

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to the BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open where it was re-reviewed and accepted.

## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Reduction in stillbirths at term after new birth induction paradigm. Results of a national intervention
<b>AUTHORS</b>	Hedegaard, Mette; Lidegaard, Øjvind; Skovlung, Charlotte; Mørch, Lina; Hedegaard, Morten

## VERSION 1 - REVIEW

<b>REVIEWER</b>	Heazell, Alexander
<b>REVIEW RETURNED</b>	10-May-2014

<b>GENERAL COMMENTS</b>	<p>This manuscript addresses an important topic for obstetricians, intervention to reduce stillbirth rates. Such studies are hampered by the relatively infrequency of stillbirth combined with the many different conditions which can lead to stillbirth. Thus, adequately powered prospective intervention studies are prohibitively large. The authors address this problem by a population registry based study of over 800,000 births. This demonstrates that since January 2000 there have been changes in national guidance and practice regarding induction of labour resulting in an increased rate of induction of labour and over the same time frame the rate of stillbirth after 37 weeks has reduced.</p> <p>The authors need to clarify their hypothesis. Was it that a more interventionalist approach to induction of labour (IOL) reduced stillbirths or that induction after 41+3 reduced stillbirths after 42 weeks? It seems that the former question is being addressed. This is critical because it affects how the authors divide their data set. Currently, they seem to have picked a somewhat arbitrary division of 3,3,3,2 and 2 year epochs. If they are addressing whether a more interventionalist policy reduces stillbirth it would be more appropriate to break the study down into a 2000-2007 group where the IOL rate was 12.4-15.5 and 2008-2012 when the IOL rate was 17.3-24.5%.</p> <p>It is not clear from the methods whether stillbirths in infants with congenital anomalies were excluded. It would be optimal if they were as timing of delivery would not be expected to achieve an impact on stillbirth rate.</p> <p>In the regression analysis the authors state that the increased proportion of women over the age of 40 giving birth would likely increase the number of stillbirths. Although this is a statistically significant increase in this group the effect on the number of stillbirths is comparatively modest. The likely increase in stillbirth risk</p>
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	<p>&gt;40 is around an odds ratio of 5. If we accept that this increases the SB rate after 37 weeks this would be 3.5 per 1,000 births after 37 weeks (using the data from 2000-2). If 3% of births were to women &gt;40 this would be responsible for approximately 12 stillbirths out of the 489 so it is extremely unlikely to materially alter the results.</p> <p>The most significant issue is how one can determine whether it is the IOL policy (intervention vs minimal) that is responsible for the very welcome reduction in stillbirths. What else changed in the period from 2000-2012. It is easily conceivable that other aspects of antenatal or intrapartum care have changed in this period including better screening for fetal growth restriction, improved management of reduced fetal movements (both of which would increase the IOL rate). There have also been advances in the management of hypertension and diabetes. This may be relevant as the perinatal mortality rate falls by 0.5 per 1,000 from 40 weeks and 0.07 from 37 weeks before the IOL rate rises significantly which would suggest that IOL policy cannot be the only factor at work here, although I accept these trends largely accelerate after 2009.</p> <p>A relatively minor comment is that some of the terms used do not translate into English particularly well. For example, in the abstract the authors refer to the newer strategy as "offensive". I think it would be better to phrase this as a more "interventional approach" as offensive can also be taken as insulting or certainly less good. We would not use the term "stillborns" instead would suggest stillborn infants or stillbirths. E.g. line 61 I would suggest the worldwide number of stillbirths is estimated... and line 98 however achieved for all stillbirths. I would also suggest changing the term "adipose women" to women with BMI &gt;30.</p>
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- This manuscript received two reviews at the BMJ but the other referee had declined to make his comments public.

### VERSION 1 – AUTHOR RESPONSE

#### Comments:

This manuscript addresses an important topic for obstetricians, intervention to reduce stillbirth rates. Such studies are hampered by the relatively infrequency of stillbirth combined with the many different conditions which can lead to stillbirth. Thus, adequately powered prospective intervention studies are prohibitively large. The authors address this problem by a population registry based study of over 800,000 births. This demonstrates that since January 2000 there have been changes in national guidance and practice regarding induction of labour resulting in an increased rate of induction of labour and over the same time frame the rate of stillbirth after 37 weeks has reduced.

The authors need to clarify their hypothesis. Was it that a more interventionalist approach to induction of labour (IOL) reduced stillbirths or that induction after 41+3 reduced stillbirths after 42 weeks? It seems that the former question is being addressed. This is critical because it affects how the authors divide their data set. Currently, they seem to have picked a somewhat arbitrary division of 3,3,3,2 and 2 year epochs. If they are addressing whether a more interventionalist policy reduces stillbirth it would be more appropriate to break the study down into a 2000-2007 group where the IOL rate was 12.4-15.5 and 2008-2012 when the IOL rate was 17.3-24.5%.

**Au:** It appears from Fig. 1 that the proportion of induced women increased gradually from year 2000 until year 2012, although with a steeper increase from 2009. Our aim (hypothesis) was to assess the influence of this gradually more effective intervention both on the stillbirth rates from 40 weeks and for

all stillbirths from 37 weeks, as the new induction paradigm moved some post-term deliveries to the weeks before term. A detailed development by time would not be apparent with a subdivision into only two time periods. Nevertheless, we also made analyses stratified into only two periods (2000-2008 and 2009-2012), which are illustrated in Fig. 2, demonstrating that the stillbirth rates were reduced in all gestational weeks after 37 weeks.

It is not clear from the methods whether stillbirths in infants with congenital anomalies were excluded. It would be optimal if they were as timing of delivery would not be expected to achieve an impact on stillbirth rate.

**Au:** We agree that stillbirths in infants with congenital anomalies probably are reduced less than the reduction for other fetuses. We discuss this issue in the article (line 242-251) and conclude that only about 12 annual stillbirths could be ascribed to the fetuses with congenital anomalies (as far as they can be detected by prenatal screening). The next problem is to define which children should be excluded. Probably the prenatal screening with succeeding induced 2<sup>nd</sup> trimester abortion is the factor which has changed during the study period, as the proportion of conceptions with anomalies probably has been fairly stable. With our assessment of this issue, we think we have handled this aspect appropriately.

In the regression analysis the authors state that the increased proportion of women over the age of 40 giving birth would likely increase the number of stillbirths. Although this is a statistically significant increase in this group the effect on the number of stillbirths is comparatively modest. The likely increase in stillbirth risk >40 is around an odds ratio of 5. If we accept that this increases the SB rate after 37 weeks this would be 3.5 per 1,000 births after 37 weeks (using the data from 2000-2). If 3% of births were to women >40 this would be responsible for approximately 12 stillbirths out of the 489 so it is extremely unlikely to materially alter the results.

**Li:** Yes, we agree. It is important, however, also to evaluate this significant although modest age trend, but our conclusion is the same as the conclusion of the reviewer (line 263-267).

The most significant issue is how one can determine whether it is the IOL policy (intervention vs minimal) that is responsible for the very welcome reduction in stillbirths. What else changed in the period from 2000-2012. It is easily conceivable that other aspects of antenatal or intrapartum care have changed in this period including better screening for fetal growth restriction, improved management of reduced fetal movements (both of which would increase the IOL rate).

**Li:** Yes, and we acknowledge this (line 252-261). The clue here is that this improvement has also occurred in other Nordic countries, without a similar reduction in stillbirths. Therefore it is unlikely that this improvement has a main responsibility for the observed reduction.

There have also been advances in the management of hypertension and diabetes. This may be relevant as the perinatal mortality rate falls by 0.5 per 1,000 from 40 weeks and 0.07 from 37 weeks before the IOL rate rises significantly which would suggest that IOL policy cannot be the only factor at work here, although I accept these trends largely accelerate after 2009.

**Li:** We agree that other factors than IOL have had their share of the decline in perinatal mortality. In contrast to several of such factors contributing to this decline mentioned in the paper, we have no reason to believe that the management of women with hypertension have changed substantially during the study period. The management of diabetes might have improved indeed, primarily, however, by earlier induction of birth for these women.

A relatively minor comment is that some of the terms used do not translate into English particularly well. For example, in the abstract the authors refer to the newer strategy as "offensive". I think it would be better to phrase this as a more "interventional approach" as offensive can also be taken as insulting or certainly less good.

Li: We have rephrased this expression with "proactive".

We would not use the term "stillborns" instead would suggest stillborn infants or stillbirths. E.g. line 61 I would suggest the worldwide number of stillbirths is estimated... and line 98 however achieved for all stillbirths. I would also suggest changing the term "adipose women" to women with BMI >30.

Li: We have replaced stillborns with stillbirths and "adipose women" with "women with BMI >30"

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Alexander Heazell University of Manchester, UK
<b>REVIEW RETURNED</b>	01-Jul-2014

<b>GENERAL COMMENTS</b>	<p>1. The background section of the abstract needs to include more information about the more proactive IOL policy rather than just the policy on IOL after 42 weeks. The effects between 37-40 weeks are just as important. I recommend the authors state that since 2009 there has been a move towards a more proactive policy including prevention of prolonged pregnancy, early treatment of PET, Diabetes etc.</p> <p>2. I am concerned that in the discussion the authors do not cite all relevant references regarding the debate as to whether IOL causes increased intervention or even harm. I think that there are now large observational studies such as that by Stock et al. that show there is no increased intervention and likely less harm from IOL rather than expectant management.</p> <p><a href="http://www.ncbi.nlm.nih.gov/pubmed/22577197">http://www.ncbi.nlm.nih.gov/pubmed/22577197</a> The data the authors present in combination with the data showing no harmful effects surely add significant weight to the argument that proactive IOL policies are likely to be beneficial.</p> <p>The authors have addressed the previous comments I have made when reviewing this paper for the BMJ.</p>
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## VERSION 2 – AUTHOR RESPONSE

1. The background section of the abstract needs to include more information about the more proactive IOL policy rather than just the policy on IOL after 42 weeks. The effects between 37-40 weeks are just as important. I recommend the authors state that since 2009 there has been a move towards a more proactive policy including prevention of prolonged pregnancy, early treatment of PET, Diabetes etc.  
Authors: We have rephrased the introduction accordingly.

2. I am concerned that in the discussion the authors do not cite all relevant references regarding the debate as to whether IOL causes increased intervention or even harm. I think that there are now large observational studies such as that by Stock et al. that show there is no increased intervention and likely less harm from IOL rather than expectant management.

<http://www.ncbi.nlm.nih.gov/pubmed/22577197> The data the authors present in combination with the data showing no harmful effects surely add significant weight to the argument that proactive IOL policies are likely to be beneficial.

Authors: We have added this relevant reference in the discussion section (line 295-297)

The authors have addressed the previous comments I have made when reviewing this paper for the BMJ.