Author's response to reviews

Title: Pre-pregnancy body mass index and weight gain: Where is the tipping point for preterm birth?

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Author's response to reviews: see over
Dear Sir/Madam:

Thank you for the opportunity to submit a revised draft of our manuscript. We found the reviewers comments constructive and have attempted to address them in the revised manuscript. This letter lists the reviewer’s concerns and details the specific changes made in response to them. We believe that the revised manuscript represents a significant improvement over the original submission and appreciate your willingness to consider this draft for possible publication.

Thank you.

Saba Masho
Reviewer’s report:

The authors assessed the effect of gestational weight gain on the odds ratio (OR) of preterm birth (PTB) in women with different pre-pregnancy BMI categories. They used data from a large cohort of American women receiving antenatal care between 1959-1974 in 12 hospitals. Their main question is how these two factors (gestational weight gain and maternal baseline BMI) interact and influence the OR for PTB.

Their research question is valid, clear and well formulated. They performed subgroup analyses for Black and White women of various BMI categories and gestational weight gains, which is interesting and pertinent, since ethnicity plays an important role in PTB and is often neglected. Additionally, they also analyzed the effects of these variable on early PTB (<32 weeks) as well as in PTB in general (<37 weeks), which is also an important point from a clinical perspective. There are important methodological details missing (such as information on recruitment, setting, type of population and how gestational age at delivery was obtained, among others) which I trust the authors can provide. In the Results and Discussion, the authors should review some sentences on the interpretation of their findings and refrain from making so many inferences based on tendencies devoid of statistical significance, concentrating instead on their more robust findings.

My main concern with this manuscript is the fact that the authors grouped different subtypes of PTB as a single outcome. It has been recommended that the investigation of possible risk factors for PTB should distinguish between PTB with and without premature rupture of membranes and indicated PTB, since the etiology, risk factors and pathways for these various subtypes of PTB may differ considerably [Hendler et al 2005, The Preterm Prediction Study: association between maternal body mass index and spontaneous and indicated preterm birth. AJOG; Goldenberg et al 2008, Epidemiology and causes of preterm birth. Lancet; Moutquin 2003, Classification and heterogeneity of preterm birth. BJOG; Savitz et al 1991, Epidemiologic characteristics of preterm delivery: etiologic heterogeneity. AJO]. I therefore strongly recommend that the authors reanalyze their data according to subtype of PTB and resubmit this manuscript.

Response: As suggested, we have re-analyzed the data. Preterm birth is now categorized as, spontaneous labor preterm births with premature rupture of membranes, spontaneous labor preterm births without premature rupture of membranes, and indicated preterm births. Additionally, the recommended manuscripts and other relevant articles are incorporated into the introduction.

Abstract

MAJOR COMPULSORY REVISIONS: The 2nd and 3rd sentences of Results should be corrected to reflect significant difference in the ORs identified in this study (see comments on Results and Discussion below).

The 1st sentence of Conclusion is incorrect, based on the findings reported in the tables (see comments on Results and Discussion below). The second sentence should be removed since it is not supported by the findings of this study which was not designed to answer this specific research question (i.e., the adequacy of IOM 2009 gestational weight gain recommendations).

Response: The abstract is revised to reflect the changes in the analysis and results.

Introduction

The authors present well the importance of the topic as well as current controversies and knowledge gaps in the area. The research question is well stated and clear.

MINOR ESSENTIAL REVISION: Some important references on the topic of maternal prepregnancy BMI and/or gestational weight gain versus PTB are missing and should be added. This studies should also be mentioned in Discussion and their findings compared with the main outcomes of the present study:
• The association between prepregnancy maternal body mass index and preterm delivery. Zhong Y, Cahill AG, Macones GA, Zhu F, Odibo AO. Am J Perinatol. 2010 Apr;27(4):293-8
• Pre-pregnancy body mass index and weight gain during pregnancy in relation to preterm delivery subtypes. Rudra CB, Frederick IO, Williams MA. Acta Obstet Gynecol Scand. 2008;87(5):510-7

Response: The introduction of this manuscript has been enhanced to include these studies and other relevant literature. Considering that the manuscript examines the different subtypes of preterm, additional literature were reviewed to enhance the manuscript. As suggested, the findings from these studies (and others) and also now included.

Methods

MINOR ESSENTIAL REVISIONS: 2nd paragraph, selection criteria for inclusion in analyses: the authors state they analyzed 52,574 pregnancies after excluding multiple births and fetal anomalies. How many, from the original cohort that enrolled women in their 1st antenatal care visit, were excluded due to miscarriage (< 20 weeks) and to fetal demise? How many were excluded from this original cohort due to missing information on essential variables, such as gestational age at delivery or maternal prepregnancy BMI or gestational weight gain? I suggest creating a flow chart to depict the representativeness of the included cases in relation to the original cohort.

Response: The study inclusion and exclusion criteria have been modified as detailed above. We have provided the numbers excluded for each each exclusion criteria. Among singleton pregnancies, 2,093 were excluded from the analysis due to fetal demise. Specifically, N=825 were excluded due to abortion at 19 weeks gestation or less, N=186 were excluded due to abortion (timing unknown), N=24 were molar pregnancies, N=822 were stillbirths at 20 weeks gestation or more, N=226 stillbirths, and N=10 were fetal deaths of an unknown type. The dataset does not differentiate between spontaneous and induced abortions. The numbers excluded for these and other exclusion criteria are now provided in detail in the methods section. Considering the detailed numbers included in the revised methods, we did not feel a flow chart was necessary, as it would be duplicative of information already provided.

- 3rd paragraph, Socio economic index: define how this was calculated (or provide a brief explanation as a footnote to Table 1). (MINOR ESSENTIAL REVISION)

Response: The methods section now includes a description of how the socio economic index was calculated as well as a citation for the detailed methodology of the index. It was computed by averaging the component scores for education, occupation, and family income. Both education and occupation were determined for the head of household and family income included income from all family members. A lower score indicates lower affluence and conversely, higher indices indicate greater affluence (possible range of 0.0 to 10.0).

MAJOR COMPULSORY REVISIONS: 4th paragraph, Gestational age (GA) at delivery, the main outcome variable: This needs to be describe in much greater details. Include information on the following:

Response: We have now provided detailed description of how gestational age was calculated and the classifications and definitions of preterm birth used in this analysis.

-What specific subtypes of PTB included in this cohort? This information is critical.
Response: The outcome for this analysis is now categorical, differentiating the three subtypes of preterm birth. Specifically, preterm birth was categorized as: spontaneous preterm birth with premature rupture of membranes; spontaneous preterm birth without premature rupture of membranes; and indicated preterm birth. The numbers and percents are provided in table 1.

- How many were Spontaneous PTB with intact membranes?

Response: N=2,278 (see table 1)

- How many were PTB after preterm rupture of membranes who went into labor spontaneously before 37 weeks?

Response: N=3,526 (see table 1)

- How many were induced PTB due to rupture of membranes or other indications such as Preeclampsia or diabetes or other maternal or fetal complications?

Response: The analysis includes 557 induced preterm births and is examined in this analysis. More detailed analysis of the induced births was not conducted due to the small number. While the reason for induction was not available in the data, conditions among induced labors include: 49.9% (N=278) with premature rupture of membranes; 17.2% (N=96) with preeclampsia; 2.2% (N=12) with diabetes; 10.6% (N=59) hypertension (chronic or during pregnancy); and 18.0% (N=100) with anemia.

- How many were elective cesarean section PTB due to medical indications? This should be clearly stated and women with induced PTB should be analyzed separately from those with spontaneous PTB.

Response: There were few cesarean sections overall in this analysis (5.2%) and the CPP study did not collect data to specify if a cesarean sections was elective or medically indicated. This analysis now examines induced preterm separately.

- How was gestational age at delivery ascertained in this cohort: by menstrual dates or by obstetric ultrasound? If it was the latter, at what gestational age was it performed? Or was gestational age assessed by physical examination of the neonate (Capurro)? In cases of discrepancy between these parameters, which one was used to determine gestational age at delivery? This information is crucial for the validity of the study.

Response: Gestational age was provided in the dataset. It was calculated by subtracting the last menstrual period from the date of delivery. This is now specified in the methods.

MINOR ESSENTIAL REVISIONS: 4th paragraph: Add reference to BMI categories used (WHO)

Response: This reference is now cited.

- 4th paragraph, Gestational Weight Gain:

-use Kg instead of pounds.

Response: All references to pounds have been replaced with kilograms.

-take into account GA at delivery

Response: Due to lack of information on weight at first trimester, we were unable to calculate the rate of weight gain per week. Although the rate adjusts for the gestational age, it has a major weakness. Considering that the weight gain per week assumes that a pregnant woman gains the same amount of weight every week, it is less practical, and difficult to interpret. For its practical application, we believe weight gain during pregnancy offers information that is clinically relevant.

-instead of using fixed, predetermined GWG categories (e.g. 5 lbs or 10 lbs)
suggest that you use quintiles of your own population.

**Response:** Gestional weight gain is now categorized into quartiles, based on the distribution of weight gain in this study sample. Quartiles were utilized, rather than quintiles due to the sample size (i.e., in stratified analysis, the numbers were too small when a 5-level category was used; however, a 4-level categorization of weight gain yielded adequate number in each cell).

**Results**

**MAJOR COMPULSORY REVISIONS:** Incorporate in manuscript the complete details of how the sample was drawn and describe the population from which it was drawn. If data are missing or the sampling plan was not followed, explain why and list all differences between data that were present in the sample and data that were missing or excluded.

**Response:** We have now provided information on how the data is drawn is clearly described in the methods section. Number of missing data is also included on table 1.

-Specifically, the authors should provide clear information on the 12 included hospitals: geographic location, N of deliveries per year, level of complexity. What was the process used for their selection? Cluster randomization? Convenience sample? What were the selection criteria? Judging by the characteristics of the participants (Table 1), these hospitals are not representative of the whole spectrum of American pregnant women. This should be stated as one of the limitations of the study in Discussion, regarding generalizability of the findings, even within the context of the United States population.

**Response:** The study methodology has been published and described in detail previously. This citation (Niswander N, Gordon M.: The women and their pregnancies; the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. Philadelphia, PA: WB Saunders; 1972) is now included in the manuscript, followed by an overview of the study methods. Additionally, the discussion section now acknowledges the limitations to generalizability of the results due to the 12 hospitals where the sample was drawn being in University-associated medical centers in urban areas.

**MINOR ESSENTIAL REVISION:** On the 5th paragraph of Methods, hypertensive disorders are apparently all grouped together. However on Table 1, the authors report the prevalence of Hypertension (presumably chronic) and Preeclampsia separately. The diagnostic criteria for these conditions should be described in Methods. And since the study spanned a period of 15 years, describe differences in these criteria over time.

**Response:** Hypertensive disorders are described in the methods; which includes a diagnosis of either chronic hypertension or hypertension during pregnancy; specifically, maternal hypertension was defined as hypertension documented by evidence occurring during any part of the pregnancy (including before 24 weeks) or a diagnosis of chronic hypertension. The definition of preeclampsia was inadvertently omitted from the methods section. We have now included information on how it was assessed separately from hypertension, (as indicated in Table 1). While it is not possible to know how advances in medicine were implemented over the time of this study, the fact that there were changes over time are now acknowledged in the discussion section as a limitation.

**Table 1.**

**MINOR ESSENTIAL REVISIONS:** The total N of participants in the 4 BMI categories adds up to only 48,077 women. Therefore 4,497 women are missing, since in Methods the author state that they analyzed 52,574 pregnancies, after excluding multiple pregnancies and those with fetal anomalies. Explain this discrepancy.

**Response:** The previous methods section was inadvertently incomplete and did not provide the numbers for all exclusion criteria specifically. In this revised manuscript, the exclusion criteria are now described in detail and the numbers reported in the text are consistent and reflected in the tables. More specifically, as now stated in the methods, pregnant women with multiple births or missing plurality
(N=3,651), severe congenital anomalies at birth (N=1,073), or non-live births, including abortion, molar pregnancies, stillbirths, and unknown etiology fetal deaths (N=2,093), were excluded from this analysis. Additionally, a total of 6,750 mother-child pairs with data missing from one or more of the following study variables were also excluded: pre-pregnancy BMI (N=4,497), gestational weight gain (N=3,573), labor (N=468), or gestational age (N=212). This resulted in the inclusion of 45,824 pregnant women who delivered singleton, live-born infants with no major congenital anomalies.

- Title of columns: place BMI cut-offs for each of the 4 categories, under the name (e.g.: Underweight: BMI < 18.5).

**Response:** Table 1 has been edited to include the BMI cut-offs.

- Besides the %, provide the specific Numbers for all variables presented in this table. And also add information about how many were missing for each variable presented.

**Response:** Table 1 has been edited to include the number of missing observations for each variable.

- Parity: present this information as a categorical variable instead of a continuous variable: N and % of Nulliparous and of Multiparous women in the cohort.

**Response:** This change has been made; parity is now included in the analysis as a dichotomized variable.

- N of prenatal visits should be adjusted according to GA at delivery; for example, a woman who delivered before 32 wks would obviously have a lower N of visits than a woman who delivered at 40 wks and this does not imply that the former had an inadequate N of prenatal care visits.

**Response:** Due to lack of sufficient information on weight at first trimester, we were unable to calculate the rate of weight gain per week. Although the rate adjusts for the gestational age, it has a major weakness. Considering that the weight gain per week assumes that a woman gains the same amount of weight every week, it is difficult to interpret. For its practical application, we believe weight gain during pregnancy offers information that is clinically relevant.

- The overall prevalence of PE in this cohort is very high: 18.1%! This reinforces the importance of presenting the diagnostic criteria for this condition in Methods and also the type of hospital setting (2ary? 3ary?). Could this be explained by some specific characteristic of this cohort, such as high prevalence of nulliparas (data not presented in current Results)? Or the high prevalence of Black women (47.1%) This needs to explored a bit in Discussion.

**Response:** With the changed study inclusion criteria, and a re-examination of the coding of the preeclampsia variable (possible preeclampsia was inadvertently coded as preeclampsia; it is now coded as no preeclampsia to yield a more conservative estimate), the prevalence of preeclampsia is now 14.0%. The sample included mostly multiparous women (71.2%); thus this may not be an explanatory variable. The high prevalence of preeclampsia, and implications due to the high prevalence of Black women in the study as well as the study setting from which participants were recruited are now discussed in the manuscript.
The overall prevalence of previous PTB is very high in this cohort: 23.3%. This indicates that this cohort is not representative of the general obstetric population and probably has a large number of high-risk women. This should be clarified, explaining the characteristics of the hospitals included in this study.

Response: With the changed study inclusion criteria, and a re-examination of the coding of the previous preterm birth variable (women who did not have a previous pregnancy are now coded separately from women who had a previous pregnancy, but without a preterm birth), the prevalence of previous preterm birth is now 16.6%. Similar to the high prevalence of preeclampsia detected in this study, implications of the high prevalence of previous PTB is now included in the discussion.

Table 2.
MINOR ESSENTIAL REVISIONS: Provide what was the reference category for maternal age and for parity.

Response: While Table 2 has changed (is now “Association Between Pre-pregnancy Weight, Weight Gain During Pregnancy and Preterm Birth – Unadjusted Analysis”, in the previous version, maternal age was examined as a continuous variable, thus no reference category was necessary. Previously, parity was also included as a continuous variable; however, now that parity is being examined as a dichotomous variable, the reference category (nulliparous) was used when testing for confounding (not specified in the tables).

- Provide pregnancy weight gain in Kg instead of lbs.

Response: All references to pounds have been replaced with kilograms.

MAJOR COMPULSORY REVISIONS: The statement in text of Results (p 9) stating that being obese is protective against PTB is incorrect: the unadjusted OR presented in Table 2 is not significant (0.91, 95% CI 0.82 -1.02). The statement in text of Results stating that being obese increases the risk of early PTB (p 10) is incorrect: the unadjusted OR presented in Table 2 is not significant (1.03, 95%CI 0.86 -1.23).

Response: The results section has been re-written to reflect the change in how the data were analyzed. The text has been drafted with particular attention to ensuring that the results described in the text correspond to the data presented in tables, with only statistically significant results included in the Results.

Figures 1 and 2. Interesting and well done!

Response: Because we are now investigating the 3 different subtypes of preterm birth, the graph became crowded and we are unable to include the table.

MINOR ESSENTIAL REVISIONS: I presume these ORs are unadjusted? This should be stated in the title of the figures.

Response: This figure is no longer included in the manuscript. However, in the originally submitted manuscript, the ORs reported in the figures were unadjusted.

- And add the 95% CI for all the ORs in the footnote table, instead of the p values.

Response: This figure is no longer included in the manuscript.

Alternatively, eliminate this footnote table and present the complete data for this in Tables 3 and 4, as additional data, grouping the Black and White women into a single group.
Response: This figure is no longer included in the manuscript. The new Tables 2 and 4 includes all women, regardless of race (unadjusted and adjusted models, respectively) and Table 3 shows the unadjusted analysis stratified by race.

-Change weight gains to Kg.

Response: All references to pounds have been replaced with kilograms.

Table 3.
MAJOR COMPULSORY REVISIONS: I suggest that the authors include another group for this table (as well as table 4) presenting the same data including both groups of women (Black and White together, which corresponds to the data summarized in their Figures 1 and 2, mentioned above). That way, the reader can clearly see how the OR for PTB is affected by the interaction between prepregnancy BMI and gestational weight gain.

Response: Table 3 in the revised manuscript submitted differs from the original Table 3 submitted. In the revised manuscript, the new Tables 2 and 4 includes all women, regardless of race (unadjusted and adjusted models, respectively) and Table 3 shows the unadjusted analysis stratified by race.

-Statements referring to this table in the text (p 9-10) are incorrect and should be rephrased according to statistical significance of the ORs. For example:

  -Among underweight White women, the OR for PTB was significantly higher than normal weight White women in the first three gestational weight gain categories, but was similar in the highest (30 + lbs) category (OR 1.19, 95%CI 0.79-1.79)
  
  -In Black underweight women, the ORs for PTB was significantly higher than in normal weight Black women in the first two categories of gestational weight gain, but did not differ significantly in the last two categories (20-29 and 30+ lbs).

  -Similar incorrect statements are made regarding overweight and obese categories in both races.

Response: The text has been carefully reviewed so that the results described in the text correspond to the data presented in tables.

Table 4.
MINOR ESSENTIAL REVISION: The text referring to this table (bottom of p 10) mentions table 3 and does not specify it refers to “early PTB”. This needs to be corrected. Similarly, the paragraph on p 11 should mention “early PTB”.

Response: In the revised manuscript, early preterm birth is no longer examined, thus Table 4 has changed. Table 4 now shows the adjusted analysis.

MAJOR COMPULSORY REVISION: Once more, authors should limit themselves to pointing out statistically significant differences and not tendencies.

Response: The results section has been re-written to reflect the change in how the data were analyzed. Additionally, only statistically significant differences detected are reported in the text.

Discussion

MINOR ESSENTIAL REVISION: In addition to comparing their results with the additional references mentioned in Introduction, there are several additional studies that should be mentioned here. For example, differences in
the ORs for PTB of White and Black women of different BMI should be compared to previous studies which also addressed this question. I recommend that the authors read these references:


Response: These references are now incorporated into the manuscript.

MAJOR COMPULSORY REVISIONS: The 1st statement is incorrect. Based on Table 2, women with pre-pregnancy overweight do not have a higher risk for PTB, but in fact they have a significantly lower OR for these outcomes, when compared to normal weight women. And the ORs of obese women for PTB are similar to normal weight women.

- The 1st statement in the 2nd paragraph is incorrect. The data presented by the authors on Tables 1, 3 and 4 do not support their statement. Based on their Tables, this study showed that, compared to normal weight women, obese White and Black women have a significantly higher OR for early PTB if they gain at least 30 lbs during pregnancy

Response: The text has been rewritten and edited so that the results described in the text correspond to the data presented in tables. Additionally, early preterm birth is no longer analyzed as an outcome due to the small sample size.

- As stated by the authors, combining spontaneous and induced PTB is a weak point of their study, which in my opinion is critical. Therefore, they should reanalyze their data accordingly and rewrite their Discussion based on these findings.

Response: We have reanalyzed the data as suggested. This major methodological change and subsequent implications have been taken into account in the rewritten discussion section.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests.