

PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The impact of level of neonatal care provision on outcomes for preterm babies born between 27-31 weeks of gestation, or with a birthweight between 1000 and 1500g: a review of the literature
AUTHORS	Ismail, Abdul Qader; Boyle, Elaine; Pillay, Thillagavathie; Study Group, OptiPrem

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Sinno Simons Institution and Country: Erasmus MC, The Netherlands Competing interests: none
REVIEW RETURNED	16-Oct-2019

GENERAL COMMENTS	<p>In the manuscript entitled ‘ Does place of birth or care matter for babies born between 27 and 31 weeks of gestation? A systematic review’ Abdul Qader Tahir Ismail and colleagues describe their review of literature on behalf of the OptiPrem study. Group. The aim of the study is clear and well described: they have previously shown that the outcome of extremely low birth weight / extremely prematures is related to the kind of center/ward they are admitted to. Now they want to answer the question if the same holds for the preterm newborns that are a bit older/less vulnerable (>27 weeks-31 weeks/ 1000-1500 grams).</p> <p>They performed a literature search and the studies included were too heterogenous to perform a meta-analysis. Therefore, they reviewed the outcome (mortality and morbidity) of 9 studies that met the criteria. However, the studies were heterogenous and results may. Be biased.</p> <p>The report is important. To my opinion, the most important flaw is that the introduction is very much oriented on the UK only. It would be better if the authors could put the problem in a broader perspective. Similar units with level III, level II intensive care and high-care might exist in other countries. Babies born between 27-31 are part of discussion in more countries.</p> <p>The report is well written. The part in the discussion where they argue that one should actually be able to evaluate the outcome per week of gestation, I liked most. There is quite a difference between a 28 weeks and a 31 weeks old newborn. Although the results are limited I think the report is of value, especially if the authors could put it in a more internationally perspective. Would it not also be a good idea to have these data on how countries organize their neonatal care and how this relates to outcome in the near. future?</p>
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REVIEWER	Reviewer name: Karel allegaert Institution and Country: KU Leuven, Belgium and Erasmus MC Rotterdam, the Netherlands Competing interests: None, although i do know some of the authors involved
REVIEW RETURNED	29-Oct-2019

GENERAL COMMENTS	<p>Although I highly value the research question, I have raised concerns and comments, in an attempt to make the authors to further reflect on the analysis, and how to report the data as observed. These comments are rather 'chronological'.</p> <p>The title is somewhat miss leading, since place of birth refers to the available level of expertise at the place of birth (both obstetric as neonatal), and do the authors refer to level of care (level 2, 3). This issue of location is discussed in the intro (but with focus on neonatal care only), but is not reflected in the abstract.</p> <p>How do the authors discriminate between <27 and ≤ 27 since it reads as if the 27 wks group is in both groups ? Have the authors considered to do a similar analysis up to 29, or 30 wks ?</p> <p>Do you anticipate that – if the analysis were done based on individual data – the results may have been more robust ?</p> <p>Although I understand the 'co-use' of birth weight, this information in at best an estimated until shortly after delivery ? how do you consider this uncertainty in your analysis ? I get the point that it is an approach to ensure to avoid non-inclusion of relevant data, but it may also introduce additional uncertainties, not fully reflected in the growth chart.</p> <p>How do you consider 'bias', being inability to referral because of imminent delivery ?</p> <p>Have you considered a combined outcome variable, like mortality or severe morbidity, as commonly used in outcome studies in extreme preterm cases ?</p> <p>Needs further study is a poor 'outcome', or at least does not provide a lot of guidance. can you indicate what and how ? since the bias will likely remain ?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

In the manuscript entitled 'Does place of birth or care matter for babies born between 27 and 31 weeks of gestation? A systematic review' Abdul Qader Tahir Ismail and colleagues describe their review of literature on behalf of the OptiPrem study. Group. The aim of the study is clear and well described: they have previously shown that the outcome of extremely low birth weight / extremely prematures is related to the kind of center/ward they are admitted to. Now they want to answer the question if the same holds for the preterm newborns that are a bit older/less vulnerable (>27 weeks-31 weeks/ 1000-1500 grams).

They performed a literature search and the studies included were too heterogenous to perform a meta-analysis. Therefore, they reviewed the outcome (mortality and morbidity) of 9 studies that met the criteria. However, the studies were heterogenous and results may. Be biased.

The report is important.

- We thank the reviewer for taking the time to review our manuscript, their relevant comments and recognition of the importance of this topic.

1.1 To my opinion, the most important flaw is that the introduction is very much oriented on the UK only. It would be better if the authors could put the problem in a broader perspective. Similar units with level III, level II intensive care and high-care might exist in other countries. Babies born between 27-31 are part of discussion in more countries.

- We have changed the introduction to reflect a more international perspective to the topic (see Introduction, page 4-5).

1.2 The report is well written. The part in the discussion where they argue that one should actually be able to evaluate the outcome per week of gestation, I liked most. There is quite a difference between a 28 weeks and a 31 weeks old newborn. Although the results are limited I think the report is of value, especially if the authors could put it in a more internationally perspective.

- We thank the reviewer for their kind comments and have edited the introduction to introduce a more international perspective as per their advice (see Introduction, page 4-5).

1.3 Would it not also be a good idea to have these data on how countries organize their neonatal care and how this relates to outcome in the near future?

- We have included a table (table 1b, page 7) summarising how several countries (U.S., Canada, Australia, New Zealand, Finland, Sweden, France) organise their neonatal care.

Reviewer: 2

Although I highly value the research question, I have raised concerns and comments, in an attempt to make the authors to further reflect on the analysis, and how to report the data as observed. These comments are rather 'chronological'.

- We thank the reviewer for taking the time to review our manuscript, and for recognising the value of the research question.

2.1 The title is somewhat miss leading, since place of birth refers to the available level of expertise at the place of birth (both obstetric as neonatal), and do the authors refer to level of care (level 2, 3).

- We have changed the title as per the reviewer's advice, to specify that we are interested in the level of neonatal care, not obstetric care (see Title, page 1).

2.2 This issue of location is discussed in the intro (but with focus on neonatal care only), but is not reflected in the abstract.

- We have changed the Abstract to reflect this (see Abstract, page 2).

2.3 How do the authors discriminate between <27 and ≤ 27 since it reads as if the 27 wks group is in both groups?

- We have included clarification within the Introduction (Page 4) and in the abstract (page 2) to address this issue:

- o babies born between 27+0 and 31+6 weeks (hereafter called '27-31 weeks')

Have the authors considered to do a similar analysis up to 29, or 30 wks?

- We were specifically interested in babies born between 27-31 weeks because the way neonatal care is organised in the UK, this group of babies can be cared for in both level 3 (NICU) and level 2 (LNU) units, and internationally there isn't a similar care pathway as there is for babies born <27 weeks.
- However, we agree with what the reviewer seems to be inferring, that an analysis of a smaller gestational age range (i.e. 27-29/30 weeks) might reveal significant differences (as has been found for babies born <27 weeks), compared to using the entire 27-31 week gestational age range. While this is not possible from the available data (as shown by the lack of studies identified by our systematic review search strategy), we touch upon this in our discussion (page 15).
- We argue that grouping these babies may in fact obscure differences in outcomes for babies born at each gestational week between 27-31 weeks, given the heterogeneity of babies born within this gestational age range. We propose that future research should provide outcomes by each gestational week (which was not available from the studies identified by our systematic review), so we can better identify best place of birth/care for these babies.

Do you anticipate that – if the analysis were done based on individual data – the results may have been more robust?

- We agree that this may be a more robust approach, unfortunately this level of detail was not available to us.

Although I understand the 'co-use' of birth weight, this information in at best an estimated until shortly after delivery? how do you consider this uncertainty in your analysis? I get the point that it is an approach to ensure to avoid non-inclusion of relevant data, but it may also introduce additional uncertainties, not fully reflected in the growth chart.

- Since our review was looking at neonatal level of care, not maternal level of care, the exact birthweight was known for all babies within the 11 studies categorising babies by birthweight.
- We agree with the reviewer that if we were looking at maternal level of care, and this was being decided based on estimated birthweight from antenatal scans, this would have introduced a degree of uncertainty in our analysis

How do you consider 'bias', being inability to referral because of imminent delivery?

- We agree with the reviewer that imminent delivery can affect whether an in-utero transfer occurs, which can therefore affect the birth location for a small proportion of babies. This is why we divided the studies identified by our systematic review search strategy into three based on comparator groups as shown in Table 2 (previously Table 1). It is difficult to compare studies across those broad groups, given differences in birth location, whether in-utero or ex-utero transfer has occurred, and the level of unit where subsequent care is being delivered (and whether this information is provided to us). If we had found sufficient data, which we were able to combine in a meta-analysis, then it would have been of relevance to discuss finer points regarding unmeasured bias.

Have you considered a combined outcome variable, like mortality or severe morbidity, as commonly used in outcome studies in extreme preterm cases?

- We reported all outcomes presented by the identified studies. Some of them used a combined morbidity outcome variable. This is reflected in the morbidity column of Table 2 (previously Table 1). Due to heterogeneity of the morbidities reported, we were unable to create a 'composite morbidity and mortality outcome measure' for those babies born and cared for in a NICU vs non-NICU setting.

Needs further study is a poor 'outcome', or at least does not provide a lot of guidance. can you indicate what and how? since the bias will likely remain?

- In our new Future Perspective section (page 16) we mention the Optiprem study, which will be seeking to answer this question (regarding best place of birth/care for babies born between 27-31 weeks of age), using national data from England and looking at gestation specific outcomes.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Karel allegaert Institution and Country: KU Leuven and Erasmus MC, Rotterdam Competing interests: None
REVIEW RETURNED	19-Jan-2020

GENERAL COMMENTS	thank you for the extensive revision. In my assessment, this has resulted in a clearer paper with unfortunately no clear answer to the question raised. is there a potential copyright issue with the WHO growth chart reproduction ?
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REVIEWER	Reviewer name: Sinno Simons Institution and Country: Erasmus UMC - Sophia Children's Hospital Rotterdam, the Netherlands Competing interests: None
REVIEW RETURNED	22-Jan-2020

GENERAL COMMENTS	The authors did a great job and significantly improved the manuscript. The UK neonatal infrastructure is well explained as is the aim of the study. Methods and results nicely describe the thorough review. Discussion put the problem into perspective that is also relevant for other countries. The organization of healthcare needs improvement and this study shows important lacking data for the neonatal care units. Off coarse it would be even better to compare internationally... I have no additional suggestions for improvement.
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