

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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obgyn@greenjournal.org.

Date: Jan 11, 2019
To: "Catherine Deneux-Tharaux" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-18-2218

RE: Manuscript Number ONG-18-2218

Twin pregnancy and severe maternal morbidity: a population-based study in France

Dear Dr. Deneux-Tharaux:

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 Feb 01, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Congratulations on a well-planned and executed study. Use of the path analysis and separation of direct effect twin pregnancy on SAMM and the indirect effect mediated by cesarean section is important for understanding the true causes of SAMM. I do not have a lot of comments on this article.

Table 1 shows SAMM divided into "underlying causal condition." However, dividing at least the large categories into what the morbidity was would be informative. For example, dividing hemorrhage into blood transfusion, hysterectomy, etc.

Reviewer #2: This is a secondary analysis of a large prospective study looking at the association of severe acute maternal morbidity (SAMM) in twin pregnancies compared to a random sample of patients without SAMM. As written in the abstract it appears as though this is a case control study starting with the outcome or cases and then comparing to those without SAMM. The objectives and study design need to be clearly defined in the abstract. If the original study was prospectively collected why not start with an exposed cohort "twins" vs. non exposed singleton pregnancy?

Abstract:

Line 90-94 The wording of the objectives is not clear. "Overall and by timing" is confusing and could be left out.

The use of the word causal condition implies a conclusion based upon higher level of evidence such as an RCT. The association of twins and SAMM is enough but there needs to be reference to the comparison group ie singleton pregnancies.

Line 98 Why was a random sample of non SAMM patients chosen? If there is data on 182, 000 deliveries why not use the entire data set?

Line 104-107 The results suggest a population comparison looking at the denominators. Exactly where is the comparison of controls 3,500 come into the analysis?

Introduction:

Line 128-129 After describing specific adverse outcomes such as postpartum hemorrhage and hypertension it does not follow that our knowledge of maternal outcomes is insufficient. Severe health effects and organ dysfunction are vague and need to be described in more detail. How does this study differ in its limitations cited reference 10-14?

Line 138-139 Characterization of intermediate factors in the causal pathway needs to be described or reworded. This is confusing given the limitations of this study design.

Materials and methods:

Line 164 The appendix description of SAMM has many broad and diverse criteria. The classification is counted categorically regardless of the number of items. Is there a validated severity scale looking at these outcomes? This is further described as near misses as noted.

Line 168 How was a 2% random sample chosen? Also how was it distributed in comparison to the cases between the 119 units described?

Line 177 How was the cause determined? Was this ICD 9 codes or chart review? If so was there multiple reviewers with an internal way to adjudicate differences?

Line 197 Is there information on country of origin and race/ethnicity? This is less clear for those born in France.

Line 243-245 Why was data imputed vs. excluded as suggested in materials and methods?

Line 272-273 Explain more the decomposed analysis by Erickson et al. This attribution of cesarean sections to direct or indirect effects on SAMM is not clear.

Results:

Line 302-304 If maternal mortality occurred in 13 patients this seems as though in the near miss category this is a significant clinical difference. Is there more information on the maternal deaths?

Line 329-331 Explain the clinical indications for cesarean section and management of twins. This is important for the reader to put the secondary path analysis into context regarding attributable risk and SAMM.

Discussion:

Given the lack of data on indications for cesarean delivery and practice patterns this limits the secondary objectives and attributable risk along with generalizability.

Table 1

It is unclear what or how maternal mortality is included in the near miss WHO criteria. Do you have separate details on all maternal mortalities? In the results section it implied known were twins.

Table 2

Why was single mother chosen as a demographic of interest?

Reviewer #3: Madar et al have performed a population-based nested case control study evaluating the association between twin pregnancy and severe maternal morbidity and secondarily evaluating the role of cesarean delivery as a mediator between twin pregnancy and severe maternal morbidity. Overall, this manuscript is well written and answers an important question in a meaningful way. I have only a few minor comments and suggestions.

- The authors discuss the WHO near-miss criteria. It would be helpful to elaborate more (or include in Appendix 1 where the SAMM criteria are lists) so that the reader is aware of how the WHO near-miss criteria differ from your SAMM criteria and in which ways these represent more severe morbidity.

- I think it would be meaningful to note the incidences of each type of SAMM (as described in appendix 1) by singleton vs. twin delivery - the description of Appendix 3 seems to say that this is what Appendix 3 shows, but it is in fact describing underlying causal conditions, rather than a description of the types of SAMM.

- The path analysis evaluating mode of delivery is very interesting, although slightly difficult to interpret for those not familiar with this type of analysis. You write it out very clearly on lines 276-278, noting what question in particular this type of analysis will answer. I would again use that kind of terminology and clear writing to discuss this in the discussion (lines 344-346). The term mediated is clear to those who understand this analysis, but not clear to those unfamiliar so I think it would be helpful to use different words here.

Reviewer #4: The study design, although observational, has several strengths. The authors report on secondary outcomes from the EPIMOMS study which was a large (involving 6 different regions) prospectively collected cohort which is current (2012-3), and represents a significant percent (~20%) of all deliveries in France during that time. The use of singletons

collected at the same time and from the same centers as a comparison group for major outcomes is another strength of the analysis.

This manuscript provides more accurate data than what is currently available for counseling and would be highly cited in the literature and in clinical practice.

Some minor comments should be addressed by the authors:

1. I am confused about why the authors selected a small control group for analysis instead of using all patients without SAMM as the control group. Or alternately if committed to using a subset of patients as a control group, why not select them to be matched for potential confounders?
2. On page 10, line 171, the control group is listed as 3651, but reported as 3650 in the rest of the manuscript - please explain or correct
3. Psychiatric disorders were included as a SAMM, but specifically referred to previously as an exclusion (page 11 - 185-6) - please clarify
4. Is being a single mother a risk factor for SAMM (page 12, line 234)? That is not my understanding. Please cite a reference if this is going to be a variable in the analysis, or eliminate it from the regression model.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

This case-control study compared SAMM among 2500 cases and a random subset of 3650 out of 182,309 deliveries without SAMM. The main outcome of interest was the association of SAMM and twin birth, which comprised 197 of the cases and 59 of the controls. The SAMM cohort differed in multiple demographic and risk factors (Table 2) and the majority of cases (> 65%) defined as SAMM were due to maternal hemorrhage. The Authors adjusted for the baseline differences using multilevel logistic regression and multiple imputation (table 3) and also using only cases and controls with complete data (Table 4).

While it is clear that twin birth was associated with higher risk of SAMM, there are limitations based on the data available in this analysis and therefore on the precision of estimates as to how much of the increased risk was due to twin birth vs other factors. First, the high proportion (> 50%) of missing data among the cases and (> 25%) among the controls, with no enumeration in Tables as to which data were missing and how much data were missing from the twin cohorts. Second, the number of twin births among the control cohort was only 59, or ~ 1.6% and we are not told how many of the latter had missing data, there is a limitation on the ability of multivariable regression to have adjusted for the many differences outlined in Table 2.

There should be a fuller accounting/enumeration of the missing data, acknowledgment of that as a limitation to generalizing the conclusions. Also, a much larger data base for controls was available and the proportion of twins among that cohort was low. So I do not understand why a larger control group was not chosen to allow greater precision in estimation of various factors besides cesarean delivery that might have contributed to SAMM. The cohorts of twins are so small that any interaction terms among the risk factors and twin births cannot be estimated with any precision, nor could NS interaction terms be generalized, due to low statistical power.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- The objective for the abstract should be a simple "to" statement without background. The Journal style doesn't use the virgule (/) except in numeric expressions. Please edit here (Line 92) and in all instances.

- Perhaps: Compared to women with singleton pregnancies, women with twins have a four fold increased risk for

severe maternal complications both before and after delivery. [do you want to mention here the contribution of CS? as you will have shortened the introduction quite a bit you should have space]

- can you tell us how the random sampling occurred?

- Please describe the data collection method for both the SAMM/non SAMM patients. Who entered the data? Was there a validation process to check for accuracy? Do these 6 regions all use a similar electronic medical record which could be queried? Paper charts? Given the high rate of missing data (noted in statistical review) a more thorough description of data collection is important.

- please provide these criteria in a box. please cite the box here as Box 1. Put the actual box at the end of the file with your tables.

- as this method will be unknown to most of our readers, please provide a description of this method. This can be in supplemental digital content but reference its' existence.

- as noted by two reviewers, please explain why marital status was considered here.

- what does this mean? Like GDM or gestational hypertension? If I am correct, you were trying to compare women with twins to non twins with both groups having no co-morbidities or pre-labor indications for cesarean. Why not do a matching process?

- could you give some examples of indirect and direct effects?

- a maternal death is not a "Near miss". Please clarify

- followed.

- please provide effect size and CI's

2. 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.
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3. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

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. 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 website 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.

6. 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 and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. 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 26 typed, double-spaced pages (6,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. 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.

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).

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.

14. Figure 1: Please add exclusion information between the first two boxes.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifauth.htm>.

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

16. 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 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 Feb 01, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2017 IMPACT FACTOR: 4.982

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

In compliance with data protection regulations, please contact the publication office if you would like to have your personal information removed from the database.



Paris, January 31, 2019

Dear Editor,

Thank you for your response on January 11th 2019, concerning our manuscript ONG-18-2218 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.

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 have been explained.

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

Yours sincerely,

Catherine Deneux-Tharaux

REVIEWER COMMENTS:

Reviewer #1: Congratulations on a well-planned and executed study. Use of the path analysis and separation of direct effect twin pregnancy on SAMM and the indirect effect mediated by cesarean section is important for understanding the true causes of SAMM. I do not have a lot of comments on this article.

We thank the reviewer for his/her comment.

Table 1 shows SAMM divided into "underlying causal condition." However, dividing at least the large categories into what the morbidity was would be informative. For example, dividing hemorrhage into blood transfusion, hysterectomy, etc.

We agree with this comment and have now added this information in the revised Table 1.

Reviewer #2: This is a secondary analysis of a large prospective study looking at the association of severe acute maternal morbidity (SAMM) in twin pregnancies compared to a random sample of patients without SAMM. As written in the abstract it appears as though this is a case control study starting with the outcome or cases and then comparing to those without SAMM. The objectives and study design need to be clearly defined in the abstract. If the original study was prospectively collected why not start with an exposed cohort "twins" vs. non exposed singleton pregnancy?

As explained in the methods section, the design is a case-control study nested in a cohort.

Although all deliveries were counted and minimal information was available for all (including multiple/singleton status), detailed information was collected for all women with SAMM, but only for a representative sample of women without SAMM within this cohort of parturients. This design has the assets of a cohort (in particular no selection bias due to a lack of comparability of cases and controls since they are selected from the exactly same source population) while allowing to minimize the number of women surveyed and the related costs. This design has been clarified in the abstract and further explained in the Methods section lines 176-183 of the revised manuscript.

Abstract:

Line 90-94 The wording of the objectives is not clear. "Overall and by timing" is confusing and could be left out.

We believe it is important to mention that the risk of SAMM has been analyzed not only for all SAMM globally, but also by timing and by cause of the SAMM events. Regarding the wording, the manuscript has been edited for language. That is why we would prefer to keep the sentence as it is, unless the editor asks for rewording.

The use of the word causal condition implies a conclusion based upon higher level of evidence such as an RCT.

Here the term "causal condition" is used in its clinical meaning, i.e the condition that is responsible for SAMM according to the clinicians, as explained on the "Methods" section.

The association of twins and SAMM is enough but there needs to be reference to the comparison group ie singleton pregnancies.

The reference group is clearly mentioned in the sentence “After controlling for confounders, the risk of SAMM was higher in twin than in singleton pregnancies (adjusted odds ratio [adjusted OR] 4.2, 95%CI 3.1-5.8)” line 109.

Line 98 Why was a random sample of non SAMM patients chosen? If there is data on 182, 000 deliveries why not use the entire data set?

As explained above, the Epimoms study was designed as a population-based case-control study nested in a cohort. Although all deliveries were counted and minimal information was available for all (including multiple/singleton status), detailed information was collected for all women with SAMM, but only for a representative sample of women without SAMM within this cohort of parturients. This design has the assets of a cohort (in particular no selection bias due to a lack of comparability of cases and controls since they are selected from the exactly same source population) while allowing to minimize the number of women surveyed and the related costs. This design has been further explained in the Methods section lines 176-183 of the revised manuscript.

Line 104-107 The results suggest a population comparison looking at the denominators. Exactly where is the comparison of controls 3,500 come into the analysis?

As explained above, we used the total population as denominators for the descriptive part of the analysis, i.e the calculation of rates of SAMM, overall and by multiple/singleton status. However, for the explanatory part of the analysis, i.e the analysis of the association between multiple pregnancy and SAMM after adjustment for confounders, we used the control group of 3650 women (and not 3500 as mentioned in the comment) as the needed detailed information was only available for this sample of women without SAMM. This design has been further explained lines 199-214 of the revised of the revised manuscript, and revised Figure 1.

Introduction:

Line 128-129 After describing specific adverse outcomes such as postpartum hemorrhage and hypertension it does not follow that our knowledge of maternal outcomes is insufficient. Severe health effects and organ dysfunction are vague and need to be described in more detail.

In this section, we mean that, although twin pregnancy has been associated with obstetric complications, its impact on severe maternal outcomes with severity characterized by parameters directly related to organ dysfunction is still poorly documented. We feel this is clearly exposed in the introduction, but are willing to rephrase this section if the editor asks for.

How does this study differ in it's limitations cited reference 10-14?

As stated in the introduction lines 147-152,” Most of the few previous studies reporting an increased risk of severe maternal outcomes in twin pregnancies have notable methodological limitations, including their analysis of retrospective or administrative databases, failure to control for confounders, and use of an outcome definition that is limited to selected obstetric complications and fails to take the woman’s health into account (ref 10-14)”. Indeed, we believe our study design addresses each of the mentioned limitations, ie. prospective study designed for SAMM study, availability of detailed information allowing for controlling for many confounders,

comprehensive SAMM definition mainly based on organ dysfunctions. Those strengths are mentioned in the discussion lines 413-428.

Line 138-139 Characterization of intermediate factors in the causal pathway needs to be described or reworded. This is confusing given the limitations of this study design.

Beyond this mention in the Introduction, the methods to characterize intermediate factors in the causal pathway are further detailed in the Methods section lines 302-304 and 328-341. We believe it would not be appropriate to further detail this approach in the introduction, but let the editor decide whether this is needed.

Materials and methods:

Line 164 The appendix description of SAMM has many broad and diverse criteria. The classification is counted categorically regardless of the number of items. Is there a validated severity scale looking at these outcomes? This is further described as near misses as noted.

We initially characterized the severity of the SAMM events by isolating the subgroup of women with SAMM meeting the WHO near-miss criteria; as suggested by the editor, these WHO near-miss criteria are now detailed in the newly Box 1, cited line 236.

We agree with the reviewer that the number of SAMM events per woman is another way of characterizing the severity of the SAMM profile. We have added this information in the revised Table 1 and Appendix 4 (previously appendix 3).

Line 168 How was a 2% random sample chosen? Also how was it distributed in comparison to the cases between the 119 units described?

The EPIMOMS study was initially designed based on an anticipated rate of SAMM of 1%, resulting in 1,800 cases of SAMM among the expected 180,000 deliveries. The size of the control sample was chosen in order to have sufficient power to study the association between various potential risk factors and SAMM, that is, to be able to show a risk multiplied by 1.5 or more for a factor with a prevalence of 5% or more among controls with $\alpha=0,05$ and $1-\beta=0.9$. 3,600 controls were thus needed, or 2% of expected deliveries. Control selection was independent of SAMM case identification; the 1/50 ratio for control selection was the same in each maternity unit, whatever the number or rate of SAMM, in agreement with the population-based approach. This design avoided matching cases and controls by characteristics related to hospitals. This unmatched design was purposely chosen to select a generalist control sample allowing various risk factor analyses. This has been further detailed in the methods section lines 199-205.

Line 177 How was the cause determined? Was this ICD 9 codes or chart review? If so was there multiple reviewers with an internal way to adjudicate differences?

As mentioned in the Methods section lines 213-214, the cause of SAMM was the one identified by the clinician team in charge of the patient, and reported in the medical chart.

Line 197 Is there information on country of origin and race/ethnicity? This is less clear for those born in France.

In France, we do not collect information on "race/ethnicity" unless the purpose of the research makes this collection specifically relevant. Social inequalities related to geographical origin are characterized by the migrant status (i.e being born outside the residence country) and the geographical zone of the birth country, in agreement with international recommendations (Urquia

ML et al; ROAM collaboration. International migration and adverse birth outcomes: role of ethnicity, region of origin and destination. J Epidemiol Community Health. 2010 Mar;64(3):243-51)

Line 243-245 Why was data imputed vs. excluded as suggested in materials and methods?

We excluded women with missing data for the exposure of interest “multiple/singleton pregnancy”, because those women were only a few, and we preferred not to impute this key variable. All other missing values for variables included in the multivariable model were imputed. This has been clarified lines 224 and 293-297 of the methods section.

Line 272-273 Explain more the decomposed analysis by Erickson et al. This attribution of cesarean sections to direct or indirect effects on SAMM is not clear.

The method proposed by Erickson and Buis is already detailed in the 10-line paragraph following this sentence. We believe it is long enough given the word limit of the manuscript and readers unfamiliar with this approach may refer to the article cited for further information.

Results:

Line 302-304 If maternal mortality occurred in 13 patients this seems as though in the near miss category this is a significant clinical difference. Is there more information on the maternal deaths?

The 13 maternal deaths all occurred in women with singleton pregnancy, as mentioned line 359-360. This does not result in a significant difference between the two groups, as expected given the rarity of this outcome. That is why maternal deaths have been included in the more severe “near-miss” outcome and not isolated as a specific outcome, although we agree you don’t expect deaths under the term “near-miss”; we have now explained this analysis strategy in the revised manuscript lines 236-238, and added this precision in footnotes of tables.

Line 329-331 Explain the clinical indications for cesarean section and management of twins. This is important for the reader to put the secondary path analysis into context regarding attributable risk and SAMM.

The objective of the path analysis is not to assess the relevance of the indications for cesarean, but to provide additional information to balance risks and benefits of the cesarean procedure. That is why we don’t think the description of caesarean indications is useful here, as it may introduce confusion in the message. In addition, given the design of this study, such a description would be done separately in women with samm and in control women, which would further complicate the information provided. That is why we prefer not to add these details, unless the editor asks for.

Discussion:

Given the lack of data on indications for cesarean delivery and practice patterns this limits the secondary objectives and attributable risk along with generalizability.

As explained in our answer above, the objective of the path analysis is not to assess the relevance of the indications for cesarean, but to provide additional information to balance risks and benefits of the cesarean procedure. That is why we don’t think the description of caesarean indications is useful here, as it may introduce confusion in the message

Table 1 It is unclear what or how maternal mortality is included in the near miss WHO criteria. Do you have separate details on all maternal mortalities? In the results section it implied known were twins.

As explained above, the 13 maternal deaths all occurred in women with singleton pregnancy, as mentioned line 359. This does not result in a significant difference between the two groups, as expected given the rarity of this outcome. That is why maternal deaths have been included in the more severe “near-miss” outcome and not isolated as a specific outcome, although we agree one does not expect deaths under the term “near-miss”; we explained this analysis strategy in the manuscript. We have now explained this analysis strategy in the revised manuscript lines 236-238, and added this precision in footnotes of tables.

Table 2

Why was single mother chosen as a demographic of interest?

Single mother is considered here as a social variable. Indeed, being a single mother is associated with social isolation and with decreased economic resources¹, and as such is a marker of social vulnerability, itself a risk factor for severe maternal complications², possibly through poorer access to care³. Indeed, in our univariable analysis, the risk of SAMM was significantly higher in single mothers (Table 2) and it remained so in the multivariable model of the sensitivity analysis (aOR = 1.4 [1.1-1.8], data not shown since the focus here was on multiple pregnancy).

¹Chardon, O, Daguët, F & Vivas, E (2008) Les familles monoparentales. Des difficultés à travailler et à se loger. *Insee Première* no. 1195 – juin 2008; available at http://www.insee.fr/fr/themes/document.asp?ref_id=ip1195

²Linard M, Blondel B, Estellat C, Deneux-Tharaux C, Luton D, Oury JF, Schmitz T, Mandelbrot L, Azria E. Association between inadequate antenatal care utilisation and severe perinatal and maternal morbidity: an analysis in the PreCARE cohort. *BJOG* 2018; 125:587–595.

³Gonthier, C., Estellat, C., Deneux-Tharaux, C., Blondel, B., Alfaïate, T., Schmitz, T., ... & Azria, E. (2017). Association between maternal social deprivation and prenatal care utilization: the PreCARE cohort study. *BMC pregnancy and childbirth*, 17(1), 126.

Reviewer #3: Madar et al have performed a population-based nested case control study evaluating the association between twin pregnancy and severe maternal morbidity and secondarily evaluating the role of cesarean delivery as a mediator between twin pregnancy and severe maternal morbidity. Overall, this manuscript is well written and answers an important question in a meaningful way. I have only a few minor comments and suggestions.

- The authors discuss the WHO near-miss criteria. It would be helpful to elaborate more (or include in Appendix 1 where the SAMM criteria are listed) so that the reader is aware of how the WHO near-miss criteria differ from your SAMM criteria and in which ways these represent more severe morbidity.

We agree with this comment and have now added a list of WHO near-miss criteria in Box 1, cited line 236, as suggested by the Editor.

- I think it would be meaningful to note the incidences of each type of SAMM (as described in appendix 1) by singleton vs. twin delivery - the description of Appendix 3 seems to say that this is what Appendix 3 shows, but it is in fact describing underlying causal conditions, rather than a description of the types of SAMM.

Appendix 4 (previously appendix 3) has been revised and now shows various SAMM criteria within the main categories of SAMM causes.

- The path analysis evaluating mode of delivery is very interesting, although slightly difficult to interpret for those not familiar with this type of analysis. You write it out very clearly on lines 276-278, noting what question in particular this type of analysis will answer. I would again use that kind of terminology and clear writing to discuss this in the discussion (lines 344-346). The term mediated is clear to those who understand this analysis, but not clear to those unfamiliar so I think it would be helpful to use different words here.

We have proposed another wording of this sentence lines 408-411 of the revised manuscript, “ In other words, if twin pregnancies had the same probability of cesarean delivery as singleton pregnancies, the association found between twin pregnancy and intra or postpartum SAMM would be reduced by a fifth. “

Reviewer #4: The study design, although observational, has several strengths. The authors report on secondary outcomes from the EPIMOMS study which was a large (involving 6 different regions) prospectively collected cohort which is current (2012-3), and represents a significant percent (~20%) of all deliveries in France during that time. The use of singletons collected at the same time and from the same centers as a comparison group for major outcomes is another strength of the analysis. This manuscript provides more accurate data than what is currently available for counseling and would be highly cited in the literature and in clinical practice. Some minor comments should be addressed by the authors:

1. I am confused about why the authors selected a small control group for analysis instead of using all patients without SAMM as the control group. Or alternately if committed to using a subset of patients as a control group, why not select them to be matched for potential confounders?

The Epimoms study was designed as a population-based case-control study nested in a cohort. Although all deliveries were counted and minimal information was available for all (including multiple/singleton status), detailed information was collected for all women with SAMM, but only for a representative sample of women without SAMM within this cohort of parturients. This design has the assets of a cohort (in particular no selection bias due to a lack of comparability of cases and controls since they are selected from the exactly same source population) while allowing to minimize the number of women surveyed and the related costs.

The EPIMOMS study was initially designed based on an anticipated rate of SAMM of 1%, resulting in 1,800 cases of SAMM among the expected 180,000 deliveries. The size of the control sample was chosen in order to have sufficient power to study the association between various potential risk factors and SAMM, that is, to be able to show a risk multiplied by 1.5 or more for a factor with a prevalence of 5% or more among controls with $\alpha=0,05$ and $1-\beta=0.9$. 3,600 controls were thus needed, or 2% of expected deliveries.

Finally, because the objective was to collect data to document various potential risk factors of SAMM, an unmatched generalist control sample appeared as the most relevant design.

The sampling method was to randomly select a number x between 1 and 50 and then to select the corresponding xth parturient from the delivery logbook starting with the first delivery of the 1 year study period; then 1 every 50 deliveries was subsequently selected; in case this process selected a woman with SAMM, the delivery just before was selected as a control. This process was conducted similarly in each unit.

These methodological aspects have been further described in the revised manuscript lines 176-183 and 199-205.

2. On page 10, line 171, the control group is listed as 3651, but reported as 3650 in the rest of the manuscript - please explain or correct

These two numbers are indeed correct. First we described the EPIMOMS source population, which includes a random sample of 3651 women without SAMM (line 199). Then we explained how the study population was selected from this source population; because information on multiple pregnancy was missing in one woman without SAMM, the control group for this analysis included 3650 women (and not 3651), as mentioned lines 221-228 and Figure 1.

3. Psychiatric disorders were included as a SAMM, but specifically referred to previously as an exclusion (page 11 - 185-6) - please clarify

SAMM cases due to psychiatric disorders are included in the Epimoms SAMM definition and in this analysis, as described in Appendix 1 and Table 1. The exclusions mentioned lines 223-226 concerned 30 women for whom obstetric data were not available, in particular, the pregnancy type (single or multiple). It turned out that these cases were due to extra-obstetrical events that occurred in the antepartum, mainly psychiatric disorders or traumas, explaining that obstetrical information may be missing in these women lost to follow-up after the event. However, most SAMM cases due to psychiatric disorders (n= 95) were included, as reported in Table 1. Moreover, we have rephrased the sentence line 224 in the Methods section to avoid any ambiguity.

4. Is being a single mother a risk factor for SAMM (page 12, line 234)? That is not my understanding. Please cite a reference if this is going to be a variable in the analysis, or eliminate it from the regression model.

Single mother is considered here as a social variable. Indeed, being a single mother is associated with social isolation and with decreased economic resources¹, and as such is a marker of social vulnerability, itself a risk factor for severe maternal complications², possibly through poorer access to care³. Indeed, in our univariable analysis, the risk of SAMM was significantly higher in single mothers (Table 2) and it remained so in the multivariable model of the sensitivity analysis (aOR = 1.4 [1.1-1.8], data not shown since the focus here was on multiple pregnancy).

¹Chardon, O, Daguët, F & Vivas, E (2008) Les familles monoparentales. Des difficultés à travailler et à se loger. *Insee Première* no. 1195 – juin 2008; available at http://www.insee.fr/fr/themes/document.asp?ref_id=ip1195

²Linard M, Blondel B, Estellat C, Deneux-Tharaux C, Luton D, Oury JF, Schmitz T, Mandelbrot L, Azria E. Association between inadequate antenatal care utilisation and severe perinatal and maternal morbidity: an analysis in the PreCARE cohort. *BJOG* 2018; 125:587–595.

³Gonthier, C., Estellat, C., Deneux-Tharaux, C., Blondel, B., Alfaïate, T., Schmitz, T., ... & Azria, E. (2017). Association between maternal social deprivation and prenatal care utilization: the PreCARE cohort study. *BMC pregnancy and childbirth*, 17(1), 126.

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

This case-control study compared SAMM among 2500 cases and a random subset of 3650 out of 182,309 deliveries without SAMM. The main outcome of interest was the association of SAMM and twin birth, which comprised 197 of the cases and 59 of the controls. The SAMM cohort differed in

multiple demographic and risk factors (Table 2) and the majority of cases (> 65%) defined as SAMM were due to maternal hemorrhage. The Authors adjusted for the baseline differences using multilevel logistic regression and multiple imputation (table 3) and also using only cases and controls with complete data (Table 4).

While it is clear that twin birth was associated with higher risk of SAMM, there are limitations based on the data available in this analysis and therefore on the precision of estimates as to how much of the increased risk was due to twin birth vs other factors.

First, the high proportion (> 50%) of missing data among the cases and (> 25%) among the controls, with no enumeration in Tables as to which data were missing and how much data were missing from the twin cohorts.

There seem to be a misunderstanding regarding the proportion of missing data. Indeed, there were 2227 (89.1%) cases and 3048 (83.5%) controls with no missing data for covariates included in the main multivariate model, ie a rate of missing data of 10.9% in cases and 16.5% in controls. This is now clearly explained lines 293-207 of the revised manuscript, and an additional Appendix 3 has been added showing the numbers and characteristics of women with and without missing data. Because of these moderate rates and the plausibility of the MAR hypothesis, we used multiple imputation for these missing values.

The secondary path analysis was conducted on non missing data but included only cases with intra or postpartum SAMM (antepartum SAMM was not relevant for this analysis, as explained), which explains the variation in numbers. For the path analysis, the proportion of women with missing data was 14.3% for cases and 18.7% for controls. Overall, these proportions of missing data are in a reasonable range and we don't think they introduce a bias in our results.

Second, the number of twin births among the control cohort was only 59, or ~ 1.6% and we are not told how many of the latter had missing data, there is a limitation on the ability of multivariable regression to have adjusted for the many differences outlined in Table 2.

Among the 59 women with twin pregnancy in the control group, 6 had missing data and were imputed. This proportion is moderate and similar to the global rate of missing data among controls, as described above. Anyhow, because it is a case-control design, and given the high number of women with the SAMM outcome, the number of variables included in the multivariable model seems appropriate.

There should be a fuller accounting/enumeration of the missing data, acknowledgment of that as a limitation to generalizing the conclusions. Also, a much larger data base for controls was available and the proportion of twins among that cohort was low. So I do not understand why a larger control group was not chosen to allow greater precision in estimation of various factors besides cesarean delivery that might have contributed to SAMM. The cohorts of twins are so small that any interaction terms among the risk factors and twin births cannot be estimated with any precision, nor could NS interaction terms be generalized, due to low statistical power.

Again, there was a misunderstanding regarding the proportion of missing data. The proportion of women with missing data was 10.9% for cases and 16.5% for controls in the main analysis, i.e in a reasonable range to draw conclusions. This has been clarified in the revised manuscript lines 293-297 and in an additional Appendix 3.

Regarding the study design, as mentioned above, the Epimoms study was designed as a population-based case-control study nested in a cohort. Although all deliveries were counted and

minimal information was available for all (including multiple/singleton status), detailed information was collected for all women with SAMM, but only for a representative sample of women without SAMM within this cohort of parturients. This design has the assets of a cohort (in particular no selection bias due to a lack of comparability of cases and controls since they are selected from the exactly same source population) while allowing to minimize the number of women surveyed and the related costs. These methodological aspects have been further described in the revised manuscript lines 176-183 and 199-205.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- The objective for the abstract should be a simple "to" statement without background. The Journal style doesn't use the virgule (/) except in numeric expressions. Please edit here (Line 92) and in all instances.

These changes have been made.

- Perhaps: Compared to women with singleton pregnancies, women with twins have a four fold increased risk for severe maternal complications both before and after delivery. [do you want to mention here the contribution of CS? as you will have shortened the introduction quite a bit you should have space]

This has been revised.

- can you tell us how the random sampling occurred?

The sampling method was to randomly select a number x between 1 and 50 and then to select the corresponding xth parturient from the delivery logbook starting with the first delivery of the 1 year study period; then 1 every 50 deliveries was subsequently selected; in case this process selected a woman with SAMM, the delivery just before was selected as a control. This process was conducted similarly in each unit. Please let us know if you want us to provide more details on this process in the manuscript.

- Please describe the data collection method for both the SAMM/non SAMM patients. Who entered the data?

Was there a validation process to check for accuracy? Do these 6 regions all use a similar electronic medical record which could be queried? Paper charts? Given the high rate of missing data (noted in statistical review) a more thorough description of data collection is important.

First, as mentioned in our answer to the statistical editor's comment, there was a misunderstanding regarding the proportion of missing data (confusion between populations

analyzed in Table 3 and Table 4, this latter restricted to intrapartum SAMM). The proportion of women with missing data was 10.9% for cases and 16.5% for controls in the main analysis. This has been clarified in the revised manuscript lines 293-297 and in an additional Appendix 3.

Regarding the data collection method, it was similar for SAMM and non SAMM patients and in all regions. Information was extracted from paper charts by research midwives trained for this study, and entered in a standardized electronic report form developed for the study. In addition, for women with SAMM, the SAMM criteria and the cause of SAMM were entered by the clinician in charge. Data monitoring was performed during the study period, targeting in particular inconsistencies and missing values. In consequence the rate of missing values in the study database likely reflects the missing values in source medical charts. This data collection method has been further detailed in the revised manuscript lines 210-214.

- please provide these criteria in a box. please cite the box here as Box 1. Put the actual box at the end of the file with your tables.

This has been done.

- as this method will be unknown to most of our readers, please provide a description of this method. This can be in supplemental digital content but reference its' existence.

This has been done, by expanding the context of Appendix 2

- as noted by two reviewers, please explain why marital status was considered here.

Single mother is considered here as a social variable. Indeed, being a single mother is associated with social isolation and with decreased economic resources¹, and as such is a marker of social vulnerability, itself a risk factor for severe maternal complications², possibly through poorer access to care³. Indeed, in our univariable analysis, the risk of SAMM was significantly higher in single mothers (Table 2) and it remained so in the multivariable model of the sensitivity analysis (aOR = 1.4 [1.1-1.8], data not shown since the focus here was on multiple pregnancy).

A mention has been added in the text line 283-284.

¹Chardon, O, Daguët, F & Vivas, E (2008) Les familles monoparentales. Des difficultés à travailler et à se loger. *Insee Première* no. 1195 – juin 2008; available at http://www.insee.fr/fr/themes/document.asp?ref_id=ip1195

²Linard M, Blondel B, Estellat C, Deneux-Tharaux C, Luton D, Oury JF, Schmitz T, Mandelbrot L, Azria E. Association between inadequate antenatal care utilisation and severe perinatal and maternal morbidity: an analysis in the PreCARE cohort. *BJOG* 2018; 125:587–595.

³Gonthier, C., Estellat, C., Deneux-Tharaux, C., Blondel, B., Alfaiate, T., Schmitz, T., ... & Azria, E. (2017). Association between maternal social deprivation and prenatal care utilization: the PreCARE cohort study. *BMC pregnancy and childbirth*, 17(1), 126.

- what does this mean? Like GDM or gestational hypertension? If I am correct, you were trying to compare women with twins to non twins with both groups having no co-morbidities or pre-labor indications for cesarean. Why not do a matching process?

Examples of « obstetric conditions that developed during pregnancy, were symptomatic and present before labor but without SAMM at this stage, and responsible for a postpartum SAMM» have now been added “(for example gestational hypertension or placenta praevia)”, lines 315-316.

Regarding the selection of controls and the choice of a completely unmatched group, as explained above in response to R2's comment, because the objective of the Epimoms study was to collect data to document various potential risk factors of SAMM, an unmatched generalist control sample appeared as the most relevant design.

- could you give some examples of indirect and direct effects?

Indirect here means « mediated by cesarean »; such an indirect effect could be for example a severe hemorrhage due to vascular wound during cesarean.

Direct effect here means “not mediated by cesarean”; such a direct effect could be for example an eclampsia.

- a maternal death is not a "Near miss". Please clarify

Given the extreme rarity of maternal deaths, this most severe event has been included in the more severe “near-miss” outcome and not isolated as a specific outcome, although we agree one does not expect deaths under the term “near-miss”; we further explained this analysis strategy in the manuscript line 236-239.

- followed.

This has been revised.

- please provide effect size and CI's

The effect size for the exposure of interest – multiple pregnancy- is provided in Table 3 through the crude OR and its 95% CI. Regarding the other variables listed in Table 2, they are presented for descriptive purpose. However, we feel that providing ORs for each of them would make Table 2 less readable, and somehow out of purpose since their characterization as risk factors for SAMM is not the objective of this analysis. That is why we did not change Table 2, but are willing to revise it if the editor asks for.

2. 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.

3. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

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. 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 website 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.

6. 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 and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize>. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. 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 26 typed, double-spaced pages (6,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. 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.

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).

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.

This has been done.

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.

This has been done.

14. Figure 1: Please add exclusion information between the first two boxes.

This has been done.

15. Authors whose manuscripts have been accepted for publication have the option to pay an article

processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at <http://links.lww.com/LWW-ES/A48>. The cost for publishing an article as open access can be found at <http://edmgr.ovid.com/acd/accounts/ifaauth.htm>.

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

16. 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 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 Feb 01, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

From: [REDACTED]
To: [Randi Zung](#)
Subject: RE: Your Revised Manuscript 18-2218R1
Date: Saturday, March 9, 2019 4:18:00 AM
Attachments: [18-2218R1 ms \(3-4-19v4\) \(1\) rev.docx](#)

Dear Randi,

Sorry for the delayed answer. I was off for holidays.

Please find below my answers to the last comments, and attached the revised manuscript.

Let me know if you need anything else

Best regards

Catherine

Le 2019-03-04 19:31, Randi Zung a écrit :

[Dear Dr. Deneux-Tharaux:](#)

Dr. Chescheir has reviewed your edited revision. She has the following comments (highlighted in green in the v4 file), and stated below:

1. Abstract-Objective: Sorry this wasn't clear. It needs to be one sentence. Please review the edit made here to delete the sentence about secondary outcomes. Do you approve ?

Yes we approve.

1. Abstract-Methods: Do you mean « Between 22 weeks of gestation and 42 days postpartum » (which would be from 3 weeks and 41 days) or do you mean « From 22 weeks of gestation and 42 days postpartum » ?

We mean “from 22 weeks of gestation and up to 42 days postpartum”. We lean including 42 days. The sentence has been revised accordingly.

1. Line 210: Similar to the comment in the Abstract-Methods, please correct the sentence here.

Revised here also.

1. Line 419-420: How is a maternal death considered a « near miss » ?

As we explained in the Method section, “To isolate the most severe fraction of severe acute maternal morbidity cases, a secondary outcome was defined to include maternal near-misses as defined by WHO¹⁵ (see criteria in Box 1); given the extreme rarity of maternal deaths, they were included in this more severe “near-miss” outcome and not isolated as a specific outcome; for brevity and clarity, this group will be referred to as the “near miss” group in the manuscript.”

To clarify this denomination, we added “...” in the Results section when mentioning this group.

1. Line 432: Do you mean IVF or infertility treatment ?

We mean IVF, as shown in Table 2.

Please send your next version back to me when you are finished addressing these comments.

Thanks,

Randi

From: Catherine deneux tharaux [REDACTED]
Sent: Friday, February 15, 2019 4:20 AM
To: Randi Zung <RZung@greenjournal.org>
Subject: Re: Your Revised Manuscript 18-2218R1

Dear Randi,

Please find below our answers to the Editors comments, and attached the revised manuscript with tracked changes.

Please let me know if anything unclear.

Best,

Catherine Deneux-Tharaux

Le 07/02/2019 à 14:43, Randi Zung a écrit :

Dear Dr. Deneux-Tharaux:

Your revised manuscript is being reviewed by the Editors. Before a final decision can be made, we need you to address the following queries. Please make the requested changes to the latest

version of your manuscript that is attached to this email. **Please track your changes and leave the ones made by the Editorial Office.** Please also note your responses to the author queries in your email message back to me.

1. General: The Editor has made edits to the manuscript using track changes. Please review them to make sure they are correct.

This has been done

2. Comment from Dr. Chescheir: Thank you for your revision of your manuscript regarding the EPIMOM study results of severe maternal acute morbidity in twins v singletons. Please note that the manuscript is significantly longer than what is typically allowed for an original research paper, almost 600 words over. In the edits, I've made some suggestions of ways to reduce all but the discussion by about 300 words. The discussion has some redundancy in it including some repetition of the results that you can work with to further decrease the word count.

Please recognize that I've made suggestions that must be acceptable to you so don't feel like you must accept these, particularly if they have altered your meaning in any way. I could never write a paper in a 2nd language myself, so I'm a bit awed that anyone can. If you can find a way to save 400 of the almost 600 that you are over, I'll be happy with that.

Thanks a lot for your suggestions and help in reducing the manuscript's length. We have removed about 400 words. However, at the same time, you asked for more details about control selection, and you replaced the acronym SAMM by Severe acute maternal morbidity which has added more than 200 words to the manuscript since this term has about 70 occurrences. Would you accept to keep this SAMM acronym?

3. Title: We'd like to make your title more specific. Do you agree with using, « Singleton Compared With Twin Pregnancy and Severe Acute Maternal Morbidity » instead?

The title has been revised according to the second edit you sent

4. Line 9: What does « EPIMOMS » stand for ? Please write it out in the byline.

This has been done

5. Electronic Copyright Transfer Agreement: François Goffinet and Aurélien Seco will need to complete our electronic Copyright Transfer Agreement, which was sent to them through Editorial Manager. Please let us know if the coauthors need this message resent to them.

They both have now completed the electronic form

6. Please review your Appendixes file and let us know if you have any edits. We are still working on the figure in Appendix 3.

We have reviewed the Appendices and Figure1. Here are our few comments :

Appendices :

- misspelling of the first author's name in the footer: it should be "Madar" instead of "Hadar"

- Appendix 3:

Explanation of the SAMM acronym is missing

The title of the article cited as a reference is written twice

Figure 1 :

- second "box" : delete one space in the number 176,118

- second "box" : replace morbidity by morbidity

7. Line 47: What are you thanking them for? Please be specific.

We have now specified the reasons for acknowledging them.

8. Line 97: The objective for the abstract should be a simple "to" statement without background. This was requested and noted by you in my original comments back to you.

We feel that this is the case; we had deleted all back ground in the R1 version. Please let us know what phrasing you would like.

9. Line 132 (Overall manuscript length): Your paper needs to be shortened quite a bit. It is about 4100 words without references, etc. About 500-600 words need to come out. As I go through this, I'm going to make some suggestions about ways of doing this, Very important that you realize these are suggestions only and that they absolutely must not change your

meaning. If you want to find others ways of accomplishing this goal, I'm good with that. The suggestions I've made directly get you down to about 3800 words from 4100. The discussion needs to be condensed quite a bit as you have some redundancy there.

Thanks a lot for your suggestions and help in reducing the manuscript's length. We have removed about 400 words. However, at the same time, you asked for more details about control selection, and you replaced the acronym SAMM by Severe acute maternal morbidity which has added more than 200 words to the manuscript since this term has about 70 occurrences. Would you accept to keep this SAMM acronym?

10. Line 135: The CDC defines Assisted Reproductive Technologies as « Although various definitions have been used for ART, the definition used by CDC is based on the [1992 Fertility Clinic Success Rate and Certification Act](#) that requires CDC to publish the annual [ART Success Rates Report](#). According to this definition, ART includes all fertility treatments in which both eggs and embryos are handled. In general, ART procedures involve surgically removing eggs from a woman's ovaries, combining them with sperm in the laboratory, and returning them to the woman's body or donating them to another woman. They do NOT include treatments in which only sperm are handled (i.e., intrauterine—or artificial—insemination) or procedures in which a woman takes medicine only to stimulate egg production without the intention of having eggs retrieved. »

As such, I think you could change ART to « infertility treatments ». I think ovulation induction is more common than IVF and its variants and a more likely contributor these days at least to twins.

We agree and have made the recommended change.

11. Line 140: You could shorten the lines highlighted in yellow to say « Both neonatal and maternal complications are more common with twins than singletons, including premature birth, hypertensive disorders of pregnancy, obstetric hemorrhage and abnormal placentation? (FN 5-9) However, our knowledge of the association of twins with maternal severe health effects and organ dysfunction is incomplete »

Thanks for this suggestion. We have revised the manuscript accordingly.

12. Line 146: Was this only in LMIC?

Actually, among the 29 participating countries, 2, Japan and Qatar, were high income ones. These 2 countries accounted for only 2% of near-miss cases. So overall, this study mostly reflects LMIC context. We have rephrased the sentence.

13. Methods: Please describe the randomization method used for selection the controls, as you did in your response to comments,

We have added this description.

14. Line 183: Representative or random?

Random. It has been changed in the text

15. Line 189: What do you mean by « surveyed » ? Were patients asked questions on a survey or do you mean « included »?

We meant “included”; this has been changed.

16. Line 201: I deleted $n=2540$ and $n=3651$ as these are part of the Results.

OK

17. Line 211: I'd like to suggest an alternative phrasing here :In order to show an odds ratio of > 1.5 or < -1.5 for a factor with a prevalence of 5% or more among controls with an with $\alpha=0.05$ and $1-\beta=0.9$. 3,600 controls (or 2% of the cohort) were needed.”

Thanks for this suggestion. We have revised the manuscript accordingly.

18. Line 215: Please state here how you randomly selected the controls.

We have added this description.

19. Line 221: This reads like your control group had to have had some maternal morbidity, just not severe. I understood the control group to be without severe acute maternal morbidity—could they have been without any?. Please clarify here and where you describe your control group.

Yes women in the control group could have non-severe maternal morbidity. This has

been clarified in the description of controls.

20. Line 258-273: Move these lines to a Box. Please cite the Box in the text here and put the Box at the end of the Tables. Please number this accordingly. If this is the only Box in the manuscript, this would be Box 1.

Thanks for the suggestion. This has been moved to Box 2.

21. Line 392: Please provide the unadjusted OR's and 95%CI here and for all data presented in the text. We prefer this information to the P values.

The unadjusted OR has been added below and is also provided in Table 3. Mentioning it also here would be redundant. That is why we just removed the p value here.

22. Line 395: Need ORs etc. You are describing this a « different » and you need to show the data that supports that.

There is no comparison here; we just describe the distribution of timing and causes among women with SAMM. In consequence, there is no possibility to calculate an OR since there is only one group. The sentence has been rephrased.

23. Line 397 and Line 399: Please provide the denominator.

Denominator has been added

24. Line 408: Provide OR and %Cis instead of the p-value.

We have added the unadjusted OR with 95% CI

25. Line 425: As indicated earlier, please put the crude OR, 95% CI above and then here around line 550, describe results of your multivariable analysis with aOR, 95%CI. The line starting here (line 550) would now read something like, « In the multivariable analysis, severe maternal acute anemia occurred with an aOR 4.2 (95%CI 3.1-5.8) » Construct this paragraph similarly for all of the reported aOR's and move the crude OR's (all with 95% CI) to the preceding paragraphs.

We have rephrased the paragraph to follow this suggestion.

26. Line 455: Generally, one reports the limitations and strengths of a study just prior to the concluding paragraph. Lines 600-637 appear to be a reiteration of some of your methods, which can be deleted or condensed as well as a description of your study's strengths and weakness. These paragraphs should be moved.

We have removed the concluding paragraph which was indeed redundant

27. Line 527: Based on what was already known, do you think obstetricians DON'T already closely monitor women with twins ? Perhaps you could provide something more specific ? Since hemorrhage was such a big contributor to the rates of SAM, perhaps you could give a specific example such as monitoring antepartum for severe maternal anemia with supplementation either PO or if needed, IV to try to prevent severe maternal anemia at the time of delivery ? That may not be example you want to give, but something concrete as an example other than « close monitoring » seems appropriate.

We have now provided more specific examples of close management of twin pregnancy.

28. Line 538: This is just a reiteration of your results. Could you draw some conclusions here ? If I recall, over ½ of your twins in the control group and 71% or so in your case group of twins were delivered by CS. Perhaps you could say something to the effect of increasing utilization of vaginal birth for twins, unless there is an obstetric or fetal indication otherwise.

Thanks for the suggestion. We have now removed the reiteration of results and insisted on the potential benefit of increasing vaginal birth in twin pregnancy.

29. Line 546: You have already said this above. Please condense, and provide specific examples.

We have removed this concluding paragraph which was indeed redundant

To facilitate the review process, we would appreciate receiving a response by February 15.

Best,

Randi Zung

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Randi Zung (Ms.)

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From: [REDACTED]
To: [Eileen Chang \(Temp\)](#)
Subject: Re: O&G Figure REvision: 18-2218
Date: Tuesday, February 19, 2019 11:55:31 AM

Dear Eileen,

The figure looks perfectly fine.

Thanks

Catherine

Le 19/02/2019 à 17:49, Eileen Chang (Temp) a écrit :

Hi Catherine,

Thank you for your response.

I have made the necessary edits and I have attached the new version for your review.
Also, thank you for catching the spelling and spacing errors!

If you could get back to me with any comments on the new version as soon as you can
that would be great.

Best,
Eileen

From: Catherine deneux tharaux [REDACTED]
Sent: Friday, February 15, 2019 3:38 AM
To: Eileen Chang (Temp) <echang@greenjournal.org>
Subject: Re: O&G Figure REvision: 18-2218

Dera Eileen,

Two small comments on this figure:

- second "box" : please remove one extra space in the number 176,118
- second "box" : replace morbidity by morbidity

Thanks

Catherine Deneux-Tharaux

Le 12/02/2019 à 19:24, Eileen Chang (Temp) a écrit :

Good Afternoon,

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

PLEASE NOTE: Any changes to the figure must be made now. Changes 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 Friday, 2/15. Thank you for your help.

Best wishes,

Eileen