

# OBSTETRICS & GYNECOLOGY



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

**Date:** Jun 18, 2019  
**To:** "Roxanne Hastie" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-19-929

RE: Manuscript Number ONG-19-929

The predictive value of the signs and symptoms preceding eclampsia: a systematic review

Dear Dr. Hastie:

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 Jul 09, 2019, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

Reviewer #1:

**TITLE:** The predictive value of the signs and symptoms preceding eclampsia: a systematic review

**TYPE:** Original Research/Systematic Review

**Precis:** This systematic review evaluates the predictive value of signs and symptoms that occur prior to the onset of eclampsia.

**Other:**

Author contributions are provided.

Funding sources (mostly Fellowships) were disclosed.

Human Subjects: This study was exempt from review.

Acknowledgements/Competing interests: None.

**Abstract:**

1. The abstract follows the recommended structure. It is specific to the paper. It also notes that the study is registered with PROSPERO.

**Introduction:**

2. Indicates why the topic is important. Eclampsia is a life-threatening pregnancy complication which disproportionately affects lower income countries. While magnesium sulfate is the drug of choice to prevent and treat eclampsia many women who should receive it do not. The specific objective of the study is stated.

3. Line 84: Please clarify what "NNT [10 10 " means.

4. Lines 96-98: This sentence seems to contain redundancies.

**Sources:**

5. Data sources included MEDLINE, ClinicalTrials, Cochrane Database of Systematic Reviews and EMBASE. PRISMA guidelines were followed and the checklist is included in the supplementary materials. The search dates and language was included. A computer-based predefined search strategy was used and is also included in the supplementary materials.

#### Study Selection:

6. The number of reports identified and the basis of selection is provided. The screening process is described. Eligibility is as follows: randomized and non-randomized, prospective and retrospective studies were included. A diagnosis of eclampsia was required as was a comparator arm (no eclampsia). Signs and symptoms prior to eclampsia were required. The method of data extraction is described (they used an online systematic review management system called Covidence) and standardized data extraction forms. The quality of the studies was assessed using QUADAS-2 guidelines (makes use of 4 domains: participants, index test, reference standard, flow/timing). Diagnostic accuracy measures: Sensitivity, specificity, likelihood ratio and confidence intervals were calculated for each sign and symptom. Reports were separated for cohort and case-control studies.

#### Results:

7. Number screened and number included is presented and a flow diagram included.

8. Point of clarification: 2791 studies were identified after the first round of duplicates were removed. 60 were left, so the other 2731 did not meet the eligibility criteria?

9. Table 1 summarized study characteristics. Over 5000 women were included with 17.5% having the outcome of interest.

10. Review of bias is included in a supplemental table. None of the studies were low-risk for bias (retrospective and case-control designs, knowledge of eclampsia diagnosis prior to recording signs and symptoms). As such there was significant potential for bias across all domains assessed.

11. Data on individual signs and symptoms was presented. Test parameters were largely inconsistent. Pooled estimates were not possible due to heterogeneity. Visual disturbances had the highest LR+. Pooled sensitivity was high but specificity was low. Subgroup analyses are reported (one for high risk populations such as preeclampsia with severe features or HELLP, one for case-control studies). Test characteristics improved but CIs were wide.

12. Symptoms yielded poor predictive test characteristics. Line 209: Please clarify - perhaps there is a word missing: "Overall, investigating individual symptoms and symptoms yielded poor predictive test ..."

#### Discussion:

13. A summary of the evidence is presented along with the limitations to the evidence. The studies identified were largely retrospective with methodologic flaws and marked heterogeneity between studies. The authors felt that it was inappropriate to provide pooled estimates. Three symptoms (visual disturbances, epigastric pain and headache) modestly increased the likelihood of eclampsia but the high negative likelihood ratios indicate that the absence of any of these does not reduce the chance of eclampsia in a clinically significant manner. While this may be the first systematic review evaluating the predictive value of prodromal eclampsia symptoms its findings are limited by the quality of the existing data. Clinical application of the limited findings are discussed and need for larger, prospective studies to evaluate signs and symptoms of predictors for eclampsia is articulated.

14. Line 261: Can the authors give examples of what individual signs and symptoms previously thought to be associated with eclampsia they excluded from their search strategy?

#### References:

15. Pertinent literature is cited.

#### TABLES and FIGURES:

16. Tables include results of individual studies and sensitivity testing.

Reviewer #2: The manuscript by Hastie et al is a vigorous attempt to determine which specific symptoms if present would allow the clinician to predict the likelihood for the development of eclampsia. The authors with their extensive review were not able to determine which specific symptoms would have a high probability to alert the clinician to the development of eclampsia. This finding was as expected. Any senior clinician appreciates that preeclampsia is the great imitator and therefore it would be highly unlikely that any specific findings would alert the clinician to the impending onset of eclampsia as there are no specific findings always associated with the diagnosis of preeclampsia. The value of the manuscript is that it adequately documents to the obstetrician that she/he must always be alert to the possibility of the patient developing eclampsia. The introduction section should be decreased by 50% and there is much repetition in the discussion section.

that should be removed. Figure 2 is complicated and should be removed.

Reviewer #3: Manuscript Review

ONG-19-929

The predictive value of the signs and symptoms preceding eclampsia: a systematic review

The stated purpose of this systematic review was to assess the positive and negative predictive values for signs that are either present or absent preceding episodes of eclampsia. Symptoms frequently noted across studies included visual disturbances, epigastric pain and headache. By attempting to identify symptoms (or signs) that consistently predict the onset of eclampsia, the authors intended to provide data that would allow clinicians to better inform decision making regarding administration of Magnesium Sulfate for eclampsia prevention.

The conclusions regarding the (lack of) quality of the selected studies for review included the fact that "5 out of 11 studies did not state or clearly define a diagnosis of eclampsia; two studies did not define the control population well; and only 2 studies assessed the signs and symptoms of interest without knowledge of eclampsia diagnosis, creating a potential high risk of bias due to the knowledge of diagnosis prior to recording signs or symptoms."

In terms of likelihood ratios, visual disturbances was most accurately associated with development of eclampsia when present, but the negative predictive value was poor when absent.

The best predictor was diastolic BP greater than or equal to 110 mm Hg, but "it is important to note this estimate is based on a single small case-control study and thus potentially unreliable".

#### Comments

The stated purpose for this systematic review was to provide clinicians with data that would allow them to determine which patient is a candidate for administration of Magnesium Sulfate based on presence or absence of signs and symptoms that may be present prior to the onset of eclampsia. One would presume that a significant number of the patient's present in the studies were already receiving Magnesium Sulfate, particularly the subgroup with HELLP syndrome. However, this is not noted in the review. Without knowledge Individual Patient Data, it is impossible to draw any accurate conclusions from the selected studies. Magnesium sulfate in itself may be associated with visual disturbances. Furthermore, all eclamptic seizures theoretically may have occurred in patients who were not receiving Magnesium Sulfate.

The study may be improved by reviewing studies not presented in English, because as the authors noted, a higher incidence of eclampsia occurs in countries with lesser resources. An individual patient data meta-analysis would be useful.

#### STATISTICAL EDITOR'S COMMENTS:

1. Although the LR(+) and LR(-) are important metrics, I would suggest that for our readers, the emphasis should be on sensitivity and specificity of the signs/symptoms. That is, although from ~ 1/3 to 1/2 of women with eclampsia had either of the three findings, among those who did not have eclampsia, from ~1/5 to ~1/10 did have either of the signs/symptoms. Therefore, although there was a statistical association, it was not strong enough in either a positive or a negative sense to reliably predict whom would develop eclampsia. (or similar wording)
2. Also, were there any of these studies which evaluated a combination of the three findings as having better predictive characteristics, in that the sensitivity might decrease, but perhaps the specificity would now become useful?

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

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

3. 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.

4. Was this study presented as an abstract at a meeting? If so, please note the name, dates, and location of the conference on the title page of your manuscript.

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: Review articles should not exceed 25 typed, double-spaced pages (6,250 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, 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. Provide a short title of no more than 45 characters (40 characters for case reports), including spaces, for use as a running foot.

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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 Jul 09, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982

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

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