Author's response to reviews

Title: Does advanced maternal age confer a survival advantage to infants born at early gestation?

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Author's response to reviews: see over
Reviewer 1:

Major Compulsory Revisions
- Methods 79th paragraph: please clarify why you use the extended definition of perinatal death. Early neonatal mortality refers to a death of a live-born newborn within the first seven days of life, while late neonatal mortality covers the time after 7 days until before 28 days. The sum of these two represents the neonatal mortality. According to the definition used in Europe perinatal mortality include only the early neonatal mortality. Perinatal mortality is defined by WHO as weight specific (# 1000 g) fetal deaths and early neonatal deaths per 1000 births (live births + stillbirths). This journal has readers worldwide. Any research that is reported is obscured by country-specific definitions of perinatal mortality.

In fact there are 2 distinct definitions of perinatal mortality. The definition provided by the reviewer, which is preferred in the demographic and other literature, includes stillbirths and early neonatal deaths. The alternative obstetric definition of perinatal mortality includes stillbirths and all neonatal deaths (Williams Obstetrics. Cunningham FG, et al. (Eds) 23rd Edition McGraw Hill. New York. 2010. page 3). We used this extended definition of perinatal mortality (fetal death or death during the first 28 days after birth) because our objectives were to compare birth outcomes between older and younger mothers in the setting of an industrialized country (the USA). The health care resources in such settings typically include neonatal intensive care and related technology that can prolong survival even among infants born at the borderline of viability. Such infants may survive beyond 7 days after birth but may die in the late neonatal period. Although we do not believe the use of early neonatal deaths versus all neonatal deaths in the definition of perinatal death is likely to make any significant difference to our study’s results, we chose to use the extended definition as we believe this is more appropriate in this context. We have added a citation to the Williams Textbook of Obstetrics to support our definition of perinatal mortality.
- What is the reason why Figures 1 and 2 and 3 are showing data from the 28th gestational week only? (Study population included all infants born between 22 and 43 weeks of gestation.)

The fetal, neonatal and perinatal rates per 1000 total births at 22-27 are markedly higher than the rates at ≥28 weeks. If graphed, the scale would have to extend to 1000, which in effect would eliminate any visible differences between the contrasted lines representing gestational age-specific rates for older vs younger mothers. All rates are therefore presented only in Table 2 for the interested reader.

Minor Essential Revisions
- Methods 71st paragraph: please define it clearly to the reader what you mean under clinical estimate of gestation at birth, as you did in Discussion 204th paragraph.

We have now clarified this in the Methods section. “We included all infants born between 22 and 43 weeks of gestation, based on the clinical estimate of gestation at birth as this estimate is more accurate than gestational age based on menstrual dates."14-17 This estimate is provided by the health care provider, without specification of the source (i.e., whether based on clinical examination, ultrasound, etc).”

Discretionary Revisions
- Discussion 209th- 213th paragraph: please rephrase these two sentences. Write it down why fetus-at-risk model reflects an appreciation of latent periods, concentrating on especially from an epidemiologic standpoint.

We have rewritten the Discussion section in order to clarify this issue. "Disparate results obtained from traditional vs fetuses-at-risk approaches highlight two different perspectives: prognostic (i.e., predictive or acausal) and causal.21 The traditional approach provides an accurate prognostic perspective for the newborn infant and has utility in predicting neonatal death. Under the traditional model, gestational age serves as an excellent predictor for neonatal mortality and infants born to older mothers at early gestation can be said to have a more favourable prognosis as compared with infants born to younger mothers. The fetuses-at-risk model, on the other hand, provides insights into the biologic role of maternal age (and other factors responsible for intersecting perinatal mortality curves such as smoking, plurality, hypertension in pregnancy) from a fetal perspective. It represents a causal model31,32 and suggests that older maternal age is causally associated with a higher risk of fetal and neonatal death at early and late gestation. Our study also demonstrates that (causal) etiologic studies restricted to births at early gestation (or low birth weight births) may yield biased results if they use traditional measures of gestational age-specific perinatal mortality since they ignore the biologic continuum of pregnancy.11,12,33,34 Whereas results based on the traditional model yield valid prognostic estimates, any causal inference based on these associations (whether related to the effect or older maternal age, smoking or hypertensive disorders in pregnancy) is likely biased. The reason for the acausal nature of traditional models and the causal nature of the fetuses-at-risk model relates to how these two models treat gestational age: in the traditional model gestation age is a determinant, whereas in the fetuses-
at risk model it represents survival time.\textsuperscript{27,31} Treating gestational age as survival time permits the estimation of incidence rates which are central to causal inference.”

Reviewer 2:

\textit{My impression is that this is a worthy study carried out in an area where the evidence is still sketchy. My largest concerns are (1) the age of the data set 2003-2005 and (2) the discussion, which is focused on fetuses at risk, without a clear definition of what is a fetus at risk (parameters/ risk factors)? The premise appears to be to isolate fetuses at risk from all fetuses and to consider the impact of advanced maternal age on this group. Additionally, this is a complex paper and the information therein is not readily accessible. For example, the sentence- lines 99-102, page 5 is still not clear to me after 3 readings.}

\textbf{Major Compulsory Revisions}

1. Some discussion of the age of the dataset, why that particular period was chosen rather than a more recent dataset? Are there likely to be differences in more contemporary data?

Fetal death files and period-linked birth/infant death files were needed for this study, because such files include fetal and infant deaths (up to 1 year of age) and all requisite birth information as well. The linkage of live birth file information with infant death file information requires linkages and additional time before it can be completed by the National Centre for Health Statistics (NCHS). When the analysis was performed, the latest available file was for year 2005. Currently, the most recent linked file available is for year 2006. We added a sentence in the Methods:

“The most recent available period linked file that linked infant deaths (up to 1 year of age) to birth certificates was for year 2005.”

We do not believe that more recent information would make any difference to the results.

2. Inclusion of a clear definition of a fetus at risk?

All live fetuses (in-utero) are at risk of fetal death. Analysis using ongoing singleton pregnancies (i.e. all unborn fetuses) as denominators is also referred to as a fetuses-at-risk analysis, or fetuses-at-risk approach. This is in contrast to traditional analysis, that uses all births at any gestation (not all fetuses whether born or unborn at that gestation) as denominators. It is generally accepted that the fetuses-at-risk approach is the appropriate formulation for gestational age-specific fetal mortality. Some controversy exists about the denominator for neonatal death rate, however. We argue, that in-utero fetuses are not only at risk of fetal death, but also at risk of birth and subsequent neonatal death. In the obstetric practice, the difference between fetal death and neonatal death after a birth of a compromised fetus is minimal. Causes of neonatal death are mostly perinatal in origin, including asphyxia, trauma or
prematurity due to a preterm birth. More support for this position is available in the cited literature. We have reworded some of the text to make this issue more clear.

3. Clarification of dense sections of the text, such as- lines 99-102, page 5. We have reworded the sentences included between lines 99 and 102.

“To contrast the effects of maternal age on perinatal outcomes at early versus later gestation, two separate models were constructed for births at early (22-33 weeks) and late gestation (34-43 weeks). Under the traditional approach, logistic regression models for early gestation fetal, neonatal or perinatal death included only live births and fetal deaths at 22-33 weeks. In contrast, under the fetuses-at-risk approach, all ongoing pregnancies at 22 weeks gestation (i.e. all births at ≥22 weeks) were included in the logistic regression models examining death at early gestation. In this early gestation model, the outcome included fetal death, neonatal death or perinatal death at 22-33 weeks gestation only. Fetal and neonatal deaths and all live births that occurred after 33 weeks gestation were treated as survivors in this early gestation model and censored at 33 weeks. Logistic regression models examining fetal, neonatal and perinatal death at later gestation (≥34 weeks) included all ongoing pregnancies at 34 weeks gestation. The numerator and denominators were identical under the traditional and fetuses-at-risk approach in this analysis, as the total number of births at ≥34 weeks represented the number ongoing pregnancies at 34 weeks gestation. The only difference between the two approaches was for neonatal death; only live births were included in the denominator under the traditional model, whereas all births were included in the fetuses-at-risk formulation.”

4. Results: It is not clear what percentage of older vs younger women fall into the ‘fetus at risk’ category. This information would help make sense of the findings. This has been made more clear after the definition of fetuses-at-risk was clarified. All fetuses were at risk for fetal, neonatal and perinatal death.

5. The discussion should include some explanation of why the traditional model supports better outcomes at earlier gestations, among older mothers generally. Could this be because they are generally healthy, better educated and their risks reflect these variables? Although advanced maternal age may not confer any real benefits in terms of obstetric outcomes, does it contribute to additional risk among healthy women?

We conclude in the discussion that the traditional model shows a prognostic perspective in terms of neonatal survival at preterm gestation that is conditional upon live birth. This phenomenon has been known as a paradox of intersecting mortality curves and has been reported for other conditions such as smoking, multiparity, or pre-eclampsia. Thus fetuses and infants of smokers who are born at early gestation or low birth weight also appear to have a survival advantage compared with the fetuses/infants of non-smokers born at early gestation/low birth weight. These observations do not imply a causal relationship – smoking does not protect against fetal and neonatal death at early gestation just as older maternal age does not confer a survival advantage at early gestation. We have added more detail to this discussion in our revised manuscript.
6. Conclusion: my impression is that the conclusion overstates the findings, and the first statement needs to be qualified as ‘among fetuses at risk’. The 2nd sentence, referring to a lesser risk of neonatal death at lower gestation among older women, clearly is of some significance and cannot be dismissed as erroneous. I think this finding points to the need for additional study in this area.

We have modified our conclusion and it now reads as follows:

“In summary, our study demonstrates that contrasts of perinatal mortality rates among older versus younger mothers demonstrate the general phenomenon of intersecting perinatal mortality curves. The traditional perinatal model provides a varying prognostic perspective on the effect of older maternal age, with protection against neonatal/perinatal death observed at early gestation and an increased risk of neonatal/perinatal death observed at later gestation. On the other hand, the fetuses-at-risk model provides a consistent causal perspective on the effect of older maternal age, with an increased risk of fetal, neonatal and perinatal death observed at all gestational ages. This underscores the need for a proper conceptualization of gestational age-specific perinatal mortality in studies examining causal associations.”