

OBSTETRICS & GYNECOLOGY



NOTICE: This document contains comments from the reviewers and editors generated during peer review of the initial manuscript submission and sent to the author via email.

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

Date: Feb 14, 2020
To: "Samuel Gentle" [REDACTED]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-20-145

RE: Manuscript Number ONG-20-145

Association of Antenatal Corticosteroids and Magnesium Therapy with Neurodevelopmental Outcome in Extremely Preterm Infants

Dear Dr. Gentle:

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

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

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Mar 06, 2020, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The purpose of this manuscript is to report if "preterm infants with a gestational age between 22 0/7 and 26 6/7 weeks, there would be lower rates of death or severe NDI in infants exposed to both ANS and MgSO4 compared to infants exposed to ANS alone." This was a prospective, cohort study.

1. How many of these preterm deliveries resulted from induction secondary to a maternal or fetal medical condition? How many were due to spontaneous preterm labor or rupture of membranes? Can the authors determine how many subjects received MgSO4 for pre-eclampsia or fetal neuroprotection (they noted without further specification of indication for pre-eclampsia or fetal neuroprotection)?
2. The authors note that gestational age at delivery was based on the "best estimate of gestational age in weeks and days, using a hierarchy of best obstetrical estimate over best neonatal estimate." Who determined the best gestational age? Did one or more than one person determine best gestational age? Could the authors provide a supplemental figure of the hierarchy that was used to determine best gestational age? How good is their method at determining gestational age?
3. The authors note that "Neurodevelopmental follow-up assessments included the Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III), administered by certified psychologists or developmental specialists." How many psychologists and developmental specialists administered the Bayley-III? What is the intra- and inter-observer variability in the Bayley-III for certified psychologists and developmental specialists involved in this study?
4. "Annually certified examiners assessed for cerebral palsy by neurological examination including evaluation of muscle tone, movements, reflexes, protective reactions, and gross and fine motor function." How many certified examiners performed these assessments? What is the intra- and inter-observer variability for the "Gross Motor Function Classification System"? Could the authors expand on the Gross Motor Function Classification system?

Reviewer #2: From this group of experienced investigators affiliated with NRN and NICHD, one would expect a well conducted study, a well written report and valuable information derived from the question being asked. This is exactly what they provided. I read the manuscript with great interest.

From this group of well versed investigators and thinkers, one would expect some insight, some "personal take", some

message. This is exactly what is completely missing. The Discussion and Conclusion sections are devoid of any inferences. The results are reiterated, previous related reports are reminded, and that is all.

Why does this report need to be published? What does it mean? What does it tell us? Are there any clinical practice implications or future research directions to be suggested? I am struggling to answer these questions myself because the authors do not say anything. This is unfair to the Journal's readership, not all of them academics or epidemiologists fully cognizant of the current body of knowledge. Should we change anything in clinical practice? Probably not much because an observational study cannot invalidate the findings of multiple RCTs and there was still benefit on mortality with the combination of ANS and MgSO₄. However, the results of this study and the recent individual participant data metaanalysis (PLoS 2017) may be closer to "real life" conditions than a strict RCT protocol. Do we still call the administration of MgSO₄ "neuroprotection" when that is not clearly the case? I have seen enough harm occurring when delivery was delayed because people believe that in order to protect from CP, the fetus needs to be exposed to MgSO₄ for 12-24 hours. Should we be more balanced, less dogmatic in our use of MgSO₄ neuroprotection? I agree that this is more of a question for the ACOG publications' committee, but there is a need to place into context newly emerging evidence, such as the one provided by this study and the individual participant data metaanalysis (PLoS 2017). Do the authors have any opinion on that?

Some minor editing:

- Line 214: delete the second "been".
- Line 219: you need a reference for "A metaanalysis of...preterm infants". I think it is (1).
- Line 255: Why "meta-analyses" (plural) when you have only one reference? Also be consistent throughout the manuscript - either "meta-analysis" or "metaanalysis".
- Lines 286-288: "The reason more infants within the cohort were exposed to MgSO₄ (75.4%) compared to the number of infants exposed to ANS (89.0%) is unknown...". Something is wrong here; 75.4% is not more than 89.0%.

Reviewer #3: The paper reviewed adds important information that should be absorbed and acted upon.

This is, however, a difficult read for me. Any effort to summarize, or utilize a list of important outcomes beyond the authors current efforts, would be helpful.

Reviewer #4:

General Comments

1. This manuscript is well written and organized.
2. The hypothesis is clear and the methods and statistics selected are appropriate.
3. The study was adequately powered.
4. The conclusions have clinical relevance to current obstetric practice.

Comments on Discussion section:

The audience for this journal is obstetricians. We are in a unique position to counsel patients on a prenatal intervention that may directly impact their offspring future health. The ability to predict intact survival and limit severe NDI is important for prenatal counseling. I would like to see discussion in this paper on how this may impact counseling a patient who is about to deliver an extremely premature infant. While we may be preventing neonatal and perinatal death, this study suggests we may not be impacting rates of severe NDI at these early gestational ages which has profound implications for patients, offspring and families.

Table 1 seems to suggest that women of low socioeconomic means and education level were less likely to receive interventions. This suggests some health disparity inequality and, while I appreciate it is adjusted for in the analysis, it would be nice to see that highlighted in the discussion as well.

Specific Comments RE: Discussion Section

In general, this section could use some editing for clarity and be reduced in length. A more top level summary of data of related literature and how this study's results differs or support prior research instead of inclusion of very specific numbers (example, inclusion of sample sizes and specific statistics).

Line 237-239: This line alludes to the small sample size of 22-24 week deliveries including in this study,. A table with the breakdown of distribution of gestational age by week (separately for weeks 22 and weeks 23) would be helpful. Was there a difference in de I understand Table 1 shows that the interquartile range for each group was similar, however as one of

the authors' conclusions involves 22-24 weeks gestational age neonates however the number of infants in this small subgroup is not clearly stated.

Line 253-Line 266: This is a nice summary of the available literature. How does this study's results compare (in the authors' opinion)?

Line 287-288: need clarification here. the number exposed to magnesium cited is lower than the number cited for exposed to steroids

Line 306-307: The final sentence in the conclusion is confusing and should be rewritten for clarity.

Table VI is not discussed in the paper. Please include in results section.

STATISTICAL EDITOR COMMENTS:

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

lines 52-54, 129-131: The hypothesis is a comparison of outcomes after magnesium sulfate and antenatal corticosteroids vs antenatal corticosteroids alone. Instead, the comparisons are between magnesium sulfate and antenatal corticosteroids and other groups. If indeed there is one primary, then those results should be clearly designated as the primary and the others should be designated as secondary ones. On the other hand, if there were meant to be comparisons of magnesium sulfate and antenatal corticosteroids vs 3 other groups, then the inference threshold needs to be adjusted from the .05 level and 95% CIs cited.

General: The MgSO₄ only group has N = 89, so the %s should be rounded to nearest integer %, not to 0.1% precision.

Tables I, II, IV, VI (is Table V missing?): The stats test used identify whether the distributions or proportions among the 4 groups differ from random allocation, the tests do not evaluate the primary outcome (comparison of the first and second groups). A more appropriate test would have been to separately teach group vs the referent of antenatal corticosteroids + magnesium sulfate. The tests cited are not able to discern which group contributed to the non-random allocation.

EDITOR'S COMMENTS:

We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting.

Line 52: could you add what population you are studying in your objective? Maybe something like "...that antenatal exposure of very premature fetuses to both..."

Line 65: PRESENTATION OF STATS INFORMATION P Values vs Effect Size and Confidence Intervals

While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, 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.

This is true for the abstract as well as the manuscript, tables and figures.

Please provide absolute values for variables, in addition to assessment of statistical significance.

We ask that you provide crude OR's followed by adjusted OR's for all relevant variables.

Line 71: please spell out all abbreviations on first use.

Also, throughout your abstract and manuscript introduction you indicate that you are comparing outcomes of ANS +Mag vs ANS alone but you also report data on MAG alone. Your conclusion does not mention MAG alone.

Line 86: what is a factorial trial?

Line 93: Could you make it clear why on line 87 you use the gestational age range of 24 +0 to 33 + 6 but here you are studying 22 + 0 and 26 + 6.

Do you mean for your hypothesis to read "Lower rates of death OR severe NDI"? or do you mean "Death AND NDI"?

Line 108 and elsewhere: . Please note that your study was conducted from date 1 to date 2, not between those dates. As written, it would exclude the dates given .

In the results section, please refer back to my notes about presentation of statistical data associated with the abstract comments.

Line 1919: "Rate of severe NDI did not differ between exposure groups" vs Line 209: Exposure to ANS and MgSO4 was associated with lower rate of NDI ...compared to ANS alone". Both statements can't be true.

Line 214: This is known as a primacy claim: yours is the first, biggest, best study of its kind. In order to make such a claim, please provide the data bases you have searched (PubMed, Google Scholar, EMBASE for example) and the search terms used. IF not done, please edit it out of the paper.

I agree with the reviewers that your discussion would be improved by providing less presentation of the data from the other trials (not completely eliminating it , but providing more focused information that relates to your study) and providing more discussion comparing your findings with these.

EDITOR COMMENTS:

1. Throughout, please make sure you are using the correct age terminology.

For 8 weeks of gestation until birth, use "fetus"
 For birth to 1 month, use "neonate" or "newborn."
 For 1 month to 1 year (12 months), use "infant."

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

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

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

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

*The manuscript's guarantor.

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

5. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at <https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality->

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

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 limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

9. 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.

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

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.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

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. 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 reference you are citing is still current and available. If the reference you are citing has been updated (ie, 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 (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at <https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance>.

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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.

15. 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 21 days from the date of this letter. If we have not heard from you by Mar 06, 2020, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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