct as added?

Yes, the year is correct as added

5. LINE 79: This will not be clear to readers. Do you mean "for the indication of preterm twins"?

YES

6. LINE 87: Per journal style, we will use the acronyms « PVD » and « PCD » only as they pertain to the group names. Otherwise, they will be spelled out.

OK

7. LINE 168: See query in abstract

YES, I mean "for the indication of preterm twins"

8. LINE 275: Please spell out

Inverse probability of treatment weighting

9. LINE 283: Your Discussion is currently 979 words. Please try to shorten it so it's closer to 750 words.

The length of the Discussion after your changes is not 979 words but 707 words (version 1). However, we have proposed some additional deletions to reduce the length of the Discussion to 569 words (version 2). Nevertheless, we would like to underline that our preference is to leave a length of 707 words for the Discussion, i.e. the length after your changes and without our proposed deletions (version 1).

Each of these points are marked in the attached manuscript. Please respond point-by-point to these queries in a return email, and make the requested changes to the manuscript. When revising, please leave the track changes on, and do not use the "Accept all Changes" function in Microsoft Word.

Please let me know if you have any questions. Your prompt response to these queries will be appreciated; please respond no later than COB on **Thursday, October 4th**.

Sincerely,
-Daniel Mosier

Daniel Mosier
Editorial Assistant
Obstetrics & Gynecology
The American College of Obstetricians and Gynecologists

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Washington, DC 20024
Tel: 202-314-2342
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From: [REDACTED]
To: [Stephanie Casway](#)
Subject: RE: O&G Figure Revision: 18-1599
Date: Wednesday, October 10, 2018 4:12:18 AM

Dear Stephanie Casway,

Thank you very much for your email and for your help for the editing of our Figure.

I reviewed the figure and legend carefully.

Everything is OK for me. There is no error.

Best regards,

Loïc Sentilhes

Expéditeur: Stephanie Casway <SCasway@greenjournal.org>

Date: 9 octobre 2018 à 20:55:33 UTC+2

Destinataire: [REDACTED]

Objet: O&G Figure Revision: 18-1599

Good Afternoon Dr. Sentilhes,

Your figure has been edited, and PDFs of the figure and legend are attached for your review. Please review the figure and legend CAREFULLY for any mistakes.

PLEASE NOTE: Any changes to the figures must be made now. Changes made at later stages are expensive and time-consuming and may result in the delay of your article's publication.

To avoid a delay, I would be grateful to receive a reply no later than Thursday, 10/11.
Thank you for your help.

Best wishes,

Stephanie Casway, MA
Production Editor
Obstetrics & Gynecology
American College of Obstetricians and Gynecologists
409 12th St, SW
Washington, DC 20024
Ph: (202) 314-2339
Fax: (202) 479-0830

scasway@greenjournal.org

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