

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends in the incidence and mortality of multiple births by socioeconomic deprivation and maternal age in England: Population-based cohort study
AUTHORS	Smith, Lucy; Manktelow, Bradley; Draper, Elizabeth; Boyle, Elaine; Johnson, Samantha; Field, David

VERSION 1 - REVIEW

REVIEWER	Dr Saima Aziz Siddiqui Dow University of Health Sciences Karachi, Pakistan
REVIEW RETURNED	05-Jan-2014

GENERAL COMMENTS	<p>1) In Objective section of Abstract, only neonatal mortality is described as objective whereas results section of abstracts also describes still births so still births are also main outcome measure and to be included in objective.</p> <p>2) Sentence in conclusion section of abstract i.e "Improved monitoring of multiple pregnancies and an increased proportion of di-chorionic twins are likely to have led to the reductions in stillbirths over this time" is not to be mentioned, as authors themselves have accepted the limitation of not finding sustained information about chorionicity in data.</p> <p>Results particularly Poisson regression analysis to be reviewed by statistician.</p>
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- The reviewer also provided marked PDF copy which is available upon request to the publisher.

REVIEWER	K. S. Joseph Professor University of British Columbia Vancouver, Canada
REVIEW RETURNED	03-Feb-2014

GENERAL COMMENTS	The authors used data on plurality, year of birth, maternal age, and deprivation decile to examine temporal trends and the effects of socioeconomic status and maternal age on the frequency and perinatal mortality of multiple births in England between 1997 to 2008. The results showed temporal increases in the frequency of twin births, declines in triplet and higher order multiple births, declines in perinatal mortality among multiple births and socioeconomic disparities in the frequency and perinatal mortality
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among multiple and singleton births.

Major comments

1. The paper quantifies the temporal trends in the frequency and perinatal mortality of twin and triplet births along with socioeconomic and maternal age effects. This is important because of the evolving nature of these trends which are heavily influenced by medical practices and the regulation of such practices (including funding).
2. The key variables in this analysis of twin/triplet frequency and mortality are calendar year, maternal age and socioeconomic status. A comprehensive picture of all these influences would be obtained if the authors provided crude rates and crude rate ratios showing the effects of year/period, maternal age and deprivation and also the effects of each adjusted for the other two. Currently Table 1 provides crude rates of multiple birth rates by calendar year, Table 2 provides these crude rates by deprivation scores, Table 3 provides rate ratios of the of multiple birth rates given most deprived versus least deprived adjusted for (stratified by) by maternal age and adjusted for calendar year and Table 4 shows crude rates of stillbirths and neonatal deaths among singletons and twins by calendar period. The comprehensive detail requested would be mean more Tables, some of which can be provided in an appendix.

Minor comments

1. Abstract, lines 29-32 The authors state that "Women over 40 years of age from the least deprived areas had a 50% increased rate of multiple births compared to similar aged women from the most deprived areas (Rate ratio 0.66 95% CI (0.61 to 0.73)." This is correct but perhaps it is better worded as "Women over 40 years of age from the most deprived areas had a 34% lower rate of multiple birth compared with similar aged women from the least deprived areas (rate ratio 0.66, 95% CI 0.61 to 0.73)."
2. It may be preferable to delete the reference to dichorionic twins from the Conclusion section of the Abstract as data on chorionicity was not presented in the paper. Speculation regarding the role of chorionicity is best presented in the Discussion section and elsewhere but not in the Conclusions.
3. Page 7, line 13 "....neonatal deaths (death before 28 days of life)...." should be edited to....."neonatal deaths (death before 28 days after birth).....".
4. A brief explanation of the term "super output area of mother's residence" would benefit the international readership of the Journal.
5. The births in a twin set or higher order multiple births set are not independent observations in terms of risk of stillbirth, neonatal death, etc. It is therefore appropriate to adjust the variance for the correlated nature of these observations (which will result in larger confidence intervals depending on the degree of the correlation). Since the data source did not possess information to reconstruct the multiple birth sets, the authors should mention this as a limitation of their study.
6. Could fetal reduction in multi-fetal pregnancies at 10-13 weeks gestation have impacted rates of triplet pregnancies in more recent years? A brief mention of this along with whether the reduced fetus (which typically gets delivered at a later gestation along with the healthy fetus(es)) requires registration as stillbirth would be informative.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Dr Saima Aziz Siddiqui
Institution and Country Dow University of Health Sciences Karachi, Pakistan

1) In Objective section of Abstract, only neonatal mortality is described as objective whereas results section of abstracts also describes still births so still births are also main outcome measure and to be included in objective.

Amended

2) Sentence in conclusion section of abstract i.e "Improved monitoring of multiple pregnancies and an increased proportion of di-chorionic twins are likely to have led to the reductions in stillbirths over this time"

is not to be mentioned, as authors themselves have accepted the limitation of not finding sustained information about chorionicity in data.

Amended to exclude this reference to chorionicity.

Results particularly Poisson regression analysis to be reviewed by statistician.

Reviewer Name K. S. Joseph
Institution and Country Professor
University of British Columbia
Vancouver, Canada

Please state any competing interests or state 'None declared': None declared.

The authors used data on plurality, year of birth, maternal age, and deprivation decile to examine temporal trends and the effects of socioeconomic status and maternal age on the frequency and perinatal mortality of multiple births in England between 1997 to 2008. The results showed temporal increases in the frequency of twin births, declines in triplet and higher order multiple births, declines in perinatal mortality among multiple births and socioeconomic disparities in the frequency and perinatal mortality among multiple and singleton births.

Major comments

1. The paper quantifies the temporal trends in the frequency and perinatal mortality of twin and triplet births along with socioeconomic and maternal age effects. This is important because of the evolving nature of these trends which are heavily influenced by medical practices and the regulation of such practices (including funding).

2. The key variables in this analysis of twin/triplet frequency and mortality are calendar year, maternal age and socioeconomic status. A comprehensive picture of all these influences would be obtained if the authors provided crude rates and crude rate ratios showing the effects of year/period, maternal age and deprivation and also the effects of each adjusted for the other two. Currently Table 1 provides crude rates of multiple birth rates by calendar year, Table 2 provides these crude rates by deprivation scores, Table 3 provides rate ratios of the of multiple birth rates given most deprived versus least deprived adjusted for (stratified by) by maternal age and adjusted for calendar year and Table 4 shows crude rates of stillbirths and neonatal deaths among singletons and twins by calendar period. The comprehensive detail requested would be mean more Tables, some of which can be provided in an appendix.

We have added in risk ratios to 2 of the tables and added in an additional 3 tables to allow for this. We also noticed an error in our denominator data which has led to amendments to Table 4 (now table 7). Since there are interactions in the models for the rate of multiplicity we felt the adjusted effects of

year, mother's age and deprivation were best demonstrated in figures 2a and 2b rather than a very complex table which would be hard to visualise. We are happy for the editors to decide whether any of these tables should be in an appendix rather than the main paper.

Minor comments

1. Abstract, lines 29-32 The authors state that "Women over 40 years of age from the least deprived areas had a 50% increased rate of multiple births compared to similar aged women from the most deprived areas (Rate ratio 0.66 95% CI (0.61 to 0.73)." This is correct but perhaps it is better worded as "Women over 40 years of age from the most deprived areas had a 34% lower rate of multiple birth compared with similar aged women from the least deprived areas (rate ratio 0.66, 95% CI 0.61 to 0.73)."

Amended

2. It may be preferable to delete the reference to dichorionic twins from the Conclusion section of the Abstract as data on chorionicity was not presented in the paper. Speculation regarding the role of chorionicity is best presented in the Discussion section and elsewhere but not in the Conclusions.

Amended

3. Page 7, line 13 "...neonatal deaths (death before 28 days of life)...." should be edited to...."neonatal deaths (death before 28 days after birth).....".

Amended to read "death of a live-born baby within the first 28 days of life"

4. A brief explanation of the term "super output area of mother's residence" would benefit the international readership of the Journal.

Amended to give more detail. "Super output areas are the smallest areas for which these deprivation data are available and are based on census geography with around 1500 residents in each; although some degree of heterogeneity will exist within them, the small size of the areas limits this."

5. The births in a twin set or higher order multiple births set are not independent observations in terms of risk of stillbirth, neonatal death, etc. It is therefore appropriate to adjust the variance for the correlated nature of these observations (which will result in larger confidence intervals depending on the degree of the correlation). Since the data source did not possess information to reconstruct the multiple birth sets, the authors should mention this as a limitation of their study.

We acknowledge this statement and have added the following: "Unfortunately, in the analysis of stillbirths and neonatal deaths we could not take account of the correlated nature of the outcomes of multiple births from the same pregnancy. The confidence intervals presented here are consequently likely to have been narrower had this adjustment been possible, but this is unlikely to have impacted upon our conclusions."

6. Could fetal reduction in multi-fetal pregnancies at 10-13 weeks gestation have impacted rates of triplet pregnancies in more recent years? A brief mention of this along with whether the reduced fetus (which typically gets delivered at a later gestation along with the healthy fetus(es)) requires registration as stillbirth would be informative.

This is a very useful comment and we have added text to include this: "A possible additional factor influencing the rate of triplets could be the increased frequency of fetal reduction in multi-fetal

pregnancies in the first trimester. In the UK death of an unborn fetus would not be registered if delivered before 24 weeks of gestation. For those deliveries where a fetal reduction occurred before 24 weeks gestation and the fetus was known to have died the death should not be registered as a stillbirth but there may be some variation in interpretation of the legislation.”