Author's response to reviews

**Title:** Variations in Preterm Birth Rates by Level of Prenatal Care and Ethnicity in New Mexico

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**Version:** 2  **Date:** 29 September 2011

**Author's response to reviews:** see over
September 29, 2011

Rachel Neilan, MSc
Executive Editor, *BMC Pregnancy and Childbirth*

Dear Ms. Neilan:

With respect, we submit our revised manuscript, "Variations in Preterm Birth Rates by Level of Prenatal Care and Ethnicity in New Mexico," for consideration as a research article in *BMC Pregnancy and Childbirth*. Based on the reviewers’ suggestions, we have made extensive changes to the manuscript, including rewriting the introduction and discussion to focus on the specific variables that were found to contribute to preterm birth, re-plotting the figures for consistent representation of the data, re-organizing Table 1 to increase clarity, and changing the title of the manuscript to better reflect the exploratory nature of the study. We believe that these changes have elevated this manuscript. Attached is a point-by-point response to all of the reviewer concerns.

We sincerely apologize for the delayed submission of the revised version of the manuscript. The extensive critiques and suggestions provided by the three reviewers as well as the fact that a majority of the authors are no longer at the same institution contributed to the extended period to revise the manuscript. We respectfully request that this manuscript be reviewed as a revised manuscript and not a *de novo* submission.

Thank you for considering our manuscript for publication in *BMC Pregnancy and Childbirth*. I verify that this manuscript is not under consideration in whole or in part for publication by any other source.

Sincerely yours,

Kimberly K. Leslie, M.D.
Professor and Chair
Gwin et al., “Variations in Preterm Birth Rates by Level of Prenatal Care and Ethnicity in New Mexico”

Responses to Reviewer Comments

We thank the reviewers for their careful reading of our manuscript. In response to the suggestions and concerns, we have made substantial changes to the original submission, including a new title, a complete rewrite of the introduction and discussion, clarification of multiple aspects of the study, and modifications to the figures and tables. We believe that these changes have resulted in a manuscript that clearly explains the purpose of our exploratory study and puts the major findings in the context of the field. Below we respond to each of the reviewer comments point-by-point. Please note that, since the changes to the text were extensive, we did not highlight changes within the text of the manuscript.

Reviewer 1: Lynne Messer

MAJOR COMPULSORY REVISIONS

1. The authors have data on an interesting and underrepresented population but are overly generic in their presentation of the material. The background replicates the epidemiology of preterm birth that is well-known among reproductive / perinatal researchers and therefore does not make a meaningful contribution to the literature. The authors could reframe their background material to highlight the significant contribution they are poised to make (the associations among Hispanics and Native Americans) and have a much better paper. In a related matter, it is not helpful to provide the laundry list of possible consequences of prematurity. Without some reference to the population of interest, it seems like a throwaway paragraph.

We have streamlined the introduction according to all of the reviewers’ appropriate concerns and suggestions (see also our responses to Reviewer 2 comment #2 and Reviewer 3 comments #1 & 2).

2. The authors need to be careful about suggesting genetic explanations to complex and multifactorial problems. If they are going to indicate “….researchers to postulate that there might be a genetic component to preterm birth.” they need to provide a reference for that claim. Further, lots of other researchers have noted the probable social causation of adverse birth outcomes. I think it makes the authors look a little simplistic to present only one side of the argument. In describing the preterm birth trajectories over time, the authors note the increases among Hispanic and Native American women. Since this information is going to be important for your material, it would be better to spend more than one sentence describing this trend and lose some of the generic background material that has been included.

We agree and have modified the introduction as suggested to focus on PTB in specific racial and ethnic groups, in particular Hispanics and Native Americans.
3. The authors provide somewhat frequent assertions throughout the paper (e.g., ...”and because it has been previously shown to be a good indicator of SES” without providing any references to the previous literature. This should be corrected throughout the paper.

We appreciate this comment and have added appropriate citations to the manuscript.

4. Regarding the maternal conditions, many of these variables are poorly collected on the birth record. It is not clear why the authors would want to include all of them, given their rarity. Just because the variable is available on the birth record is not a good reason to include it. Further, literature exists as to the quality of various elements of the birth record. The authors could refer to it to guide your choice of variables to include / exclude. It would also be helpful if the authors would provide definitions of many of these, since not all are sufficiently common to be widely known.

We believe the reviewer is referring the maternal conditions considered high risk (previously shown as the table on pg. 8, now listed within the text on pg. 7). Each of these conditions is a risk factor for preterm birth. We segregated cases with known maternal risk factors from those without so that we could study the incidence of spontaneous preterm birth as well as preterm birth in cases with maternal complications in our population. We acknowledge that there could be maternal conditions that are not listed on the birth record and have discussed this in the limitations of the study. Also, we agree with the reviewer about the accuracy and reliability of data on birth records and have acknowledged this and cited additional literature to this effect.

5. In the results, it is not clear if any of the result are adjusted. Please clarify.

The results were adjusted. This has been clarified in the methods section as well as the figure legends.

6. In the discussion, ties to Native American and / or Hispanic findings would be helpful. A summary of the statistically significant results (many of the paragraphs) is not that helpful, given the considerable literature devoted to the epidemiology of preterm birth.

We have shortened the conclusions and focused on the correlation between ethnicity or level of prenatal care and PTB, which we consider the most interesting findings our study and areas for future study.

MINOR COMPULSORY REVISIONS

7. Why did the authors not use a “==high school” education categorization? Graduating from high school is an important transition in the U.S. and those with “some high school” are very different from those “completed high school.” The fact that a temporal trend is noted in the data suggests an indicator variable for “year” is warranted. It is not clear if the authors included this variable in their models.

We agree with the reviewer as to the importance of years of high school; however, these data were not available on the birth records.
8. Odds ratios should be graphed on the log, not natural, scale.

We appreciate this comment; however, we plotted the odds ratios on a natural scale to facilitate the interpretation of the odds ratio itself. However, to aid interpretation, we included a reference line at OR=1.0 in all graphs.

Reviewer 2: Marcelo L Urquia

Major compulsory revisions

1. The title does not accurately reflect the contents of the manuscript, which reports variations in PTB by predictors available in birth certificates. As some of the observed associations are well documented (U-shaped maternal age association with PTB, inverse education gradient), it is not clear what is the contribution of this study to the literature. The manuscript would benefit from a rethinking of the points authors are trying to make. It is not clear if this study was conceived to answer specific research questions regarding the interplay between prenatal care, ethnicity and preterm birth (if this is the case please be explicit as there is no clear hypothesis) or was just a descriptive study looking how PTB varied by common risk factors (which better reflects what the manuscript is about). In any case, authors should make clear what this paper adds to the literature.

We appreciate the reviewer’s observation and have changed the title to better reflect the focus and key conclusions of the study. There was not a specific research hypothesis and instead was designed as an exploratory, descriptive study as the reviewer describes. Our overall goal was to identify sub-populations at increased risk of PTB. This observational study has the limitations that follow from lack of experimental controls. It was not possible to statistically control for other causes because the agency providing data (New Mexico Department of Health) required de-identified and aggregated (by county and year) information. We have made this clear throughout the manuscript. Furthermore, we have streamlined the introduction to better reflect the focus of this manuscript. Please also see our responses to Reviewer 1 comment #1 and Reviewer 3 comment #1.

2. Background: Authors did not make explicit their causal assumptions regarding the mechanisms linking prenatal care and preterm birth, particularly if this is the focus of the study. It might be possible that prenatal care and preterm birth are associated just because they are common effects of some unknown causes (e.g., unwanted pregnancy). In fact, associations between prenatal care and preterm birth have been found in observational but not in experimental studies (Kramer et al 2001, Socioeconomic disparities in preterm birth: causal pathways and mechanisms. Paediatric and Perinatal Epidemiology, 15(S2)). Consideration of alternate explanations may enrich the interpretation of results.

The reviewer brings up an interesting point about causality. We have revised the background material to present the controversy in the field, i.e., whether the level of prenatal care is causal in decreasing PTB. We also added this point to the discussion section. Essentially, despite the fact
that other factors may be at play, our observational study did reveal a correlation between increased prenatal care and decreased PTB rates in high-risk patients, which is consistent with previously published observational studies.

3a. Methods: Page 8: Please provide more details regarding the measurement of gestational age. Was the LMP estimate or the clinical estimate? Did the measure change over the study period? Is it possible that the secular trends of increasing ultrasound use affect the observed trends in PTB during the study period? The possibility of artefacts in the measurement of PTB should be addressed in the discussion.

In our definition of preterm birth, we used a variable termed “estgest” in our database, which is the physician’s estimated gestational age in weeks. We recognize that “calgest”, which is the calculated gestational age in weeks based upon the LMP, is an alternate variable used to define PTB; however, we believe the “estgest,” which takes into account ultrasound confirmation is the most accurate. In addition, because the clinicians relied on the “estgest” based upon clinical judgment, there were many missing “calgest” values in our database. We have added a statement to the methods section describing this information. With regards to how the use of ultrasound affects PTB trends between 1991-2005, it is certainly possible that more ultrasounds were performed in the later period of the study compared to the early period; however, this is a reality which is always a factor when evaluating gestational age in a longitudinal dataset. As suggested, we have added a statement to the discussion section reflecting this possibility.

3b. A breakdown of the excluded records (11%) by their criteria may be informative.

The reviewer makes an interesting point and these data would indeed be informative. However, the list is fairly long given that a number of different anomalies were excluded in addition to plural births. Thus, we have added this statement to the methods section in lieu of adding a table of criteria for exclusion that encompasses the 11% of excluded records.

4. Results: A table with the characteristics of the study population was not provided. Would it be possible that medical conditions included in the definition of high risk pregnancy were underreported among those who had missing or inadequate prenatal care? If so, many high risk pregnancies might have been misclassified as low risk pregnancies. Would not be more appropriate to use a logarithmic scale in the Y-axis in Figures 2 to 5?

The only data source possible was DOH birth records. Those are not complete medical records and thus misclassifications are undoubtedly present, as they are with any such large database study. We have included this in our discussion of study limitations. Please also see our responses to Reviewer 1 comment # 4. With regards to the presentation of data, please see our response to Reviewer 1 comment # 8.

5. Conclusions: I am not sure that this cross-sectional study has “demonstrated”, as claimed, “that increased pregnancy surveillance by obstetric providers helps modify the risk for PTB among women with complicated pregnancies”, since the observed associations may be due to confounding. In addition, authors ignored the conflicting literature regarding the role of prenatal care on preterm birth.
We thank the reviewer for pointing out that we overstated our conclusion. While our hope is that this observational study will better guide physicians to identify populations with a greater need for intervention, we realize that a controlled trial would be necessary to demonstrate that prenatal care can reduce PTB rates for women with complicated pregnancies. We have revised the concluding statement based on the reviewer’s points.

6. References # 1 to 4 and 6 to 8 seem to be improperly formatted.

The reference list has been updated.

Reviewer 3: Jason L Salemi

Major Compulsory Revisions:

1. In general, the stated focus of this manuscript, “…to elucidate the maternal risk factors that contribute to PTB…” does not match the title, which focuses more intently on adequacy of prenatal care and maternal ethnicity. There has been a considerable amount of research done into risk factors for prenatal care and this study, as written, appears as an exploratory analysis, which then evolved into a title which implies a focus on specific factors, but only because those factors had a statistically significant association with risk of PTB in the analysis. The Background, Methods, Results, and Discussion all point towards this global investigation of risk factors, and without a stated focus on any factors in particular, the study does not add a great deal in substance. The paper would benefit from a considerable re-working; I offer comments below.

We appreciate this insightful suggestion and have changed the title and streamlined the introduction and discussion. Please also see our responses to Reviewer 1, comment #1 and Reviewer 2, comment #1.

2a. Background: The background is extremely long, is heavily undercited, and lacks measures of association that offer a quantitative (as well as qualitative) assessment of the literature. For example, the authors state that “most research in the US has focused on the higher risk of PTB among black women as opposed to white women” and “there have been many studies that have shown that maternal age of less than 18 years increases the risk of PTB before…” and “Many studies have shown an association between socioeconomic status and the risk of either LBW or PTB.” None of these claims are supported or cited, and they should be backed by multiple citations. Although these are just a few examples, this is an issue throughout the introduction. I would advise that the authors review and offer a more substantive intro with appropriate citations.

We have condensed the background information to substantively describe known risk factors for PTB (e.g., prenatal care, socioeconomic variables) and the rates of PTB in the ethnic groups included in our study. Citations for this information were added.
2b. The background is also too long, in my opinion. There is an entire discussion of the causes of PTB; however, the reader seems to be thrown out facts without a real sense of carrying the reader forward to the purpose of the current study. Why are adequacy of PNC and ethnicity in the title? Were those the factors the authors were primarily interested in? If so, then a reworking with emphasis on these factors would benefit the paper considerably.

We agree with the reviewer that the causes of PTB distract from the focus of the paper, which is to identify populations at high risk for PTB. This paragraph has been removed from the manuscript. In addition to developing the introduction to reflect the focus of the paper (e.g., socioeconomic factors – race & ethnicity; prenatal care; education level), we have changed the title of the manuscript to better reflect the motivation for the study and the key findings.

2c. Lastly, there are few numbers offering a quantitative assessment of the literature. For example, “New Mexico is a Southwestern US border state with a premature birth rate that exceeds the national average”. In this case it would help the reader to express what those PTB rates are since “exceed” could mean many things.

We appreciate this suggestion and have added the recent PTB rates in NM as compared to the US and other relevant statistical comparisons to the introduction.

3a. Methods: In general, the methods section is adequate; however, there are a few major issues that need to be clarified. First, this section states that the study is a retrospective cohort, whereas the abstract calls it a cross-sectional study design. The design of the study should be consistently expressed throughout.

We apologize for this mistake. Indeed our study is a cross-sectional study, not a retrospective study. This has been corrected in the methods section.

3b. Second, although the study is restricted to singletons, the lengthy time frame for the study (15 years) makes it certain that the same mother may have several offspring in the dataset. The authors do not mention any steps that would limit the analysis to one record per unique woman. Did the analysis take into account the inherent clustering of the data, or was there reason to suspect this was not needed? Often, studies in which multiple outcomes for a given mother may be included in an analysis, a technique which accounts for the clustering (e.g. Generalized Estimating Equations) is used as opposed to multivariable logistic regression. Also, although Figure 2 and the supplementary table(s) allude to effect modification (by implying the joint effect of two factors [adequacy of PNC and pregnancy risk] on the risk of PTB. Since the title of the article implies a focus on adequacy of PNC, was an interaction term or some other statistical method used to assess effect modification? Lastly, did you consider alternative ways of determining/categorizing adequacy of prenatal care, such as the G-Index (Greg Alexander).

The reviewer brings up an interesting point since several studies have demonstrated that increased incidence of PTB correlates with short durations between gestational periods (<6 months). In our study, however, we did not limit analysis to one record per unique woman, nor did we analyze the duration between gestational periods for two reasons: 1) since this is an exploratory study, the focus of the analysis was on estimation rather than hypothesis testing; and
2) because it is in general difficult to correctly model the correlation structure among multiple outcomes for a given mother, we took the simple approach, which is to treat the multiple outcomes as independent. This information has been added to the methods section and discussed as a limitation to this study. Next, in Figure 2, we did examine the interaction between two variables: medical risk factors and prenatal care. We chose these variables based on the clinical implications and have described this analysis in the methods section. Also, to address the reviewer’s point about the interaction, the title of the manuscript has been changed. Finally, we did not explore alternate measures of prenatal care, though this would indeed be interesting.

4. Results: The results section seems to have haphazard/sporadic use of ORs and 95% CI intervals. There are sections that qualitatively describe associations found and the actual measure of association with a confidence interval would support this section better. Second, what method was used to detect for the trend referenced? Was it for a linear trend, nonlinear, etc? Third, why was a stratified analysis performed only for adequacy of prenatal care (stratified by pregnancy risk)? Why were stratified analyses NOT done for other variables? This need to be explained in the methods section. Did the adjusted model have an interaction term in it, or were separate analyses performed for high and low risk pregnancies?

For the first comment, we believe the reviewer is referring to second and last paragraphs of the results section. Please note that we only included ORs and 95% CIs for parameters that were not included in Table 1. For results that are included in the table, we give a qualitative description of the data and refer the reader to “Table 1” in addition to the figure within the text for the actual ORs and 95% CIs. The trend described for Figure 1 is a linear trend; year was treated as a continuous variable and we examined the coefficient of that variable by logistic regression. This is now described in the methods. Please note in Figure 2 that we did not perform a stratified or separate analysis but instead determined the result of the interaction between maternal risk and level of prenatal care on preterm birth.

5. Discussion: Similar to the introduction, the discussion section needs to focus on important findings and do a better job of citing to back claims. It tries to cover all of the factors under study and does not provide a meaningful coverage of the literature and does not carry the reader forward to potential hypotheses or next steps.

We have also condensed the discussion section and put our most interesting findings in the context of the field. See also our response to Reviewer 1, comment # 6.

6. Figures/Tables: I would suggest either a table that provides a breakdown (frequencies and percentages) of demographic and perinatal characteristics by preterm birth status or adding crude (unadjusted) ORs to Table 1. Also, table 1 needs to be cleaned up. It should not be in multiple sections according to the variable under study. All of the information should be in a single table with the referent levels of each variable included as a row and with either “ref” or 1.00 placed in the OR column. The figures also have poor detail. I would suggest, at a minimum, labels next to each dot with the point estimate value. Also, the figures seem to be of varying types (different shapes for estimates and varying ways of presenting the confidence interval). I would standardize. Lastly, in the figure and table, it is unclear why only adequacy of PNC is involved in a stratified analysis with pregnancy risk. This should be made clear in the methods.
Regarding these comments, we refer the reviewer to our responses to Reviewer #2 comment 3b and Reviewer #1 comment 8. As requested, we have streamlined Table 1 for easier interpretation. In response to the last comment, we did not perform a stratified analysis (see also our response to this reviewer’s comment 4).

Minor Essential Revisions:

7. Figures/Table: In general, titles of figures and tables should be able to “stand alone” in that they should be descriptive enough for a reader to understand even if not supplemented by the paper. For example, Figure 1 could be renamed to “Rate of Preterm Birth Among Singleton Deliveries in New Mexico, 1991-2005”.
Table 1 should be something like, “Unadjusted and adjusted odds ratios and 95% confidence intervals from logistic regression analysis for risk of preterm birth by important demographic and perinatal characteristics, New Mexico, 1991–2005”

We have changed the figure and table titles as suggested.

8. There is overuse of the phrase “not surprisingly” and “elucidated”. Please consider removing the former and finding synonyms for the latter.

We have made these changes.

9. The last sentence of the Background states that aim of the paper and includes “…and to discuss the wider implications of these findings with respect to PTB internationally”. I’m not certain this can truly be done considering this study; however, since it is stated here, it should be adequately covered in the Discussion section and currently it is not.

We have removed this statement.

10. Methods, 2nd paragraph: in the definition of PTB, what about a 22 week, zero day old baby? Is that included or excluded. That is, did you mean to say “…of less than 37 weeks zero days but greater than or equal to 22 weeks zero days”?

The convention is that “less than” refers to “less than or equal to”.

11. Methods, 2nd paragraph: Please clarify what you mean by gestational age based on LMP being “inconsistent”. Please provide the specific case in which the clinical estimate was used and what you mean by “adjusted in the dataset”. I assume you just replace the age based on LMP to the age based on clinical estimate, but this is not clear.

Please see Reviewer #2 comment #3a

12. Methods: The paper would benefit from a clearer understanding of how many and what percentage of records were excluded for congenital anomaly outcomes and for multiple gestation.
See Reviewer #2, comment #3b

13. Methods: The table with maternal conditions considered high risk should be transformed into prose and inserted in the Methods section. A table is not needed.

We have made this change.

14. Discussion, 2nd paragraph: suggest changing “Women with missing...” to “Women with no...”. Missing means missing data to some and I believe you mean to imply those with NO reported prenatal care.

We have changed this phrase to “a lack of”.

15. Discussion, 2nd paragraph: You interpret the finding, among high risk pregnancies, that intensive care decreases the risk for PTB. However, you do not discuss the finding that the exact opposite happens among normal-risk pregnancies. What does this mean to the authors?

The reviewer raises an interesting point. We point out in the discussion that only observational studies and not case-controlled trials have demonstrated that an increased level of prenatal care correlates with decreased PTB. Hence, other factors must be at play here.

16. In the discussion, ORs are included by saying, for example, “…to an odds ratio of 0.89”. I suggest finding a more eloquent way of expressing the difference in odds of PTB among groups. For example, “Group A was found to have over twice the odds of PTB as group B.”

We have made the suggested changes.