

BMJ -
Decision on
Manuscript
ID
BMJ-2018-
048089

Body: 21-Jan-2019

Dear Miss Magnus

Manuscript ID BMJ-2018-048089 entitled "The role of maternal age and pregnancy history in risk of miscarriage"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

dr. Wim Weber
European editor, The BMJ
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****Report from The BMJ's manuscript committee meeting****

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: John Fletcher (chair), Jamie Kirkham (statistical advisor), Elizabeth Loder, José Merino, Wim Weber, Daoxin Yin.

Decision: Put points

Detailed comments from the meeting:

We thought your study addressed an interesting and important research question. We had the following concerns.

This is a straightforward analysis with no unexpected findings - miscarriage rates are in line with the literature. The J-shaped risk of miscarriage according to maternal age seems typical of what would be expected. The pattern observed for maternal ages 22-23 (Figure 2) may appear slightly distorted due to the differing y-axis scale (differences are quite minor despite the fluctuation observed).

Much of the statistical analysis focuses on the issue of calculating accurate miscarriage rates in the presence of induced abortions. A number of assumptions are made about including the relevant numerator/denominator in the miscarriage rate computations. The authors seem to come to a satisfactory solution around this and demonstrate their rates are largely unaffected by induced abortions and subsequently exclude these from the formal stats inference.

Table 1 - We do not understand the 100% miscarriage rate when there is missing data.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:

In this manuscript, the authors present results from a large Norwegian birth registry specifically focused on reporting rates of miscarriage and risk factors associated with miscarriage in their population. This is a robust and well characterized data set that the authors do a nice job of explaining and utilizing. I have a few comments/questions.

1. In the "What this study adds" section 1st bullet- it would be helpful to clarify what the comparison is to for the "increased risk of miscarriage among both younger and older mothers..."

2. Abstract Conclusion- recommend changing final phrase to "some adverse pregnancy outcomes."

3. Introduction- consider moving the 3rd paragraph above the 2nd one for flow.

4. There were several outcomes from prior pregnancies that were noted in the Methods that did not show up in the Results. These include post-term, SGA, and LGA. these need to show up in the results table.

5. Figure 2 why is there a 2nd figure focusing in on age 23-33? What does it add that the first panel does not have?

Additional Questions:

Please enter your name: David Haas

Job Title: Professor of OB/GYN

Institution: Indiana University School of Medicine

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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If you have any competing interests (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:

This study examined the burden of miscarriage in the Norwegian population and evaluated the association between miscarriage and maternal age and pregnancy history.

The authors used national data from Norwegian registries to meet their objectives.

The study has major flaws including the following:

1. The authors claimed that the data were collected prospectively which means that the registries were primarily designed to provide data to meet the objectives of this study among other objectives. However, the collected data were very deficient in many aspects including confounding factors for miscarriage such as paternal age, previous induced abortion, BMI, co-morbidity such as maternal diabetes, employment and the nature of maternal work if she is doing night shift, socioeconomic status in addition to ethnic origin of the mother and her immigration status. The latter condition is important considering that 16% of the Norwegians are immigrants some are from The Middle East where consanguineous marriages are recognized with increased possibility of congenital abnormalities. The deficient data on all proven factors associated with miscarriage makes the conclusion about the effect of maternal age and pregnancy history uncertain especially that the odds for these outcomes were small.

2. The results of this study showed another major issue which the missing data from each of the tables 2-5. The large number of missing data introduces the possibility of bias and threatens the validity of the conclusion reached by the authors especially that there are no comparisons in the main determinants between the missing group and the analyzed group.

Additional Questions:

Please enter your name: Hayfaa Wahabi

Job Title: Associate professor Evidence-based healthcare and knowledge translation

Institution: King Saud University. Riyadh, Saudi Arabia

Reimbursement for attending a symposium?: No

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If you have any competing interests (please see BMJ policy) please declare them here: No competing interest

Reviewer: 3

Recommendation:

Comments:

This paper does not present many surprises but the risk estimates are solidly supported by a comprehensive, national database and reflect pregnancy outcomes for women in a high income country with good access to medical and reproductive health care. The inter-generational links between pregnancy complications are new to me. The persisting elevated burden of miscarriage borne by teenaged women is also interesting.

I attach a document listing some suggested revisions. I have asked the authors to check some suspected typographical errors, give more information in table and figure footnotes, provide supplementary information about gestation at miscarriage which allow comparison with other publications' definitions of first trimester or second trimester miscarriage and substantiate a few statements which currently lack numeric data and/or referenced source data.

Title:

The role of maternal age and pregnancy history in risk of miscarriage. No suggested changes

First author:

Magnus, Maria Christine

MS number

BMJ-2018-048089

Dot points: What is already known, what this study adds

These are clearly enunciated. No changes suggested

Abstract

Well-structured. Main results expressed clearly. No changes suggested

Introduction

The authors convince the reader that miscarriage is important but that ascertaining its incidence and associated risks is not as simple as first imagined.

The aims of quantifying miscarriage risk and relating it to maternal age and previous pregnancy complications are convincingly stated.

No changes suggested

Methods

1st paragraph:

Methods described well. Clear and repeatable information. No changes suggested
Pregnancy outcomes and identification of unique pregnancies:

Uses a 42 day rule to determine if an ICD miscarriage related code was for a new pregnancy. I think this is reasonable and replicable. No changes suggested

Statistical analysis:

This is readable to the academic clinician reviewer who has some basis statistical training but does not claim to be a biostatistician.

The sensitivity analyses assessing according to inter-pregnancy interval, adjustment for smoking and sensitivity analysis for previous pregnancy complications are of clinical interest.

Results

This is generally well presented and complements the figures and tables. Please see comments below about figures and tables, including 1 possible typographical error and my request for more information about error bars, abbreviations and definitions.

Discussion and conclusions

Para 1:

- Confirm some observations with new precision, contemporary, comprehensive national data from a high income country

Para 2

- Strengths
- Page 12, line 27 Correct typographical error "recognizes" should be "recognize" to agree with the plural subject "most women".

- Weaknesses: under-ascertainment of miscarriage due to requirement for specialist medical attention. The statement "... in Norway, most women who recognize (s) a miscarriage are likely to receive care from a specialist" is not substantiated. The authors' 3rd paragraph draws on other "prospective studies with full ascertainment of early miscarriages", stating that overall risk of miscarriage in such studies was similar to that found in the current study. The reader would be more convinced if

- o The numeric risks of miscarriage from REFS 5 -7, 2, 4, 8 were listed or tabulated so that the reader can judge for themselves if they agree with the authors' assertion that "... miscarriage in Norway was 12.8%. This risk is ... similar... to reports..."

- o Future research could estimate the extent of under-ascertainment of miscarriage due to omitting miscarriages which were managed in a non-specialist setting, e.g. by general medical practitioners, community nurses or midwives

Consider additional information (probably as supplementary material) for international comparisons of miscarriages at different gestational age bands or "trimesters": for example:

< 10 weeks: biological change from 1st trimester to mid-trimester as per Silver, RM.

Nomenclature for Pregnancy Outcomes. Time for a Change Obstet Gynecol 2011;118:1402-8. DOI: 10.1097/AOG.0b013e3182392977

< 12 weeks: health services change to Norwegian pregnancy register

< 14 weeks: ICD coding change to "midtrimester"

All <20 weeks: Norwegian definition of miscarriage

All < 22 weeks: Some other countries' definition

All < 24 weeks: UK and other international definition

References:

No suggested changes

Figure 1

This flow diagram is generally presented clearly.

Please correct typographical errors where h and t are transposed in the word "Stillbirths" in the 2nd box to the right of the 4th row and in the lowermost box.

I recommend using a footnote to define abbreviations NPR and MBRN +/- ICD10. NPR and MBRN may not be immediately understood by an international reader, particularly a reader who reads this figure (or reproduces it with permission) separate from the main article.

Figure 2

This pair of diagrams illustrate well the j-shaped curve of risk of miscarriage with age with part b expanding on the decade of age 23 to 33 years with detail including an indication of estimate uncertainty as vertical bars around a central point.

What do the vertical bars mean in 2(b)? Are they upper and lower limits those of a confidence interval?

Table 1

Please check the lowermost, rightmost cell, corresponding to "Total" (age group) and "Proportion miscarriages including induced abortions that would have resulted in a miscarriage in the numerator and all induced abortions in the denominator % (N)". The figure is 1.28 but I wonder if this should be 12.8, that is, perhaps the decimal point is misplaced?

Otherwise this table is useful and readable.

Table 2

This well illustrates the number and % of miscarriages for women sub-grouped by the registered outcome of the prior pregnancy. It also shows the age-adjusted odds ratio for miscarriage relative to the reference group of women with no previous registered pregnancy.

No changes suggested.

Table 3

This table effectively illustrates the dose-association curve of previous miscarriage number 0 to 3 and the age-adjusted odds ratio for miscarriage.

No changes suggested.

Table 4

This table well illustrates that previous pregnancy complications, other than previous post-term gestation, are associated with small but measurable increases in age-adjusted odds ratio for miscarriage.

The table would be more understandable as a stand-alone item if terms were defined in a footnote. In particular, I recommend that "Small" and "Large" fetal growth are defined as < 10th and > 90th centiles, citing birthweight or fetal weight standards so that the reader can find this. The footnote could include all other definitions +/- references for preterm, post-term, congenital malformations, pre-eclampsia, gestational diabetes.

Table 5

This table illustrates inter-generational risks for pregnancy complications and miscarriage in the next pregnancy. Other than adding footnoted definitions to improve readability of the table as a stand-alone item of data (the same suggestions as for Table 4), I do not suggest changes.

Supplementary methods

This seems reasonable. I would also value a statistician to review

Supplementary table: eTable 1

Risk of miscarriage according to the previous pregnancy ended in a live birth, stillbirth, miscarriage or a neonatal death (that is excluding induced abortion). This is readable and adjusted both for maternal age and for inter-pregnancy interval. No changes suggested

Supplementary table: eTable 2

Risk of miscarriages by whether the previous pregnancy was a live birth, with a pregnancy complication, adjusting for age, inter-pregnancy interval and smoking. No changes suggested

Additional Questions:

Please enter your name: Elizabeth A. McCarthy

Job Title: Senior Lecturer

Institution: University of Melbourne

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

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