Author's response to reviews

Title: Birth-weight, insulin levels, and HOMA-IR in newborns at term.

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Author's response to reviews: see over
**Response to Reviewers and Editor’s comments**

**Reviewer's report**

**Title:** Birth-weight, insulin levels, and HOMA-IR in newborns at term.

**Version:** 1  **Date:** 25 November 2011

**Reviewer:** Deborah Ehrenthal

**Reviewer's report:**

**Major Compulsory Revisions:**

This reports a small study of the association of insulin and HOMA IR levels at birth with birthweight groupings. This is an interesting and important area for research. The author's use of a homogenous population adds to its value. It seems to confirm earlier observations.

1. The authors state that insulin secretion is reduced in type 2 DM. Impaired might be a more accurate characterization.  
   **Response. We made the suggested change (Page 3, line 3)**

   **Response. We thank the reviewer by the suggestion. It is an interesting article closely related with the focus of our manuscript.**  
   **We added a couple of paragraphs in the Introduction section (2nd and 3rd Paragraphs, page 3.). Also we added the references 8-11, 15 of the current version.**

3. Revisions recommended to the methods:
   - Specify what defined a “healthy mother”.
   - Describe if glucose tolerance testing is a part of routine care in the community- were the women tested?  
   - Please define for the reader the “HOMA-IR index” and why you used it.  
   **Response.**
   - **We modified the paragraph about health maternal status (Page 4, 5th paragraph), in the current version it is clearly stated the inclusion criteria to the study.**
   - **The glucose tolerance testing is a part of routine care in the Hospital; diagnosis of gestational diabetes in this study was based in the OGTT, we added a sentence to recognize it (Page 4, 5th paragraph, line 4)**
• The acronym HOMA-IR index was defined (Page 2, line 5-6; Page 4, 1st line)

• Do you have mother’s height so you can calculate BMI?
• Your discussion mentions “matching” the mothers but I did not see this described in your methods.
• You selected only babies at term and classified them as LBW, HWB and NBW. How was gestational age determined? Did you consider classifying them as SGA/AGA/LGA? Response.

• We added the BMI in the studied groups (Tables 1 and 2; and a paragraph in the Methods section (Page 5, 5th paragraph)
• We appropriately defined the matching criteria in the Methods Section (Page 5, 1st paragraph).
• We totally agree with the Reviewer. Gestational age was determined by ultrasound; we added a paragraph (Page 4, 5th paragraph, line 2), and change LBW, NBW, and HBW by SGA, AGA, LGA.

4. Revisions recommended to the results:
• The authors should consider including the data they used to develop the cut-offs for the HOMA IR unless it has been previously published.
• Please show tests of significance from the ANOVA that make it clear where there are differences in the insulin levels with the NBW infants for each of the LBW and HBW groups (there is a p-value that the post-hoc Bonferroni will give you when comparing the different groups)
• You include an OR but do not explain if it is the results from a bivariate or multivariable logistic regression. What else did you include in your model? Was it only maternal prepregnancy weight? Any infant characteristics such as sex?
• The point estimate for the OR for the association of HOMA IR was 1.9, which was not significant likely due to the small sample size. I would be careful stating that there was no association, rather that you were unable to adequately test that due to the small sample size.

Response.

• We added data about the independent group of newborns studied in order to obtain the cutoff points for insulin and HOMA.IR. For the purpose of presentation, we divided the study in two phases: the first, a cross-sectional non-comparative study to determine the cutoffs points and, the second, a cross-sectional comparative study (Page 4, 3rd and 4th paragraph). We added the 4th and 5th paragraph, and the last two lines on Page 6 as well as the lines 1-2 on Page 7 to show the results of 1st phase of the study. Furthermore, we added the Tables 1 and 2 in the current version, and the lines 4-5 in the 10.
• Data of the Bonferroni post-hoc test were added at bottom of Table 3.
• We clarify the data about of regression analysis model. Given that only maternal weight before pregnancy showed statistical significance in the bivariate analysis, the regression model was adjusted only by this variable and sex of newborn (Page 6 2nd paragraph).
• We modify the paragraph (Page 7, 5th paragraph) about the results of regression analysis in order to show the association of LGA and the *tendency of association* of SGA with insulin and HOMA-IR. This limitation was recognized (Page 10, 4th paragraph)

5. Revisions recommended to the discussion:
• The authors should discuss their findings in the context of other studies of newborns, rather than to studies of children and adolescents. It is fine to draw that connection later, but they are not comparable to their study.
• More caution in their statement about the absence of association with HOMA IR and LBW is warranted given their lack of power.
• Be careful with the speculations about the placental mechanism and provide more detailed rationale if you plan to include them.

Response.

• We agree with this important observation. In this regard, we modify Discussion section to focus on our results (Page 8, paragraphs 1 and 2; Page 9 2nd paragraph and lines 6-8 in the last paragraph; Page 10, line 1, and lines 1-2, in the 2nd paragraph).
• Totally in agree; we modify the 5th paragraph in Page 7 and 4th paragraph in Page 10
• Because in this study are not shown data to support this hypothesis, we deleted the paragraphs and references related with it.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I have no competing interests to declare.
Reviewer's report

Title: Birth-weight, insulin levels, and HOMA-IR in newborns at term.

Version: 1 Date: 10 January 2012

Reviewer: George Datto

Reviewer's report:

The authors present a cross sectional study of cord blood insulin and HOMA-IR level in a small population of Mexican term infants. They do a good job in defining and excluding confounding maternal variables which helps with their small sample size.

The following are major concerns:

1. The authors do not have a citation that defines normal versus abnormal insulin and HOMA levels in newborns. Although addressed in their manuscript, this data needs to be published first.
   - Response. According suggestion by Editor, data about the independent group of newborns studied in order to obtain the cutoff points for insulin and HOMA.IR were added. For the purpose of presentation, we divided the study in two phases: the first, a cross-sectional non-comparative study to determine the cutoffs points and, the second, a cross-sectional comparative study (Page 4, 3rd and 4th paragraph). We added the 4th and 5th paragraph, and the last two lines on Page on 6 as well as the lines 1-2 on Page 7 to show the results of 1st phase of the study. Furthermore, we added the Tables 1 and 2 in the current version, and the lines 1-2 in the paragraph 4th Page 9.

2. When analyzed as a continuos variable, HOMA-IR was not significantly different between the three birth weight groups. (Table 1) Contradicts their conclusions.
   - Response. Given that HOMA-IR is not parametrically distributed, we normalized its distribution using Logn (Page, 1st paragraph) and we reanalyze data using one way ANOVA. In the current version is noted a p value of 0.04 for HOMA-IR.

Based on these major issues, the conclusions of the paper can not be accepted.

Level of interest: An article of limited interest

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests
Editor’s comments
This is an interesting article and findings that have potential to meaningfully contribute to the existing literature. Major revisions are required before acceptance can occur. Please see the reviewers' comments in addition to the following:

1. There has been previous research into HOMA-IR levels in newborns. Most significantly is the study by Catalano in 2009 Diabetes Care. This work should be reference and discussed what the author's study adds to this previous finding. The work by Catalano determined a cut-off value of approximately 3.

Response. We added the 2nd paragraph on Page 8 and the reference 25 in the current version.

2. The authors state that they studied 150 newborns to establish their own normal values of insulin and HOMA-IR.

3. a. Was this research covered under the human subjects protection/IRB given to the other data presented in this study or was this a separate study?

b. The findings from these 150 NBW infants if not previously published should be published as part of this study. This would means presenting the data in a far more explicit manner. This could be the Part I - establishing the norms. Part II could be the data presented in the current manuscript.

c. If these 150 NBW infants was approved research and included with the current manuscript, the combined data would make for a strong study worth publication.

Response. The cross-sectional non-comparative analysis is also approved by the Mexican Social Security Institute Research Committee and the mother’s informed consent was obtained. Thus, we added data about the independent group of newborns studied in order to obtain the cutoff points for insulin and HOMA.IR. For the purpose of presentation, we divided the study in two phases: the first, a cross-sectional non-comparative study to determine the cutoffs points and, the second, a cross-sectional comparative study (Page 4, 3rd and 4th paragraph). We added the 4th and 5th paragraph, and the last two lines on Page on 6 as well as the lines 1-2 on Page 7 to show the results of 1st phase of the study. Furthermore, we added the Tables 1 and 2 in the current version, and the lines 4-5 in the 10.

• 3. Multiple regression: the authors need to state what variables were included in the multiple regression equation. It is not clear if it is maternal pre-pregnancy weight or additional variables. If additional variables were not included than possibly controlling for maternal diabetic status may be helpful.
Response. We clarify the data about of regression analysis model. Given that only maternal weight before pregnancy showed statistical significance in the bivariate analysis, the regression model was adjusted only by this variable and sex of newborn (Page 6 2nd paragraph).

4. The authors state that the data is "matched". Possibly this is a confusion of terms, but there is no evidence of matching. Was there a difference in diabetic status between the NBW and HBW groups? If excluding the LBW group, was there a different in prepregnancy weight? Further delineation of the underlying maternal status for each group would be helpful.

Response. We appropriately defined the matching criteria in the Methods Section (Page 5, 1st paragraph). We modified the paragraph about health maternal status (Page 4, 5th paragraph), in the current version it is clearly stated the inclusion criteria to the study.

- 5. Absent a power analysis and associated risk of a type II error caution should be made before concluding that there is a lack of an association between HOMA-IR and LBW. Subgroup comparisons (NBW vs HBW and NBW vs LBW) should be presented for all factors.

Response. Totally in agree; we modify the 5th paragraph in Page 7 and 4th paragraph in Page 10

- 6. Discussion should include other studies in this same age group.

In this regard, we modify Discussion section to focus on our results (Page 8, paragraphs 1 and 2; Page 9 2nd paragraph and lines 6-8 in the last paragraph; Page 10, line 1, and lines 1-2, in the 2nd paragraph) and added the references 8-11, 15, and 25.