Prepregnancy Body Mass Index, Vaginal Inflammation, and the Racial Disparity in Preterm Birth

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The authors sought to quantify the overall and race/ethnic-specific relations between prepregnancy body mass index and both preterm birth and vaginal inflammation. Data from a cohort of 11,392 women who enrolled in the multicenter Vaginal Infections and Prematurity Study (1984–1989) at 23–26 weeks’ gestation were used. Compared with a prepregnancy body mass index of 22, a body mass index of 16 increased the risk of preterm birth by 90% (odds ratio = 1.9, 95% confidence interval (CI): 1.5, 2.6), and a body mass index of 18 increased the risk by 40% (odds ratio = 1.4, 95% CI: 1.2, 1.7). Ethnicity substantially modified the magnitude of the body mass index effect and the shape of the preterm birth risk curve, with underweight having a greater impact on preterm birth among Blacks and Hispanics than among Whites. Low body mass index increased the risk of a high level of neutrophils (>5 per oil immersion field) and a high vaginal pH measurement (≥5.0) among Black women; for a body mass index of 16 versus 22, the odds ratio = 1.7 (95% CI: 1.1, 2.6). Compared with Black women with a body mass index of 22, Blacks with a body mass index of 16 had a 1.7-fold increased risk for a high level of neutrophils and a high vaginal pH measurement, while those with a body mass index of 18 had a 1.3-fold increased risk.

African continental ancestry group; body mass index; European continental ancestry group; Hispanic Americans; inflammation; pregnancy; premature birth; vagina

Abbreviation: CI, confidence interval.

Preterm birth continues to be the most important problem in modern obstetrics, accounting for the majority of newborn death and handicap. There is dramatic ethnic disparity in the United States, with Black women having approximately twice the frequency of preterm birth compared with White women. This disparity is particularly notable among the earliest preterm births (<32 weeks) that result in a disproportionate frequency of mortality and morbidity, such as cerebral palsy.

Low maternal prepregnancy weight and weight for height have consistently been associated with preterm birth. Indeed, the relation between low prepregnancy body mass index and spontaneous preterm birth is remarkably consistent among North American White women (1), urban (2) and rural (2) Black women, and urban Latinas (3, 4). Low body mass index also modifies the association between low pregnancy weight gain and the risk of preterm birth (5).

A biologically plausible point of convergence at which body mass index might influence the risk of preterm birth is immunity and inflammation. There is an abundance of data supporting a relation between obesity and altered inflammation, either locally or systemically (6–8). We and others have previously reported that the inflammatory milieu of the lower genital tract early in pregnancy can be a marker of risk of subsequent preterm birth (9, 10). We noted that the concomitant presence of elevated vaginal pH and neutrophils in the vagina in early pregnancy is associated with an increased frequency of early preterm birth with preterm...
labor or premature rupture of the membranes. The relation between body mass index and reproductive tract immunity has not been elucidated to date. This study had two objectives. First, we sought to quantify the relation between prepregnancy body mass index and the risk of spontaneous preterm birth in a racially/ethnically diverse cohort of women from the general obstetric population. We planned a priori to evaluate this relation overall and stratified by race/ethnicity. Our second major goal was to evaluate the relation between prepregnancy body mass index and the inflammatory milieu of the vagina in early pregnancy, overall and by race/ethnicity.

**MATERIALS AND METHODS**

**Patient population**

We used data from the Vaginal Infections and Prematurity Study, a seven-center cohort study (1984–1989). Our cohort comprised 13,917 women who enrolled between 23 and 26 weeks’ gestation. Women were enrolled from antepartum clinics at Columbia University and Harlem Hospital Center, New York, New York; University of Washington, Seattle, Washington; University of Oklahoma Health Science Center, Oklahoma City, Oklahoma; University of Texas Health Science Center, San Antonio, Texas; and Louisiana State University Medical Center and Tulane University, New Orleans, Louisiana. Women who met the eligibility criteria, who agreed to participate, and who gave written informed consent as approved by each local institutional review board were enrolled into the study and followed up until delivery as described in detail elsewhere (11, 12).

Women were ineligible if they were less than 16 years of age, had autoimmune or immunosuppressed medical conditions, had pregestational insulin-dependent diabetes, or were taking selected medications. Roughly equal numbers of White, Black, and Hispanic patients were enrolled.

**Data collection**

Enrollment into the Vaginal Infections and Prematurity Study occurred at a routine prenatal visit between 23 and 26 completed weeks’ gestation. At this time, eligible women were administered a standard questionnaire inquiring in detail about demographic, medical, behavioral, and sexual factors. Data were collected on paper forms and were sent to the independent Data Coordinating Center at Research Triangle Institute, where they were computerized and subjected to detailed quality control procedures. The gestational age at screening for study eligibility was determined by the examining physician’s best estimate. This estimate was based on the last menstrual period, supplemented by other evidence such as uterine size, detection of fetal heart tones, and ultrasonography, when done. At the initial visit and at subsequent study visits, in accordance with a standardized protocol, a pelvic examination was performed using a clean, nonlubricated speculum. Genital specimens were collected and processed as described previously (11, 12). All women had cervical swabs obtained for Neisseria gonorrhoeae, Chlamydia trachomatis, and Trichomonas vaginalis, and they had vaginal swabs obtained for pH and Gram’s stain for diagnosis of neutrophils and bacterial vaginosis by use of bacterial morphotypes evaluated by the Nugent 10-point scoring system (11–13). Vaginal neutrophils were counted in five nonconsecutive fields without cervical mucus and averaged. Only areas that had a single layer of epithelial cells were evaluated. A random sample of vaginal smears (n = 50) was evaluated by five different study smear readers in a blinded fashion. The degree of agreement with respect to those smears having less than or equal to five or more than five neutrophils per oil immersion field was 95 percent, suggesting that the interobserver reproducibility of neutrophil detection performed in the manner described is excellent.

Prepregnancy body mass index (weight (kg)/height (m)\(^2\)) was based on self-reported weight and measured height. Maternal race was self-reported. Preterm birth was defined as spontaneous delivery occurring after preterm labor with intact membranes or preterm prelabor rupture of the fetal membranes. We excluded women with the diagnosis of preeclampsia and women whose fetuses had intrauterine growth restriction. “Preeclampsia” was defined as a persistent blood pressure of 140/90 mmHg and proteinuria of at least +++. “Intrauterine growth restriction” was defined as birth weight less than the 10th percentile. After making these exclusions, we were left with an available cohort of 11,392 women. Two gestational-age cutpoints for preterm birth were selected: less than 36 and less than 34 weeks’ gestation. We chose less than 36 weeks to reduce the likelihood of misclassification of preterm births. “High vaginal pH” was defined as pH of at least 5.0 (9, 10). Women were classified as having a high level of neutrophils if there were more than five neutrophils per high-power field.

**Statistical analysis**

Multivariable logistic regression was used to estimate the independent effect of prepregnancy body mass index on the risk of preterm birth at less than 36 and less than 34 weeks’ gestation in the total population and stratified by ethnicity. After inspecting curves produced by use of nonparametric regression smoothing with LOWESS (locally weighted regression scatterplot smoother), we observed a curvilinear association between body mass index and the logit of preterm birth. Therefore, rather than using traditional body mass index categories, we specified body mass index as a spline function in nearly all models. Spline regression more closely approximates nonparametric regression (14, 15), which makes no assumptions about the exposure-disease relation. In each model, we explored many linear and quadratic splines. We performed a likelihood ratio test for the null hypothesis that the spline parameter of the multivariable model was equal to zero (\(\alpha = 0.10\)). If the hypothesis was rejected, the spline function was maintained in the model. A body mass index of 22 often marked a point of inflection in the preterm birth risk curve. Thus, for consistency, 22 was chosen as the reference value for all models.

In a similar fashion as described above, we used multivariable logistic regression to assess the independent relation between prepregnancy body mass index and the risk of high neutrophils and high vaginal pH. This association was...
examined in the total population and stratified by ethnicity. Spline regression was used where appropriate.

To determine which covariates should be entered into the final multivariable models, we used directed acyclic graphs (16, 17), theory-based causal diagrams that rely on the investigators’ a priori subject-matter knowledge of the causal relations of variables to one another, rather than relying on statistical associations. All models were adjusted for potential measured confounders: maternal age, race, parity, smoking status, education, marital status, and height.

RESULTS

A majority of the women in this study were aged 20–24 years, multiparous, and nonsmokers; had normal weight before pregnancy; and reported an annual income of less than $5,000 (table 1). Smoking and underweight were more common among White women than among the other ethnic groups. Hispanics were more likely to be older, multiparous, and less educated, whereas Blacks most often reported being unmarried and having a household income of less than $5,000. The incidence of preterm birth at less than 36 weeks’ gestation was 6.7 percent in the total sample and was 6.0 percent, 7.9 percent, and 5.9 percent among White, Black, and Hispanic women, respectively. Preterm birth at less than 34 weeks’ gestation occurred in 2.7 percent of the cohort and in 2.2 percent, 3.5 percent, and 2.4 percent of White, Black, and Hispanic women, respectively.

Prepregnancy body mass index and preterm birth

We observed a curvilinear association between prepregnancy body mass index and the risk of preterm birth at less than 18.5 kg/m², with a peak risk at approximately 25.0–29.9 kg/m². The risk then decreased with a further increase in body mass index (table 1).
than 36 weeks in the total sample (figure 1; table 2). Compared with a prepregnancy body mass index of 22, a body mass index of 14 almost tripled the risk of preterm birth, and a body mass index of 16 nearly doubled the risk. Prepregnancy body mass index values of 18 and 20 were associated with 40 percent and 20 percent increases in the risk of preterm birth, respectively, compared with a body mass index of 22. Beyond a body mass index of 22, there was no significant effect of body mass index on the risk of preterm birth.

Ethnicity substantially modified the magnitude of the body mass index effect and the overall shape of the 36-week preterm birth risk curve (figure 1; table 2). Among White women, the risk of preterm birth decreased as prepregnancy body mass index increased. Compared with White women with a body mass index of 22, White women with a body mass index of 16 had a 30 percent increase in the risk of preterm birth, while White women with a body mass index of 35 had a 50 percent reduction in risk. In contrast to Whites, Black women had a higher odds ratio of preterm birth at low body mass index values and did not evidence the same significant reduction in risk at high body mass index values. A similar strong effect of underweight was observed for Hispanic women. At body mass index values greater than 22, the data suggested a possible increasing risk of preterm birth among Hispanics with high body mass index values, but the results did not reach statistical significance.

We observed a curvilinear relation between body mass index and the risk of preterm birth at less than 34 weeks’ gestation that was similar in shape and magnitude to the effect at less than 36 weeks among the total population, as well as for each ethnic group (table 2).

**Prepregnancy body mass index and vaginal inflammation**

Roughly 8.5 percent of the total population had high neutrophils and a high vaginal pH, but the condition was more

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**FIGURE 1.** The unadjusted association between prepregnancy body mass index (kg/m²) and preterm birth at less than 36 weeks’ gestation overall and stratified by race in the US multicenter Vaginal Infections and Prematurity Study (1984–1989). The solid lines and dashed lines represent the point estimates and 95% confidence intervals, respectively.
common among Black women (10.5 percent) than among White women (8.9 percent) or Hispanic women (5.6 percent) (p < 0.001 for each). Prepregnancy body mass index was not significantly associated with the risk of high neutrophils and high vaginal pH in the total population or among Whites (table 3). However, having a low body mass index increased the risk of high neutrophils and high vaginal pH among Black women. Compared with Black women with a body mass index of 22, Blacks with a body mass index of 14 had a 2.2-fold increased risk of high neutrophils and high vaginal pH, while those with a body mass index of 16 had a 1.7-fold increased risk. There was no relation between body mass index and the risk of high neutrophils and high vaginal pH at body mass index values of 20 or more. Among Hispanics, the point estimates suggested a possible increased risk among individuals with low and very high body mass index values, but the results only bordered on statistical significance.

**DISCUSSION**

Our study confirmed previous reports that prepregnancy underweight promotes the risk of spontaneous preterm birth. Previous investigators have described the relation between low prepregnancy weight/body mass index and preterm birth, with odds ratios ranging from 1.2 to 3.9 compared with normal-weight women (1–4, 18, 19). These reports vary widely in design; in the socioeconomic, geographic, and racial/ethnic composition of the study population; and in the definition of prepregnancy underweight. Of note, the prior studies that report the odds ratio of less than 2.0 did not differentiate spontaneous from indicated preterm birth (2, 19). The biologic relation between spontaneous preterm birth and indicated preterm birth from fetal growth restriction or preeclampsia may be very different. Considering them together may fail to detect a relation or underestimate the strength of that relation.

**TABLE 2. Relation between prepregnancy body mass index and the risk of preterm birth in the total sample and stratified by race/ethnicity in the US multicenter Vaginal Infections and Prematurity Study (1984–1989)**

<table>
<thead>
<tr>
<th>Prepregnancy body mass index (kg/m²)</th>
<th>Total (n = 11,392)</th>
<th>Whites (n = 3,768)</th>
<th>Blacks (n = 4,242)</th>
<th>Hispanics (n = 3,382)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted odds ratio*</td>
<td>95% confidence interval</td>
<td>Adjusted odds ratio†</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td></td>
<td>14 2.8‡</td>
<td>1.8, 4.5</td>
<td>1.5§</td>
<td>1.2, 1.9</td>
</tr>
<tr>
<td></td>
<td>16 1.9</td>
<td>1.5, 2.6</td>
<td>1.3</td>
<td>1.1, 1.6</td>
</tr>
<tr>
<td></td>
<td>18 1.4</td>
<td>1.2, 1.7</td>
<td>1.2</td>
<td>1.1, 1.4</td>
</tr>
<tr>
<td></td>
<td>20 1.2</td>
<td>1.1, 1.2</td>
<td>1.0</td>
<td>1.0, 1.2</td>
</tr>
<tr>
<td></td>
<td>22 1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td></td>
<td>24 0.9</td>
<td>0.9, 1.0</td>
<td>0.9</td>
<td>0.9, 1.0</td>
</tr>
<tr>
<td></td>
<td>26 0.9</td>
<td>0.9, 1.1</td>
<td>0.8</td>
<td>0.7, 0.9</td>
</tr>
<tr>
<td></td>
<td>30 1.0</td>
<td>0.8, 1.2</td>
<td>0.7</td>
<td>0.5, 0.8</td>
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<tr>
<td></td>
<td>35 1.0</td>
<td>0.7, 1.2</td>
<td>0.5</td>
<td>0.4, 0.8</td>
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<tr>
<td></td>
<td>40 0.9</td>
<td>0.6, 1.3</td>
<td>0.4</td>
<td>0.2, 0.7</td>
</tr>
</tbody>
</table>

- * Adjusted for maternal age, race/ethnicity, parity, smoking status, height, education, and marital status.
- † Adjusted for maternal age, parity, smoking status, height, education, and marital status.
- ‡ Body mass index specified as a quadratic spline with a knot at 25.
- § Body mass index specified as a linear term.
- ¶ Body mass index specified as a linear spline with a knot at 22.
- # Body mass index specified as a quadratic spline with a knot at 22.

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TABLE 3. Relation between prepregnancy body mass index and the risk of high neutrophils and high vaginal pH in the total sample and stratified by race/ethnicity in the US multicenter Vaginal Infections and Prematurity Study (1984–1989)

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<tr>
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</tr>
<tr>
<td>14</td>
<td>1.7†</td>
<td>0.9, 3.0</td>
<td>1.0§</td>
<td>0.9, 1.2</td>
</tr>
<tr>
<td>16</td>
<td>1.5</td>
<td>0.9, 2.3</td>
<td>1.0</td>
<td>0.9, 1.2</td>
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<tr>
<td>18</td>
<td>1.3</td>
<td>1.0, 1.7</td>
<td>1.0</td>
<td>0.9, 1.1</td>
</tr>
<tr>
<td>20</td>
<td>1.1</td>
<td>1.0, 1.3</td>
<td>1.0</td>
<td>1.0, 1.1</td>
</tr>
<tr>
<td>22</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
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<tr>
<td>24</td>
<td>1.0</td>
<td>1.0, 1.0</td>
<td>1.0</td>
<td>1.0, 1.0</td>
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<tr>
<td>26</td>
<td>1.0</td>
<td>0.9, 1.1</td>
<td>1.0</td>
<td>0.9, 1.1</td>
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<tr>
<td>30</td>
<td>1.0</td>
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<td>1.0</td>
<td>0.8, 1.2</td>
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<td>35</td>
<td>1.0</td>
<td>0.8, 1.2</td>
<td>1.0</td>
<td>0.7, 1.3</td>
</tr>
<tr>
<td>40</td>
<td>0.9</td>
<td>0.6, 1.3</td>
<td>0.9</td>
<td>0.6, 1.4</td>
</tr>
</tbody>
</table>

* Adjusted for maternal age, race/ethnicity, parity, smoking status, height, education, and marital status.
† Adjusted for maternal age, parity, smoking status, height, education, and marital status.
‡ Body mass index specified as a linear spline with a knot at 20.
§ Body mass index specified as a linear term.
¶ Body mass index specified as a linear spline with a knot at 25.

Uniquely, we demonstrated that the impact of low body mass index on spontaneous preterm birth is greater among Black and Hispanic parturients than among their Caucasian counterparts. These disparities were present not only in preterm birth overall but also when only early preterm births less than 34 weeks were included. Our findings are in contrast to those of Hickey et al. (18), who noted that low pregravid body mass index is associated with an increase in the prevalence of late preterm delivery (33–36 weeks) and of spontaneous preterm labor among Black and White, but not Hispanic, women. Hickey et al. may not have detected the effects of weight for height on risk of prematurity, and other studies may have found a diluted effect of underweight because they categorized body mass index rather than evaluating it on a continuum. Categorical analysis has numerous pitfalls, including making the biologically implausible assumption of a constant risk within a category and a large jump in risk as a patient moves into the next category. Categorization also causes a loss of statistical power and, importantly, may not identify relations that are present at the extremes of the exposure distribution. By performing semiparametric analyses that did not use traditional body mass index categories, we were able to describe the curvilinear shape of the body mass index–preterm birth risk curve. Using this technique, we demonstrated that the risk of prematurity is markedly elevated at very low body mass index values (e.g., 14–16 kg/m²) and not constant within the category traditionally defined as “underweight.” If we had categorized body mass index conventionally, we would not have detected certain associations. For example, the odds ratios for preterm birth at less than 36 weeks’ gestation among underweight, overweight, and obese White women compared with their normal-weight counterparts were 1.3 (95 percent confidence interval (CI): 1.0, 1.6), 0.8 (95 percent CI: 0.7, 1.0), and 0.9 (95 percent CI: 0.7, 1.0), respectively.

While a number of investigations have reported a relation between obesity and systemic markers of inflammation (20–23), to our knowledge, there are no published reports of the relation between underweight and inflammation, either locally or systemically. In our study, we posited that lower genital tract inflammation might provide a link by which body mass index exerts influence on the risk of preterm birth. Based on the literature, the notion of infection/inflammation as a link between underweight and preterm birth is supported through an indirect observation from a study of bacterial vaginosis treatment by Hauth et al. (24). In their study, women with a prepregnancy weight of less than 50 kg were screened for bacterial vaginosis. If bacterial vaginosis was present, subjects were randomly assigned to metronidazole and erythromycin antibiotic therapy or placebo. The frequency of preterm birth among underweight women with bacterial vaginosis treated with placebo was 33 percent compared with 14 percent among antibiotic-treated women (p = 0.04). Thus, treatment of bacterial vaginosis among underweight women reduced the risk of preterm birth. This contrasts with findings from several investigators demonstrating that bacterial vaginosis treatment in a general obstetric population is ineffective (25).

Our study is the first to evaluate directly the relation between a marker of nutritional status, prepregnancy body mass index, and lower genital tract inflammation. In our exploration of the relation of prepregnancy body mass index to the vaginal inflammatory milieu, we noted important racial/ethnic disparities. Underweight only increased the risk of high vaginal pH and neutrophils among Black women. While there was a trend toward a significant association
among Hispanics, this relation was notably absent among Whites. These data suggest that there are racial differences in how nutritional status, as represented by body mass index, might influence the vaginal immunologic environment and ultimately the risk of spontaneous preterm birth.

We noted a decreased risk of spontaneous preterm birth with higher body mass index among White women. With a cohort of more than 70 percent Caucasian women, Sebire et al. (26) noted a decreased frequency of delivery at less than 32 weeks among women with a body mass index greater than or equal to 30 (odds ratio = 0.73, 95 percent CI: 0.65, 0.82) compared with women with a body mass index of less than 30. These authors did not differentiate spontaneous from indicated preterm birth. In a recent secondary analysis from the National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units’ Preterm Prediction Study, where 65 percent of the sample was Black, Hendler et al. (27) found decreased odds of spontaneous preterm birth at less than 37 weeks among women with a prepregnancy body mass index greater than or equal to 30 (odds ratio = 0.57, 95 percent CI: 0.39, 0.83) compared with women with a body mass index of less than 30 (27). Obesity is detrimental for numerous aspects of human health and disease. Still, high body mass index is associated with better outcomes in both congestive heart failure and atherosclerotic heart disease among people with chronic renal disease (28, 29). It has been hypothesized that these “epidemiologic paradoxes” may be the result of obesity-related changes in systemic inflammation (28, 29). Perhaps the relation between obesity and a decreased frequency of preterm birth is, in part, mediated via effects on reproductive tract inflammation. Our data lend credence to this speculation and support further investigations into this hypothesis.

Our study was limited by a lack of information on subjects’ weight gain during pregnancy. Schieve et al. (5) have demonstrated that weight gain may modify the effect of prepregnancy body mass index on the risk of prematurity and perhaps would have modified some of the relations noted in our study. Additionally, body mass index is a relatively crude measure of maternal nutritional status. Fatty acids, antioxidants, trace elements, and other nutrients all have potent biologic effects and influence inflammation both in vitro and in vivo. We were not able to describe nutritional status with this level of detail in our cohort. Nevertheless, the Vaginal Infections in Prematurity Study cohort provided us with a very large racially and geographically diverse population with valuable markers of the vaginal inflammatory milieu.

Our study was of insufficient sample size and was not designed to address the interaction among low body mass index, heightened inflammation, and preterm birth rates and whether these relations differ by race. These relations are of tremendous interest, and understanding them may contribute to our comprehension of the racial disparity in preterm birth. Still, we speculate that our findings of ethnic differences in the contributions of both body mass index to preterm birth and body mass index to the vaginal inflammatory milieu may explain, in part, the racial disparity in preterm birth.

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