**Author’s response to reviews**

**Title:** Neonatal and obstetric outcomes in diet- and insulin-treated women with gestational diabetes mellitus: a retrospective study

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**Author’s response to reviews:**

Rebuttal to the comments of the reviewers with respect to manuscript ID BEND-D-16-00115: “Neonatal and obstetric outcomes in diet- and insulin-treated women with gestational diabetes mellitus: a retrospective study”.

Reviewer 1:

The manuscript by Koning at al explored fetal and maternal outcomes in GDM women who were treated with insulin vs. diet control. They found that the outcomes were comparable, although the rate of LGA was higher than that of non-GDM pregnancy. The manuscript provided useful data, especially in tracking outcomes of GDM.

We thank the reviewer for his/her positive comment.
I have the following comments.

1) The rationale of the study stemmed from the fact that Dutch National guideline was implemented in 2010. This is supposedly more "stringent" but it really is not stringent as GDM was diagnosed using fasting glucose ≥126, which is the criteria in 1999. I think the author needs to explain what was the old criteria and what were the changes in 2010 criteria (to reflect that it was more "stringent") so that the readers will have a better understanding of the main manuscript idea.

2) As per comment in #1, it would be helpful to cite some previous outcome data in GDM prior to the criteria change.

The reviewer is correct that there is no comparison with a population using older screening methods. Actually, the research questions we have aimed and tried to answer are more focussed on the clinical outcomes, given the fact that patients are referred for treatment after they have been identified and/or diagnosed according to the new 2010 Dutch guidelines. This new guideline focused on a more active screening and treatment policy provided by "usual care" in the preceding years. As such, our population is a careful description of current clinical practice and treatment outcomes, rather than a before-after comparison. We have changed the text in the abstract and introduction accordingly.

3) The newborns of the mother on insulin therapy had lower birth weight but also lower GA at birth. This is likely related to the higher rate of induction of labor. Please clarify the normal practice or criteria used to induce labor.

The reviewer is correct, in the insulin group there was a higher rate of induction of labour, and lower birth weight and lower gestational age at birth. To adjust for this difference, we have used several ways to estimate birth weight in relation to gestational age/time of delivery, which included also the birth percentiles (see table 2). The birth percentiles are adjusted for gestational age, parity, ethnicity, and gender. After these corrections we observed no differences in birth weight between the insulin group and the diet-group.

Furthermore, as proposed by the reviewer we have described the normal practice/criteria of induction of labour more clearly in the method section (line 141). At last, in table 3 we did not report a p-value for the variable “induction of labour”. This p-value is not applicable because the use of insulin therapy is an indication for induction of labour at or around 38 weeks.

4) Interestingly, infants of diet-controlled GDM women had a higher rate of birth weight 4000-4499 gm, despite their moms having lower BMI. I think the author needs to speculate why this was the case. Was it due to difference in gestational age, or perhaps different glucose levels? Information on glucose control is crucial.

The reviewer poses an interesting comment and is correct that information about glucose control is important. As we described in the method section, after 1-2 weeks the blood glucose values of the women were evaluated. Women with fasting blood glucose level ≥5.3 mmol/l and/or post prandial blood glucose level ≥7.8 mmol/l received additional insulin therapy to obtain adequate
blood glucose control. The diet- and insulin-treated women were both followed to the date of delivery. If applicable based on SMBG, diet was adjusted and insulin dose increased to maintain BG levels within the target range. There was regular e-mail and/or telephone contact by the diabetes nurse, at least weekly, in order to assist patients to achieve and maintain glycaemic targets.

We believe that the higher birth weight in the diet-group is not because of a large difference in glucose control between the two groups, all women were monitored and treated similarly. Moreover, after correction for gestational age, parity, ethnicity, and gender there were no differences in birth weight between the two groups (also no significant differences in LGA infants (P > 90)).

In addition, to further establish glycaemic control we evaluated the third trimester HbA1c values (week 32-36 of gestation). For a small sample of women (n=212) the HbA1c values were measured in the third trimester of their pregnancy. The median HbA1c were higher in the insulin group compared (n=125; median 5.7% (39 mmol/mol), inter quartile range 5.4-6.0% (36-42 mmol/mol)) with the diet-group (n=87; median 5.5% (37 mmol/mol), inter quartile range 5.3-5.6% (34-38 mmol/mol)). These data do not support the higher glucose levels in the diet-group. Women in the diet-group were treated correctly and further treatment like additional insulin therapy was not indicated.

5) The author only included birth weight in comparing GDM and non-GDM pregnancies. Were other outcomes not available? If so, please state clearly.

The reviewer correctly points out that other outcomes of non-GDM pregnancies were not available. Not all of the neonatal and obstetric outcomes in the general population are available from public datasets with sufficient detail (discussion section, line 355).

As proposed by the reviewer we provided additional information about the outcomes for non-GDM pregnancies in the method section and below table 2.

6) I think it's important to stress that the current criteria likely is not stringent enough. There is evidence that IADPSG criteria is associated with improved outcomes. In addition, the timing of screening may identify higher risk GDM women. Please see these two additional references for more information.


We thank the reviewer for this point. We agree that adjustment of the diagnostic criteria in the current Dutch guideline is needed. On the other hand, we should realize that despite this, our treatment goal was rather strict and similar to the IADPSG criteria (FBG <5.3, PPBG<7.8).

We thank the reviewer for the two additional references, we have added these references in the discussion section and we have changed the text in the discussion section accordingly.

Reviewer 2:

This is a interesting paper as it gives us obstetric outcomes based on clinical care in a routine setting using the older WHO criteria which had a much higher fasting cut off.

We thank the reviewer for her/his positive comment.

1) The details of glycemic control achieved is not stated though the protocol to add insulin and the amount and type of insulin used is mentioned. Since a large part of the outcome is focusing on birth weight, it is important to see if there was good control achieved in the two groups especially in those with the higher birth weight babies.

The reviewer poses an interesting comment and is correct that information about glycaemic control is an important point. See also our answer to the 4th point raised by reviewer 1. Moreover, after correction for gestational age, parity, ethnicity, and gender there were no differences in birth weight between the two groups (also no significant differences in LGA infants (P >90)). In the discussion section we have speculated about the higher percentage of LGA infants in the whole GDM cohort compared with the general obstetric population.

2) The way the birth weights are described is a little confusing. In line 221 insulin group had lower birth weight but in 227 no difference in two groups with respect to LGA and then in 229 difference in frequency suggesting higher weight in the insulin group is confusing at first read. Could be explained in a better fashion.

We thank the reviewer for this point. In the revised manuscript we have changed the text in the result section for clarity.

3) The authors suggest that the larger LGA percentage compared to ACHOIS and Langer could be due to the higher fasting cut off and no milder GDM in their group. Equally, the high fasting cut off may have potential GDM in the untreated group.

The reviewer is correct that the routine care group (untreated group) in the ACHOIS study and study by Landon et al. the percentages of LGA were much higher compared with their treatment groups. We compared our LGA percentages only with the treatment groups of the two studies and not with the untreated groups (because the aim of our study was to evaluate the pregnancy outcomes after treatment).
Especially in the Landon study only women with milder GDM (defined as a fasting glucose level <5.3 mmol/l) were included in the study. Compared with the Landon study, we included women with a slightly higher fasting glucose value, but lower post GTT value. Moreover, the difference in LGA can also be explained by the difference in the definition for LGA. In the Landon study the percentage neonates with a birth weight >4,000 gram was almost similar with the percentage observed in our population. However, the differences between the percentage neonates with a birth weight >4,000 gram and percentage LGA neonates is small in the Landon study, as they did not correct for gender, ethnicity and parity. In our study LGA was defined as a birth weight above the 90th percentile and specifically adjusted for gender, parity and ethnicity. Therefore, we found a higher percentage of LGA neonates.

In the revised manuscript we paid attention to this point in order to clarify the differences in LGA neonates.

4) It seems that the timing of delivery was the same for the diet and insulin group. was there a difference in gestational age of delivery as per protocol between the diet and insulin groups? induction of labour for diet group was nearly 60% was that at 40 weeks?

The timing of delivery was not the same for the diet and insulin group. The women in the insulin group (median 38.1, inter quartile range 38.0-38.4) had a lower gestational age at birth compared with diet-group (median 38.6, inter quartile range 38.0-39.6). The interquartile range (75th percentile) of the diet group is higher (more women delivered their child around 40 weeks).

This difference is related to the higher rate of induction of labour in the insulin therapy group. Insulin therapy was one of the indications for induction of labour. In both centres labour was induced at or around 38 weeks in women on insulin therapy with taking blood glucose control as well as fetal growth into consideration. In the revised manuscript we changed the text in the methods and results section, to make this more clearly.