Author's response to reviews

Title: Differences in pregnancy outcomes and characteristics between insulin- and diet-treated women with gestational diabetes

Authors:

Katrien Benhalima (katrien.benhalima@uzleuven.be)
Karolien Robyns (karolien.robyns@uzleuven.be)
Paul Van Crombrugge (Paul.Van.Crombrugge@uzleuven.be)
Natascha Deprez (Natascha.Deprez@olvz-aalst.be)
Bruno Seynave (Bruno.Seynave@olvz-aalst.be)
Roland Devlieger (roland.devlieger@uzleuven.be)
Johan Verhaeghe (johan.verhaeghe@uzleuven.be)
Chantal Mathieu (chantal.mathieu@uzleuven.be)
Frank Nobels (Frank.Nobels@olvz-aalst.be)

Version: 3
Date: 25 September 2015

Author's response to reviews:

Answers to the reviewers:

Reviewer Kerstin Berntop:

1. ‘Methods, line 109: It is referred to the Fifth International Workshop Conference criteria but not all readers may be aware of these since criteria differ world-wide. It could be understood that the glucose challenge test was offered to all women, but when in gestation? A difference is obvious from Table 2 and raises the question whether there were special indications for earlier or later CTG? It would also be more informative if 50g is added “Women received a 50g glucose challenge test (CTG)”.

Answer: We now more clearly specified that ‘a 50g glucose challenge test (GCT) was used between 24-28 weeks and those testing positive [threshold after 1-h # 140 mg/dl (7.8 mmol/l)] had a 3-hour 100g oral glucose tolerance test (OGTT) within two weeks after the GCT using the Carpenter & Coustan criteria for GDM’. We also added that ‘Although there are no specific recommendations in both centers on which women should receive screening for GDM before 24 weeks of pregnancy, screening for GDM with a 50g GCT is sometimes performed before 24 weeks of pregnancy in high risk women such as women with a history of GDM.’

2. Methods, line156-162: It could be understood that the HbA1c is reported as NGSP (%) but this should be clarified. Since there is a world-wide agreement on
reporting HbA1c according to the IFCC-reference system (mmol/mol) the corresponding value for IFCC (mmol/mol) should be added.

Answer: We have now added that ‘Hba1c is reported in compliance with the National Glycohemoglobin Standardization Program (NGSP).’ In the manuscript we now systematically report HbA1c both in % and mmol/mol.

3. Results, line 193-194: Since fasting glucose levels predicted insulin treatment (according to multivariable regressions, line 228) it could be expected that some women only had fasting hyperglycemia and in need of long-acting insulin alone. It would therefore be of interest to clarify how many women received short-acting insulin alone, long-acting insulin alone, or both.

Answer: It was now added that ‘Of all women on insulin, 69.1 % (92) received only short acting insulin, 2.3% (3) received only long-acting insulin and 28.6% (38) received both short -and long acting insulin. Of all women on short acting insulin, 57.1% (76) received short acting insulin at each meal.’

4. Results, line 201-202: Add mg/dl after glucose levels line 201, as well as the corresponding value for mmol/l since many countries report according to the SI system and readers may not be familiar with values in mg/dl. The same refers to HbA1c line 202, give % as well as mmol/mol. The same refers to Table 2, which indeed lacks information on mg/dl after the respective fasting, 1-h, 2-h, 3-h glucose variable as well as % after HbA1c in the first column. Values of the corresponding mmol/l and mmol/mol in parenthesis after the respective glucose and Hba1c level is suggested to be added.

Answer: As suggested, we added mmol/l after each glucose value and added mmol/mol to each HbA1c value (both in the manuscript as in Tables).

5. Results, line 228-234: The multivariable regression analysis should be more clearly described. In methods, line 169-171, it is described that the clinical variables most significantly associated with the need for insulin in univariable analysis were included in the multivariable logistic regression analysis, but which were they? It is suggested that Table 3 is replaced by a table showing the results of the univariable and multivariable analyses and that the information in the present Table 3 is given in the text alone.

Answer: In the section of statistical analysis, it was now clearly specified that ‘the Treatment with corticoids was a significant variable in the univariable analysis but this was not included in multivariable logistic regression since it could not be excluded that treatment with corticoids preceded the use of insulin in some
patients.' We have now added in Table 3 the p-values of the variables included in the multivariable logistic regression.

6. Discussion, line 261-279: This information is not especially relevant for the present study which does not include women on other drugs than insulin. This section could be shortened down, only including information relevant for the study, such as that metformin might have a positive effect on weight gain in these women.

Answer: This section in the discussion was now shortened to ‘Some studies have suggested that metformin may be a safe and acceptable alternative for the treatment of GDM with less maternal weight gain compared to insulin and with no increase in congenital anomalies, despite it crossing the placenta [8,26,27]. However there is a paucity of long-term follow up data on children exposed to oral agents in utero. More research is therefore necessary to evaluate whether the addition of metformin to insulin can improve pregnancy outcomes in women with GDM and whether this is also safe on the long term.’

7. One or two sentences could be added on line 300 discussing the clinical implications of the present findings of fasting glucose levels as predictors of insulin treatment with an optimal cut-point of 88.5 mg/dl (4.9 mmol/l), close to the IADPSG cut-off. Does this change anything considering indications for insulin treatment (now fasting level 95 mg/dl or 5.3 mmol/l)? How about the corresponding 2-h level (120 mg/dl or 6.7 mmol/l)?

Answer: In the discussion we have now added that ‘This FPG cut-off is lower than the general recommended FPG target for the treatment of GDM of < 95mg/dl (5.3 mmol/l) and is also closer to the FPG cut-off proposed by the ‘International Association of Diabetes and Pregnancy Study Groups’ (IADPSG) for the diagnosis of GDM compared to the Carpenter & Coustan criteria we used. This might suggest that a lower FPG target for the treatment of GDM might be indicated but there is a need for large randomized intervention trials evaluating the benefit of lower glycaemic targets for the treatment of GDM on pregnancy outcomes.’

8. Discussion, line 314-320: In what way is this information relevant for the finding presented on line 2013-214, that less than one third had abnormal fasting glycemia while 2-h and 3-h glucose levels were more frequently abnormal? Does the 3-h value add anything concerning insulin treatment and outcomes?

Answer: In the discussion we have now added that ‘However, in contrast to the FPG, the 2-and 3-hour glycaemia were not anymore significantly associated with the use of insulin in the multivariable logistic regression.’
Reviewer Melissa Whitworth:

1. Need to justify using center as a variable when they have stated that the same treatment protocols are used in both centers.

   Answer: In the section of the statistical analysis, we have now added that ‘Although the treatment protocol for GDM was similar in both centers, a center was also used as a variable to adjust for differences in population characteristics and for potential differences in obstetrical management between both centers.’

2. The results section is very difficult to read as there are lots of results given in text format. Results which are given in the tables should not be repeated in the text. If the results from lines 187-192 are in table 1 remove from text. If not please put in a table instead. Similarly for table 2 and lines 199-211.

   Answer: The results of the general cohort and the differences between both centers, were now included in an additional table (Table 1) and therefore only briefly mentioned in the results. The other sections in the results were now also shortened with referral to the Tables.

3. Line 114-116 Need to explain more clearly what determined use of insulin-e.g. how many ‘high’ BMs etc

   Answer: To better explain when insulin is started, the following was added ‘To uniform the initiation for insulin therapy as much as possible, the ‘Weekly Average Glycaemia’ (WAG) is calculated based on the self-monitoring values of the blood glucose (fasting and postprandial) during the first weeks after the diagnosis. Therapy with Insulin is initiated when the fasting WAG and/or the postprandial WAG is above target during two weeks in a row.’

4. Line 248-251-p values are missing

   Answer: The p-values were not added in the discussion.

5. Line 282-286 They state as a positive finding that those on insulin have an earlier diagnosis of GDM and are more likely to have previously had GDM but as they will be doing their GTT tests earlier on women with previous GDM is this really a positive finding?

   Answer: In the method section, we now more clearly specified that ‘a 50g glucose challenge test (GCT) was used between 24-28 weeks and those testing positive [threshold after 1-h # 140 mg/dl (7.8 mmol/l)] had a 3-hour 100g oral glucose tolerance test (OGTT) within two weeks after the GCT using the Carpenter & Coustan criteria for GDM’. We also added that ‘Although there are no specific recommendations in both centers on which women should receive screening for GDM before 24 weeks of pregnancy, screening for GDM with a 50g GCT is sometimes performed before 24 weeks of pregnancy in high risk women’.
such as women with a history of GDM.’

6. Line 269-279 do not seem relevant as they have not used oral agents

Answer: This section in the discussion was now shortened to ‘Some studies have suggested that metformin may be a safe and acceptable alternative for the treatment of GDM with less maternal weight gain compared to insulin and with no increase in congenital anomalies, despite it crossing the placenta [8,26,27]. However there is a paucity of long-term follow up data on children exposed to oral agents in utero. More research is therefore necessary to evaluate whether the addition of metformin to insulin can improve pregnancy outcomes in women with GDM and whether this is also safe on the long term.’

7. Need to settle on one spelling of Caesarean.

Answer: The spelling was corrected.