

December 5, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13691-review.doc).

Title: Birth defects in pregestational diabetes: defect range, glycemic threshold and pathogenesis

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Name of Journal: *World Journal of Diabetes*

ESPS Manuscript NO: 13691

1. The manuscript has been improved according to the suggestions of reviewers:
Format has been updated
2. Revision has been made according to the suggestions of the reviewer:

(1) "Title and terminology: "Pregestational" implies maternal. I did a PubMed search and found only one article that uses the term of "pregestational maternal diabetes" compared to 82 articles that use the term of "pregestational diabetes". Suggest to use the latter."

We thank and accept reviewer comment. "Pregestational maternal diabetes" was changed to "pregestational diabetes."

(2) "In citing articles that report rate and range of birth defects, information on glycemic control should be provided. In this way, readers can make a judgement on whether glucose lowering treatment had an impact on the rate and range of birth defects that were observed in a specific study."

We thank the reviewer for this comment. Many studies evaluated the rate and/or range of congenital anomalies associated with pregestational diabetes. However, not all of them published the data related to maternal glycemic control at early pregnancy (which has negative effects on organogenesis) or maternal treatment, compliance and effect throughout pregnancy. Be that as it may, whenever the data was obtained, we added it in the relevant places in manuscript.

Galindo et al: data about glycemic control was added to text: "...They noted positive correlation between high levels of haemoglobin A1c (HbA1c) >7% at early pregnancy and major congenital anomalies..."

Wender-Ozegowska *et al*: range of malformation is described under "range of birth defects" section while relation to HbA1c levels is described in the "Glycemic threshold for birth defects" section.

The other references mentioned in this section did not provide data about maternal glycemic control.

(3) Under the “Glycemic threshold for birth defects” subheading, these sentences of “Hanson et al. [25] studied 532 type 1 PGMD women and compared their malformation rate to 222 nondiabetic women. The rate of malformations did not differ significantly between the diabetic and the control groups (4.3% vs 2.4%).” should be part of the previous subheading “Range of birth defects”

We thank the reviewer for this comment; Hanson et al. in this study from 1990 aimed to evaluate the relationship between haemoglobin A1C in early type 1 (insulin-dependent) diabetic pregnancy and the occurrence of spontaneous abortion and fetal malformation in Sweden. Therefore the main issue in this paper was not the range of defects but the association with levels of haemoglobin A1C. We emphasized Hanson’s finding in our manuscript by illustrating the relation between HgA1c levels at first trimester and the risk for congenital malformation: *“Hanson et al. [25] studied 532 type 1 PGD women and compared their malformation rate to 222 nondiabetic women. The rate of malformations did not differ significantly between the diabetic and the control groups (4.3% vs 2.4%) although significant different was find in levels of first trimester HgA1c. The median value of HgA1c was 7.7% in the diabetic and 5.3% in the control group ($p < 0.001$). However, when higher levels of HgA1c were evaluated (HgA1c greater than 10.1% - equal to 8 SD above the normal mean control value), there was statistically significant higher occurrence rate of congenital malformation ($p < 0.01$).”*

(4) “Also under the “Glycemic threshold for birth defects” heading. In the last paragraph, the sentence of “In conclusion, It is clear that glycemic control is associated with congenital anomalies,” needs editing. “... associated with...” is better to be changed to “... associated with a reduced risk of ...”. In addition, “It” should be “it”, and the last “,” should be “.”.

We accept this comment. Changes were made to *“In conclusion, it is clear that glycemic control is associated with a reduced risk of congenital anomalies.”* as suggested.

(5) “Be accurate in citing literature. Under the “Glycemic threshold for birth defects” subheading. Last paragraph on page 12. The authors cited the studies of Greene et al. [34] and Zabihi et al. [35]. However, Zabihi’s study did nothing with HbA1 when I read through the paper. In Gneene’s study, the abstract says “The risk for major malformation was 3.0% with Hb A1 less than or equal to 9.3% and 40% with Hb A1 greater than 14.4% (risk ratio 13.2; 95% confidence interval 4.340.4).” These figures are different from those cited in the manuscript. Please confirm.”

We accept and thank reviewer comment. The corresponding sentence was changed to: *“Greene et al. [34] showed an increase in PGD-induced birth defects correlating to the level HgA1c. Their risk for major malformation was 3.0% when HgA1c taken at first trimester was less than or equal to 9.3% and 40% with HgA1c was greater than 14.4% (risk ratio 13.2; 95% confidence interval 4.3-40.4).”*

(6) “HbA1c or HgA1c. Consistence in the usage of the term my help avoid confusion to readers.”

We accept this comment and changed all to HgA1c.

(7) "The use of abbreviation of neural tube defects is inconsistent throughout the manuscript and should be corrected."

We accept this comment and made appropriate changes in manuscript.

3. References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Diabetes*.

Sincerely yours,

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