Author's response to reviews

Title: Mild Gestational Diabetes in Pregnancy and the Adipoinsular Axis in Neonates born to mothers in the ACHOIS randomised controlled trial.

Authors:

Louise K Pirc (louise.pirc@nwahs.sa.gov.au)
Julie A Owens (julie.owens@adelaide.edu.au)
Caroline A Crowther (caroline.crowther@adelaide.edu.au)
Kristyn Willson (kristyn.willson@adelaide.edu.au)
Miles J DeBlasio (miles.deblasio@adelaide.edu.au)
Jeffrey S Robinson (jeffrey.robinson@adelaide.edu.au)

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Author's response to reviews:

Dear Dr. da-Silva,

Re: MS 7273104501081313

Mild gestational diabetes in pregnancy and the adipoinsular axis in neonates born to mothers in the ACHOIS randomised controlled trial.

Thank you for your email and providing the peer reviewers comments on our manuscript. We appreciate the suggestions the reviewers have made to improve the manuscript. We have amended the manuscript in response to the queries raised by the reviewers and attached the revised manuscript. Detailed below point by point is our response to the issues raised.

As requested we have included a statement in the methods section on ethical approval and informed consent and checked that our revised manuscript conforms to the journal style.

Thank you for reconsidering our paper.

Wish best wishes
Yours sincerely

Professor Caroline Crowther

Reviewer 1 David Pettitt

1. Description of the study design.
In the abstract and the methods section we have clarified that the 95 women with mild GDM had been recruited to the ACHOIS trial at one of the collaborating hospitals and also agreed to take part in this cord blood study.

2. In several cases the authors claim "tendencies" with non-significant p-values.
In presenting some of the results of this study, that has a relatively small sample size, we consider describing trends p<0.1 can be helpful. However where such trends are presented we now clearly state that this does not reach our defined statistical level of significance of p<0.05.

3. The statement "maternal treatment for mild GDM partially prevented these adverse effects for the infant" seems unsupported by the data.
We have removed this sentence from the first paragraph of the discussion.

Reviewer 2 Robert Fraser

1. What lability is shown in the various metabolites measured in relation to events in labour?
Women were recruited to the cord blood study at a single institution. In the treated group 4 women were
treated with insulin therapy and 1 in the routine care group. The policy of the hospital for care of women with GDM is not to continue insulin during labour and not to provide a glucose infusion. We consider the numbers in the study too small to permit exploring metabolite concentrations by events occurring in labour.

2. How labile are cord blood levels of adiponectin and leptin?
We have not assessed this directly but many studies over a number of years and information provided with kits for the measurement of these hormones have shown that the measured levels of these hormones in plasma and serum do not change following incubation at 4°C for up to at least 14 days and unchanged after up to 5 freeze thaw cycles. This indicates that their levels are very stable in human plasma and serum generally.

3. The authors should standardise throughout that what they are measuring here is cord blood or fetal levels rather than 'neonates'.
We have standardised using the word "baby" or "fetal" rather than neonate throughout the text.

4. Units of serum insulin in Table 2 given as micrograms/ml. More conventionally these would be microunits/ml.
We have changed the units of serum insulin to microunits/ml in Table 2 as was meant.
Julie/Jeffrey/Miles is this correct? Are the other units correct?

Reviewer 3 David McCance

1. Details should be given of the number of subjects who required insulin in each of the treated and routine groups.
In the treated group 4 women were treated with insulin therapy and 1 woman in the routine care group. Given the small numbers of cases treated with insulin presenting as a subgroup is not warranted.

2. Details should be given of the glucose levels achieved during delivery and whether a glucose infusion was employed.
As is the hospital policy glucose levels are not routinely monitored in women with GDM and no glucose infusion is given.

3. It would be helpful if more details were given as to how the control subjects were obtained?
Women who had a normal OGTT during the time course of the cord blood study were invited to participate. The controls were not matched to the GDM cases. The controls were not all Caucasian. We have added further details to the methods section as requested.

4. Several of the data are only borderline significance and should not be given undue prominence. As described under Reviewer 1 point 2, we have downplayed these findings.

5. The authors should give power calculations for what difference they would be able to detect for each variable.
Kristyn: please could you calculate or do we have already? Maybe just for the diponectin?

6. Did the method of delivery differ between groups?
Kristyn: Please could you run analyses for caesarean birth/vaginal birth.
The mode of delivery did not differ between groups. We have added this to the manuscript.

7. Treatment of GDM improved the plasma glucose compared with controls but did not 'normalise' it as stated in the abstract and results.
We have removed this statement from the results and the abstract.

8. No reference is made to the tables throughout the manuscript.
We have referenced the tables in the results section as suggested.

9. No details of smoking are given in Table 1.
These details have now been added.
Kirstyn: please can you provide.

10. The references in the text (by author name) differs from the numerical format in the bibliography. This has been corrected.