

Manuscript ID BMJ.2018.043743 entitled "Prenatal biochemical screening and long-term risk of maternal cardiovascular disease"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We would be pleased to offer publication in the BMJ so long as you are able to revise to our satisfaction.

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. We are looking forward to reading the revised version.

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.

Thanks!

John Fletcher
Dr John Fletcher
Associate 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: Chair: John Fletcher, Statistical advisor: Julie Morris
Also present Georg Roeggla, Jose Merino, Elizabeth Loder, Daoxin Yin

Decision: Put points

Detailed comments from the meeting:

1. 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.
2. Please also respond to these additional comments by the committee:
3. Our statistician made the following observations:
 - It is not clear why a CVD composite (which covers a number of different events) was chosen as the primary outcome. Is it not more appropriate to select just one event?
 - One pregnancy per woman was chosen at random (to simplify the statistical analysis). Analyses are said to have been adjusted for gravidity, but would a previous history of abnormal prenatal screening results (for those with gravidity greater than zero) be a possible confounder? For those women with greater than one pregnancy during the study period, what proportion had more than one abnormal screening result?

- Table 4. The analyses here relating to the number of abnormal analytes show results for 855,536 women. How is this possible when PAPP-A was carried out on only 499,790 women and DIA on only 98,160 women (Table 1)? What assumptions have been made here?
- Table 2. It is not clear how the smaller incidence of the CVD composite outcome for those with abnormal readings on hCG compared to those with normal readings (5.8 per 10,000 vs 6.0 per 10,000) leads to a unadjusted hazard ratio of 1.3.

4. The editors all thought that your observations are at the beginning of a story and do not have any direct clinical implications at the moment. We do not often publish research that has no direct clinical application but have made an exception this time because we think some of our readers will enjoy thinking about the information available from screening tests in a new way. Your discussion is suitably reserved about practical implications.

5. Some editors were unsure why you had excluded births with congenital or chromosomal anomalies from the analysis. Please can you add a short explanation as to why this is a good idea?

6. Please can you present a table of the frequency of the various cardiovascular outcomes in this study? As these are women of childbearing age the pattern of cardiac outcomes may be different from the older men that are so frequently the participants in research with cardiovascular outcomes.

7. If the numbers are large enough to make sense, please can you present the main analysis using the most common single cardiac conditions as outcomes as well as the composite?

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:

Interesting manuscript with interesting findings. Authors describe that placental vascular disease is intimately linked with maternal vascular disease and prenatal biochemical screening is closely related to long term maternal cardiovascular events risk. If similar trends are seen on other population based studies, findings from widely available prenatal biochemical screenings can be used for preventative and cardiovascular risk factor modification strategies among those at higher risk of CVD events.

Specific questions:

1- On Page 5 line 47: "Of all remaining deliveries, we randomly selected one pregnancy per woman as the index pregnancy in order to simplify the data analyses." Why not select the first pregnancy as the index pregnancy?

2- On Page 7 line 42: "HRs were adjusted for maternal age (continuous), gravidity (1, 2+, missing), neighbourhood income quintile (1, 2, 3, 4, 5, missing), rural residence (rural, urban, missing), ethnicity (Asian, "Oriental", Black, Caucasian, Hispanic, other, missing) and gestational age (continuous) – each at the time of prenatal biochemical screening – as well as maternal diabetes mellitus, chronic hypertension, renal disease, tobacco/drug use and dyslipidemia within 365 days before or after the start of the index pregnancy (i.e. within 2 years preceding time zero)." What % had preeclampsia or eclampsia? Did they have higher CVD events on followup?

Additional Questions:

Please enter your name: Rajoo Dhangana

Job Title: Assistant Professor, Vascular and Interventional Radiology

Institution: University of Pittsburgh Medical Center

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 is a very interesting cohort study to investigate whether there is any association between abnormal prenatal biochemical screening and premature CVD after pregnancy. The study is conducted with sound methodology and statistical analysis, and is presented succinctly. There are a couple of points that need to be considered.

1. The uptake of the prenatal screening has big variation geographically, thus the cohort went for the screening could be biased. The models were adjusted for rural residence, but it would be more useful if the cluster of regions could be taken into account.
2. The study randomly selected one pregnancy per woman as the index pregnancy, and analysed all the data by adjusting for gravidity. Although the authors have acknowledged it as a limitation, it could be investigated as a sensitivity analysis. A stratified analysis by gravidity for the selected cohort could clarify whether there is any effect of abnormal screening results from repeat pregnancies.

Additional Questions:

Please enter your name: Jianhua Wu

Job Title: Lecturer in Medical Statistics

Institution: University of Leeds

Reimbursement for attending a symposium?: Yes

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: Yes

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Reviewer: 3

Recommendation:

Comments:

Summary

Based on the background that abnormal prenatal biochemical screening is related to a higher risk of preeclampsia, which is also linked to premature CVD; the authors hypothesised that abnormal prenatal biochemical screening may be related to premature CVD after pregnancy. Using a population-based cohort study comprising of 1,209,690 pregnancies recruited from the entire province of Ontario, the authors assessed the associations of five prenatal biochemical screening analytes with the risk of CVD. Each of the analytes was associated with an increased risk of CVD, with the highest risk for dimeric inhibin-A. Three or more abnormal analytes (compared with no abnormal analytes) was also associated with an increased risk CVD.

General Comments

The authors seem to have performed the first study that assessed the associations of prenatal biochemical screening analytes with the risk of CVD. It is an important research question, well analysed and written. Findings may have policy implications for the identification of women who are at risk of future CVD. Further studies are needed to replicate these findings. I do however have some concerns:

1. What was the basis for the definition of composite CVD outcome which was used as the primary outcome? Peripheral arterial disease and heart failure are normally outcomes that are assessed separately.

2. Why were the major adverse cardiovascular events (MACE) not rather considered as the primary outcomes? Why was all-cause mortality included in the definition for MACE?

The authors will need to review their outcomes again as not appropriate. In their conclusions, the authors recommend replication of these findings in other studies. Can this easily be done given the nature of the primary outcome specified?

Specific comments

What is already known on this subject

1. This section needs to be revised as it does not reflect the title. The authors could provide some background evidence that led to their hypothesis

2. "Abnormal prenatal biochemical screening for trisomies and birth defects has been completed among millions of women" This statement is very vague and need to be completed or revised.

Abstract

1. Remove "also" from the first sentence.

2. "It is unknown if abnormal prenatal biochemical screening is associated with premature CVD after pregnancy, the goal of the current study." Please revise this and be specific about the aim of the study. Do the same in background.

3. Please provide the mean/median follow-up time in years in place of/in addition to person-years

4. Please specify that the estimates were multivariate-adjusted

Background

Third paragraph lines 29-39. Most of this does not belong here.

Methods

1. The authors indicated in the abstract that the goal of the study was to evaluate if abnormal prenatal biochemical screening is associated with PREMATURE CVD after pregnancy. The term PREMATURE was however not defined/discussed in the methods section.
2. Did the authors adjust for BMI at prenatal screening?

Results

1. How robust are these results? Did the authors consider undiagnosed CVD as partly explaining their findings? The authors should conduct a sensitivity analyses which excludes the first two years of follow-up.
2. Consider doing a sensitivity analysis on exclusion of pre-existing renal disease, chronic hypertension, or dyslipidaemia, which are all risk factors for CVD. Exclusion is a much appropriate way of demonstrating robustness rather than adjustment.
3. The authors have a large and rich data source and should be able to conduct subgroup analyses by relevant characteristics such as age (average vs advanced maternal age), ethnicity (compare major ethnicities), type of pregnancy etc

Additional Questions:

Please enter your name: Setor Kunutsor

Job Title: Research Fellow

Institution: University of Bristol

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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Reviewer: 4

Recommendation:

Comments:

This well written manuscript focuses on a very interesting issue regarding cardiovascular women health: the relationships between obstetric antecedents and the development of cardiovascular disease. Specifically, the aim of this study was to analyze the possible relationships between some prenatal maternal serum measurements (used to screen for trisomy and neural tube defects) and long-term cardiovascular health.

The introduction clearly shows the background of the problem and the hypothesis. The primary endpoint was hospitalization because of cardiovascular disease. Events directly related to obstetric complications (for example preeclampsia or eclampsia) were adequately excluded.

The study shows that cardiovascular events rate was related with abnormal prenatal maternal serum alphafetoprotein (AFP), total human chorionic gonadotropin (hCG), unconjugated estriol (uE3), dimeric inhibin-A (DIA) and pregnancy-associated plasma protein A (PAPP-A), all collected during the second trimester of gestation. The association was particularly strong between composite cardiovascular endpoint and high DIA. Remarkably, the rate of cardiovascular events showed a stepwise increase with the number of abnormalities.

The authors conclude that "women with abnormal prenatal biochemical screening, especially DIA, may be at higher risk of CVD". Cardiovascular relative risk was more pronounced as the number of abnormal screening analytes increased, particularly in the co-presence of a newborn congenital anomaly, preterm birth or maternal placental syndrome.

Since no prior studies analyze the use of prenatal biochemical screening to estimate long-term cardiovascular health of a woman, I think this manuscript is innovative and very interesting. Indeed, the study highlights the possibility that some remote and relatively brief events could be related with long-term development of chronic diseases.

However, some doubts should be addressed. My main criticism to the study is regarding to how the traditional risk factors were analyzed. Specific definitions of covariates (diabetes mellitus, chronic hypertension, dyslipidemia) should be showed in the main text. Also, the way used to analyze these variables in the regression model should be clarified (enter vs stepwise, enter and excluded p values, collinearity). Furthermore, showing more data of the regression model could be useful to the reader in order to understand the results. No data were provided regarding the treatment of traditional risk factors. In the same way, how women with previous cardiac, cerebrovascular or peripheral disease were identified should be specified.

Regarding the clinical relevance of the findings, I disagree with the authors. In order to evaluate the utility of adding prenatal screening to the traditional risk evaluation, an analysis showing risk reclassification becomes necessary. In other words, how many women would change their risk level if the values of prenatal screening were added to conventional risk estimators?

Finally, I would suggest showing the results using Kaplan-Meier curves as well (for example: no, 1, 2, 3... abnormal prenatal biochemical screening).

Additional Questions:

Please enter your name: Martin R Salazar

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Institution: Hospital San Martín, La Plata, Argentina

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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