Author's response to reviews

Title: Amniotic fluid embolism incidence, risk factors and outcomes: a review and recommendations

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Author's response to reviews: see over
Dear Sir,

Re: Amniotic fluid embolism incidence, risk factors and outcomes: a review and recommendations

We have revised our manuscript further as requested. We have amended the authors’ contributions section to read as follows:

MKn conceived the study, participated in the workshop, presented data, contributed to discussions and drafted the manuscript/paper. CB participated in the workshop, presented data, contributed to discussions and participated in revising the manuscript. MKr participated in the workshop, presented data, contributed to discussions and participated in revising the manuscript. GL participated in the workshop, presented data, contributed to discussions and participated in revising the manuscript. JO participated in the workshop, presented data, contributed to discussions and participated in revising the manuscript. CR participated in the workshop, presented data, contributed to discussions and participated in revising the manuscript. CS participated in the workshop, presented data, contributed to discussions and participated in revising the manuscript. ES participated in the workshop, presented data, contributed to discussions and participated in revising the manuscript. JvR participated in the workshop, presented data, contributed to discussions and participated in revising the manuscript. JZ participated in the workshop, presented data, contributed to discussions and participated in revising the manuscript. All authors read and approved the final manuscript.

We look forward to hearing from you.

Yours sincerely,

Marian Knight
Response to Reviewer and Editor Comments

Reviewer: Shali Mazaki-Tovi
Reviewer’s report:
The aim of the study was to determine incidence, risk factors and outcomes of amniotic fluid embolism (AFE) and to investigate whether any variation identified could be ascribed to methodological differences between the studies. The available data sources on the incidence of AFE in Australia, Canada, the Netherlands, the United Kingdom and the USA were investigated. Data regarding the risk factors and outcomes of AFE were also reviewed (where information was available). The authors reported that the incidence of AFE ranged from 1.9 cases per 100 000 maternities (UK) to 6.1 per 100 000 maternities (Australia). The lowest incidence rates were obtained through validated case identification (range 1.9-2.5 cases per 100 000); rates obtained from retrospective analysis of population discharge databases were significantly higher (range 5.5-6.1 per 100 000). Older maternal age and induction of labour were consistently associated with AFE. The authors concluded that comparisons of AFE incidence estimates should be restricted to studies using similar methodology and that comparisons of AFE incidence between and within countries would be facilitated by development of an agreed case definition. The authors recommended that groups conducting population-based studies regarding AFE should develop an agreed strategy to allow combined analysis of data and that future specific studies on AFE should aim to collect information on management and longer-term outcomes for both mothers and infants.

The manuscript is interesting and well-written. However the major weakness of the study for the BMC Pregnancy and Childbirth is lack of originality. The new information provided by this manuscript is very limited.
We believe the results of this study are new and important. This review highlights the benefits of detailed comparison of AFE incidence and ascertainment methods from different population-based studies and has identified a number of difficulties with making direct international comparisons. The methodology used by individual studies impacts on estimates of disease incidence and case fatality, and may also account for inconsistencies in reported risk factors. There is a need for consistent study methodologies, including agreed case definition and case validation criteria. The use of such unified methodologies will allow for valid international comparisons of incidence in the future, and may permit pooling of international data to provide more reliable information on associated factors, management and outcomes, thus allowing for development of preventive and treatment strategies to improve outcomes of this rare but serious condition.

Additional major concern is the heterogeneity in the databases, definitions of AFE and the inconsistency in the availability of information in the datasets used in this study. These limitations along with the rarity of AFE led to conclusions and recommendations that have limited clinical value and a marginal contribution to the study of this important condition. As noted above, we (and the other reviewers) disagree with this viewpoint. Published population-based studies of incidence and risk factors are inevitably compared, and we believe that highlighting the impact of differences in methodology and definitions will lead to more consistent, comparable and
robust studies in the future. We therefore feel that publication of this review will make an important contribution to the literature.

Reviewer: Offer Erez
Reviewer’s report:
The study by Knight et al is a large review on the prevalence and risk factors for amniotic fluid embolism that is based on population based data from the United Kingdom, Netherlands, Australia, and the USA. Given the rarity of this condition the reports in the literature are inconsistent and differ by definition and mode of the data collection. In light of this situation the effort made by the authors is impressive.
The manuscript is well written and it is sound in term of its statistical methods, recommendations, and need only a minor revision.

Specific comments
1. Methods section, on page 6, 2nd paragraph- I would like to suggest the authors to add references to the factors previously reported in the literature, and to specify the factors themselves.

   We have specified the factors and added the references as suggested:
   Putative risk factors, identified from factors previously reported in the literature (maternal age, parity, smoking status, race/ethnicity, diabetes, multiple pregnancy, previous caesarean delivery, hypertensive disorders, placenta praevia, placental abruption, presentation at delivery, chorioamnionitis, polyhydramnios, induction of labour, mode of delivery, manual removal of placenta, macrosomia, gestational age at delivery) [1-4, 22], were examined using univariable or full multivariable logistic regression analysis where possible and results presented as odds ratios (ORs) with 95% confidence intervals.

2. Results section, on page 8, first paragraph- the representation of the data regarding the role of induction of labor is inconsistent. There is a contradiction between the opening sentence of the paragraph stating " The only factors consistently associated with AFE across all five countries were induction of labour and maternal age…" and the what is written in the rest of the paragraph, since for example in the USA there was no statistical significant association between induction of labor and amniotic fluid embolism. Thus, I would like to suggest the authors to rephrase their opening sentence and to limit the statement to maternal age only.

   We would prefer to retain the sentence as originally written, since both these factors are consistently associated with raised odds of AFE. We have, however, clarified that in the case of both age and induction of labour, there was one country in which the association was not statistically significant:
   The only factors consistently associated with AFE across all five countries were induction of labour and maternal age; although with both of these factors, in one country the association was not statistically significant.

3. Why do the authors presents the incidence of amniotic fluid embolism in the Netherlands between the years 2004-2006 on Table 2 and the morality ratio between the years 1983-1992 and 1993-2005 in Table 3 this is a bit confusing, please explain.

   The data are presented in this format since these are the groupings in which the data are available. Data were collected on severe maternal morbidity in the Netherlands solely between 2004 and 2006;
the maternal deaths data represent results from the Dutch national confidential enquiries into maternal deaths, which have historically been analysed in two time periods, 1983-1992 and 1993-2005. We have clarified this in the methods section, p5:

Fatal cases were identified from the Dutch Confidential enquiries into the causes of maternal mortality between 1983-1992 and 1993-2005 [15]. Incident cases (fatal and non-fatal) were identified through the LEMMoN study of severe maternal morbidity between 2004 and 2006 [16].

4. Table 5 is too long it is needed to be divided into sub tables dealing with maternal factors, pregnancy factors, induction and delivery.
We have divided the table as suggested into tables 5-8.

5. Did the authors include in their study any information regarding the level of the hospitals in which the patients were treated and did this factor had an impact on the outcome of the patients?
We did not include an analysis of hospital level in our study, because of the variety of health systems covered (public/private), and the difficulty with identifying patient transfers in some of the data sources.

6. On page 11, 1st paragraph, two lines from the bottom please add references to the USA studies cited here.
We have added the reference as suggested.

Reviewer: Edi Vaisbuch
Reviewer's report:
Summary
This study is a collaborative effort to define the incidence, risk factors and outcomes of amniotic fluid embolism using population-based regional or national data from five high resource countries – Australia, Canada, The Netherlands, United Kingdom and United States. The authors report an incidence of amniotic fluid embolism from 1.9/100,000 cases (UK) to 6.1/100,000 (Australia) with the lowest estimated incidence rates were validated case identification existed. Case fatality rates ranged from 11 to 43%. Older maternal age and induction of labour were the only factors consistently associated with amniotic AFE. The authors present key recommendations for future studies on amniotic fluid embolism and encourage the development of an agreed case definition and an agreed set of criteria among countries to minimize inclusion of false positive cases for database studies.

General comments
I read this study with great interest. It is an interesting, clear, thoughtful and very well written study. The results are clearly presented and the discussion is well organized. I have only a few small suggestions:
Specific comments:
1. Was the definition used in each country for maternal death the same as that used by the WHO (death within 42 days of termination of pregnancy)? I am not sure if all readers are aware
of the exact definition, thus I would suggest adding to the methods the definition used. (Discretionary Revision)
We have clarified in the methods section that the definition used was as the reviewer surmised:

- The definitions and codes used to identify cases in each country are shown in table 1.
- Maternal death was defined throughout as death of a woman while pregnant or within 42 days of the termination of pregnancy.

2. In Table 5 please add to the table footnote what RR and aOR represent. (Discretionary Revision)
We have added this as suggested.

Editor comment:
Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.
We have formatted the paper according to the guidance.