PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Epidemiology of Placenta Previa Accreta: A Systematic Review and Meta-analysis
AUTHORS	Jauniaux, Eric; Grønbeck, Lene; Bunce, Catey; Langhoff-Roos, Jens; Collins, Sally L

VERSION 1 – REVIEW

REVIEWER	Igor Locatelli University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia
REVIEW RETURNED	19-May-2019

GENERAL COMMENTS	I have read the manuscript entitled: »Epidemiology of Placenta Previa Accreta: A Systematic Review and Meta-analysis« and review it with a particular emphasis on the statistical methods and analyses used. General opinion. The systematic research was comprehensive and all of the elements of the Prisma Checklist have been presented. Prospero registration was also performed. However, I have some concerns about the interpretation of the study results especially regarding huge heterogeneity that was observed and that remained unexplained. Furthermore using median values of the prevalence/incidence reported in the individual studies is not correct. The manuscript should be upgraded in this view. Specific comments: 1. Methods and outcomes used. • Page 8, last paragraph of the method section. State more clearly which outcomes and measures were obtained from the studies and used in forest plots/tables. As huge heterogeneity was expected before conducting the review, random effect models should be applied. However, you have mentioned using fixed effect models but I guess this was not used. Pleas clarify. If not used, do not mention in the methods. • Page 8, last paragraph of the method section. Normal distribution of the data. Explain why is this important and how was this information incorporated in your results? Random effect model uses weighted mean value (corrected for tau) for pooled estimates and you have that value reported in the forest plots (figures 2 to 5), however you reported the pooled estimate using different approach – just by using median value. Why did you use STATA to calculate the pooled effect size, if in the end you report just the median value with IQR? I think that approach by using median values is not correct and it certainly does not capture the statistics behind the meta-analysis. • Heterogeneity in terms of Tau should also be reported. • Page 11, last paragraph of the results section. You have stated that mortality data was also reported in some studies. Why

	mortality was not used as a reporting outcome eg. performing a forest plot? 2. Table 1. • State more clearly which prevalence is reported. Looking at the data for prevalence reported in table 1, you see that are the same as reported in figure 4 (= figure on the page 32) where prevalence for PP an PAS are reported. However in the table 1 caption you used slightly different word. I suggest you to unify the wording placenta previa and placenta previa accreta (instead of placenta previa and PAS). • I luck reporting NOS data (risk of bias assessment) for individual study and not just in aggregated form as reported in figure 2. • In the table 1 you could also add information about diagnostics used in the studies, inclusion of the data for major/minor placenta previa. 3. Figure 2. • Why did you put high risk category in the middle? Risk of bias is expected to represent categories in this way: Low, unclear, high. 4. Figure 3 and 4 and 5. • Explain ES • Explain the parameter on the X axis, negative values on x axis are abundant. • State that random effect model was used and represent tau. If used? • Figure 3. 0.89 is the pooled prevalence. This should be reported in the manuscript text or you should use different meta-analysis method if you do not believe in this estimate. 5. Subgroup analyses • By making subgroup analysis according to the study design (retrospective vs. prospective) no additional heterogeneity was explained. So it looks like that study design does not influence the study results. Looking at table 1 it can be ad oculum estimated that the country origin influences the heterogeneity of the study results. The studies performed in Arabic countries have higher estimates compared to the other countries. Furthermore the majority of the studies come from that region indicating that PAS could be more relevant health problem in these countries, and more research in this area was done there. However, this could influence your conclusions, since you have decided to use median number as pooled estimate. It looks like your finding is biased due to publication bias. To overcome this, several subgroup analyses according to country regions (or women health policy) should be performed. Only 3 studies were performed in EU/USA. I believe that for these countries the estimates of prevalence for PAS could be taken from data registry. Moreover, your final estimates should be compared to such data if existed. This is a major issue in this manuscript. • Did you also test a diagnostic tool used in the studies in the subgroup analysis?

REVIEWER	Zhengping Liu Foshan Institute of Fetal Medicine, Southern Medical University Affiliated Maternal & Child Health Hospital of Foshan, Foshan, Guangdong, China
REVIEW RETURNED	23-May-2019

GENERAL COMMENTS	The authors provided comprehensive estimates for the prevalence of placenta previa and that of placenta previa with PAS, as well as the incidence of PAS in women with placenta previa. This is interesting enough to attract the readers' attention and has some

	clinical and public significance. However, there were several methodological concerns that the authors should address. 1. How did the authors define these prevalence and incidence? Among those included studies, some reported prevalence among deliveries whereas others reported prevalence among pregnancies. Please explain the rationality of the synthesis of these two kinds of value. 2. There was neither sensitivity analysis nor publication bias tests seen throughout the manuscript. Minor comments: 1. The number of references is confused, please check it. 2. The description seemingly doesn't match the figure 2, please check it. 3. Table 1, the population in the study of Wortman et al. is 148,031 births, not 138,031. Please confirm this. 4. The important articles (Medicine (Baltimore). 2016 Oct;95(40):e5107; Trop Med Int Health. 2013 Jun;18(6):712-24; Medicine (Baltimore). 2017 Apr;96(16):e6636) should be cited.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Igor Locatelli

Institution and Country: University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia

Specific comments:

1. Methods and outcomes used.

• Page 8, last paragraph of the method section. State more clearly which outcomes and measures were obtained from the studies and used in forest plots/tables. As huge heterogeneity was expected before conducting the review, random effect models should be applied. However, you have mentioned using fixed effect models but I guess this was not used. Pleas clarify. If not used, do not mention in the methods.

A: Changed as suggested.

• Page 8, last paragraph of the method section. Normal distribution of the data. Explain why is this important and how was this information incorporated in your results? Random effect model uses weighted mean value (corrected for tau) for pooled estimates and you have that value reported in the forest plots (figures 2 to 5), however you reported the pooled estimate using different approach – just by using median value. Why did you use STATA to calculate the pooled effect size, if in the end you report just the median value with IQR? I think that approach by using median values is not correct and it certainly does not capture the statistics behind the meta-analysis.

• Heterogeneity in terms of Tau should also be reported.

• Page 11, last paragraph of the results section. You have stated that mortality data was also reported in some studies. Why mortality was not used as a reporting outcome eg. performing a forest plot?

A: We included the methods that we planned to use in advance of looking at the data to show that our decisions in analysis were not driven by data. This follows guidance in the Cochrane Handbook. It was our intention to use random effect estimates unless there were too few studies to allow for a robust estimate, in this case we would use the fixed effect model. A meta- analysis synthesises information from different studies to yield a pooled estimate however for this to be valid it is important to explore the heterogeneity between studies to see

if they are combining similar information. The Forest plots are included in order to illustrate to readers just how high this inconsistency between studies is. We believed it to be too high and so instead provided study specific estimates to give readers a sense of the data that we had found.

2. Table 1.

- State more clearly which prevalence is reported. Looking at the data for prevalence reported in table 1, you see that are the same as reported in figure 4 (= figure on the page 32) where prevalence for PP an PAS are reported. However in the table 1 caption you used slightly different word. I suggest you to unify the wording placenta previa and placenta previa accreta (instead of placenta previa and PAS).

A: Changed as requested.

- 1-3 I luck reporting NOS data (risk of bias assessment) for individual study and not just in aggregated form as reported in figure 2. & In the table 1 you could also add information about diagnostics used in the studies, inclusion of the data for major/minor placenta previa. Why did you put high risk category in the middle? Risk of bias is expected to represent categories in this way: Low, unclear, high.

A: We agree that Figure 2 is confusing and would be more appropriated for a Quadas assessment for diagnostic studies. The characteristics and quality assessment using the NOS are presented in appendix 2.

4. Figure 3 and 4 and 5.

- Explain ES

A: ***ES, effect size. CI, confidence interval***

- Explain the parameter on the X axis, negative values on x axis are abundant.
- State that random effect model was used and represent tau. If used?
- Figure 3. 0.89 is the pooled prevalence. This should be reported in the manuscript text or you should use different meta-analysis method if you do not believe in this estimate.

A: We apologies if inclusion of the Forest plot has caused confusion. Our reason for including the Forest plot is to show the inconsistency across studies. We have used I-square rather than τ^2. We accept that τ2 is more useful for comparisons of heterogeneity among subgroups, but values depend on the treatment effect scale. I^2 places focus on the effect of heterogeneity and is therefore preferable when assessing inconsistency across studies. Because there is such high inconsistency we do not believe that the pooled figure should be cited which is why we have provided study specific estimates.

5. Subgroup analyses

- By making subgroup analysis according to the study design (retrospective vs. prospective) no additional heterogeneity was explained. So it looks like that study design does not influence the study results. Looking at table 1 it can be ad oculum estimated that the country origin influences the heterogeneity of the study results. The studies performed in Arabic countries have higher estimates compared to the other countries. Furthermore the majority of the studies come from that region

indicating that PAS could be more relevant health problem in these countries, and more research in this area was done there. However, this could influence your conclusions, since you have decided to use median number as pooled estimate. It looks like your finding is biased due to publication bias. To overcome this, several subgroup analyses according to country regions (or women health policy) should be performed. Only 3 studies were performed in EU/USA. I believe that for these countries the estimates of prevalence for PAS could be taken from data registry. Moreover, your final estimates should be compared to such data if existed. This is a major issue in this manuscript.

- Did you also test a diagnostic tool used in the studies in the subgroup analysis?

A. That is correct but it would be highly biased to separate countries according to their geographic location as a parameter for poor quality clinical research (PAS is a worldwide research issue) and the main reason for high prevalence of placenta previa with, and without, PAS is the high birth rates and high c-section rates in many countries outside Europe and North-America. We have added a paragraph in the discussion to highlight this issue (and one of the suggested references). However, to perform the analysis proposed would require an epidemiological study which included local/national birth & c-section rates, unfortunately no such study currently exists.

Reviewer: 2

Reviewer Name: Zhengping Liu
Institution and Country:
Foshan Institute of Fetal Medicine, Southern Medical University Affiliated Maternal & Child Health Hospital of Foshan, Foshan, Guangdong, China

The authors provided comprehensive estimates for the prevalence of placenta previa and that of placenta previa with PAS, as well as the incidence of PAS in women with placenta previa. This is interesting enough to attract the readers' attention and has some clinical and public significance.

Methodological comments.

1. How did the authors define these prevalence and incidence? Among those included studies, some reported prevalence among deliveries whereas others reported prevalence among pregnancies. Please explain the rationality of the synthesis of these two kinds of value.

A: Prevalence is the number of placenta previas with PAS in a defined population of pregnancies or births & incidence is the number of PAS in women presenting with a placenta previa.

2. There was neither sensitivity analysis nor publication bias tests seen throughout the manuscript.

A: These were performed using the NOS for cohort studies, see appendix 2.

Minor comments:

1. The number of references is confused, please check it.

A: All references were checked. A reference number was missing in the introduction and one was attributed to a different author in the discussion. Thank you for spotting it.

2. The description seemingly doesn't match the figure 2, please check it.

A: Checked and correct and displayed in Appendix 2 for clarification. Figure 2 was therefore removed.

3. Table 1, the population in the study of Wortman et al. is 148,031 births, not 138,031. Please confirm this.

A: This was a typo. Thank you for spotting it. Please note that this does not change the results of analysis.

4. The important articles (Medicine (Baltimore). 2016 Oct;95(40):e5107; Trop Med Int Health. 2013 Jun;18(6):712-24; Medicine (Baltimore). 2017 Apr;96(16):e6636) should be cited.

A: We are aware of these articles 2 of which are from the reviewer own references. The first 2 are systematic reviews of placenta previa without PAS and thus are not directly relevant to our study but we have added the reference in Trop Med Int Helath by Cresswell et al as it supports the answer to comment No 5 of reviewer 1. The third articles (Prevalence of abnormally invasive placenta among deliveries in mainland China: A PRISMA-compliant Systematic Review and Meta-analysis. Fan D, Li S, Wu S, Wang W, Ye S, Xia Q, Liu L, Feng J, Wu S, Guo X, Liu Z.

Medicine (Baltimore). 2017 Apr;96(16):e6636) is a systematic review including exclusively articles in Chinese and thus we were not able to assess them. In addition, we were very surprised by an unusual exclusion criterion used by the authors to select the articles included in their study i.e. "All studies were conducted in mainland China and because of cultural differences from mainland China, studies from Taiwan, Hong Kong, and Macao were excluded !!!!:

VERSION 2 – REVIEW

REVIEWER	Igor Locatelli University of Ljubljana, Faculty of Pharmacy, Ljubljana, Slovenia
REVIEW RETURNED	29-Jul-2019

GENERAL COMMENTS	The authors have addressed all my comments. I do not completely agree with the responses, since it is still strange to perform a meta-analysis (as it is promised in the article title) and then represent the results as median values of effect sizes with IQR (the last two sentences in the results section of the abstract). However, in the manuscript this peculiarity is more or less explained.

REVIEWER	Zhengping Liu Foshan Institute of Fetal Medicine, Southern Medical University Affiliated Maternal & Child Health Hospital of Foshan, Foshan, Guangdong, China
REVIEW RETURNED	23-Jul-2019

GENERAL COMMENTS	I have carefully read the revised manuscript. It's a lot better than before, however, I have two other concerns that the authors should address.

	The placenta accreta spectrum (PAS) separated into three categories: placenta creta, placenta increta, and placenta percreta. Their clinical results varied widely. The author only gave the total results of PAS. It is better to be able to give individual results. In addition, the Newcastle Ottawa Assessment Scale is a fine choice, but looking at table 1, all of the included articles have gained at least one star. Please indicate in the methods section which factor you chose as main confounding factor to adjust for (and if adjusted for, add one star for those specific papers), and indicate which is the second most important factor and add one star for those studies adjusting for that factor.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name: Zhengping Liu

The placenta accreta spectrum (PAS) separated into three categories: placenta creta, placenta increta, and placenta percreta. Their clinical results varied widely. The author only gave the total results of PAS. It is better to be able to give individual results.

We thank the reviewer for this comment as it further highlights the heterogeneity of the data published in the international literature on the differential diagnosis of the different grades of PAS and the need for standardisation of clinical protocols. Table 3 was added to display the detailed results of the nine studies that provided data on the depth of villous invasiveness.

In addition, the Newcastle Ottawa Assessment Scale is a fine choice, but looking at table 1, all of the included articles have gained at least one star. Please indicate in the methods section which factor you chose as main confounding factor to adjust for (and if adjusted for, add one star for those specific papers), and indicate which is the second most important factor and add one star for those studies adjusting for that factor.

Table 1 corresponds to Figure 2 of the first version of our manuscript. Methodology modified as requested.

VERSION 3 – REVIEW

REVIEWER	Zhengping Liu Foshan Institute of Fetal Medicine, Southern Medical University Affiliated Maternal & Child Health Hospital of Foshan, Foshan, Guangdong, China
REVIEW RETURNED	01-Sep-2019

GENERAL COMMENTS	Thanks for authors revised their manuscript. However, some comments must be considered for further modification. 1. Authors provided the frequency of the subgroup of PAS in table 3. However, I prefer to think about the prevalence or incidence.

	2. “In addition, the Newcastle Ottawa Assessment Scale is a fine choice, but looking at table 1, all of the included articles have gained at least one star. Please indicate in the methods section which factor you chose as main confounding factor to adjust for (and if adjusted for, add one star for those specific papers), and indicate which is the second most important factor and add one star for those studies adjusting for that factor.” There was no response the above comment. I want to know “which factor authors chose as main confounding factor to adjust for in the comparability part in the Newcastle Ottawa Assessment Scale (and if adjusted for, add one star for those specific papers), and indicate which is the second most important factor and add one star for those studies adjusting for that factor.” 3. The authors said they extraction author institution, year of publication, …diagnosis of PAS at birth in Appendix 1. However, I cannot find the Appendix 1. 4. In the Appendix Electronic search strategy, the authors provided the search strategy. However, it is not right. Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. 5. The publication bias test and sensitivity analysis are still not given. 6. The last one but the most important one issue, the data was presented as the median and interquartile range in the manuscript. However, in the forest plot, it presented the ES and 95%CI. They are in conflict with each other. In addition, for rare occurrences, what is the method to calculate the prevalence or incidence? And what is the method to pool the prevalence or incidence? The statistical method used in this manuscript seems incorrect. Please contact statistical experts for confirmation.

VERSION 3 – AUTHOR RESPONSE

1. Authors provided the frequency of the subgroup of PAS in table 3. However, I prefer to think about the prevalence or incidence.

R: We calculated the prevalence for each grade of PAS and added a line in the results section.

2. “In addition, the Newcastle Ottawa Assessment Scale is a fine choice, but looking at table 1, all of the included articles have gained at least one star. Please indicate in the methods section which factor you chose as main confounding factor to adjust for (and if adjusted for, add one star for those specific papers), and indicate which is the second most important factor and add one star for those studies adjusting for that factor.”
There was no response the above comment. I want to know “which factor authors chose as main confounding factor to adjust for in the comparability part in the Newcastle Ottawa Assessment Scale (and if adjusted for, add one star for those specific papers), and indicate which is the second most important factor and add one star for those studies adjusting for that factor.”

R: The reviewer is suggesting here that we select which of the various categories of an agreed score system is of most importance. The scores do not do this because they consider each aspect to be an element of concern.

3. The authors said they extraction author institution, year of publication, …diagnosis of PAS at birth in Appendix 1. However, I cannot find the Appendix 1.

R: Appendix 1 remained unchanged between R1 and R2 and the reviewer may not have seen it during R2. In order not to overload the readers of the main text we suggest to also move Table 1 into supplementary material as Appendix 2. The tables containing the main have been renumbered accordingly.

4. In the Appendix Electronic search strategy, the authors provided the search strategy. However, it is not right. Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.

R: It seems that the reviewer has seen Appendix 1. As advised when we submitted our paper to BMJ open, we have deposited our data on Dryad digital repository which should enable other to repeat our analysis if they so wish.

5. The publication bias test and sensitivity analysis are still not given.

R: Our main message is that we believe there is too much heterogeneity to rely upon a meta analysed result. It is only if we are presenting a pooled estimate which we are advocating is the "truth" that we would need to consider publication bias and sensitivity analyses.

6. The last one but the most important one issue, the data was presented as the median and interquartile range in the manuscript. However, in the forest plot, it presented the ES and 95%CI. They are in conflict with each other. In addition, for rare occurrences, what is the method to calculate the prevalence or incidence? And what is the method to pool the prevalence or incidence? The statistical method used in this manuscript seems incorrect. Please contact statistical experts for confirmation.

R: The reviewer appears to lack expertise in this area and it would be preferable for him/her not to comment on this.