6-May-2016

Dear Dr. Farrar

Manuscript ID BMJ.2016.032237 entitled "Hyperglycaemia and risk of adverse perinatal outcomes: A systematic review and meta-analysis"

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.

Tiago Villanueva
Assistant Editor
tvillanueva@bmj.com

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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: Jose Merino (Chair), Angie Wade (Statistician), Elizabeth Loder, Wim Weber, Alison Tonks, Amy Price, Tiago Villanueva, Jessamy Bagenal, Georg Roggla (written notes), Rubin Minhas (written notes)

Decision: Put points

Detailed comments from the meeting:

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.

Please also respond to these additional comments by the committee:

- Our statistician made the following comments:
A major aim is to determine whether there are thresholds and visual inspection plays a prominent role in this. The supplementary figures 2-1 are crucial to this investigation and should be moved to the main part of the paper (or at least the primary ones). The treatment of the IPD should be clarified. More information should be given on the selection of studies (figure 1 shows the large numbers of exclusions, for which there is no explanation).

- One editor was broadly in favour despite the relative lack of novelty. She felt that you give us the findings but don't seem to come off the fence about the implications. She added that additional analyses by ethnicity would be even better, if possible, as one of the reviewers says.

- Another editor felt this was not particularly novel, but would be useful and worth pursuing.

- Another editor was concerned about relative lack of novelty, but felt it was a nice summary and was moderately positive.

- Another editor felt that this was an important topic but she was concerned by the reviewer who says "While I appreciate the significant amount of work done by the authors to conduct this analysis, I do not think this study contributes new information to the literature. It is confirmatory of the findings of the HAPO study and other smaller studies. As noted in the "what this study adds" section, their findings are confirmatory."

- Another editor made the following comments:
I would have liked to see the results of this study with and then exclusive of HAPO 2008/2010 and Subramaniam with 56786 participants with GDM diagnosis (not reported-supplementary materials) to see how and if the analysis changed or was novel.
This was NIHR funded so benefit to NHS is the target and it is unlikely to be as multinational as a reviewer had hoped for plus in LMIC this problem is seldom measured/treated. You could still analyze this across nationalities and report it since it was mentioned in your discussion it needs to be clearly reported.
The patient statement that Cochrane uses consumers so there is patient involvement is not appropriate as the "outcomes" are a common medical threshold and not the work of patients at all. This is like saying the outside IRB had a patient rep so our study has PPI. It is just not accurate.
This paper could benefit from a plain language summary edited by patients as it is a hard read.

- Another editor wondered whether including published studies along with IPD of some selected cohorts introduces bias. He pointed out that the analyses were not adjusted for any covariates.

- Another editor was on the fence. For him, the issue of concern with this paper is that we already know that lowering glucose is beneficial but the trouble is that we don't know how this is best achieved.

- Another editor said that while one reviewer points out that the study is confirmatory, the underlying studies are not particularly heterogeneous, and though the message might be deduced from them, there may be some value in this summary.

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:
This manuscript is a systematic review and meta-analysis of adverse pregnancy outcomes associated with maternal OGTT or GCT results below the currently established thresholds for GDM and after excluding women with diabetes. The authors objective was to determine a clear threshold at which adverse outcomes occur, acknowledging that the HAPO study found no clear threshold and that there was a dose response relationship between glucose and the outcomes. The HAPO Study, which included women from many different ethnic groups and countries of origin intended to create criteria to define GDM that could be used universally although it as likely, as the authors point out, that there is potentially some variability in this relationship based on other factors such as ethnicity.

The review included 28 studies and over 260,000 non-diabetic women, non-GDM women, although given that GDM was identified using different criteria across the multiple studies that were included some of the women in the study had GDM based on some criteria other than what was used clinically at in that specific study.

While as figure 1 shows many potential studies were identified, the vast majority were excluded. It is not clear to me how those decisions were made. I am aware of at least one other potential cohort with several publications that would meet inclusion criteria stated in the manuscript but was not included so perhaps a summary of the rationale for exclusion could be included.

In supplementary file 1 it is not clear to me why only UK countries were added as search terms. There are studies included that are from places other than the countries specified in the search such as studies from the US.

This study found the same results as the HAPO study and other similar studies – that there is a dose response relationship between glucose based on OGTT and adverse outcomes.

While I appreciate the significant amount of work done by the authors to conduct this analysis, I do not think this study contributes new information to the literature. It is confirmatory of the findings of the HAPO study and other smaller studies. As noted in the "what this study adds" section, their findings are confirmatory. The second phrase, the fact that there is no clear threshold, is not added by this study as it is already known.

Note that in Table 1, the definition of IADPSG and ACOG need to be provided unless the journal includes these in a list of common abbreviations.

Additional Questions:
Please enter your name: Jean Lawrence

Job Title: Senior Research Scientist

Institution: Kaiser Permanente Southern California

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None

Reviewer: 2

Recommendation:

Comments:
In the present manuscript, entitled "Hyperglycaemia and risk of adverse perinatal outcomes: A systematic review and meta-analysis", the authors conducted a systematic review and meta-analysis in 26 published studies and 2 cohort data to assess the association between maternal glucose level at 24-28 gestational weeks and adverse perinatal outcomes. This manuscript provide important evidence on the relationship between maternal hyperglycemia levels and perinatal outcomes with a critical question on whether the current diagnostic criteria on gestational diabetes (GDM) are supported by scientific evidence and can be generalized to difference populations. In general, the manuscript is well organized and well written. Statistical analyses are appropriate and well conducted. Tables and figures are presented in high quality. The specific comments I have are.

1. With all the results presented in the main and supplementary materials, I would strongly suggest to add the dose-response meta-analysis if the study number for a particular outcome is equal or greater than 5. The method is well developed and has been widely used to assess both linear and non-linear relationship in meta-analysis. (Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135(11):1301-9).
2. It is important to understand how the relationship between maternal hyperglycemia level and perinatal outcome by race/ethnicity. Even by authors' own study, it has been suggested that Pakistani women were different from White British women. Although there is not statistical evidence that heterogeneity exists among the studies, I would think the stratified analysis by race/population is very helpful and valuable.
3. It has been debated that how the glucose values of 1-h 50-g OGCT can be used to predict both short-and long-term risk of maternal hyperglycemia since women are not fasting before they take the test. I think the pooled 50-g OGCT results in this analysis is very interesting and deserve more discussions regarding the implications in this manuscript.
4. Page 7, line 31: "In case where only one study reported a specific o for a test or timing of glucose measure, a simple logistic regression model was applied to data…". It is not clear how that could be done. If the author has access to the raw data of that particular study, then I can understand. But if there is only published results, how technically that can be done. Please clarify.

Additional Questions:
Please enter your name: Liwei Chen

Job Title: Assistant Professor

Institution: Clemson University

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Reviewer: 3

Recommendation:

Comments:
The authors carried out a systematic review and meta-analysis to determine whether there is a threshold of maternal glucose above which adverse perinatal outcome were elevated. 28 studies with some 263,000 women were included in the meta-analysis and showed that there was a positive linear relationship between maternal plasma glucose levels and perinatal outcomes such as caesarean delivery, labour induction, large-for-gestational age birth, macrosomia and shoulder dystocia. The absence of a clear glycemic threshold above which adverse perinatal outcomes were substantially higher was interpreted to mean that any plasma glucose cut-off for the diagnosis of gestational diabetes

has to be "somewhat arbitrary".

Comments
1. The theoretical question regarding the existence of a threshold for adverse perinatal effects of maternal plasma glucose is an interesting one. However, there are empirical grounds to suggest that there is no reason to expect such a threshold. For instance, the adult blood pressure-adverse effect relationship shows no such threshold. The lack of a threshold is seen both for blood pressure associated adverse effects and also for reductions in adverse effects associated with pharmacotherapy. Similarly, rates of cardiovascular disease increase with plasma glucose (in adults) and this relationship is continuous without a clear threshold effect. Finally, (as the authors mention in the Introduction) the larger, well done studies on the relationship between maternal plasma glucose and adverse outcomes, such as the HAPO study, did not show any threshold for adverse effects. In any case, the absence of a clear threshold is not necessarily a problem for setting a diagnostic cut-off.

2. The systematic review and the meta-analysis follows a standard methodology and include a detailed search of the literature, an examination of included studies for potential bias and analyses ascertaining heterogeneity in the results of different studies. I agree with the argument that the unadjusted relation between plasma glucose and adverse effects is the appropriate relationship to study in this context.

3. In the Abstract, lines 43-46, the authors state that
"In general, associations were stronger for fasting compared with post-load glucose. For example, the odds ratios for LGA per 1mmol/L of fasting and 2-hour post-load glucose (following a 75g OGTT) were 2.14 (95% CI 1.17 to 2.68,), and 1.21 (95% CI 1.18 to 1.24), respectively."
The odds ratio for LGA per 1 mmol per L of fasting glucose (i.e., 2.14, 95% CI 1.17 to 2.68) is not significantly different from the odds ratio for LGA per 1 mmol per L of 2-hour post-load glucose (i.e., 1.21, 95% CI 1.18 to 1.24). Even though the point estimate of the former is larger than the point estimate of the latter, the 95% CI of the former includes the point estimate of the latter implying a P value greater than 0.05 for the difference in the 2 odds ratios. Perhaps the authors should use a different example to make this point.

4. The authors mention in the Discussion section that absence of blinding of maternal glucose levels may have resulted in some flattening of the association between plasma glucose levels and adverse outcomes. A stratified analysis of studies with and without such blinding may be provide some insight into this issue.

Minor comment
5. On page 8, lines 30-31. The authors mention that the main risk of bias in studies on the relationship between maternal glucose and adverse perinatal outcomes arises due to a lack of blinding of outcome assessors to the maternal glucose level. According to the authors this could have resulted in a bias due to confounding by indication. In my opinion, the lack of blinding could have led to a surveillance bias or detection bias (and potentially to a self-fulfilling prophesy) but not to confounding by indication. Confounding by indication refers to different phenomenon wherein higher rates of an adverse outcome (e.g., maternal death) are associated with a treatment (e.g., caesarean delivery). This occurs because the treatment (e.g., caesarean delivery) is closely correlated with an indication (e.g., serious pregnancy complication such as severe preeclampsia, abruption, etc) that is responsible for higher rates of the adverse outcome (maternal death).

Additional Questions:
Please enter your name: K.S. Joseph

Job Title: Professor

Institution: University of British Columbia

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A fee for speaking?: No

A fee for organising education?: No

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END

Date Sent: 26-May-2016