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

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RE: Manuscript Number ONG-22-1305

Prevalence, Indications, Risk Indicators and Outcomes of Emergency Peripartum Hysterectomy Worldwide: A Living Systematic Review and Meta-analysis

Dear Dr. Kallianidis:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 09, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: The authors have performed an updated metaanalysis of an important topic that contributes to maternal morbidity worldwide. The writing is clear and a systematic approach has clearly been performed in this study. I have the following comments:

1) The authors report throughout the manuscript that they are reporting on the prevalence of emergency peripartum hysterectomy (EPH). Even though this was the terminology used in the original meta-analysis that they are updating, the authors actually describe the incidence, and this terminology should be clarified. Prevalence is the count of cases (new and ongoing) in a total population, which could be used to describe the number of women living s/p emergency hysterectomy. Incidence is the count of new cases in a population at risk (i.e. count of EPHs in a total number of delivering patients) and incidence is therefore the more accurate term.

2) Similarly, throughout the manuscript, the authors report a maternal mortality rate, but what they actually report is a mortality to case ratio - the number of deaths per a given number of emergency peripartum hysterectomies. Mortality rate is defined as a count per total population, which is not what is reported here.

3) Lines 196-198- Reports of individual surgical measures aimed to prevent hysterectomy are listed, but I am curious, in how many studies were multiple or sequential measures described (as often occurs in practice?)

4) The weighted mean number of units of blood transfused and days in hospital are reported. These measures are most often not normally distributed, and weighted medians therefore may be more appropriate.

5) The authors report that the proportion of patients who receive blood transfusion is markedly lower in low income countries, and increases as does the income status of the country, with a slight difference between mid-high to high income countries. Conversely, mortality is reported as highest in the lower income countries, and gradually decreases with income status. While these may not directly correlate, it begs the question whether access to safe blood transfusion may...
be a reasonable, modifiable intervention to reduce maternal mortality associated with EPH in the lower income settings, rather than concluding that there is lack of appropriate management. It is possible that providers in the LMICs are providing care as best and in as timely a manner as they can with the resources available to them, and identification of most efficient and cost effective ways to reduce mortality is paramount.

Reviewer #2: This is the update of a systematic review published by the same authors in 2016. The original review presented descriptive data from 128 studies on Emergency Peripartum Hysterectomy (EPH). In this updated version, 26 studies published since 2016 were added.

The authors used the same methodology as the previous review. They applied strict inclusion and exclusion criteria and risk of bias was presented. The information is well organized and the manuscript well written.

The results are similar to the original review. The authors mention the availability of population studies after 2016 as the main reason to publish this update (lines 53 to 56), but it is unclear if otherwise there's a true need for a revision of this data. There's no mention of new clinical questions that need to be answered or if the update would influence the original findings sufficiently to justify a review. The authors suggest that the inclusion of population studies increase the validity of the findings without acknowledging the multiple limitation of this type of methodology (line 254). Among other things, that data collection is not performed by the researchers, data quality information is unavailable and important data might be missing.

Reviewer #3: The investigators conducted a systematic review and meta-analysis, updated through December 2021 from one published in Obstetrics & Gynecology on the same topic in 2016, to describe and compare prevalence of emergency peripartum hysterectomy across income settings, and secondly, to describe indications, outcomes and management of emergency peripartum hysterectomy globally.

There were 26 new articles (n=7,741 patients) since 2015 that met inclusion, doubling the number of patients in the prior publication, with 8 new countries represented. The justification for updating the review so soon after the prior publication is that several population-based studies that will better capture prevalence and were nearly absent in the prior review, have been since published and included.

Overall, this is well-presented, important data, and an exhaustive review.

Comments and suggestions:
1. The abstract does not mention management of emergency peripartum hysterectomy as being a study objective, while it is described as such at the end of the Introduction.

2. While the current review is expected to be more valid than the prior, given how recent the prior review was it would be helpful to contextualize how the inclusion of population-based data shifted findings. Are the investigators' recommendations outlined in the discussion different than they were in 2016? This could all be mentioned in the discussion.

3. Some differences in emergency peripartum hysterectomy across income settings may be driven by maternal health status (e.g., malaria- or nutritional deficiency-induced severe anemia; lines 259-262).

4. The reasons for increased peripartum emergency hysterectomy for placental pathology in high income countries could be stated. (lines 281-284).

5. Was this study registered in the PROSPERO database?

STATISTICAL EDITOR COMMENTS:

Tables 1, 4, 5, 6: As in the other Tables, need to include footnote explaining to reader that the prevalence estimates and their CIs are weighted estimates, not based on the aggregated n/N entries provided in Tables.

Tables 1, 3: Hard to generalize conclusions re: low-income strata or compare to other strata, since there were only 1 or two studies of that income group vs 34 to 75 studies (table 1) or 35 to 77 studies (table 2). Much larger samples, more precise estimates and more stats power to compare among the other three income strata.
General: Since some of these data were previously analyzed, should compare cohorts by suitable strata of year of study, to
demonstrate whether the prevalence rates have changed over time.

EDITORIAL OFFICE COMMENTS:

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in the study.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if
applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

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"patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive
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6. Have any of the figures been previously published in another source?
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Review: 4,000 words

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avoided in titles.
* Abbreviations, jargon, trade names, formulas, and obsolete terminology should not be used.
* Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," "A Systematic Review," or "A Cost-
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Reviews: 300 words

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such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate
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noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test
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Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three
decimal places (for example, "P = .001").

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

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Sep 09, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Jason D. Wright, MD
Editor-in-Chief

In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r). Please contact the publication office if you have any questions.
Dear Editor,

Thank you for giving us the opportunity to improve our manuscript according to the relevant comments made by the reviewers. Hereby, we submit our revision.

We have considered every comment and adjusted the manuscript accordingly. Where necessary, we have provided additional explanation. We feel that readability of the entire manuscript, and completeness of the discussion section in particular, have improved considerably, with more complete information on possible reasons for the observed differences in prevalence and indications. The passage on recommendations has now also been updated compared to the previous edition of this review.

The third reviewer and the statistical editor both suggest a comparison of prevalence over time. As more closely explained below, we feel that such a comparison would not be possible at this time given the heterogeneity and low quality of the different data sets of so many regions and hospitals, with so many possible time-dependent confounding factors. However, in future updates of this review, given the fact that an increasing number of population-based studies of higher quality are becoming available, we feel that such an analysis might very well be possible and would add importantly to the analysis. We thank the reviewer and statistical editor for this suggestion and will add the time analysis as a study objective for the next update.

We appreciate the time you and the reviewers have invested in improving the manuscript, and are looking forward to your response.

Kind regards,

Thomas van den Akker
REVIEWER COMMENTS:

**Reviewer #1:** The authors have performed an updated meta-analysis of an important topic that contributes to maternal morbidity worldwide. The writing is clear and a systematic approach has clearly been performed in this study. I have the following comments:

1) The authors report throughout the manuscript that they are reporting on the prevalence of emergency peripartum hysterectomy (EPH). Even though this was the terminology used in the original meta-analysis that they are updating, the authors actually describe the incidence, and this terminology should be clarified. Prevalence is the count of cases (new and ongoing) in a total population, which could be used to describe the number of women living s/p emergency hysterectomy. Incidence is the count of new cases in a population at risk (i.e. count of EPHs in a total number of delivering patients) and incidence is therefore the more accurate term.

Thank you for this comment. Before the publication of the first article in 2016, we discussed the correct term to use with our epidemiology consultants extensively and decided that the correct term to use was **prevalence**. In literature both prevalence and incidence are used as terms to describe the epidemiological features of PPH. The question which term to use also depends on what the emphasis is: if it is the event itself the hysterectomy, then incidence is a better term as the event itself hardly has any duration. After consulting our epidemiologist again, we decided to change the terminology to incidence throughout the whole manuscript.

2) Similarly, throughout the manuscript, the authors report a maternal mortality rate, but what they actually report is a mortality to case ratio - the number of deaths per a given number of emergency peripartum hysterectomies. Mortality rate is defined as a count per total population, which is not what is reported here.

We agree that maternal mortality rate is indeed not the correct term. We indeed present the number of maternal deaths per 1000 EPH’s. We have therefore adjusted the terminology to maternal case fatality rate (number of deaths among the number of cases) (page 11, lines 236-243). We use rate rather than ratio, as ratio would suggest a comparison between two different rates. We have adjusted the term perinatal mortality rate to perinatal case fatality rate accordingly. (page 11, lines 245-248)

3) Lines 196-198- Reports of individual surgical measures aimed to prevent hysterectomy are listed, but I am curious, in how many studies were multiple or sequential measures described (as often occurs in practice?)

The question of the reviewer rightly implies that, probably, multiple surgical measures were performed sequentially prior to peripartum hysterectomy, especially in high-income settings where life-support measures such as mass transfusion and ICU care are readily available. Unfortunately, in the included studies only the aggregated numbers/proportions of interventions were given, and in this meta-analysis we are therefore able to present pooled data only. Numbers on multiple or sequential measures would unfortunately only be available in case we had individual patient data. We have added this to the limitations of the study. (page 15, lines 330-332)

4) The weighted mean number of units of blood transfused and days in hospital are reported. These measures are most often not normally distributed, and weighted medians therefore may be more appropriate.
We agree with the reviewer that medians are the appropriate presenting method for not normally distributed data. Unfortunately most of the included studies report means rather than medians. For example, with regard to ‘days in hospital’ 16 studies presented the median, and 63 the mean. We therefore opted to include the means as given in the reports and use weighted means in our meta-analysis.

5) The authors report that the proportion of patients who receive blood transfusion is markedly lower in low income countries, and increases as does the income status of the country, with a slight difference between mid-high to high income countries. Conversely, mortality is reported as highest in the lower income countries, and gradually decreases with income status. While these may not directly correlate, it begs the question whether access to safe blood transfusion may be a reasonable, modifiable intervention to reduce maternal mortality associated with EPH in the lower income settings, rather than concluding that there is lack of appropriate management. It is possible that providers in the LMICs are providing care as best and in as timely a manner as they can with the resources available to them, and identification of most efficient and cost effective ways to reduce mortality is paramount.

Thank you for this valuable addition. We agree that accessibility to safe blood transfusion is vital in order to reduce maternal morbidity and mortality especially with the knowledge that hemorrhage is one of the most important causes of maternal death globally. We strongly agree with the reviewer that our meta-analysis may reflect limitations in available resources including blood for transfusion rather than inappropriate management. In lines 297-302, we discuss the differences in transfusion rates and quantities between different income settings. Although an inverse relation with mortality seems sensible, this would be hard to conclude from our data, with only limited data from LMICs. We have now added this recommendation to our discussion “Access to safe blood transfusion is likely to be an efficient and cost-effective intervention to reduce maternal mortality associated with EPH in the lower income settings.”(page 13, lines 302-304).

Reviewer #2: This is the update of a systematic review published by the same authors in 2016. The original review presented descriptive data from 128 studies on Emergency Peripartum Hysterectomy (EPH). In this updated version, 26 studies published since 2016 were added.

The authors used the same methodology as the previous review. They applied strict inclusion and exclusion criteria and risk of bias was presented. The information is well organized and the manuscript well written.

The results are similar to the original review. The authors mention the availability of population studies after 2016 as the main reason to publish this update (lines 53 to 56), but it is unclear if otherwise there’s a true need for a revision of this data. There’s no mention of new clinical questions that need to be answered or if the update would influence the original findings sufficiently to justify a review. The authors suggest that the inclusion of population studies increase the validity of the findings without acknowledging the multiple limitation of this type of methodology (line 254). Among other things, that data collection is not performed by the researchers, data quality information is unavailable and important data might be missing.

Thank you for your positive comments. Since the first study in 2015, 26 new articles have been published (n=7,741 patients). We understand the concerns about the limitations of
population based studies. However, by including these in our study update, we believe that a much more reliable and complete overview is given on the global prevalence of hysterectomy. And only by including more of these in the future, will we be able to unravel the reasons why there are such differences in management and outcome. We have added the limitations of population based studies explicitly now in the discussion (page 15 line 329-331).

Reviewer #3: The investigators conducted a systematic review and meta-analysis, updated through December 2021 from one published in Obstetrics & Gynecology on the same topic in 2016, to describe and compare prevalence of emergency peripartum hysterectomy across income settings, and secondly, to describe indications, outcomes and management of emergency peripartum hysterectomy globally.

There were 26 new articles (n=7,741 patients) since 2015 that met inclusion, doubling the number of patients in the prior publication, with 8 new countries represented. The justification for updating the review so soon after the prior publication is that several population-based studies that will better capture prevalence and were nearly absent in the prior review, have been since published and included.

Overall, this is well-presented, important data, and an exhaustive review.

Comments and suggestions:

1. The abstract does not mention management of emergency peripartum hysterectomy as being a study objective, while it is described as such at the end of the Introduction.

   Thank you for pointing out this omission. We have now, adjusted the objectives in the abstract to read: “To describe incidence, indications, risk indicators, outcomes and management of emergency peripartum hysterectomy (EPH) globally and compare between different income settings.”

2. While the current review is expected to be more valid than the prior, given how recent the prior review was it would be helpful to contextualize how the inclusion of population-based data shifted findings. Are the investigators' recommendations outlined in the discussion different than they were in 2016? This could all be mentioned in the discussion.

   The addition of the recently published population based studies (for 9 European countries), and also the new cohort studies from new countries adds to the validity of the presented prevalence for these countries, as there is no more accurate way to calculate a country’s true prevalence. For all other countries, the national prevalence is updated by pooling together all available point estimates, usually from hospital-based or regional studies. (see also answer to the statistical editor below) As such, the inclusion of 26 new articles means a shift in global prevalence from 0.9 to 1.1 per 1,000 births, bearing in mind that we used a random effects model for all weighted pooled prevalence figures.

   Thank you for this valuable remark concerning the recommendations in the last paragraph of the discussion. We now have once again revisited this section on recommendations and amended it to reflect the newer data. (page 15 lines 337-359)

3. Some differences in emergency peripartum hysterectomy across income settings may
be driven by maternal health status (e.g., malaria- or nutritional deficiency-induced severe anemia; lines 259-262).

Agreed. We have added 'maternal health status' to the factors that can contribute to the differences across income settings. (page 12, ling 264)

4. The reasons for increased peripartum emergency hysterectomy for placental pathology in high income countries could be stated. (lines 281-284).

We have now added further details as to the possible explanation of increase in placenta accreta spectrum, now reading: "Worldwide, placental pathology was the commonest indication for EPH. This is likely to be caused by increasing rates of cesarean section, as the risk of placenta accreta spectrum and thus hysterectomy increases with the number of previous caesarean sections"

5. Was this study registered in the PROSPERO database?

Given the fact that this is an update from a previous review, we failed to register this review in the PROSPERO database, and unfortunately already completed reviews cannot be registered. However, given the fact that we plan to update this review every 5-10 years, we will endorse this recommendation and will certainly register future updates.

STATISTICAL EDITOR COMMENTS:

Tables 1, 4, 5, 6: As in the other Tables, need to include footnote explaining to reader that the prevalence estimates and their CIs are weighted estimates, not based on the aggregated n/N entries provided in Tables.

We have added this explanation to the tables now stating “Weighted prevalence per [...] using random effects model”

Tables 1, 3: Hard to generalize conclusions re: low-income strata or compare to other strata, since there were only 1 or two studies of that income group vs 34 to 75 studies (table 1) or 35 to 77 studies (table 2). Much larger samples, more precise estimates and more stats power to compare among the other three income strata.

We wholeheartedly concur with the statistical editor on this point. Unfortunately, low-income countries remain underrepresented in our updated review. Primarily due to the lack of scientific output from these countries. Therefore we explicitly mention this in the third paragraph of the discussion (page 12, lines 273-280 as well as in our second recommendation in the discussion (page 15, lines 342-344).

General: Since some of these data were previously analyzed, should compare cohorts by suitable strata of year of study, to demonstrate whether the prevalence rates have changed over time.

We agree that changes in prevalence over time may be present, especially with the rise in global rates of caesarean section and subsequently in placenta accreta spectrum and changing medical practices. The previous global prevalence was 0.9 per 1,000 births, and now 1.1.
Ideally prevalence of the same settings/countries/hospitals should be compared stratified by time-intervals. However, no updated studies were published from the exact same previous settings. Rather, new data from other hospitals or regions form the same countries were included (see beneath), adding to the validity of the point estimates of a country’s true prevalence. As such, a comparison of new and old studies would be susceptible to great bias (other regions, hospitals, populations) and is unlikely to reflect true changes over time. The answer lies in future publication of more population based studies of high quality, in order to compare true change of prevalence over time.

New included studies, from countries for which previous data was known:

1 for: Cameroon, Iceland, Ireland, Italy, Jordan, Nigeria, Pakistan, South Africa, US
2 for: Australia and China
4 for: Turkey
1 population based studies from Denmark, Finland, France, Italy, Norway, UK