OBSTETRICS & GYNECOLOGY

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

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

Personal or nonessential information may be redacted at the editor's discretion.

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

Date: Jul 17, 2020
To: "Kathleen Brookfield" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-1643

RE: Manuscript Number ONG-20-1643

A randomized trial of an alternate dosing protocol for magnesium sulfate in obese preeclamptic women

Dear Dr. Brookfield:

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).

Due to the COVID-19 pandemic, your paper will be maintained in active status for 30 days from the date of this letter. If we have not heard from you by Aug 16, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Thank you for the opportunity to review your work. Authors examined 2 Mg dosing regiments for women with preE to determine sub-therapeutic values in an RTC.

I have the following questions:

1. Dosing regiments
a. Please explain why chose 1g/hr. maintenance dose. I understand that it is institutional standard as stated in methods but why so? Most places use 2 g/hour with exceptions of impaired renal function, and they do not adjust dosing for obesity. It is no surprise that patients in this arm were not therapeutic. For example, study from ref 19 studied 4/2 regiment and found that many obese women were subtherapeutic and look longer to become therapeutic. Backtracking to 4/1 regimen makes this study less generalizable.

Same question echoes to the limitations part of the discussion. From the reader's perspective, one of the limitations is that 4/1 dosing regimen is not used in most institutions. That makes this study less generalizable. To me, it seemed that authors wanted to dis-prove an institutional practice which they did not agree with, which would have been a great idea if most other hospitals were using the same policy. It seems like what is the point of the study to disprove a practice that very few are engaged in? Please explain/expand.

b. If many women in 6/2 group were still subtherapeutic, would it be of use to consider alternative dosing such as 6/2.5 or 6/3? Our maybe 2 loading doses (like 4g then 4g/hr., then 3g/hr., then 2/g changing every hour on the hour)? That would be a very interesting research question, esp. in the setting of uncertainty of lower cut off point for therapeutic levels.
c. What do you think is the balance in dosing of % subtherapeutic vs. toxicity? If we keep increasing dosing regiments, at what point will concerns with toxicity will become a problem?

2. PK of Magnesium in obesity
a. For ease of understanding and readability, it might help to review basic PK in the setting of Mg use, such as obese women have greater volume of distribution, etc. Is it known how adipose tissue alters PK of Mg? Is it stored in it (like anesthesia meds) so that it takes long her to clear it out hence affecting maintenance dose? I would then tie those concepts to implications (i.e If higher BMI means that it takes longer to reach therapeutic levels, then giving higher loading dose means that therapeutic levels will be reached sooner; toxicity concerns etc.).
b. What was the rationale behind checking Mg levels at 1 hr., 4 hours and at the time of delivery vs. at other time

intervals?
3. Sample size
a. lines 159-161. Please summarize findings of these studies and how it lead to your N calculation of 80% subtherapeutic in 4/1 group and 35% in 6/2 so that reader would not have to pull those articles to be able to follow.
b. What would significant % difference be based on 80% power? it is not specified in lines 172-173.
c. Secondary outcomes: why was P value of 0.01 chosen instead of 0.05?
d. Primary outcome: why was 4 hours chosen over 1 hour and time of delivery?

4. Clinician discretion
a. Did any of the women receive additional boluses? Was it up to clinicians to readjust maintenance dose? In other words, was this regimen controlled at the time of randomization only and then mag dosing was left up to the clinicians to adjust and manage?
b. Did any of the women with pre-eclampsia without severe features get magnesium? Was severe criteria eligibility verified by study staff or was it left up to the clinicians?
5. Results
a. Line 187. Why did the on patient receive loading dose only and no maintenance?
b. Lines 196-197. Sample size prediction was based on assumption that 4/1 group would be subtherapeutic 80% of the time, while your study found that 100% of them were; likewise, 6/2 group was predicted to be 35% subtherapeutic yet 37% of them were therapeutic in your study. That is a very close estimate! Speaks to good data you relied on while calculating N.
c. Line 212. Highest level mentioned-which group was this? Was there a cluster of higher MG levels in 6/2 group?
d. Lines 229-243. Discussion of using lower Mg levels to be considered therapeutic. 4.8-8.4 vs. 3.6. 95/31% vs. 37/0 % seems like a very big difference is quite striking. It might help to emphasize that no matter what therapeutic cut off you use (assume due to lack of consensus, but if there is consensus, please explain), 6/2 is superior to 4/1 in that paragraph.

Reviewer #2: This manuscript describes a randomized control trial performed to compare 2 standard magnesium dosing regimens for obese women with severe preeclampsia, and evaluate which more frequently led to a serum magnesium level in the desired therapeutic range to avoid eclamptic seizures. As a secondary measure, they compare undesirable side effects between dosing regimens. Their primary finding is that the higher dosing schedule more frequently reaches desired therapeutic target, without an increase in adverse effects. As such, this is an important finding for the field of obstetrics. The results of this study are therefore worthy of publication.

As a premise for their study, the authors cite very compelling pharmacokinetic data which suggest that maternal body weight influences serum magnesium level independent of renal function, and suggest that alternate dosing structures may be required for obese women.

The authors are very clear and specific in their report of their research question, and desired outcome variables. They sought specifically to evaluate serum levels, and secondarily maternal side effects and neonatal outcomes. By doing this, they were able to keep their sample size low to facilitate their RCT. The RCT, as conducted, then is rigorous with appropriate methodology and statistical analysis. Their convenience strategy of randomizing women before they actually met criteria for severe features was acceptable based on the fact that the groups were ultimately relatively even for eventual ruling in.

However, in several very specific ways, their study design limits the clinical utility of their outcomes and concern me that clinicians will use this data inappropriately. I would expand the limitations section of the discussion to better address these issues:

1. The data they cite regarding therapeutic levels of magnesium required to avoid eclamptic seizure is from 1955 and 1957, which was upheld in 1981. The authors use this therapeutic window, but point out that this therapeutic window must be flawed in some ways, as so many women fail to meet this target but do not experience eclamptic seizures. (They even assumed as part of their research design that 80% of obese women would be subtherapeutic on standard dosing). The manuscript they cite, the Du manuscript, reports modeled predicted eclampsia rates at varied magnesium levels using different dosing regimens. However, it is not clear that precise magnesium therapeutic level required to avoid a seizure is actually accurate. The discussion of magnesium utility to avoid seizures in lines 254-265 focuses on the threshold to seize among obese patients. But it does NOT discuss that thus far, there has been no evidence that obese women seize more often due to under-dosing of magnesium. They admit their sample size is too small to evaluate for undesirable side effects. When applied to a population level, it is possible that higher dosing of magnesium may incur risk without additional seizure-reducing benefit in the name of meeting a flawed serum target.

2. All obesity is not the same. The authors point out that they used a BMI cut off of 35, and simply qualify women as "obese." A figure demonstrating deceasing serum magnesium levels with increasing BMI would go a long way convincing the reader that BMI works on serum magnesium levels in the way the authors claim. In truth, a prospective cohort study of therapeutic levels across all BMIs would be better at evaluating appropriate dosing strategy. This could help identify a specific inflection point when dosing should be altered. Perhaps magnesium should be dosed as mg/kg. As the authors point out in another limitation, a cohort study could eliminate the questions of race and metabolism. It could also identify whether eclamptic seizures were avoided at specific thresholds in a contemporary cohort. This should be at least proposed

in the manuscript as an area for future study.

The discussion of the manuscript should be altered with these qualifiers and ideally a new figure. I also recommend removing the final sentence, the suggestion that higher dosing should be considered in obese preeclamptic women, as this data is as yet insufficient to demonstrate that this is clinically necessary. This manuscript is more of a foundational than definitive work for this practice.

Reviewer #3: This manuscript is a prospective, randomized study evaluating serum Mg levels in obese patients on two different regimens of IV MgSO4 for preeclampsia with severe features. It is unclear why this higher regimen was chosen as it has already been shown not to achieve therapeutic magnesium levels for 61% of obese patients in prior references. Please comment.
Abstract
The aim of the study was to compare two regimens of magnesium sulfate infusion by assessing serum levels of magnesium in obese patients. Otherwise, the abstract is adequate.
Methods
Current recommendations are to use 4-6 g bolus followed by 1-2 grams per hour. Please comment.
Efficacy levels for seizure prophylaxis have not been established making it unclear if differences in these regimens clinically matter. The same applies to "therapeutic" levels of magnesium. Please comment.
The benefit of MgSO4 in seizure prophylaxis in developed countries has been questioned. Please comment.
Please expand on why a BMI>35 was used, as prior quoted studies (and the definition of obesity) used BMI>30.
Were there more magnesium samples drawn, other than at 0, 1, 4 hrs and delivery? The mean labor length for patients receiving the higher dose regimen was 22 hours. Were there no additional magnesium levels drawn during the remaining 18 hrs of labor? Please comment.
Why was the level at 4 hrs used for comparison? vs assessing for therapeutic level of magnesium at any predelivery point.
What is the protocol for a subtherapeutic magnesium level? It seems like there is no response to a subtherapeutic magnesium level. Please comment.
Results
While not powered for maternal side effects, the results mention no noted difference in same. There is an approximate 2x higher rate of nausea and an elevated rate of flushing in the higher dose group.
Also, the median labor time of 14.7 vs 22 hours strongly suggests an inadequate sample to evaluate the differing regimens on labor length.
As the magnesium levels in the higher dose group increased over 20% between 4 h and delivery, does this suggest patients are on an increasing slope of magnesium levels that could lead to supratherapeutic levels if labor lasted longer. Please comment.
The reader would be helped by knowing the particular severe features presented in these groups and whether it varied between them. While creatinine is reported, all normal, it would appear your population was not at substantial risk of low intravascular volume. Please comment.
Discussion
Adequate summary but no discussion about the relationship of therapeutic levels to seizure prevention.

This manuscript evaluated magnesium levels in obese (class 2 obesity and higher) preeclamptic patients with normal creatinine levels given one of two regimens of magnesium sulfate. Both regimens fall within the current ACOG recommendations for this clinical group. While it is not surprising that higher doses yield higher serum levels of magnesium, the clinical importance of this remains unclear as the study was not powered for the outcome of eclampsia.

STATISTICAL EDITOR COMMENTS:

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

Abstract: Need to conform to our template for RCTs. Specifically, need to concisely explain rationale for power/sample size calculation.

lines 62-65: The sample sizes were modest and under powered to discern differences in maternal or neonatal outcomes nor in side effects.

Table 1: Since the groups were randomized, there is no need to statistically test for group differences. Any difference is thought to be due to random chance, so eliminate the column of p-values.

lines 52-55, 168-174 and Table 2: There is only one primary outcome, the proportion having a sub-therapeutic level at 4 hrs, with a posited difference of 80% vs 35%.. That should be stated separately from the others, which are secondary outcomes. The proportions having therapeutic levels should include the point estimates along with CIs and a footnote explaining the stats significance. Also, Table 2 cites the primary outcome as the % having therapeutic level, so should clarify whether the primary was the % achieving vs not achieving a specified level. That is the proportions not achieving therapeutic levels were: 18/18 = 100% (59-100%) vs 12/19 = 63%(33-100%), with $p < 0.001$ by Fisher's test.

Table 3: The counts are low and there is low power to discern differences, so the NS findings cannot be generalized. Each

group had N = 19 or 20, so the n(%) format should round the %s to nearest integer %, not cite to 0.1% precision.

Associate Editor: We are happy to consider a revised version of your manuscript but are asking that it be formatted as a Research Letter. In your revision, please tone down the "should be used" language. What constitutes a therapuetic concentration of magnesium has not been rigorously evaluated and you do not show differences in clinical outcomes. Finally, I found many of your references to not really be on point re: magnesium concentration vis. a vis. dosing. Please carefully review your references with an eye to direct relevance and remove as appropriate.

EDITOR COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter. 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. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page. As of 7/17/20, Dr. Caughey hasn't filled out the form.

3. For studies that report on the topic of race, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes).

Use "Black" and "White" (capitalized) when used to refer to racial categories.

The category of "Other" is a grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

4. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

In addition, please use only the major headings outlined in our Instructions for Authors for Original Research and delete any subheadings. In the Abstract: Objective, Methods, Results, Conclusion; and in the body text: Introduction, Methods, Results, Discussion.

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: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

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).

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

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

9. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

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.

Please expand "PK" to read, "pharmacokinetic" throughout the manuscript.

11. Please reword the phrase, "obese preeclamptic women" to read, "obese women with preeclampsia."

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. 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.

Figure 1: Please confirm n values (those allocated to each group do not add up to those randomized [31+35=66]).

14. 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.

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

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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 in a word processing format such as Microsoft Word. 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.

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 30 days from the date of this letter. If we have not heard from you by Aug 16, 2020, we will assume you wish to withdraw the manuscript from further consideration..

Sincerely,

The Editors of Obstetrics & Gynecology

2019 IMPACT FACTOR: 5.524

2019 IMPACT FACTOR RANKING: 6th out of 82 ob/gyn journals

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August 10, 2020

To the Editor:

Thank you for reconsideration of publication of the enclosed manuscript entitled, "A randomized trial of an alternate dosing protocol for magnesium sulfate in obese preeclamptic women," which sought to prospectively validate existing PK data and retrospective studies that have addressed this issue. Multiple revisions have been made to the manuscript in an attempt to address all of the reviewers' concerns and comments. Additionally, it is noted that the Associate Editor would have preferred a manuscript in a Research Letter format. The authors were not able to condense the manuscript to 600 words while addressing the multiple comments from the other reviewers, and we would ask that the editors reconsider publication in the form of an Original Research paper.

As previously noted, the study was approved by the Oregon Health & Science University Institutional Review Board and the trial was registered at ClinicalTrials.gov (NCT02835339) prior to enrollment. This study was presented, in part, as an oral presentation at the Society for Maternal Fetal Medicine 40th Annual Meeting. Grapevine, TX. February 2020.

The lead author (Kathleen Brookfield, M.D., Ph.D.) 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.

The authors have submitted solely to Obstetrics & Gynecology. The manuscript is not under review with another journal and will not be submitted

elsewhere until a decision is rendered.

Please see the point-by-point responses to the reviewers below and please do not hesitate to contact me with any questions or concerns.

Sincerely,

Kathleen F. Brookfield, M.D., Ph.D., M.P.H.

Assistant Professor

Obstetrics & Gynecology

Oregon Health & Science University

RE: Manuscript Number ONG-20-1643

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Dear Dr. Brookfield:

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REVIEWER COMMENTS:

Reviewer #1: Thank you for the opportunity to review your work. Authors examined 2 Mg dosing regiments for women with preE to determine sub-therapeutic values in an RTC.

I have the following questions:

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a. Please explain why chose 1g/hr. maintenance dose. I understand that it is institutional standard as stated in methods but why so? Most places use 2 g/hour with exceptions of impaired renal function, and they do not adjust dosing for obesity. It is no surprise that patients in this arm were not therapeutic. For example, study from ref 19 studied 4/2 regiment and found that many obese women were subtherapeutic and look longer to become therapeutic. Backtracking to 4/1 regimen makes this study less generalizable.

Same question echoes to the limitations part of the discussion. From the reader's perspective, one of the limitations is that 4/1 dosing regimen is not used in most institutions. That makes this study less generalizable. To me, it seemed that authors wanted to dis-prove an institutional practice which they did not agree with, which would have been a great idea if most other hospitals were using the same policy. It seems like what is the point of the study to disprove a practice that very few are engaged in? Please explain/expand.

Response: The use of magnesium sulfate 4/1 is based on the Magpie trial, (now reference #25) While magnesium sulfate regimens worldwide and within the United States are quite variable, the authors involved with this manuscript have utilized the original 4/1 Zuspan regimen at OHSU and UCSF. OHSU was the only institution in the U.S. that participated in the Magpie trial, and the authors acknowledge that many other institutions in the U.S. use other regimens, however, anecdotally, the 4/1 regimen is in use at other centers in the U.S. as well. Internationally, regimens utilized are also quite variable. In a 2017 WHO multi-country survey of 147 health facilities across 15 countries in Latin America, Africa and Asia, 25% of facilities used the standard Zuspan regimen and 7% used the standard Pritchard regimen; but most countries used variations of either regimen. Ref: Long Q, Oladapo OT, Leathersich S, Vogel JP, Carroli G, Lumbiganon P, et al. Clinical practice patterns on the use of magnesium sulphate for treatment of pre-eclampsia and eclampsia: a multi-country survey. BJOG 2017;124(12):1883-90. (Ref #31) The authors certainly appreciate that variations of the Zuspan regimen are common, but this only furthers our point that with the changing face of obesity in the U.S., there is a growing segment of the population that may benefit from an alternate regimen. Still, we have included a statement about this in the discussion and acknowledge this may limit generalizability.

b. If many women in 6/2 group were still subtherapeutic, would it be of use to consider alternative dosing such as 6/2.5 or 6/3? Our maybe 2 loading doses (like 4g then 4g/hr., then 3g/hr., then 2/g changing every hour on the hour)? That would be a very interesting research question, esp. in the setting of uncertainty of lower cut off point for therapeutic levels.

Response: Thank you for this comment. A dosing regimen of 6/3 may well result in a greater proportion of “therapeutic” levels and therapeutic levels achieved in a shorter time period, however, previous modeling work has suggested that regimens that include a maintenance dose of 3g/hr have a greater potential to reach supratherapeutic levels. (Ref Du et al #20). Of note, we did not previously simulate the exact regimens suggested above. Due to this potential safety issue, and the fact that the 6/2 regimen is a widely utilized regimen for neuroprotection in the United States, we chose the 6/2 regimen as the alternate dosing regimen for this trial. The reviewer’s point is well-taken though, that perhaps for a subset of superobese women with normal renal function, increased dosing might be tolerated and result in a greater proportion of therapeutic women.

c. What do you think is the balance in dosing of % subtherapeutic vs. toxicity? If we keep increasing dosing regiments, at what point will concerns with toxicity will become a problem?

Response: Simulation studies of different magnesium sulfate regimens suggest that AUC, which is achieved with various loading and maintenance doses over time, plays a crucial role in achieving the serum magnesium levels that have been associated with toxicity. The authors' opinions are that avoiding toxicity (0%) should be the most important factor to consider in the effort to individualize dosing protocols as multiple studies suggest the traditionally cited "therapeutic level" of 4.8 mg/dL may not be necessary to prevent eclamptic seizures. Our prior research, as noted in Refs 17 and 18 (Du et al studies), suggests even when women with a higher body weight are administered intravenous magnesium sulfate in doses greater than 6g loading over 20 minutes and 3g/hr maintenance, they approach a supratherapeutic level associated with magnesium toxicity. This was a factor that was considered when choosing the alternate dosing regimen for the study. The reviewer's point is well-taken though that there is not a "one-size-fits-all" balance that can be applied to every woman administered magnesium sulfate.

2. PK of Magnesium in obesity

a. For ease of understanding and readability, it might help to review basic PK in the setting of Mg use, such as obese women have greater volume of distribution, etc. Is it known how adipose tissue alters PK of Mg? Is it stored in it (like anesthesia meds) so that it takes long her to clear it out hence affecting maintenance dose? I would then tie those concepts to implications (i.e If higher BMI means that it takes longer to reach therapeutic levels, then giving higher loading dose means that therapeutic levels will be reached sooner; toxicity concerns etc.).

Response: For the sake of keeping the manuscript succinct, we have added one summary sentence in the introduction regarding determinants of magnesium PK. Elimination of magnesium is through renal excretion. The reviewer makes an excellent point, however, that we are making an assumption when we administer magnesium sulfate and measure serum magnesium, that this truly reflects what we are trying to measure. We do not know if magnesium measured in adipose, CSF, other tissues, etc. may give more useful data regarding seizure thresholds.

b. What was the rationale behind checking Mg levels at 1 hr., 4 hours and at the time of delivery vs. at other time intervals?

Response: The time points of 1 and 4 hours are common in the PK literature to demonstrate the steepest slope of the concentration-time curve in ascent to steady state. In our previous PK modeling, 4 hours was the time point when most average weight women reached a serum magnesium level of around 4.8 mg/dL. Time of delivery was chosen as another time point so that there would be some variation in the timing of when the additional samples were collected, and with the thought that the majority of eclamptic seizures occur in the antepartum/intrapartum time period, hence this would be the time frame when achieving therapeutic serum levels would be of the most importance. While not the aim of the study, data was collected in a fashion that could potentially yield a magnesium PK model specifically for women with obesity.

3. Sample size

a. lines 159-161. Please summarize findings of these studies and how it lead to your N calculation of 80% subtherapeutic in 4/1 group and 35% in 6/2 so that reader would not have to pull those articles to be able to follow.

Response:
A more complete summary is now included in the methods.

b. What would significant % difference be based on 80% power? it is not specified in lines 172-173.

Response: The power calculation assumed a two sided confidence interval of 95%, with a risk ratio of >2.

c. Secondary outcomes: why was P value of 0.01 chosen instead of 0.05?

Response: Although the main secondary outcome in the study was proportion therapeutic at delivery, we did assess multiple neonatal outcomes as well and sought to adjust for these multiple comparisons.

d. Primary outcome: why was 4 hours chosen over 1 hour and time of delivery?

Response: In our previous PK modeling, 4 hours was the time point when most average weight women reached a serum magnesium level of around 4.8 mg/dL, albeit with a dosing regimen of 4/2. (Ref #16) Additionally, 4 hours was one of the reported time points retrospectively assessed in the Tudela et al study utilized in sample size estimates. (Ref #19)

4. Clinician discretion

a. Did any of the women receive additional boluses? Was it up to clinicians to readjust maintenance dose? In other words, was this regimen controlled at the time of randomization only and then mag dosing was left up to the clinicians to adjust and manage?

Response: Women were administered the study drug per protocol with the exception of the single patient who received a 4g IV bolus only and no maintenance dose. The maintenance dose was not administered due to the clinician's decision to hold the maintenance dose for a patient with a creatinine of 1.1 mg/dL. We did leave it up to the clinician's discretion to alter dosing, but in practice, the patient just mentioned is the only participant who did not complete the assigned protocol.

b. Did any of the women with pre-eclampsia without severe features get magnesium? Was severe criteria eligibility verified by study staff or was it left up to the clinicians?

Response: Women without severe features of preeclampsia do not receive magnesium sulfate at OHSU. Eligibility was only verified in the sense that study staff confirmed with the treating clinician they had made a diagnosis of preeclampsia with severe features and intended to treat with magnesium sulfate, and that patients did not meet exclusion criteria for the study. We have added the severe features experienced to Table 1.

5. Results

a. Line 187. Why did the on patient receive loading dose only and no maintenance?

Response: The maintenance dose was not administered due to the clinician's decision to hold the maintenance dose for a patient with a creatinine of 1.1 mg/dL.

b. Lines 196-197. Sample size prediction was based on assumption that 4/1 group would be subtherapeutic 80% of the time, while your study found that 100% of them were; likewise, 6/2 group was predicted to be 35% subtherapeutic yet 37% of them were therapeutic in your study. That is a very close estimate! Speaks to good data you relied on while calculating N.

Response: Thank you for this comment. We agree that without the prior published retrospective data and PK modeling, it would have been difficult to predict these proportions, and still, we underestimated the proportion who would be subtherapeutic at the 4 hour mark.

c. Line 212. Highest level mentioned-which group was this? Was there a cluster of higher MG levels in 6/2 group?

Response: The highest level of 7.4 mg/dL was in a woman who received the 6/2 regimen. Although no women were supratherapeutic, the highest levels were clustered in women who received the 6/2 regimen, as expected. There was not visually a "cluster" of higher levels for women with BMI closer to 35 when examining a plot of the data at the four hour mark, but the sample size is notably not large enough to examine meaningfully stratified by BMI.

d. Lines 229-243. Discussion of using lower Mg levels to be considered therapeutic. 4.8-8.4 vs. 3.6. 95/31% vs. 37/0 % seems like a very big difference is quite striking. It might help to emphasize that no matter what therapeutic cut off you use (assume due to lack of consensus, but if there is consensus, please explain), 6/2 is superior to 4/1 in that paragraph.

Response: Thank you for this comment. We agree that there is no consensus about the true therapeutic level and that whichever level is used, the 6/2 regimen is more likely to achieve that target. This has been added to line 243.

Reviewer #2: This manuscript describes a randomized control trial performed to compare 2 standard magnesium dosing regimens for obese women with severe preeclampsia, and evaluate which more frequently led to a serum magnesium level in the desired therapeutic range to avoid eclamptic seizures. As a secondary measure, they compare undesirable side effects between dosing regimens. Their primary finding is that the higher dosing schedule more frequently reaches desired therapeutic target, without an increase in adverse effects. As such, this is an important finding for the field of obstetrics. The results of this study are therefore worthy of publication.

As a premise for their study, the authors cite very compelling pharmacokinetic data which suggest that maternal body weight influences serum magnesium level independent of renal function, and suggest that alternate dosing structures may be required for obese women.

The authors are very clear and specific in their report of their research question, and desired outcome variables. They sought specifically to evaluate serum levels, and secondarily maternal side effects and neonatal outcomes. By doing this, they were able to keep their sample size low to facilitate their RCT. The RCT, as conducted, then is rigorous with appropriate methodology and statistical analysis. Their convenience strategy of randomizing women before they actually met criteria for severe features was acceptable based on the fact that the groups were ultimately relatively even for eventual ruling in.

However, in several very specific ways, their study design limits the clinical utility of their outcomes and concern me that clinicians will use this data inappropriately. I would expand the limitations section of the discussion to better address these issues:

1. The data they cite regarding therapeutic levels of magnesium required to avoid eclamptic seizure is from 1955 and 1957, which was upheld in 1981. The authors use this therapeutic window, but point out that this therapeutic window must be flawed in some ways, as so many women fail to meet this target but do not experience eclamptic seizures. (They even assumed as part of their research design that 80% of obese women would be subtherapeutic on standard dosing). The manuscript they cite, the Du manuscript, reports modeled predicted eclampsia

rates at varied magnesium levels using different dosing regimens. However, it is not clear that precise magnesium therapeutic level required to avoid a seizure is actually accurate. The discussion of magnesium utility to avoid seizures in lines 254-265 focuses on the threshold to seize among obese patients. But it does NOT discuss that thus far, there has been no evidence that obese women seize more often due to under-dosing of magnesium. They admit their sample size is too small to evaluate for undesirable side effects. When applied to a population level, it is possible that higher dosing of magnesium may incur risk without additional seizure-reducing benefit in the name of meeting a flawed serum target.

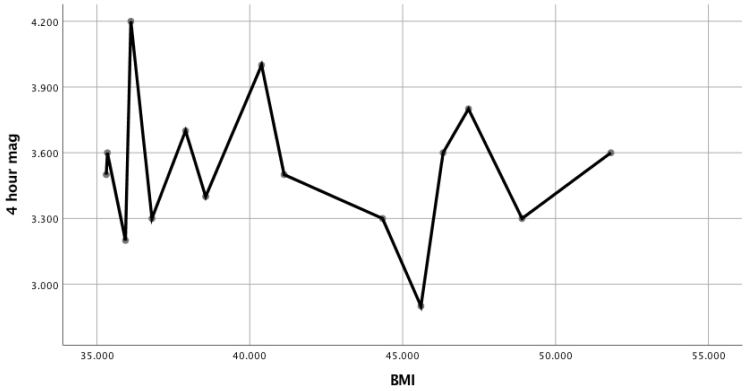
Response: We fully agree with the reviewer's assertion that there is a lack of evidence that lower serum magnesium levels in obese women lead to more eclampsia, and the study is certainly not powered to assess this. We have added to the discussion that these findings should be applied with caution given there may not be additional benefit for obtaining higher serum levels and the risk of additional toxicity should be considered in these women.

2. All obesity is not the same. The authors point out that they used a BMI cut off of 35, and simply qualify women as "obese." A figure demonstrating deceasing serum magnesium levels with increasing BMI would go a long way convincing the reader that BMI works on serum magnesium levels in the way the authors claim. In truth, a prospective cohort study of therapeutic levels across all BMIs would be better at evaluating appropriate dosing strategy. This could help identify a specific inflection point when dosing should be altered. Perhaps magnesium should be dosed as mg/kg. As the authors point out in another limitation, a cohort study could eliminate the questions of race and metabolism. It could also identify whether eclamptic seizures were avoided at specific thresholds in a contemporary cohort. This should be at least proposed in the manuscript as an area for future study.

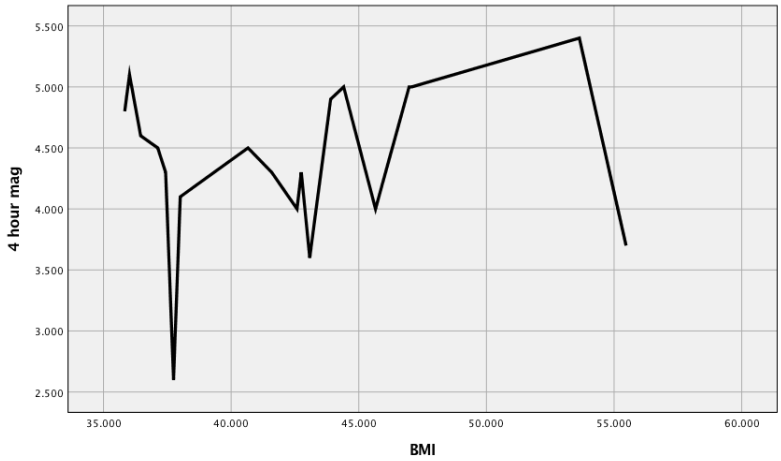
The discussion of the manuscript should be altered with these qualifiers and ideally a new figure. I also recommend removing the final sentence, the suggestion that higher dosing should be considered in obese preeclamptic women, as this data is as yet insufficient to demonstrate that this is clinically necessary. This manuscript is more of a foundational than definitive work for this practice.

Response: Such a figure was previously published in the Brookfield et al study (Ref 16) with maternal weight rather than BMI, using a 4/2 regimen in a much larger sample. For the sake of brevity as requested by the editors, the authors cannot include such a figure in the current manuscript, but have constructed one for both dosing regimens here. More than one woman had same BMI/same serum magnesium at 4 hour mark (there are overlapping data points) The sample size is not large enough in the current study to stratify the data in a meaningful way by BMI.

4/1 Group



6/2 Group



We have modified the discussion to highlight the above limitations and toned down the language throughout the manuscript that would suggest this should become standard practice.

Reviewer #3: This manuscript is a prospective, randomized study evaluating serum Mg levels in obese patients on two different regimens of IV MgSO4 for preeclampsia with severe features. It is unclear why this higher regimen was chosen as it has already been shown not to achieve therapeutic magnesium levels for 61% of obese patients in prior references. Please comment.

Response: We understand the reviewer's concerns that a large proportion of obese women have been demonstrated to be subtherapeutic in prior retrospective studies. The choice of 6/2 regimen is based on multiple factors: 1.) Our institution uses this regimen routinely for fetal neuroprotection, hence we would not have to further justify a higher dosing regimen as "new" and ethical to the IRB. 2.) Along these same lines, there is some evidence from modeling in the previous Du et al papers, that maintenance doses of 3g/hr or more are associated with more magnesium toxicity, which the investigators wanted to avoid. 3.) We assumed the previously studied population would likely have a higher proportion of Class III obesity rates than the population studied in the current paper, hence felt there may be a lower proportion of women with subtherapeutic levels than what was previously reported. We have attempted to make this clearer throughout the methods section.

Abstract
The aim of the study was to compare two regimens of magnesium sulfate infusion by assessing serum levels of magnesium in obese patients. Otherwise, the abstract is adequate.
Methods
Current recommendations are to use 4-6 g bolus followed by 1-2 grams per hour. Please comment.

Response: We believe the current study findings suggest within the guidelines mentioned above, that more obese women are more likely to obtain therapeutic serum magnesium levels when administered dosing on the higher end of these ranges.

Efficacy levels for seizure prophylaxis have not been established making it unclear if differences in these regimens clinically matter. The same applies to "therapeutic" levels of magnesium. Please comment.

Response: We fully agree with the reviewer's assertion that there is a lack of evidence that lower serum magnesium levels in obese women lead to more eclampsia, and the study is certainly not powered to assess this. We have attempted to address this in the discussion by brief review of findings from exposure-response modeling of Magpie data (Du et al Ref # 18). We have also added to the discussion that these findings should be applied with caution given there may not be additional benefit for obtaining higher serum levels and the risk of additional toxicity should be considered in these women.

The benefit of MgSO4 in seizure prophylaxis in developed countries has been questioned. Please comment.

Response: Evidence from prospective randomized trials has demonstrated the benefit of magnesium sulfate administration for prevention of eclampsia in women with preeclampsia with severe features. The authors agree the incidence of eclampsia is much higher in low and middle-income countries; however, the reasons for this are multifactorial, and include the fact that institutions in the U.S. have magnesium sulfate readily available for administration. We have edited the manuscript as above, to reflect acknowledgement of the following: regimens utilized in the U.S. may differ from those used internationally and the true "therapeutic level" and hence optimal dosing regimens are unknown in the obese and non-obese populations.

Please expand on why a BMI>35 was used, as prior quoted studies (and the definition of obesity) used BMI>30.

Response: The prior Tudela et al study used BMI > 30 and the Brookfield et al study used maternal body weight as opposed to BMI. It was determined on review of the prior Brookfield et al study that the maternal weight cut-off for the most profound changes observed in magnesium disposition would most closely correlate with a BMI of 35 (for the range of conceivable maternal heights). Though we recognize this is Class II obesity, we felt it would be most reflective of differences in serum levels when utilizing the different regimens. Additionally WHO BMI obesity definitions do not account for weight gain in pregnancy, so the higher threshold was felt more appropriate in this setting.

Were there more magnesium samples drawn, other than at 0, 1, 4 hrs and delivery? The mean labor length for patients receiving the higher dose regimen was 22 hours. Were there no additional magnesium levels drawn during the remaining 18 hrs of labor? Please comment.

Response: Beyond the prespecified time points, serum magnesium levels were obtained only if they were drawn in conjunction with a routine preeclampsia lab panel. This was done to avoid multiple unnecessary blood draws. Therefore, many patients have more serum magnesium level data than that of the time points mentioned, which can be used for constructing an obesity specific PK/PD model, but was not the primary intent of this study.

Why was the level at 4 hrs used for comparison? vs assessing for therapeutic level of magnesium at any predelivery point.

Response: The time points of 1 and 4 hours are common in the PK literature to demonstrate the steepest slope of the concentration-time curve in ascent to steady state. In our previous PK modeling, 4 hours was the time point when most average weight women reached a serum magnesium level of around 4.8 mg/dL. Time of delivery was chosen as another time point so that there would be some variation in the timing of when the additional samples were collected, and with the thought that the majority of eclamptic seizures occur in the antepartum/intrapartum time period, hence this would be the time frame when achieving therapeutic serum levels would be of the most importance. While not the aim of the study, data was collected in a fashion that could potentially yield a magnesium PK model specifically for women with obesity. The 4 hour mark was also reported in the Tudela et al study, which was utilized in the power calculation.

What is the protocol for a subtherapeutic magnesium level? It seems like there is no response to a subtherapeutic magnesium level. Please comment.

Response: Serum magnesium levels were only drawn for study participants and are not routinely drawn outside of a study protocol at our institution. If women experienced symptoms concerning for magnesium toxicity, a serum magnesium level was drawn, and the dosing decreased/discontinued if the treating clinician felt this was warranted. Dosing was not altered in response to subtherapeutic serum magnesium levels.

Results
While not powered for maternal side effects, the results mention no noted difference in same. There is an approximate 2x higher rate of nausea and an elevated rate of flushing in the higher dose group.

Response: We modified the discussion to reflect the absolute rates of nausea and flushing were higher for women in the alternate dosing group. It is difficult for us to comment on the clinical significance of these numbers as they generally represented 1 or 2 women reporting the side effect in an overall small sample.

Also, the median labor time of 14.7 vs 22 hours strongly suggests an inadequate sample to evaluate the differing regimens on labor length.

Response: We agree and these point estimates had fairly wide confidence intervals. They were not statistically different for the purposes of comparing baseline characteristics and comparison of the regimens on labor length was not the intent of the study.

As the magnesium levels in the higher dose group increased over 20% between 4 h and delivery, does this suggest patients are on an increasing slope of magnesium levels that could lead to supratherapeutic levels if labor lasted longer. Please comment.

Response: PK data in concentration-time profiles were not specifically constructed for this population, however, a rudimentary look at the data from this trial supports what has previously been published with different regimens that suggests the steady state concentration of

magnesium is approximately 7mg/dL and that women with normal renal function do not approach supratherapeutic levels when administered a 2g/hr regimen. Many of the previous models have not extrapolated beyond 24 hours of magnesium administration, hence the caution of our group in using maintenance doses > 2g/hr out of concern for toxicity in some women.

The reader would be helped by knowing the particular severe features presented in these groups and whether it varied between them. While creatinine is reported, all normal, it would appear your population was not at substantial risk of low intravascular volume. Please comment.

Response: A breakdown of severe features was added to Table 1 and there are no differences between the two dosing groups. While not included in the table for the sake of brevity, there were no differences between the two groups in those women meeting criteria for severe features by specific lab abnormality (creatinine, LFTs, thrombocytopenia).

Discussion
Adequate summary but no discussion about the relationship of therapeutic levels to seizure prevention.

This manuscript evaluated magnesium levels in obese (class 2 obesity and higher) preeclamptic patients with normal creatinine levels given one of two regimens of magnesium sulfate. Both regimens fall within the current ACOG recommendations for this clinical group. While it is not surprising that higher doses yield higher serum levels of magnesium, the clinical importance of this remains unclear as the study was not powered for the outcome of eclampsia.

Response: As stated above, we fully agree with the reviewer's assertion that there is a lack of evidence that lower serum magnesium levels in obese women lead to more eclampsia, and the study is certainly not powered to assess this. We have attempted to address this in the discussion by brief review of findings from exposure-response modeling of Magpie data (Du et al Ref # 18). We have also added to the discussion that these findings should be applied with caution given there may not be additional benefit for obtaining higher serum levels and the risk of additional toxicity should be considered in these women.

STATISTICAL EDITOR COMMENTS:

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

Abstract: Need to conform to our template for RCTs. Specifically, need to concisely explain rationale for power/sample size calculation.

Response: Abstract has been edited using template as model. Rationale is detailed within the manuscript body.

lines 62-65: The sample sizes were modest and under powered to discern differences in maternal or neonatal outcomes nor in side effects.

Response: The statement regarding no differences in maternal side effects or neonatal outcomes was removed from the abstract.

Table 1: Since the groups were randomized, there is no need to statistically test for group differences. Any difference is thought to be due to random chance, so eliminate the column of p-values.

Response: The p-values were removed.

lines 52-55, 168-174 and Table 2: There is only one primary outcome, the proportion having a sub-therapeutic level at 4 hrs, with a posited difference of 80% vs 35%.. That should be stated separately from the others, which are secondary outcomes. The proportions having therapeutic levels should include the point estimates along with CIs and a footnote explaining the stats significance. Also, Table 2 cites the primary outcome as the % having therapeutic level, so should clarify whether the primary was the % achieving vs not achieving a specified level. That is the proportions not achieving therapeutic levels were: 18/18 = 100% (59-100%) vs 12/19 = 63%(33-100%), with $p < 0.001$ by Fisher's test.
Response: Throughout manuscript, provided consistency in use of “subtherapeutic” levels, as this was what data the power calculation was based on and modified the table.

Table 3: The counts are low and there is low power to discern differences, so the NS findings cannot be generalized. Each group had N = 19 or 20, so the n(%) format should round the %s to nearest integer %, not cite to 0.1% precision.

Response: A note was made for Table 3 that the study was underpowered to detect differences between the two groups for neonatal outcomes. The N(%) was rounded to the nearest integer. P values were noted to be non-significant in table legend.

Associate Editor: We are happy to consider a revised version of your manuscript but are asking that it be formatted as a Research Letter. In your revision, please tone down the "should be used" language. What constitutes a therapuetic concentration of magnesium has not been rigorously evaluated and you do not show differences in clinical outcomes. Finally, I found many of your references to not really be on point re: magnesium concentration vis. a vis. dosing. Please carefully review your references with an eye to direct relevance and remove as appropriate.

Response: Although the total N is small, the complexity of the background information and details of enrollment requested by other reviewers made it impossible to summarize and reformat the manuscript in 600 words. We have done our best to cut down on unnecessary words and reviewed the citations for inclusion of truly relevant references.

EDITOR COMMENTS:

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

2. Obstetrics & Gynecology uses an "electronic Copyright Transfer Agreement" (eCTA). When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page. As of 7/17/20, Dr. Caughey hasn't filled out the form.

3. For studies that report on the topic of race, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, the reasons that race/ethnicity were assessed in the study also should be described (eg, in the Methods section and/or in table footnotes).

Use "Black" and "White" (capitalized) when used to refer to racial categories.

The category of "Other" is a grouping/label that should be avoided, unless it was a prespecified formal category in a database or research instrument. If you use "Other" in your study, please add detail to the manuscript to describe which patients were included in that category.

Response: We have now addressed these issues in the footnote for Table 1.

4. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the article (after the References section).

Response: The data sharing statement was added to the end of the manuscript.

In addition, please use only the major headings outlined in our Instructions for Authors for Original Research and delete any subheadings. In the Abstract: Objective, Methods, Results, Conclusion; and in the body text: Introduction, Methods, Results, Discussion.

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: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

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).

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

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

9. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

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.

Please expand "PK" to read, "pharmacokinetic" throughout the manuscript.

Response: This was done throughout the manuscript.

11. Please reword the phrase, "obese preeclamptic women" to read, "obese women with preeclampsia."

Response: This was done throughout the manuscript.

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: Tables were edited to conform to journal style.

13. 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.

Figure 1: Please confirm n values (those allocated to each group do not add up to those randomized [31+35=66]).

Response: One person withdrew from the study shortly after consent and immediately after randomization (she changed her mind about participation). This was added to the Figure legend.

14. 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 in a word processing format such as Microsoft Word. 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.

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 30 days from the date of this letter. If we have not heard from you by Aug 16, 2020, we will assume you wish to withdraw the manuscript from further consideration..

Sincerely,

The Editors of Obstetrics & Gynecology