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)*

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Date: Jan 18, 2022
To: "Wentao Li" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-2385

RE: Manuscript Number ONG-21-2385

Timing of Delivery for Twins with Growth Discordance and Growth Restriction: An Individual Participant Data Meta-analysis

Dear Dr. Li:

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

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 08, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

This paper is a very well written and comprehensive evaluation of the literature on timing of delivery in twins with growth abnormalities. There are some questions about the methods and results.

Specific comments:

1. In the Precis, abstract, and introduction, the authors state that they intend to determine the optimum time for delivery. Determining the optimum time for delivery would require a clinical trial. There are clinical trials among the papers you used, and it would be useful to know what these trials showed. Indeed, the use of observational studies on an equal footing with clinical trials requires an explanation.
2. For figure 1, please identify the abbreviations used in the MOOSE diagram.
3. It seems odd that 93 studies were excluded for lack of full text availability. Librarians today can retrieve almost anything, and translation services are available for foreign language papers.
4. In considering neonatal mortality from prematurity, was there adjustment for changes in neonatal mortality with improved neonatal care over time?
5. In your presentation of results, all of your 95% confidence intervals include the null value. I am not convinced that any optimum time for delivery was identified for any subgroup. Specifically:
   5a. Line 153: Please change the sentence "From 38(+0-6) the stillbirth risk seems to outweigh the neonatal mortality risk" inasmuch as there was no statistical difference. The stillbirth risk was statistically comparable to the neonatal mortality risk.
   5b. Line 162: Please remove the word "trend," which has a statistical definition that does not appear to be applicable to your results.
   5c. Line 185: Please remove "trended" and indicate whether risk was different or comparable between groups.
   5d. Line 191: The description "seemed to outweigh" appears to be contraindicated by your statistical results.
   5e. Line 194: Please remove reference to a trend unless you performed a trend test. There was no statistical difference.
   5f. Line 202: Again, "seemed to outweigh" is contradicted by your statistical testing.
6. Line 208: Please remove the term "adverse." Morbidity is always adverse, is it not?
7. Your I-squared values are all zero, which seems unlikely unless there was only a single study or all studies gave identical results. Can you explain?

Reviewer #2:

This review is an individual patient meta-analysis of the effects of growth discordance on perinatal mortality in twin gestations. The authors use risk difference to determine their definition of optimal week of delivery and stratified by chorionicity as well as levels of growth discordance and birthweight. The question of whether growth discordance should attach timing of delivery is relevant. Methods are well explained. The article would be strengthened by more clearly stating the absolute risks and the overall n available at each gestational week, particularly when the number of ongoing pregnancies is few.

Methods: Given general awareness of long term morbidity in premature birth, can you explicitly state why you chose not to evaluate this? I suspect it is due to available data. However, given that there are other decision analysis based papers on timing of twin delivery that do incorporate long term morbidity, it should be addressed.
Methods, line 50-51: why did you choose 24 weeks for definition of stillbirth? There is significant variation in the definition of stillbirth, ranging from 20-28 weeks depending on the nation. Can you explain why you chose 24?
Results, lines 132-135: can you state how many had discordance >20 or >30% as these are clinically relevant?
Results, lines 136-137: consider adding a figure or range of gestational ages at delivery so we understand the n involved in calculations (and how significantly a single event is likely to skew results).
Results, section line 144: can you state the range of absolute risk of stillbirth and risk of neonatal mortality?
Tables: Looking at absolute numbers, it is clear that single events make a big difference in the risk differences. This is worth stating in the discussion.

Reviewer #3:

The authors present a systematic review with an individual data meta-analysis. Their primary objective was to determine the optimal timing of delivery for twins with growth disorders. This report builds on and includes data from a previous report addressing a similar question for dichorionic and monochorionic-diamniotic twins without growth restriction. The authors found that growth discordance or SGA was associated with higher absolute risks of stillbirth and neonatal death. The authors concluded that the perinatal risk balanced between 36 and 37 weeks EGA which was similar to what they previously found in twin pregnancies without growth discordance. The manuscript is well written with clearly described methods and limitations. I have but a few comments and queries outlined below.
1. Do you have any information on NICU level of care in the included studies? Were they all tertiary or quaternary care medical centers? Could this have influenced delivery decisions and perinatal outcomes?
2. Do you have any data on antenatal fetal testing used in included studies? Did reports that did or did not use doppler studies on SGA twins influence delivery decisions or outcome?

STATISTICS EDITOR COMMENTS:

Table 1: Need to embolden or otherwise distinguish the risk differences that were statistically different, since most were not.

Figs 2, 3 Need to summarize in legend to figure which comparisons at EGA categories were significantly different.

Tables 2, 3, 4: The analysis and conclusions are limited by the data. First, the rates of adverse outcomes is low (varying from < 10 per 1,00 to ~ 20 per 1,000, with the majority of point estimates < 5 per 1,000. As can be seen from the CIs for risk differences, there is limited precision to these estimates and low statistical power to make comparisons. Although this is a large series, it is limited by the low counts of adverse outcomes, when subdivided by GA and degree of growth discordance.

General: The term "trends" is used on lines 155, 162, 204, 221. Unfortunately, the trends are obscured by wide CIs, ie, randomness in the data due to low frequency of adverse events. Although a useful compilation of multiple data sets, the

analyses are limited by low stats power and wide CIs.

EDITORIAL OFFICE COMMENTS:

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

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

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

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

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

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

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-

informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 6,250 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

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

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

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

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

In addition, the abstract length should follow journal guidelines. The word limit for Reviews is 300 words. Please provide a word count.

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

11. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

12. 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.

13. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

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

14. Figure 1: Please explain how the flowchart goes from (n=45+2) to (n=20).
Figures 2-3 okay
All figures: Please upload as figure files on Editorial Manager.

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

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

16. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at https://wkauthorservices.editage.com/open-access/hybrid.html.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include the following:

* A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and

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

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

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Feb 08, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Dwight J. Rouse, MD
Deputy Editor, Obstetrics

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

_____

04/02/2022

Dear Editors of *Obstetrics and Gynecology*,

RE: Timing of Delivery for Twins with Growth Discordance and Growth Restriction: An Individual Participant Data Meta-analysis
Manuscript Number ONG-21-2385

We are grateful for your consideration of this research for publication and thank the reviewers for their feedback. Below are responses to the reviewers' comments. We have made the required changes to the manuscript, read the Instructions for Authors, and hope it is now acceptable for publication in Obstetrics and Gynecology. All authors have read and approved the submission of the manuscript; the manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language. We have attached a copy of the revised manuscript with the changes tracked for your review.

Dr Ashlee Koch, 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 have been explained. All individuals included as authors and contributors who made substantial intellectual contributions to the research, data analysis, and publication or presentation development are listed appropriately.

We thank the reviewers for their valuable suggestions and look forward to your response.

Kind Regards,

Dr Ashlee Koch

MD, B. Psych (Hons)

Reviewer 1

1. In the Precis, abstract, and introduction, the authors state that they intend to determine the optimum time for delivery. Determining the optimum time for delivery would require a clinical trial. There are clinical trials among the papers you used, and it would be useful to know what these trials showed. Indeed, the use of observational studies on an equal footing with clinical trials requires an explanation.

Response: Indeed, the best evidence to evaluate an intervention comes from randomised trials. But given the low rate of perinatal death as we observed in this study and the fact that several gestational weeks around 36 to 37 weeks need to be compared, performing such a trial will be incredibly challenging even if using an adaptive design and composite outcomes. Clinical trials included in this study did not randomize twins to different delivery timings, instead, they compared various interventions regarding delivery mode or preventing preterm birth. The timing of delivery was up to local protocols or clinicians' discretion. Therefore, they were treated as prospective cohort studies nested in clinical trials in this study. The quality of evidence these trials provided is equivalent to that of observational studies for this research aim. We agree that the aim – to determine the optimal time for delivery might not be fully satisfied by the observational nature of included studies. Therefore, we have rephrased the aim in the Precis, abstract, and introduction. We also discuss this issue in the discussion section.

Changes:

- **Precis** Growth disorders in twins are associated with higher absolute risks of stillbirth and neonatal death but no evidence was found that the optimal timing of delivery should be changed. (line 117-119, page 6)
- **Abstract-Objective** The impact of growth discordance in twin pregnancies on the optimal time of delivery, with or without small for gestational age (SGA, birthweight <10th centile), is unknown. We aimed to elucidate this impact by evaluating the risks of stillbirth and neonatal death in women with different levels of growth discordance and in relation to SGA. (line 136-140, page 7)
- **Introduction** We therefore aimed to evaluate the impact of growth disorders in twins on the optimal timing of delivery by performing a systematic review and individual participant data meta-analysis. (line 194-196, page 9)
- **Methods** We included cohort studies nested in randomized controlled trials, prospective and retrospective observational studies of monochorionic and dichorionic twins…(line 220, page 11)
- **Discussion** We acknowledge that the best evidence to determine the optimal timing should be sourced from randomized trials and observational studies may be subject to confounding. Interventions including antenatal fetal testing and Doppler measurements may affect the timing of delivery in practice. However, given the low rate of perinatal death, performing such a trial will be incredibly challenging even if using an adaptive design and composite outcomes. Our study provides the best available evidence in the absence of such trials. (line 450-456, page 20-21)
- **Appendix 4 – Type of study** Trials have been relabelled as cohort study nested in single/multi-center RCT

2. For figure 1, please identify the abbreviations used in the MOOSE diagram.

Change:

- Definition of abbreviations has been added to Figure 1.

3. It seems odd that 93 studies were excluded for lack of full text availability. Librarians today can retrieve almost anything, and translation services are available for foreign language papers.

Response: There were 93 articles which were originally excluded because the full texts of the abstract were not available. An updated search for these titles was able to locate all articles. Of these articles, there were 69 duplicates which were excluded. Of the remaining 24 articles, 9 were re-classified as not being on topic based on screening of the title and abstract. The remaining 15 articles were able to be accessed, there were 7 case reports, 7 letters and 1 review article. The search strategy figure has been updated to reflect the articles that were accessed based on the title and abstract but were excluded from the next stages of the analysis.

Change:

- Figure 1

4. In considering neonatal mortality from prematurity, was there adjustment for changes in neonatal mortality with improved neonatal care over time?

Response: It is reasonable to assume that neonatal mortality improves over time due to advances in neonatal health care. To understand its impact on the results, we performed a post hoc sensitivity analysis that was restricted to cohorts that only included deliveries after 2004. 12 out of 20 cohorts were retained in the sensitivity analysis. The findings are similar to the main analysis – perinatal risks are likely balanced between 36 and 37 weeks in overall twins. Thus, we believe the impact of improved neonatal care over time on the risk difference between stillbirth and neonatal death is small given the fact that stillbirth also improved over time.

Changes:

- **Methods – Evidence synthesis** A post hoc sensitivity analysis that only included cohorts entirely after 2004 was performed in all twins to assess the impact of improved neonatal care over time. (line 292-293, page 14)
- **Results** Only including cohorts entirely after 2004 resulted in similar findings as the main analysis (Appendix 10). (line 386-387, page 18)
- **Appendix 10**

5. In your presentation of results, all of your 95% confidence intervals include the null value. I am not convinced that any optimum time for delivery was identified for any subgroup. Specifically:

5a. Line 153: Please change the sentence "From 38(+0-6) the stillbirth risk seems to outweigh the neonatal mortality risk" inasmuch as there was no statistical difference. The stillbirth risk was statistically comparable to the neonatal mortality risk.

5b. Line 162: Please remove the word "trend," which has a statistical definition that does not appear to be applicable to your results.

5c. Line 185: Please remove "trended" and indicate whether risk was different or comparable between groups.

5d. Line 191: The description "seemed to outweigh" appears to be contraindicated by your statistical results.

5e. Line 194: Please remove reference to a trend unless you performed a trend test. There was no statistical difference.

5f. Line 202: Again, "seemed to outweigh" is contradicted by your statistical testing.

Response: We agree that the interpretation of estimates not reaching statistical significance should be more conservative.

Changes:

- **Results** From 38^{+0-6} the stillbirth risk was statistically comparable to the neonatal mortality risk (risk difference 4.5/1000, 95%CI -12.8 to 21.8, I^2=0%). Similar findings with balanced perinatal risks at 37^{+0-6} were seen among twins with different levels of growth discordance. (line 331-335, page 15-16)
- **Results** From 38^{+0-6} the stillbirth risk was statistically comparable to the neonatal mortality risk (risk difference 21.1/1000, 95%CI -18.1 to 60.2, I^2=0%. In SGA twins with 10-30% growth discordance (N=363), a similar finding was observed, with balanced perinatal risks between 36^{+0-6} and 37^{+0-6}. (line 366-370, page 17)
- **Results** From 38^{+0-6} the stillbirth risk was statistically comparable to the neonatal mortality risk (risk difference 8.4/1000, 95%CI -8.0 to 24.8, I^2=0%). Similar findings with balanced perinatal risks between 36^{+0-6} and 37^{+0-6} were seen among twins with <10% (N=1,052) and 10-30% growth discordance (N=513). (line 380-384, page 17-18)

6. Line 208: Please remove the term "adverse." Morbidity is always adverse, is it not?

Change:

- **Results** The risk of neonatal morbidity outcome in one or both twins decreased consistently with advancing gestational age up to 39+0-6 in dichorionic and 37+0-6 in monochorionic twin pregnancies, after which no adverse events occurred. (line 392, page 18)

7. Your I-squared values are all zero, which seems unlikely unless there was only a single study or all studies gave identical results. Can you explain?

Response: We checked the I^2 values and found no error. We assume that I^2 of zero is prevalent for two reasons. First, methods for testing heterogeneity such as I^2 in meta-analysis are less sensitive for rare event outcomes, confidence intervals of different studies are prone to overlap. Second, when pooling the risk difference of stillbirth and neonatal death but not absolute risks, studies are likely homogenous, especially between 36 to 38 weeks. Similar findings were found in a previous IPDMA regarding delivery timing in unselected twins where all reported I^2=0%.

Reference:

- Cheong-See F, Schuit E, Arroyo-Manzano D, Khalil A, Barrett J, Joseph K, et al. Prospective risk of stillbirth and neonatal complications in twin pregnancies: systematic review and meta-analysis. bmj 2016;354.

Reviewer 2

1. Methods: Given general awareness of long term morbidity in premature birth, can you explicitly state why you chose not to evaluate this? I suspect it is due to available data. However, given that there are other decision analysis based papers on timing of twin delivery that do incorporate long term morbidity, it should be addressed.

Response: We agree that long-term morbidity is important and could have weight in considering timing of delivery. However, we did not incorporate this in our study for two reasons. First, reporting of long-term morbidity is inadequate and selective in the literature. Pooling sparse data on this is likely to be subject to significant bias. Second, we chose to suggest the optimal timing of delivery by balancing the risk of two forms of perinatal death, which are objective to assess and of equal importance in decision-making. Looking at the findings, the suggested optimal timing is between 36^{+0-6} and 37^{+0-6} weeks, we do not believe delivery at this timing will cause many long-term comorbidities that are related to preterm delivery.

Change:

- **Discussion** Long-term morbidity could also have weight in considering timing of delivery, but relevant data were mostly absent in studies. (line 429-430, page 20)

2. Methods, line 50-51: why did you choose 24 weeks for definition of stillbirth? There is significant variation in the definition of stillbirth, ranging from 20-28 weeks depending on the nation. Can you explain why you chose 24?

Response: We acknowledge the definition varies widely around the world. Stillbirth from 24 weeks was chosen in the protocol as this is the current widely accepted definition of viability from most of the countries we accessed studies from. However, as the analysis focused on delivery between 32 and 40 weeks, all concerned stillbirth happened between this interval. Thus, the definition of 24 weeks is no longer relevant to the context of the analysis. We therefore removed this time definition.

Change:

- **Methods** Stillbirth was defined as the death of the fetus before birth, whereas perinatal loss included stillbirth and neonatal death within the first 7 days. (line 227, page 11)

3. Results, lines 132-135: can you state how many had discordance >20 or >30% as these are clinically relevant?

Change:

- **Results** In 1327 (18%) dichorionic and 458 (20%) monochorionic twins, birthweight discordance was greater than 20%. (line 307-308, page 14)

4. Results, lines 136-137: consider adding a figure or range of gestational ages at delivery so we understand the n involved in calculations (and how significantly a single event is likely to skew results).

Change:

We add a figure (Appendix 4) describing the number of deliveries for dichorionic and monochorionic twins each gestational week.

5. Results, section line 144: can you state the range of absolute risk of stillbirth and risk of neonatal mortality?

Changes:

- **Results** In the population of dichorionic twins without taking SGA status or growth discordance into account (n=7,474), the prospective risk of stillbirth increased from 1.2/1000 (95% CI 0.6/1000 to 2.4/1000) at 34+0-6 to 6.0/1000 (95% CI 2.9/1000 to 12.4/1000) at 38+0-6, while the risk of neonatal death decreased from 11.5/1000 (95% CI 5.8/1000 to 22.5/1000) at 34+0-6 to 2.1/1000 (95% CI 0.7/1000 to 6.1/1000) at 39+0-6 (Appendix 7). (line 319-323, page 15)
- **Results** In pregnancies where one or both twins were SGA (N=1,814), the absolute risk of stillbirth increased from 2.5/1000 (95% CI 1.0/1000 to 6.5/1000) to 11.8/1000 (4.0/1000 to 34.0/1000) from 34+0-6 to 38+0-6, whereas the risk of neonatal mortality decreased from 17.2/1000 (95% CI 5.9/1000 to 49.5/1000) to 6.0/1000 (95% CI 1.7/1000 to 21.7/1000) (Appendix 7). (line 326-330, page 15)
- **Results** In pregnancies in which both twins had birthweights appropriate for gestational age (birthweight ≥p10; N=5,654), the absolute risk of stillbirth ranged from 0.8/1000 (95% CI 0.3/1000 to 2.1/1000) to 4.4/1000 (1.7/1000 to 11.4/1000) between 34+0-6 and 38+0-6. The risk of neonatal mortality was highest at 34+0-6 (9.6/1000, 95% CI 4.1/1000 to 22.3/1000) and lowest at 38+0-6 (0.9/1000, 95% CI 0.2/1000 to 5.1/1000) (Appendix 7). (line 336-340, page 16)
- **Results** In the population of monochorionic twins without taking SGA status or growth discordance into account (n=2,281), the prospective risk of stillbirth was 1.6/1000 (95% CI 0.6/1000 to 4.8/1000) at 34+0-6 and 7.1/1000 (95% CI 2.8/1000 to 18.1/1000) at 37+0-6. The risk of neonatal death decreased from 15.9/1000 (95% CI 6.2/1000 to 40.1/1000) at 34+0-6 to 4.0/1000 (95% CI 1.1/1000 to 14.6/1000) at 37+0-6 (Appendix 8). (line 351-356, page 16)
- **Results** In pregnancies in which one or both twins were SGA (N=699), the absolute risk of stillbirth increased from 5.8/1000 (95% CI 2.0/1000 to 16.8/1000) to 12.4/1000 (3.4/1000 to 44.2/1000) from 34+0-6 to 37+0-6, while the risk of neonatal mortality decreased from 10.8/1000 (95% CI 1.9/1000 to 58.4/1000) to 7.2/1000 (95% CI 1.3/1000 to 39.6/1000) (Appendix 8). (line 359-362, page 17)
- **Results** In pregnancies where both twins were appropriate for gestational age (birthweight ≥p10; N=1,581), the prospective risk of stillbirth was 1.4/1000 (95% CI 0.4/1000 to 5.0/1000) at 33+0-6 and 5.0/1000 (95% CI 1.4/1000 to 18.0/1000) at 37+0-6. The risk of neonatal death

decreased from 18.9/1000 (95% CI 6.4/1000 to 54.0/1000) at 34+0-6 to 2.8/1000 (95% CI 0.5/1000 to 15.7/1000) at 37+0-6 (Appendix 8). (line 374-378, page 17)

6. Tables: Looking at absolute numbers, it is clear that single events make a big difference in the risk differences. This is worth stating in the discussion.

Response: We added a paragraph discussing this issue.

Change:

- **Discussion** In the case of single or zero event, the accuracy and precision of estimation could be affected. We applied meta-analysis methods that are optimized for rare events to counteract this potential issue and the results are conservative for scenarios of single event. (line 414-417, page 19)

Reviewer 3

1. Do you have any information on NICU level of care in the included studies? Were they all tertiary or quaternary care medical centers? Could this have influenced delivery decisions and perinatal outcomes?

Response: We did not collect this information at individual level. From the 20 publications, 12 specified that delivery took place in a hospital with a tertiary level neonatal intensive care unit (NICU), 2 reported deliveries occurred in a mix of NICU/special care neonatal units, and 6 did not specify. Thus, we do not believe there are strong variations among studies in terms of the level of care.

2. Do you have any data on antenatal fetal testing used in included studies? Did reports that did or did not use doppler studies on SGA twins influence delivery decisions or outcome?

Response: Two studies provided data on the last known amniotic fluid index or deepest vertical pocket, 3 studies were able to provide data on whether the last known umbilical artery dopplers were normal or abnormal, and 1 study provided both. We do not have further clinical information regarding specific maternal/obstetric complications that may have influenced the timing of delivery.

Of the 20 datasets, 7 specified how the use of doppler studies would influence delivery outcomes. This information was sought from authors, but the majority were not able to provide this information. Monitoring and delivery policy is described in Appendix 5.

We add a paragraph discussing the implication of this issue.

Change:

- **Discussion** We acknowledge that the best evidence to determine the optimal timing should be sourced from randomized trials and observational studies may be subject to confounding. Interventions including antenatal fetal testing and Doppler measurements may affect the timing of delivery in practice. However, given the low rate of perinatal death, performing such a trial will be incredibly challenging even if using an adaptive design and composite

outcomes. Our study provides the best available evidence in the absence of such trials. (line 450-456, page 20-21)

STATISTICS EDITOR COMMENTS:

1. Table 1: Need to embolden or otherwise distinguish the risk differences that were statistically different, since most were not.

Change:

We have emboldened statistically significant results in Table 1&2.

2. Figs 2, 3 Need to summarize in legend to figure which comparisons at EGA categories were significantly different.

Response: Legends of Figure 2 & 3 have been updated to guide readers to locate statistically significant results in Table 1 & 2.

3. General: The term "trends" is used on lines 155, 162, 204, 221. Unfortunately, the trends are obscured by wide CIs, ie, randomness in the data due to low frequency of adverse events. Although a useful compilation of multiple data sets, the analyses are limited by low stats power and wide CIs.

Response: We have modified some interpretation of data as suggested by reviewer 1. Please refer to our response to comment 5 of reviewer 1. We realize that the statistical power is low for some comparisons even after collating all available data that have been reported in the literature. However, using the large number of observations, we were able to rule out big change in the timing of delivery in the presence of growth disorders, which is an intensively debated topic. Findings in this study should provide assurance to families and clinicians by providing long awaited evidence.

EDITORIAL OFFICE COMMENTS:

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

A. OPT-IN: Yes, please publish my point-by-point response letter.

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

Response: We OPT-IN.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:

* Include your title page information in the main manuscript file. The title page should appear as the first page of the document. Add any previously omitted Acknowledgements (ie, meeting presentations, preprint DOIs, assistance from non-byline authors).

* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and in the body text. For industry-sponsored studies, the Role of the Funding Source section should be included in the body text of the manuscript.

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

* Name the IRB or Ethics Committee institution in the Methods section (if applicable).

* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

Response: We have added these parts.

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

Response: We confirm.

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.

Response: We confirm this information has been included in the cover letter.

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Response: We confirm.

6. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Review articles should not exceed 6,250 words. Stated word limits include the title page, précis, abstract, text, tables, boxes, and figure legends, but exclude references.

Word count: 6248.

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

* All financial support of the study must be acknowledged.

* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.

* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.

* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."

Response: These have been added to the title page.

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

Response: This has been added to the title page. 45 characters.

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

In addition, the abstract length should follow journal guidelines. The word limit for Reviews is 300 words. Please provide a word count.

Response: We confirm the abstract is consistent with the revised manuscript. Word count: 293

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

Response: We confirm.

11. 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.

Response: We confirm.

12. 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.

Response: The tables have been updated to conform to the required style.

13. Please review examples of our current reference style at http://ong.editorialmanager.com (click on the Home button in the Menu bar and then "Reference Formatting Instructions" document under "Files and Resources). Include the digital object identifier (DOI) with any journal article references and an accessed date with website references. Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the reference list.

In addition, the American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document.

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

Response: We confirm. Available DOIs have been added.

14. Figure 1: Please explain how the flowchart goes from (n=45+2) to (n=20).

Figures 2-3 okay

All figures: Please upload as figure files on Editorial Manager.

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your

original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

Response: Multiple papers (45, plus 2 contributed by one author) were produced from the same set of data. In order to avoid duplication of the participant data, these publications were condensed into datasets, rather than numbered by individual publications. We have updated figure 1 to avoid confusion.

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

Response: We confirm.

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Response: We confirm.