Author's response to reviews

Title: Glycosylated haemoglobin and adverse pregnancy outcomes in type 1 and type 2 diabetes mellitus: Systematic review of observational studies

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Version: 2 Date: 3 July 2006

Author's response to reviews: see over
27th June 2006

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Dear Dr Le,

Re: MS – 1606448450984135: Glycated haemoglobin and adverse pregnancy outcomes in type 1 and type 2 diabetes mellitus: Systematic review of observational studies.

Thank you for your e-mail of 12th June regarding reviewers comments for the above paper. We are grateful to all the reviewers for their comments which we have taken into account and we welcome the opportunity to improve our paper. The changes we have made are detailed below, and where suggested changes were not made an explanation is given.

Reviewer 1:

We thank Reviewer 1 for the comments regarding our review. In response to the minor essential revisions we have changed the sentence in the 2nd paragraph of the discussion so that it now reads ‘Our analysis shows that poor glycaemic control is associated with a greater…’.
In Table 4 we have expanded the headings and we now hope that this helps the reader understand the content.

Reviewer 2:

We thank the reviewer 2 for raising the issue of the 1% change in HbA1c and whether this has been properly derived across the studies. One of the co-authors on our paper is an experienced statistician, Dr Peter Donnan, and we are assured that the methods used to derive this 1% change in HbA1c are appropriate.
The following paragraph is included on page 7, ‘For studies that reported the mean and SD of glycated haemoglobin we estimated the effect of a 1-unit percent change in glycated haemoglobin, assuming a normal distribution for glycated haemoglobin values. We calculated the 25th and 75th percentiles and divided the log relative risk by the difference of these 2 values to give an estimate of the effect of a 1-percent change in glycated haemoglobin. (12) We did not pool data from individual studies for these analyses as the measurement of glycated haemoglobin differed between centres.’
Reviewer 3:

We appreciate the detailed attention our paper received from reviewer 3. We thank the reviewer for mentioning that several papers which he felt were important did not meet the inclusion criteria for this systematic review. These papers did indeed use both blood glucose levels and glycated haemoglobin to look at outcomes, however the authors used levels relating to mean maternal glycated haemoglobin expressed as standard deviations from normal control mean values. Studies included in this systematic review divided their population into groups on the basis of values either above or below a certain percent. To include the data from the Mills papers in the systematic review we would need to convert their glycated haemoglobin data from standard deviations to their normal control mean. Data on the normal control mean has not been mentioned in the papers.

We have searched the papers of Judith Steel and were unable to find any which meet the inclusion criteria for our systematic review. As part of our systematic review we had investigated pre-pregnancy studies analysed by Ray in his systematic review and again none of these met the inclusion criteria for our particular systematic review. The question of whether or not women received pre-conception care is not addressed by us.

We have added several sentences in the methods section to clarify our inclusion criteria and this will hopefully give better explanation as to how the studies were selected, (4th paragraph, page 4).

We have changed the term ‘glycosylated’ to the now accepted term ‘glycated’ as requested in the minor essential revisions.

Reviewer 4:

We thank reviewer 4 for the detailed comments regarding our paper. We have applied the QUORUM statement to this review as it allowed us to follow the guidelines for the open-reporting of studies. By using the recommended QUOROM format we hope that information which would otherwise require a lot of text is conveyed more simply. There are still no widely accepted optimal strategies for searching the literature for prognostic and observational studies nor any widely agreed quality criteria for assessing prognostic and observational studies. In our review quality assessment was modified to suit a meta-analysis of observational studies rather than randomized controlled trials, examining patient selection, data extraction methods, detailed definition of variables, losses to follow up, and confounding. In response to the comments of Reviewer 3 we have further modified this quality assessment and this can be seen in Table 2 where we have included more criteria in this assessment.

The funnel plot in our review does show indication of asymmetry, however we feel that with just 12 studies the power to detect asymmetry in a funnel plot is low and no clear conclusions can be made from this result.

Heterogeneity and the appropriate use of random or fixed effect models was assessed by Cochran’s Q test and we have included information on this in the methods section. Taking into account the above points and in order to help readers understand the methods used we have edited this section, in particular the inclusion criteria and statistics section. We hope the edits have resulted in greater clarity.
In response to the reviewer’s minor essential revisions we have changed text of the results subsection of the Abstract and we hope that this now reads better.

The version of Statistical packages which were used are now stated in the Methods section.

The objectives of the review have been stated after the Background with the addition of the following sentence ‘The objective of the study was to perform a systematic review of observational studies to investigate and quantify the risk of adverse pregnancy outcomes in pregnant women with diabetes in relation to glycaemic control, whether poor or optimal’.

In Table 1, the number of women in each study with optimal and poor glycaemic control and the number of events occurring have been added.

We hope that the changes which have been made are in line with the reviewer’s comments and will allow readers to better understand the content of our review. Where suggested changes were not made we trust an appropriate explanation has been given. If you need further clarification of any aspect of the review please do not hesitate to contact Melanie Inkster at m.inkster@chs.dundee.ac.uk.

We look forward to the publication of our paper.

Yours sincerely,

Melanie Inkster
Tom Fahey
Peter Donnan
Graham Leese
Gary Mires
Deirdre Murphy