OBSTETRICS & GYNECOLOGY

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

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

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

Date: Dec 17, 2021
To: "Christopher Michael Nash" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-21-2192

RE: Manuscript Number ONG-21-2192

Duration of postpartum magnesium sulphate for the prevention of eclampsia: A Systematic Review & Meta-Analysis.

Dear Dr. Nash:

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 Jan 07, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: In this manuscript, the authors perform a systematic review and meta-analysis to address whether the duration of postpartum magnesium sulfate (24 hours versus less than 24 hours) affects the risk of eclamptic seizure. Overall, this study is intended to address a highly relevant clinical question which is encountered daily in routine obstetric care. Our field lacks evidence-based guidance for the duration of seizure prophylactic magnesium sulfate. The topic is appropriate for the readership of this journal.

I believe this manuscript would benefit by some clarifications throughout and enhanced discussion points which I have detailed in my comments below. Methodologically, I have some concerns about one of the studies included in the meta-analysis (see comments pertaining to Methods and Discussion).

Abstract:

Line 22-23 and 48-49 - Objective and conclusion statements should remain focused on the question addressed (risk of eclampsia). The study was not designed to directly test optimal duration over a range of treatment protocols, nor was it designed to test overall safety.

Line 38 - The abstract would benefit by a definition of "shorter duration" (i.e. a range of hours).

Introduction:

Line 55 - The incidence of eclampsia referenced requires a denominator - it is unclear from the current wording whether the 1-2% rate of eclampsia is in women who have received MgSO4, or are pregnant vs postpartum, etc. I am unable to find this information in the referenced review article.

Line 64-65 - The authors should re-word this statement to reflect that while there are recommendations and a standard of care for postpartum continuation of MgSO4, these recommendations are not based on direct clinical evidence. Also, what is the meaning of "milder PET"? It would be helpful to adhere to the commonly used terminology, e.g. preeclampsia with or without severe features, preeclampsia without eclampsia, etc. (here and throughout the document - lines 220 and 237).

Methods:

In general: I do not have the statistical expertise to comment in detail on the design and execution of a meta-analysis.

Their description of their methodology is understandable. Their reporting is adherent to PRISMA guidelines and they included the PRISMA checklist.

I do have a concern about the assessment of bias in the included studies. In particular, I scrutinized Anjun et al (2016) "Maternal outcomes after 12 hours and 24 hours of magnesium sulfate therapy for eclampsia". In their assessment of bias for this study, the authors believe that this study was low risk for performance bias. However, the original study notes that personnel were not blinded to the treatment arm. I am confused how the authors interpreted this information and assigned low risk of performance bias to this study.

Line 93 - Could the authors specify which of study populations included or excluded patients diagnosed with preeclampsia without severe features? Can they speak to the diagnostic criteria for preeclampsia and eclampsia that were used in the contributing studies?

Results:

Line 145 - I would prefer to see the results show as a rate or n/denominator, rather than simply the raw number of seizure episodes. This comment also applies to the discussion section (lines 177-178).

Line 160 - Can the authors specify how many studies reported the secondary outcomes of interest?

Line 165-170 - Can the authors address whether it is typical to report secondary outcomes in a meta-analysis that were only addressed by one of the studies included in the analysis? How is this contributing new information?

Discussion:

The authors need to address the timing of seizure episodes with respect to whether postpartum MgSO4 had been completed. The comparison of 12 versus 24 hours of MgSO4 therapy by Anjum et al (2016) has 10 seizure episodes in the 24 hour treatment group. However, in the primary study, all 10 of those seizures occurred during the first 2 hours of therapy. Anjum et al reported zero seizures in both treatment groups following completion of MgSO4 therapy. It would be interesting to know, and essential to address, whether the seizure events described in the other studies were before or after completion of MgSO4. I would like to know why the authors of this study chose to include in their analysis those seizure episodes which occurred before completion of MgSO4 therapy.

I am also interested in the authors' thoughts on the rate of eclampsia in the patient populations that were studied. Specifically, the Anjum et al (2016) 12h vs 24h study notes a 3.9% incidence of eclampsia in their total patient population, which limits generalizability of their results.

Line 180 - The authors mention that there was one seizure in patients who were enrolled with a diagnosis of preeclampsia without eclampsia at the time of enrollment. They should specify that the seizure occurred in the experimental group (<24 hours of MgSO4) and that there were zero seizures in the control group (24 hours of MgSO4).

Line 183 - "hospitalization rates" should be "duration of hospital stay".

Line 184-186 - I disagree with the authors' interpretation of the cited guidelines and encourage them to review in order to adjust their general summarization. For patients with preeclampsia without severe features, the guidelines acknowledge controversy/lack of clarity regarding the need for MgSO4 for seizure prophylaxis and, in the case of the ACOG guidelines, allow for clinical decision-making based on patient and local resources/systemic factors.

Line 188-191 & Conclusion section - I am confused how the authors reached this conclusion based on their analysis. First, their study is underpowered to detect the primary outcome, so I do not think it is reasonable to suggest a change in clinical practice based on their results. Also, Figure 3B shows that patients with preeclampsia and without eclampsia at the time of enrollment had 0 seizure episodes out of 492 patients in the 24h treatment group, and 1 seizure episode out of 529 patients in the <24h treatment group. Although not statistically powered to demonstrate a difference, these data are not reassuring in the <24h treatment group, and do not support a chance in clinical practice.

Line 195-206 - The authors need to more clearly delineate what is unique about this manuscript. They have provided a comparison of the included studies between their meta-analysis and those already published, but it is not clear to me how these methodological differences have translated to a robust/unique contribution to the published literature.

Reviewer #2: The paper examines the duration of postpartum magnesium sulfate for the prevention of eclampsia. The authors included 10 studies (n=1714) in their meta-analysis and subsequently showed no increased risk for postpartum seizures with a shorter duration of MgSO4. The study is important in the context of changing an established clinical practice to use a shorter duration of magnesium sulfate in the post-partum period, which in turn is likely to improve patient safety and reduce the adverse effects without increasing the risk of recurrent seizures. The authors describe the

search strategy and the inclusion criteria clearly. Please find my comments on reviewing the article here:

1) In the study by Anjum et al which has been included in the analysis of the incidence of seizure if exposed to less than 24 hours vs 24 hours(145-152) .On going through the study 10 patients had convulsions within the first 2 hours of instituting therapy in the 24 hour group and they required a 2 gram loading dose of magnesium sulphate. The primary outcome of this study was the recurrence of seizures after completion of therapy. Therefore this incidence of a seizure 2 hours into the treatment has not been considered by the authors in their outcomes and could be due to requirement of different dosing based on different variables such as the patient's BMI rather than the duration of therapy (12 vs 24 hours)

2) Did the authors consider evaluating various other side effects of magnesium sulphate as an outcome such as oliguria, presence or absence of deep tendon reflexes as these outcomes would be more meaningful in a clinical context

3) Did any of the studies included assess serum magnesium levels to assess whether they were in the therapeutic range or not as the duration of therapy has an implication on that

4) How many of the patients with mild preeclampsia (ie preeclampsia without severe features) were included by the studies as it is not a common practice to give magnesium sulphate for these patients

5) The study by Agarwal et al is an abstract published in the journal BJOG. It contributes significantly to the outcomes as 11 patients in the extended duration therapy had recurrent seizures compared to 6 in the reduced duration. Analysis of the reason, if any for this would be required from the full text of the article if that can be provided by the authors

Reviewer #3:

1. "PET" is not a recognized or standard acronym for pre-eclampsia. Please use alternative.

2. It is unclear how the authors arrived at 10 articles from the text. The authors begin with 3629 studies, then exclude 3342 studies. This would leave 287 articles. However, the authors only report reviewing 39 full text articles. It is clear from the diagram what happened, but not from the text. The text should be updated to clearly discuss how authors got to 39 articles.

3. Comment. The study is underpowered, but improves on methodology of other investigators.

4. We have moved terminology to reflect preeclampsia with or without severe features. The authors should update manuscript language to reflect this category language in place of "mild and severe" preeclampsia.

5. Instead of having clinicians consider shorter courses of magnesium sulfate (as mentioned in line 237) authors should focus recommendations on developing more trials to attain more evidence. This study is underpowered and cannot be the basis of recommendations.

STATISTICAL EDITOR COMMENTS:

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

General: The central problem with this study is the lack of statistical power. Although the samples are large, the adverse events are (fortunately) low and it is those counts that determine CIs and inference testing. For example, using the data from Fig 3A: Based on the usual criteria for alpha = 0.05 and power = 0.80, using the sample sizes given and the 24 hr cohort having an adverse outcome rate of 23/773, then the rate among the < 24 hr cohort would have to exceed that rate by > 2x. Put another way, in order to detect a relative risk of 1.5X, and assuming the same baseline rate etc, the needed samples would be > 6,000 in each group, or almost an order of magnitude higher than available. Had the hypothesis been formatted as a non-inferiority study, the same issue of inadequate power would happen.

Would need to further emphasize the limitations section and deemphasize generalizing the conclusion of no difference in the adverse outcome, based on these data.

EDITOR 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. Authors of systematic reviews are encouraged to prospectively register their study in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), an international database of prospectively registered systematic reviews. If you already have a PROSPERO registration number, please note it in your submitted cover letter and include it at the end of the abstract.

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 précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

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. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

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

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. Figures

Figures 1-4: Please upload as figure files on Editorial Manager.

Figure 3: Is this available in a higher resolution?

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 https://wkauthorservices.editage.com/open-access/hybrid.html.

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

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include 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 Jan 07, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason Wright, MD
Editor-in-Chief, Elect

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

January 4, 2022

Dear Dr. Wright,

Thank you for reviewing our manuscript and providing us with valuable feedback. Please find enclosed a revised copy of our manuscript titled "Duration of postpartum magnesium sulphate for the prevention of eclampsia: A Systematic Review & Meta-Analysis" (ONG-21-2192) for consideration of this revision for publication in Obstetrics & Gynecology.

Our study was registered prior to initiation with PROSPERO (registration number: CRD42020182432).

We confirm we have read the instructions for authors at**:**
(http://edmgr.ovid.com/ong/accounts/authors.pdf)

Please find below our responses to each comment raised by the reviewers.

Reviewer #1:

In this manuscript, the authors perform a systematic review and meta-analysis to address whether the duration of postpartum magnesium sulfate (24 hours versus less than 24 hours) affects the risk of eclamptic seizure. Overall, this study is intended to address a highly relevant clinical question, which is, encountered daily in routine obstetric care. Our field lacks evidence-based guidance for the duration of seizure prophylactic magnesium sulfate. The topic is appropriate for the readership of this journal.

I believe this manuscript would benefit by some clarifications throughout and enhanced discussion points which I have detailed in my comments below. Methodologically, I have some concerns about one of the studies included in the meta-analysis (see comments pertaining to Methods and Discussion).

Abstract:

Line 22-23 and 48-49 - Objective and conclusion statements should remain focused on the question addressed (risk of eclampsia). The study was not designed to directly test optimal duration over a range of treatment protocols, nor was it designed to test overall safety.

The above suggestion has been incorporated as follows:

*"**CONCLUSION:** This systematic review and meta-analysis suggests a shorter duration of postpartum magnesium sulphate does not increase the risk for eclamptic seizure, however data remains underpowered to render firm conclusions."*

Line 38 - The abstract would benefit by a definition of "shorter duration" (i.e. a range of hours).

The above suggestion has been incorporated into the abstract as follows:

"Shorter duration of magnesium sulphate (12 hours or less) was not associated with increased risk of eclampsia compared to 24 hour postpartum regimens (RD -0.01, 95% CI -0.02, 0.01, p=0.54, I^2 70%)."

Introduction:

Line 55 - The incidence of eclampsia referenced requires a denominator - it is unclear from the current wording whether the 1-2% rate of eclampsia is in women who have received MgSO4, or are pregnant vs postpartum, etc. I am unable to find this information in the referenced review article.

We apologize for the error in reference citation. We have corrected the reference cited and added further clarification. The above statement has been revised as follows:

"Eclampsia, new onset seizures,occurs in 2-3% of women with pre-eclampsia with severe features and 0-0.6% of those without severe features in the absence of magnesium sulphate.[4]"

Reference 4: Sibai BM. Magnesium sulfate prophylaxis in preeclampsia: Lessons learned from recent trials. Am J Obstet Gynecol 2004;190:1520-26.

Line 64-65 - The authors should re-word this statement to reflect that while there are recommendations and a standard of care for postpartum continuation of MgSO4, these recommendations are not based on direct clinical evidence. Also, what is the meaning of "milder PET"? It would be helpful to adhere to the commonly used terminology, e.g. preeclampsia with or without severe features, preeclampsia without eclampsia, etc. (here and throughout the document - lines 220 and 237).

The above comments have been incorporated as follows into the Introduction:

"Results from the MAGPIE trial have been extrapolated and common practice internationally for patients with pre-eclampsia /eclampsia is to infusion magnesium sulphate during labour and delivery and continued for 24 hours postpartum despite the lack of consensus on optimal duration.[1,2,3]"

Through the manuscript we have adjusted our terminology to pre-eclampsia with/without severe features.

Methods:

In general: I do not have the statistical expertise to comment in detail on the design and execution of a meta-analysis. Their description of their methodology is understandable. Their reporting is adherent to PRISMA guidelines and they included the PRISMA checklist.

I do have a concern about the assessment of bias in the included studies. In particular, I scrutinized Anjun et al (2016) "Maternal outcomes after 12 hours and 24 hours of magnesium sulfate therapy for eclampsia". In their assessment of bias for this study, the authors believe that this study was low risk for performance bias. However, the original study notes that personnel were not blinded to the treatment arm. I am confused how the authors interpreted this information and assigned low risk of performance bias to this study.

Blinding of participants and study personnel falls under the domain of performance bias. As per the Cochrane handbook, the role of blinding is more common and relevant in placebo/sham intervention trials. The primary outcome in our study was presence of eclampsia (seizure), an objective measure along with no placebo treatment group in any of the included trials. We felt this trial was low risk for performance bias as per Cochrane guidelines as participants/people delivering the intervention were aware of intervention, but there were no deviations from intended intervention, results were analysed in intention-to-treat manner and the appropriate analysis of treatment effect was performed.

Line 93 - Could the authors specify which of study populations included or excluded patients diagnosed with preeclampsia without severe features? Can they speak to the diagnostic criteria for preeclampsia and eclampsia that were used in the contributing studies?

The above suggestion has been incorporated as follows:

“One study included patients with pre-eclampsia without severe features; all other trials included women with either pre-eclampsia with severe features and/or eclampsia. Pre-eclampsia with severe features was defined as the presence of blood pressure greater than 160/110 on serial readings, altered liver/renal function, presence of pulmonary edema, myocardial infarction, stroke, unresolving headache and/or new onset visual changes.”

In addition, table 1 “population randomized column” was updated for each study to include classification of pre-eclampsia with or without severe features.

Results:

Line 145 - I would prefer to see the results show as a rate or n/denominator, rather than simply the raw number of seizure episodes. This comment also applies to the discussion section (lines 177-178).

The above suggestion has been incorporated as follows:

"The primary outcome of eclamptic seizure on magnesium sulphate was reported in all 10 studies (n=1714); where 10 women (1.2%) had seizure if exposed to less than 24 hours and 23 women (3.0%) had seizure if exposed to 24 hours postpartum magnesium sulphate (RD -0.01, 95% CI -0.02, 0.01, p=0.54, I^2 70%) (Figure 3a).

In studies that randomized after an eclamptic seizure, three (0.9%) had recurrent eclampsia in the less than 24 hours group compared to 12 (6.8%) in the 24 hour group (RD -0.04, 95% CI -0.14, 0.07; p=0.52, I^2 87%) (Figure 3c)."

Line 160 - Can the authors specify how many studies reported the secondary outcomes of interest?

The above suggestion has been incorporated as follows:

"Shorter duration of postpartum magnesium sulphate was associated with reduced duration of urinary catheter (four studies)[10,14,17,18] (mean difference -15.44 hours, 95% CI -19.97 - -10.91; p < 0.00001, I^2 98%) and time to ambulate (two studies) (mean difference -10.77 hours, 95% CI -17.24 - -4.31; p=0.001, I^2 96%).[14,15] Length of stay was reduced in all reported (four) studies with shorter duration magnesium sulphate.[10,12,17,18]"

Line 165-170 - Can the authors address whether it is typical to report secondary outcomes in a meta-analysis that were only addressed by one of the studies included in the analysis? How is this contributing new information?

We felt, as this paper is both a systematic review & meta-analysis, it was prudent to report all desired secondary outcomes even if only reported in one study.

Discussion:

The authors need to address the timing of seizure episodes with respect to whether postpartum MgSO4 had been completed. The comparison of 12 versus 24 hours of MgSO4 therapy by Anjum et al (2016) has 10 seizure episodes in the 24 hour treatment group. However, in the primary study, all 10 of those seizures occurred during the first 2 hours of therapy. Anjum et al reported zero seizures in both treatment groups following completion of MgSO4 therapy. It would be interesting to know, and essential to address, whether the seizure events described in the other studies were before or after completion of MgSO4. I would like to know why the authors of this study chose to include in their analysis those seizure episodes which occurred before completion of MgSO4 therapy.

The following was incorporated into the discussion to address this comment:

“Our primary outcome was risk of eclampsia postpartum when exposed to different durations of magnesium sulphate. In the pooled studies, they did not all specifically state if eclampsia occurred during magnesium sulphate infusion or after it’s completion; and we felt clinically the overall risk was a more relevant outcome.”

I am also interested in the authors' thoughts on the rate of eclampsia in the patient populations that were studied. Specifically, the Anjum et al (2016) 12h vs 24h study notes a 3.9% incidence of eclampsia in their total patient population, which limits generalizability of their results.

The following was added to our discussion to address the above comment:

“To attempt to achieve adequate power in this study, we included trials from both resource rich and resource limited countries. During the analysis it did highlight the underlying rates of eclampsia varied across countries, likely due to other underlying medical conditions, environmental and genetic factors, which unfortunately due to the limitations of a meta-analysis could not be explored further.”

Line 180 - The authors mention that there was one seizure in patients who were enrolled with a diagnosis of preeclampsia without eclampsia at the time of enrollment. They should specify that the seizure occurred in the experimental group (<24 hours of MgSO4) and that there were zero seizures in the control group (24 hours of MgSO4).

The above statement has been revised as follows:

“In studies of women with pre-eclampsia only, one patient had a seizure in the shorter duration group; while in studies randomizing those who had eclampsia, there were recurrent seizures in both experimental groups.”

Line 183 - "hospitalization rates" should be "duration of hospital stay".

The above statement has been revised as follows:

“In addition, shorter magnesium sulphate was also associated with potential maternal benefits, such as reduced duration of urinary catheter, increased mobilization and reduced duration of hospital stay.”

Line 184-186 - I disagree with the authors' interpretation of the cited guidelines and encourage them to review in order to adjust their general summarization. For patients with preeclampsia without severe features, the guidelines acknowledge controversy/lack of clarity regarding the need for MgSO4 for seizure prophylaxis

and, in the case of the ACOG guidelines, allow for clinical decision-making based on patient and local resources/systemic factors.

The above comment has been incorporated as follows into our discussion:

"Obstetrical guidelines advocate for postpartum magnesium sulphate in women with pre-eclampsia with severe features/eclampsia as seizure prophylaxis.[1,2,3] No consensus exists for its routine use in pre-eclampsia without severe features and it is left to individual clinicians to decide. In all populations, guidelines acknowledge to lack of evidence for duration of postpartum magnesium sulphate and recommend 24 hours.[1,2,3]"

Line 188-191 & Conclusion section - I am confused how the authors reached this conclusion based on their analysis. First, their study is underpowered to detect the primary outcome, so I do not think it is reasonable to suggest a change in clinical practice based on their results. Also, Figure 3B shows that patients with preeclampsia and without eclampsia at the time of enrollment had 0 seizure episodes out of 492 patients in the 24h treatment group, and 1 seizure episode out of 529 patients in the <24h treatment group. Although not statistically powered to demonstrate a difference, these data are not reassuring in the <24h treatment group, and do not support a chance in clinical practice.

The above comment has been incorporated as follows into our discussion:

"Our data remains underpowered to conclude if shorter duration of postpartum magnesium sulphate is associated with increased risk for eclampsia; while it is associated with maternal benefits, including reduced duration of urinary catheter, increased mobilization and duration of hospital stay."

Line 195-206 - The authors need to more clearly delineate what is unique about this manuscript. They have provided a comparison of the included studies between their meta-analysis and those already published, but it is not clear to me how these methodological differences have translated to a robust/unique contribution to the published literature.

The following paragraphs have been edited to incorporate the above comment into our discussion:

"Strengths of our study include the largest number of identified trials, no evidence of publication bias, trials from both resource rich and resource limited countries and the inclusion of trials including women with either pre-eclampsia and/or eclampsia. Patients in the selected papers had both pre-eclampsia with or without severe features; as the definitions varied across studies, and we hoped to capture all women with pre-eclampsia. We had hoped with our broad inclusion criteria to obtain statistical power to determine the optimal duration of postpartum magnesium sulphate. Our analysis differentiated between those with pre-eclampsia with severe features and those who had an eclamptic seizure as indication for magnesium sulphate, an outcome which has not previously been

reported. For studies with ambiguity in the methods, we contacted authors to ensure studies met our inclusion criteria. We also excluded trials at high risk for bias based on their published methodology.

Limitations of this study include despite the large number of trials, given the rarity of eclampsia; a power calculation using a 1% incidence of eclampsia, demonstrated over 9000 women would be required to demonstrate a 50% reduction in seizure with magnesium sulphate.[22] With all identified studies, our population was still only 1714; therefore we remain underpowered to truly identify if shorter duration magnesium sulphate is associated with a reduction in seizure activity. Similar, the heterogeneity across studies was high at 71%, limiting the generalizability of these findings. To attempt to achieve adequate power in this study, we included trials from both resource rich and resource limited countries. During the analysis it did highlight the underlying rates of eclampsia varied across countries, likely due to other underlying medical conditions, environmental and genetic factors, which unfortunately due to the limitations of a meta-analysis could not be explored further. Lastly, it remained challenging to capture duration of magnesium sulphate prior to delivery. Therefore we were unable to assess if duration of magnesium sulphate prior to delivery plays a role in rate of postpartum eclampsia."

Reviewer #2:

The paper examines the duration of postpartum magnesium sulfate for the prevention of eclampsia. The authors included 10 studies (n=1714) in their meta-analysis and subsequently showed no increased risk for postpartum seizures with a shorter duration of MgSO4. The study is important in the context of changing an established clinical practice to use a shorter duration of magnesium sulfate in the post-partum period, which in turn is likely to improve patient safety and reduce the adverse effects without increasing the risk of recurrent seizures. The authors describe the search strategy and the inclusion criteria clearly. Please find my comments on reviewing the article here:

1) In the study by Anjum et al which has been included in the analysis of the incidence of seizure if exposed to less than 24 hours vs 24 hours(145-152) .On going through the study 10 patients had convulsions within the first 2 hours of instituting therapy in the 24 hour group and they required a 2 gram loading dose of magnesium sulphate. The primary outcome of this study was the recurrence of seizures after completion of therapy. Therefore this incidence of a seizure 2 hours into the treatment has not been considered by the authors in their outcomes and could be due to requirement of different dosing based on different variables such as the patient's BMI rather than the duration of therapy (12 vs 24 hours)

Respectfully, we disagree with the reviewers' interpretation of our primary outcome. As stated in the methods section, our primary outcome was rate of eclampsia in those exposed to less than 24 hours compared 24 hours of postpartum magnesium sulphate. Our

outcome was not rate of eclampsia after the completion of therapy, but rather simply rate of eclampsia overall in each time group. This was chosen as our primary outcome as clinically we are concerned with preventing eclampsia overall, rather than simply preventing eclampsia after completion of magnesium sulphate.

The following was incorporated into the discussion to address this comment:

"Our primary outcome was risk of eclampsia postpartum when exposed to different durations of magnesium sulphate. In the pooled studies, they did not all specifically state if eclampsia occurred during magnesium sulphate infusion or after it's completion; and we felt clinically the overall risk was a more relevant outcome."

2) Did the authors consider evaluating various other side effects of magnesium sulphate as an outcome such as oliguria, presence or absence of deep tendon reflexes as these outcomes would be more meaningful in a clinical context

Yes, we agree, we would have liked to report on these other side-effect/complications of magnesium sulphate. These variables unfortunately were not reported in any of the included studies and therefore not available to be included in the meta-analysis.

3) Did any of the studies included assess serum magnesium levels to assess whether they were in the therapeutic range or not as the duration of therapy has an implication on that

Only one study (Agarwal et al) measured serum magnesium levels, and they unfortunately did not report the levels. Therefore we were unable to comment in our systematic review/meta-analysis regarding the serum concentration of magnesium in the various durations of postpartum magnesium sulphate.

The following was added to the results section to address this comment:

"No studies reported serum magnesium levels."

4) How many of the patients with mild preeclampsia (ie preeclampsia without severe features) were included by the studies as it is not a common practice to give magnesium sulphate for these patients

We elected to include all studies evaluation both pre-eclampsia with or without severe features as management is varied in different countries in terms of use of magnesium sulphate. The ACOG guideline also highlights the use of magnesium sulphate in those without severe features is left to the decision of individual practitioners and local resources. Therefore we wanted to increase the generalizability of our study by including all patients, rather than limiting to only those with severe features.

The above suggestion has been incorporated as follows:

“One study included patients with pre-eclampsia without severe features; all other trials included women with either pre-eclampsia with severe features and/or eclampsia.”

We have also added in the results section, one further analysis of those trials including only pre-eclampsia with severe features.

“Similarly, in studies including only women with pre-eclampsia with severe features, one had eclamptic seizure in the less than 24 hours group compared to none in 24 hours (RD 0, 95% CI -0.01, 0.01, I^2 0%).”

5) The study by Agarwal et al is an abstract published in the journal BJOG. It contributes significantly to the outcomes as 11 patients in the extended duration therapy had recurrent seizures compared to 6 in the reduced duration. Analysis of the reason, if any for this would be required from the full text of the article if that can be provided by the authors

Unfortunately, the published abstract by A Agarwal et al did not lead to a full article publication. In addition, we attempted to contact the author without success.

In this systematic review/meta-analysis, we included published abstract data that met our inclusion criteria. There is a growing body of evidence advocating for inclusion of conference abstracts in this type of review, especially if evidence is sparse as is the case for studies evaluating duration of postpartum magnesium sulphate.

Scherer RW & Saldanha IJ. How should systematic reviews handle conference abstracts? A view from the trenches. Syst Rev 2019; 8. doi: https://doi.org/10.1186/s13643-019-1188-0.

Reviewer #3:

1. "PET" is not a recognized or standard acronym for pre-eclampsia. Please use alternative.

Throughout the manuscript the abbreviation PET has been corrected to pre-eclampsia as there is no other standard accepted abbreviation.

2. It is unclear how the authors arrived at 10 articles from the text. The authors begin with 3629 studies, then exclude 3342 studies. This would leave 287 articles. However, the authors only report reviewing 39 full text articles. It is clear from the diagram what happened, but not from the text. The text should be updated to clearly discuss how authors got to 39 articles.

Figure 1 is the PRISMA flow diagram outlining the process of selected articles. The initial search strategy identified 3629 articles (3381 after removal of duplicates as

multiple databases had been searched). After the initial screen/abstract review 3342 records were excluded, as they did not meet inclusion criteria. 39 articles as outline in the flow diagram; had full text review and ultimately 10 met criteria for inclusion in this meta-analysis.

To clarify the above process; the following was added to the PRISMA flow diagram; *Records excluded at title/abstract review (n=3342).*

3. Comment. The study is underpowered, but improves on methodology of other investigators.

4. We have moved terminology to reflect preeclampsia with or without severe features. The authors should update manuscript language to reflect this category language in place of "mild and severe" preeclampsia.

We have corrected terminology throughout the manuscript to include pre-eclampsia with or without severe features to address the above comment.

5. Instead of having clinicians consider shorter courses of magnesium sulfate (as mentioned in line 237) authors should focus recommendations on developing more trials to attain more evidence. This study is underpowered and cannot be the basis of recommendations.

The above comment has been incorporated as follows into our discussion/conclusion:

"Our data remains underpowered to conclude if shorter duration of postpartum magnesium sulphate is associated with increased risk for eclampsia; while it is associated with maternal benefits, including reduced duration of urinary catheter, increased mobilization and duration of hospital stay."

"*This systematic review/meta-analysis found shorter duration postpartum magnesium sulphate did not increase the risk for eclampsia although data showed significant heterogeneity and remains underpowered to make firm conclusions. A well-designed international adequately powered clinical trial remains needed to determine the optimal duration of magnesium sulphate in women with pre-eclampsia and/or eclampsia."*

STATISTICAL EDITOR COMMENTS:

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

General: The central problem with this study is the lack of statistical power. Although the samples are large, the adverse events are (fortunately) low and it is those counts that determine CIs and inference testing. For example, using the data from Fig 3A: Based on the usual criteria for alpha = 0.05 and power = 0.80, using the sample sizes given and the 24 hr cohort having an adverse outcome rate of

23/773, then the rate among the < 24 hr cohort would have to exceed that rate by > 2x. Put another way, in order to detect a relative risk of 1.5X, and assuming the same baseline rate etc, the needed samples would be > 6,000 in each group, or almost an order of magnitude higher than available. Had the hypothesis been formatted as a non-inferiority study, the same issue of inadequate power would happen.

Would need to further emphasize the limitations section and deemphasize generalizing the conclusion of no difference in the adverse outcome, based on these data.

The above comments were incorporated in the manuscript and the conclusion statement edited to as follows:

"*This systematic review/meta-analysis found shorter duration postpartum magnesium sulphate did not increase the risk for eclampsia although data showed significant heterogeneity and remains underpowered to make firm conclusions. A well-designed international adequately powered clinical trial remains needed to determine the optimal duration of magnesium sulphate in women with pre-eclampsia and/or eclampsia."*

EDITOR 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.

We OPT-IN to publication of our 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.**

The above criteria have been added to the revised manuscript.

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.

The eCTA forms have been completed by all authors.

4. Authors of systematic reviews are encouraged to prospectively register their study in PROSPERO (https://www.crd.york.ac.uk/PROSPERO/), an international database of prospectively registered systematic reviews. If you already have a PROSPERO registration number, please note it in your submitted cover letter and include it at the end of the abstract.

Our study was registered with PROSPERO (registration number: CRD42020182432), and the registration number has been included both in the cover letter and at the completion of the abstract.

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.

Standard definitions as listed in revitalize have been used throughout our manuscript.

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.

Our manuscript meets the above-mentioned word count.

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 précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

The précis has been formatted to ensure it meets the above-mentioned criteria.

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.

The abstract included in this manuscript has been edited to meet the above-mentioned criteria and word count.

10. Only standard abbreviations and acronyms are allowed. A selected list is available online athttp://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.

Throughout the manuscript, only standard abbreviations have been used. MgSO4 has been corrected to magnesium sulphate; and PET has been corrected to pre-eclampsia.

11. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

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

The above recommendations regarding data presentation have been incorporated.

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.

The Table 1 has been reformatted to ensure it meets the journal’s Table checklist criteria.

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 athttps://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.

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The reference list has been reformatted to ensure it meets the above-mentioned suggestions.

14. Figures

Figures 1-4: Please upload as figure files on Editorial Manager.

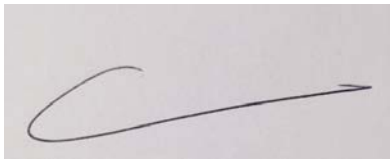
Figure 3: Is this available in a higher resolution?

Figure 3 has been exported from RevMan at the highest resolution.

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 athttps://wkauthorservices.editage.com/open-access/hybrid.html.

Thank you again for the feedback on our previous draft. Please consider our revised paper incorporating these suggestions for publication in your journal.

Sincerely,



Christopher Nash MD, MSc, FRCSC