Author's response to reviews

Title: A population-based study of race-specific risk for placental abruption

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Author's response to reviews: see over
Dear Dr. Bucceri,

Thank you for allowing us to revise our manuscript in accord with the reviewer comments. We believe we have significantly improved the manuscript by doing so. We look forward to the assessment of this revised version.

Sincerely,

Louis Muglia, MD PhD

Response to Reviewer Comments

Please find below the individual reviewer comments and our point-by-point response to each comment in italics.

Responses to Reviewer 1 (Eyal Sheiner)
Comment: The subject is interesting, although no new information is presented.

We concur that the subject is an interesting one, however, we respectfully submit that the analysis stratified by contribution of abruption to preterm births at defined times is new and has important implications.

The results of this study show again that the risk of abruption in Black mothers is higher than White parturients. Statistical analysis is well adapted to this retrospective study.
I have few comments:

Comment 1. Basically the article is too long. It is both, the introduction and discussion sections that should be shortened.

- Several paragraphs and large sections were deleted from both the Introduction section and the Discussion section to improve readability. These deleted paragraphs are shown below:
  o Page 4: Further efforts to elucidate risk factors for placental abruption are imperative due to the severity of complications it produces. Severe placental abruption resulting in stillbirth occurs in 0.12% of deliveries[12]. Live births that are complicated by placental abruption are associated with increased risks of preterm delivery, small-for gestational age, and neonatal and infant deaths[13-20]. Maternal risks associated with placental abruption include massive blood loss, intravascular coagulation, renal failure, and even maternal death[11].
  o Page 5: The determinants that were associated with these increasing trends in abruption included anemia, gestational diabetes mellitus, preterm labor, short umbilical cord, and velamentous cord insertions, although their effects varied substantially by maternal race[9].
  o Page 14: For example, Black women, relative to White women, are at greater risk of having placental abruption, especially at an early
gestational age, but given that they delivered early, their chances of having placental abruption as the cause of preterm birth is less, relative to White women.

- **Page 15:** There is a strong association between placental abruption and placental-decidual inflammation. Placental histology in abruption-associated PTB often shows chorioamnionitis with dense decidual neutrophil infiltration in the absence of infection [8, 57, 58]. Neutrophils, a rich source of elastases and metalloproteinases, are localized to sites of fibrin deposition at areas of decidual hemorrhage, leading PPROM. Thrombin from decidual hemorrhage may also directly stimulate myometrial contractions leading to SPTL.

**Comment 2.** It is unclear to me why did the authors exclude the severe cases of abruption, leading to perinatal mortality.
- *We provided our decision to exclude fetal deaths in utero, on page 16, and still believe this approach the most appropriate:* We chose to exclude fetal deaths in utero, because it likely represents a group of complicated births having different pathological mechanisms unrelated to placental abruption. Even though the most severe cases of placental abruption (causing death) may be excluded, the effect of that on the relationship between maternal race and placental abruption should be limited.

**Comment 3.** The definition "pregnancy induced hypertension" was long ago changed to "gestational hypertension".
- *Pregnancy-induced hypertension was replaced with gestational hypertension in all sections of the manuscript.*
Responses to Reviewer 2 (Pelle Lindqvist)

It is a large well written registry study. They stratified analyses for various high and low risk groups. It is an interesting topic, riskfaktors for abruptio
The authors tries to elucidate an relation between Race abruptio placentae and prematurity due to abruptio placenta.

Comment: I was not totally comfortable with the mixing of results, discussion and conclusions.
- We have now changed the organization of the text from being divided into the two sections 1) Results and discussion and 2) Conclusions; into three sections 1) Results, 2) Discussion and 3) Conclusions and have attempted to minimize overlap between these sections.

Comment: In addition, the text is quite heavy for the reader and should also benefit from “under headings”. It will be easier to read if the text was reduced substantially
Several paragraphs and large sections were deleted from both the Introduction section and the Discussion section to improve readability and conciseness as described in the Responses to Reviewer 1. Subheadings are provided in the Methods and Results sections.

Comment: The authors have examined White vs. Black women in Missouri, USA. The location of the study should be pointed out clearly.
- We made the modification shown below, in order to point out clearly the location of the study:
- We developed a study to analyze the Missouri Department of Health’s de-identified maternally linked birth-death certificate database, which includes all 1,577,082 live births or fetal deaths in Missouri from 1978 through 1997.

Comment: The difference might not be due to the race but to something related to black women in the USA. The prevalence in the USA differs with low risk in the west and high risk in the north (Faiz, AS Ethn Health 2001) In addition they found lower incidence also with registry material??
- We added underreporting to the list of possible sources of bias concerning measurement error in a birth registry database, in order to state this possible source of error explicitly, on page 16: Possible sources of bias concerning measurement error in the database comprise recall, underreporting, miscoding, misclassification and information bias. Recall bias, such as the underreporting of social habit variables (i.e. cigarette smoking, alcohol use, and illicit drug use) and inaccurate reporting and underreporting of prenatal care, weight, past medical history and obstetrics complication variables, likely results in bias towards the null since bias is most likely nondifferential across race.
Comment: It might not be the race per se, but rather the differences in food, habits, sunhabits, cold weather?
- We had many measures available for inclusion in our model, and chose only those that altered the effect of race. The climate in which White and Black mothers live is the same, because the study was exclusively done in Missouri. We indirectly assessed food and habits, by examining the effect of body mass index on the observed association using the logistic regression model, on page 11: Other variables that had a significant effect on placental abruption (but were not part of the final explanatory regression model because they did not alter the estimate of the effect of race) were age 20-30 relative to teenage pregnancy (aOR 1.16, 95% CI 1.06-1.26), advanced maternal age relative to teenage pregnancy (aOR 1.56, 95% CI 1.38-1.76), primigravida (aOR 0.77, 95% CI 0.73-0.81), pre-pregnancy BMI < 20 (aOR 1.33, 95% CI 1.24-1.42), pre-pregnancy BMI > 30 (aOR 0.82, 95% CI 0.75-0.90), renal disease (aOR 1.84, 95% CI 1.30-2.60), and alcohol use (aOR 1.30, 95% CI 1.13-1.49).

Comment: How much is due to genetic differences?
- We cannot state how much of the observed association is due to genetic differences from this data or other currently available date. This was discussed in a paragraph in the Discussion section, on page 15: Finally, the association between placental abruption and maternal race, especially abruption-associated PTB, prominent even after controlling for SES and maternal medical risk factors, may suggest the possibility of a genetic contribution along with environmental components to the pathogenesis of placental abruption. Self-reported race in general accurately reflects ancestry, but the heterogeneity of nativity in Black mothers have also been shown to influence birth outcomes[59]. Thus, self-reported race is a reasonable, but not perfect, correlate for ancestry and genetics. However, we also acknowledge that unmeasured confounding environmental risk factors must be considered, and may contribute much of the disparity we observed.

Comment: Page 3 line 2 conclusions “important” should be changed to “known”
- This sentenced was changed, on page 3: Black women have an increased risk of placental abruption compared to White women, even when controlling for known coexisting risk factors.
Responses to Reviewer 3 (T'sang-T'ang Hsieh)

Shen and co-workers conducted a population-based cohort study to assess racial effects on placental abruption and the contribution of placental abruption to preterm birth, at different gestational age categories. They confirmed most prior studies that Black women are at increased risk for placental abruption compared to White women, even when controlling for important confounding factors. Moreover, they found that the relative contribution of placental abruption to term births was greater in Black women, whereas the relative contribution of placental abruption to preterm birth was greater in White women. Overall the manuscript is well written and addresses the hypothesis with appropriate analysis. The results are well presented and interesting, and the limitations are clearly stated.

**Comment:** Two minor points needed to be revised. First, page 10, second paragraph, first line: the number “644,303” should be “664,303”.
-  *This change was made, on page 10:* The cohort analyzed included 664,303 singleton live births with 108,806 (16.4%) births to Black mothers, and 555,497 (83.6%) births to White mothers.

**Comment:** Second, this is a research article and therefore about 25-40 references should be sufficient here.
-  *We deleted some redundant references to a total of 39 references remaining.*
Other changes:

- The following sentence was added to the acknowledgement section of the manuscript, on page 17, as a standard disclaimer requested by the Missouri Department of Health and Senior Services: All of the analyses, interpretations, and conclusions that were derived from the database and included in this article are those of the authors and not the Missouri Department of Health and Senior Services, Bureau of Health Informatics.