Author's response to reviews

Title: Blood Pressure Measurement At Two Years In Offspring Of Women Randomized To A Trial Of Metformin For GDM: Follow Up Data From The MiG Trial

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Author's response to reviews: see over
Response to Reviewers comments:

We thank the reviewer for their comments and opportunity to improve the paper. In order to be clear of the revisions that have been made, I have taken each reviewer comment in order (in italics) then given my response and made note of any manuscript changes.

Reviewer 1 Saker Firas.

Reviewer's report:

_The authors in this paper tried to answer an important follow up question from the MiG Trial published in 2008; It is not clear from this paper why this question was not addressed in the MiG TOFU in 2011 since it was taking place at the same time period._

The reviewer is correct to note that the MiGTOFU study reported body composition of infants originally studied in the MiG Trial and followed in either Auckland or Adelaide. Given the novel nature of this study group, follow up is planned throughout childhood. It is intended to publish a variety of important outcomes including body composition, cardiovascular status and neurodevelopment at selected ages in childhood.

The current manuscript is focussed on blood pressure at two years of age. Although this data was collected at the same time as that reported in the body composition paper (Rowan et al. Diabetes Care 2011), it represents a smaller dataset and was considered outside the direct sphere of interest of that paper. Thus it was planned to report separately as a short report – i.e. the current manuscript.

Major concerns:

1- _The number of patients with BP measurement does not match the two papers from the MiG and MiG TOFU trials, Please include an algorithm with justification (your group were able to do anthropometric measurement on 56 % of eligible patients ) 222 represent 38 % of eligible follow up patients. Perhaps this study was done in a subgroup from New Zealand (Not clear from methodology)_

The reviewer is correct in the request for clarification on the numbers. The 170 infants reported in the current manuscript were those in whom we were able to obtain successful blood pressure measurement. This group represents about 53 % of the children reported in the previous Mig TOFU paper (Metformin n=154, Insulin n=164; Table 1. Rowan et al. Diabetes Care 2011). The explanation for the low numbers reported in the current study is that at two years of age it was not possible to collect blood pressure measurements on all children who attended for follow up. Indeed, Van Houten (J Hypertension 2009) reports a similar rate of 63 percent.

The composition of the group includes infants from the two Auckland centres and Adelaide. This fact was noted as a consequence of the primary author responding to the reviewer’s comments. Accordingly, the Adelaide group were informed, invited to contribute to the significant rewriting of the manuscript and included as authors.

Several important changes have been made to the text:

1) The text has been modified in the methods section to give details of follow up at each site.
2) The requested flow diagram has been added.
3) The results now express the 170 children as a percentage of the total number who attended for follow up.

4) The discussion section includes recognition that this number is just under 30 % of the total eligible for follow up from the original trial. The difficulty in assessing BP in two year old children is also discussed and the Van Houten (J Hypertension 2009) paper with a similar rate of 63 percent is referenced.

2- A table with other demographics and patient information comparing the two treatment groups such as birth weight, height, gender, current weight, BMI and anthropometric measurements will be useful. (you referred to the MiG TOFU except your numbers are not inclusive).

Although the treatment allocation comes from the original trial and is randomized, I agree that it is useful to the reader to see that the groups are comparable, so I have added the following information on current height, weight and sex to paragraph one of the results:

“There were no significant differences in weight at 13.7(1.9) kg versus 14.0 (2) kg and height at 90.5 (4.7) versus 90.4 (5.1) cm for insulin and metformin groups respectively. Sex was also equally distributed between the treatment groups with 41 males (47.1%) in insulin group and 40 males (48.2%) in the metformin group”.

As there are no differences in current height and weight I have not included BMI.

Minor concerns:

1- A table with unadjusted and adjusted odds ratios or CI for specific differences in the predictor variables might be helpful.

Weight and height were the only significant variables and information is given in the text on the effect size of these variables. The lack of effect for the other two important variables is illustrated in the two figures, which show unadjusted BP data divided by sex and treatment arm.

In summary: The paper provides important BP values for infants born to mothers with controlled GDM; additional clarifications are needed to explain the findings and to make it easier to follow.

Reviewer 2. Tine Dalsgaard Clausen

Reviewer's report:

The MIG-study is/was a very important RCT-study in order to evaluate the use of metformin (+/- insulin) versus insulin alone, and the follow-up of the children is essential. However, unfortunately I do not find that the present part of the follow-up in its current form is very usefull.

The study evaluates the blood pressure (BP) from n=170 (form 2 year old offspring of women being treated for GDM (including 2 different arms) in a mixed population, which is not found alike many other places in the world.

We note that the offspring of women in New Zealand and Australia may not be exactly the same as those from other centres. However, this was the population that formed the original randomised controlled trial so it cannot be altered. We have reported the ethnicity, which allows the reader to crudely compare with their own patient population.
Further, the reviewer states “Data on women with diet-treated GDM are not included”. As stated in the methods section, this study represents follow up of the original MiG trial so the group reflects the treatment given in that trial and cannot be modified. As the reviewer commented that “follow-up of the children is essential” with respect to the MIG-study, I have taken the wording as a simple statement rather than a request for extra comparison with children born following diet controlled GDM.

*It will in coming studies be difficult to evaluate whether a potential difference according to BP in another cohort should be referred to ethnic differences or effects of potential mal-treated GDM.*

There is a paucity of published data on offspring blood pressure early in childhood following GDM and it is unclear whether the above comment is suggesting a change in the manuscript or discussing potential problems with interpretation of future literature. For the current study it should be noted that neither ethnicity nor treatment arm had an effect on blood pressure at two years of age in the regression model used. However, to aid the reader in interpretation, we have included description of weight and height, which are important influencers of BP and may vary with ethnicity.

The authors claims 2 aims:

1) *To provide data on BP in 2 year old offspring of women with pharmacologically treated GDM*
2) *To study the effect of treatment on the BP of the offspring- comparing metformin-arm with insulin-arm*

*To me the secondary aim is by far the most interesting aim - though it would still have been more relevant to evaluate the effect of treatment by comparing to diet-treated GDM. I don’t find that the primary aim is interesting in itself, without comparing data on BP with a relevant reference-population.*

As stated above, and in the methods section of the manuscript, the data come from follow up of a randomised trial of metformin (+/- insulin) versus insulin alone so cannot include a diet controlled group.

In order to provide the reader with more information, I have added a recent reference that is a systematic review (Aceti et al. Diabetologia 2012) of studies examining the diabetic pregnancy and offspring blood pressure in childhood. It should be noted that the youngest age at follow up in the included studies is three years. One of the studies (Wright 2009) gives the actual data at 3 years, which has now been included in the discussion section.

*In the discussion section it is stated, that it is reassuring, that systolic and diastolic BP does not differ from “published norms”, but in my opinion this should have been discussed in much more details and have been included also in the results-section and in the abstract.*

Comparison with other published data is conventionally included in the discussion rather than results section, so I have left it there and added further text as discussed below.

The abstract contained the wording “These novel data compare favourably with published norms”. The following text has now been added to the abstract: “No difference was found between the metformin and insulin treatment arms. In a regression model, height and weight were only two factors associated with the levels of systolic blood pressure. For each additional kg the systolic blood pressure increased by 1.0 mmHg. For each additional cm of height the systolic blood pressure increased by 0.42 mmHg.”
Details are given for the reference data in the discussion but a full description of each study group is not given in the abstract due to space.

The following text has been added to the discussion section:

In a study of infants from the USA who were exposed to GDM the mean systolic BP, at 3 years of age, was reported to be 3.2 mmHg higher than that in controls born to normoglycaemic mothers after adjustment for sex, age and measurement condition. In this study population, of whom 73% were born to mothers described as white American, the mean systolic BP was 92 mmHg, which is similar to the US 50th centile. A recent systematic review (Aceti) has reported increased systolic BP following exposure to diabetes in-utero but no effect on diastolic BP. However, there were important differences in type of maternal diabetes, sex and age at follow up that require further investigation.

*What is the ethnic background in the reference-material? And how would it affect the interpretation of data from the current study?*

The ethnic background in the referenced papers varies but the majority are Caucasian. In the Wright paper 73% are described as “white”. For Van Houten no data is given in the 2009 paper but in other reports 53% of the background population are described as Dutch. In the Blake paper approximately 90% are described as Caucasian race.

Note that the discussion text has been modified to include the available extra information on ethnicity.

In my opinion, given the lack of effect from ethnicity when corrected for current size and the paucity of data at this age, there is unlikely to be a major barrier to interpretation of the presented study data.

*Furthermore, one could speculate whether BP by the age of 2 years is clinical relevant, valid and/predictive of later cardiovascular disease (which is also mentioned in the discussion section) - I would be happy for a reference and more discussion evaluating this issue.*

It is agreed that two years of age is early to observe a clinically relevant difference. However, the relationship between maternal diabetes and offspring cardiovascular health is important because maternal diabetes is common. Furthermore, this is an area where the literature is still very much evolving. If there was a statistically significant difference in blood pressure noted at two years this would be of considerable importance even if it was not yet proven clinically relevant.

A summary of this literature has been added to the discussion section.

*This follow-up includes only 23% (170/751) of the children from the original trial and only 77% of those “who attended for assessment”. The issue regarding lost-to-follow-up is only mentioned very briefly in the discussion and needs more attention than a reference to a previous publication.*

Please see previous discussion. This is an important point and is acknowledged in the text.

*The authors describe the back-wards elimination procedure - and apparently (but I am not sure) the reduced model regarding the systolic blood pressure contains only offspring height and weight - but it is not clear to me what the content of the reduced model is regarding the diastolic blood pressure. And are the estimates of BP in Figure 1 and 2 - crude estimates?*
The reported model was used to interrogate an effect on systolic blood pressure. This is supported by the systematic review (Aceti) findings.

The figures 2a and b use raw unadjusted BP data this has been clarified in the legend.