Inflammation and Dyslipidemia Related to Risk of Spontaneous Preterm Birth

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Women who deliver preterm are at increased risk for cardiovascular disease, but mechanisms are not understood. The authors considered that inflammation in women with spontaneous preterm birth (sPTB) might be related to their metabolic profile, such as lipids, and tested this in a nested case-control study from the Pregnancy Exposures and Preeclampsia Prevention Study (1997–2001). Cases were women with sPTB at 34–<37 weeks (n = 76) or <34 weeks (n = 33). Controls were randomly selected women with term births (n = 228). Early pregnancy inflammation (C-reactive protein: ≥8 μg/ml) and dyslipidemia (cholesterol: >230 mg/dl or triglycerides: >140 mg/dl) were evaluated in serum collected at <21 weeks. Late pregnancy elevated C-reactive protein (≥12 μg/ml) was measured in a subset (n = 295). Polycotomous logistic regression was used to estimate the joint effects of C-reactive protein elevations and dyslipidemia on the risk of sPTB subtypes. After adjustment for race, body mass index, periconceptional vitamin use, and gestational age at sampling, early pregnancy inflammation (odds ratio = 2.9, 95% confidence interval (CI): 1.1, 7.2) and dyslipidemia (odds ratio = 2.0, 95% CI: 1.0, 4.2) were independently associated with sPTB at 34–<37 weeks. The presence of both conditions increased risk of sPTB at <34 weeks 6.4-fold (95% CI: 1.7, 24.1). Half of the women with early pregnancy inflammation had elevated C-reactive protein late in gestation, and each was independently related to the risk of sPTB at <34 weeks. The results indicate that some metabolic factors together with inflammation may be related to the risk of sPTB.

cardiovascular diseases; cholesterol; C-reactive protein; dyslipidemias; inflammation; premature birth; triglycerides; women

Abbreviations: CI, confidence interval; OR, odds ratio; SD, standard deviation; sPTB, spontaneous preterm birth.

Epidemiologic evidence suggests that women who deliver preterm infants have a two- to threefold increased risk later in life for cardiovascular disease (1–4). Mechanisms that may link preterm birth with excess maternal cardiovascular risk are not understood, but excess inflammation is one possibility (5). Women with preterm birth, particularly early preterm birth, have elevated markers of inflammation (6–9). C-reactive protein, an inflammatory marker and a predictor of future atherosclerotic events, is elevated before 20 weeks’ gestation in women with a preterm birth (8, 9). We have demonstrated that older women who delivered small infants many years in the past have elevated C-reactive protein concentrations (10). It is possible that a proinflammatory phenotype may predispose women to preterm birth during the reproductive years and be related to increased cardiovascular disease risk later in life.

Inflammation in women with preterm birth is thought to be due to subclinical infection, but treatment during
pregnancy has been largely disappointing (11, 12). Influenced by the relation of preterm birth to maternal cardiovascular disease in later life, we considered whether inflammation in women with preterm birth might be linked to their metabolic profile, such as lipids. We recently reported that cholesterol and triglycerides were elevated at 8 weeks’ gestation in women with subsequent spontaneous preterm birth (sPTB), likely before pregnancy-induced changes (13). We hypothesized that early pregnancy dyslipidemia in women with subsequent sPTB may be related to inflammation. We also considered the possibility that women with sPTB, in particular sPTB at <34 weeks, may demonstrate an inflammatory phenotype such that inflammation would be present both early and late in pregnancy.

To test these hypotheses, we measured the concentrations of C-reactive protein, cholesterol, and triglycerides before 21 weeks’ gestation in a nested case-control study of women with spontaneous preterm singleton births after otherwise uncomplicated pregnancies. Specifically, we were interested in examining the separate and joint effects of early pregnancy C-reactive protein elevations and dyslipidemia related to risk of sPTB at <34 weeks and at 34–<37 weeks. In addition, we related early and late gestation C-reactive protein elevations to sPTB risk.

MATERIALS AND METHODS

The Pregnancy Exposures and Preeclampsia Prevention (PEPP) Study was a prospective study of women enrolled at <16 weeks’ gestation and followed through the postpartum visit. Women were recruited from clinics and private practices from 1997 to 2001. The study was approved by the institutional review board, and all participants provided written informed consent. Of the 2,211 women enrolled, we excluded women with conditions associated with indicated preterm birth risk and those with incomplete diagnostic information (figure 1). We also limited the analysis to the first birth in the cohort. Of the 1,563 eligible women with otherwise uncomplicated pregnancies, 116 delivered preterm (<37 weeks’ gestation). Cases were all women from this group with spontaneous onset of labor or preterm premature rupture of membranes with a first blood specimen drawn at ≤21 weeks’ gestation (n = 109). Controls (2:1 ratio) were randomly selected from women with uncomplicated pregnancies who delivered at ≥37 weeks’ gestation with a first blood sample at ≤21 weeks (n = 228).

Maternal biomarkers

Maternal nonfasting serum samples were collected at the first prenatal visit and during pregnancy at the usual times for clinical indications and were stored in aliquots at −80°C until assayed. The first specimen drawn before 21 weeks’ gestation (for controls, mean: 10.0 (standard deviation (SD): 3.8) weeks; for cases, mean: 10.7 (SD: 4.2) weeks; p = 0.13) was evaluated. For 295 of these women (88 percent), there was also a late pregnancy blood specimen drawn after 26 weeks or upon hospital admission for delivery but before administration of medications (for term births, mean: 39.8 (SD: 1.2) weeks; for preterm births, mean: 33.4 (SD: 3.4) weeks). As expected, the 42 women without late pregnancy specimens were more likely to deliver preterm compared with those with late specimens. They were also more likely to be Black (52 percent vs. 32 percent; p = 0.01) and to be unmarried (64 percent vs. 48 percent; p = 0.06); however, they were only somewhat more likely to have early pregnancy inflammation as measured by C-reactive protein (25 percent vs. 16 percent; p = 0.17).

C-reactive protein was measured by high-sensitivity enzyme-linked immunosorbent assay. The detection limit of the C-reactive protein assay was 0.2 μg/ml, with intra- and interassay variabilities of 4 percent and 7 percent, respectively. C-reactive protein increases with advancing gestation; therefore, inflammation before 21 weeks’ gestation (early pregnancy) was defined as C-reactive protein (≥8 μg/ml), and inflammation after 26 weeks but before delivery (late pregnancy) was defined as C-reactive protein (≥12 μg/ml). These thresholds have been associated with chorioamnionitis (14) and have been previously related to preterm birth risk (9). We also evaluated C-reactive protein as a continuous variable to explore a dose effect.

Total cholesterol and triglycerides were measured in duplicate by a colorimetric technique using commercial kits from Pointe Scientific (Canton, Michigan); the average coefficients of variation between runs ranged from 5.3 percent to 8.4 percent. On the basis of our previous work relating lipids to spontaneous preterm birth risk (13), dyslipidemia before 21 weeks was defined as elevated cholesterol (>230 mg/dl) or triglycerides (>140 mg/dl). These concentrations were >1 standard deviation above the mean value at the same gestational age for women with term births and were similar to the criteria used to define dyslipidemia in nonpregnant adults (15).

Preterm birth

Based on early pregnancy ultrasounds, gestational age was assessed upon delivery. Women were categorized as delivering at or after 34 and before 37 completed weeks and before 34 weeks to describe severity of preterm status, as inflammation has been more strongly related to early preterm birth (7). Spontaneous preterm births were defined as those occurring after spontaneous onset of preterm labor with intact membranes or following preterm spontaneous premature rupture of the fetal membranes.

Covariates

Women enrolled in the Pregnancy Exposures and Pre-eclampsia Prevention Study underwent a structured interview at their first prenatal visit. Reported prepregnancy weight and measured height were used to calculate prepregnancy body mass index (weight (kg)/height (m)²). Waist circumference was measured at this first visit. Women were diagnosed with gestational diabetes mellitus according to the Carpenter and Coustan criteria (16). The self-reported covariates considered were maternal age at delivery, education (less than high school for women older than 19 years who did not complete high school vs. high school or
greater), periconceptional multivitamin use (self-reported multivitamin use during the 6 months prior to the first prenatal visit), smoking during pregnancy (any smoking since suspected pregnancy), and race. Because of the small number of women who reported their race as other than Black or White (n = 4), results are reported for Black women vs. non-Black women (White and other). Women reported if they were born small (<2,500 g) or if a mother or sister had a pregnancy complicated by preeclampsia or transient hypertension. Women reported any leisure physical activity in the year before they became pregnant, and the intensity was reported as low, moderate, or vigorous. Women were categorized as those who reported moderate or vigorous physical activity versus low intensity or none.

Analysis

Maternal characteristics were summarized according to sPTB status (≥37 weeks, 34–<37 weeks, <34 weeks). C-reactive protein was not normally distributed so median concentrations were compared using the Kruskal-Wallis test, and correlations were evaluated using the Spearman correlation coefficient. Differences were considered significant with p < 0.05, and all tests were two sided. Polychotomous logistic regression was used to estimate the risk of sPTB (34–<37 weeks and <34 weeks) associated with having early pregnancy inflammation. We used published methods (17) to evaluate dose-response relations between C-reactive protein and risk of subtypes of sPTB. The best fit was found with C-reactive protein modeled as a continuous linear term for sPTB at 34–<37 weeks (p = 0.02) and as a restricted quadratic spline with knots at 5 and 10 µg/ml for preterm birth at <34 weeks (C-reactive protein, p = 0.01; C-reactive protein spline term, p = 0.06).

Covariates were considered confounders if they changed the odds ratio associated with early pregnancy inflammation by >10 percent. All covariates were evaluated in this fashion. A second early pregnancy model then evaluated the combined effects of inflammation and dyslipidemia, with and without adjustment for body mass index because of the strong correlation of C-reactive protein to prepregnancy body mass index (9). Effect measure modification by dyslipidemia and body mass index was assessed by the likelihood ratio test (α = 0.10). A third model limited to women with early and late pregnancy specimens (n = 295) related early and late evidence of inflammation to sPTB risk.

RESULTS

Women with sPTB at <34 weeks were more likely to be Black and to have less than a high school education compared with women with term births (table 1). They were less likely to report periconceptional vitamin use, to have engaged in moderate or vigorous physical activity before pregnancy, and to have been married. They were also 3–4 times more likely to report that a mother or sister had pregnancies complicated by hypertension or that they themselves were small at birth.

Early pregnancy inflammation and dyslipidemia

Higher C-reactive protein concentrations before 21 weeks were correlated with prepregnancy body mass index as well as early pregnancy triglycerides and cholesterol concentrations (r = 0.45, p < 0.01; r = 0.39, p < 0.01; r = 0.25, p < 0.01, respectively). The median concentrations of C-reactive protein measured before 21 weeks’ gestation tended to be higher among the sPTB groups, but these differences were not statistically significant (figure 2). However, when concentrations were considered dichotomously, women with sPTB at <34 weeks and at 34–<37 weeks were more likely to have evidence of early pregnancy inflammation (C-reactive protein ≥ 1.0 mg/dl) compared with term and preterm births.
The presence of early pregnancy inflammation (C-reactive protein: ≥8 µg/ml) conferred a 2.6- to 2.8-fold increased risk of sPTB subtypes, after adjustment for race, body mass index, periconceptional multivitamin use, and gestational age at sampling (table 2). Moreover, we observed a dose-response relation between C-reactive protein concentrations and risk of sPTB subtypes. There was a positive linear relation between C-reactive protein and risk of sPTB at 34–<37 weeks (figure 3, part A). A 5-µg/ml increase in C-reactive protein was associated with a 1.4-fold (95 percent confidence interval (CI): 1.1, 2.0) increase in the risk of sPTB, independent of confounders. For sPTB at <34 weeks (figure 3, part B), the risk increased as C-reactive protein rose from 0 to 10 µg/ml. An increase of C-reactive protein from 5 to 8 µg/ml conferred a 70 percent increase in the risk of sPTB (adjusted odds ratio (OR) = 1.7, 95 percent CI: 1.1, 2.5). Beyond 10 µg/ml, precision was poor because of sparse data.

### TABLE 1. Maternal characteristics according to preterm birth status, mean or percent, Pregnancy Exposures and Preeclampsia Prevention Study, 1997–2001

<table>
<thead>
<tr>
<th>Demographic and lifestyle</th>
<th>≥37 weeks</th>
<th>34–&lt;37 weeks</th>
<th>&lt;34 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>24.9 (6.0)*</td>
<td>24.7 (5.5)</td>
<td>24.1 (6.7)</td>
</tr>
<tr>
<td>Black (%)</td>
<td>32.5</td>
<td>34.2</td>
<td>48.5</td>
</tr>
<tr>
<td>Less than high school education (%)</td>
<td>9.2</td>
<td>6.6</td>
<td>18.2</td>
</tr>
<tr>
<td>Married or marriage like (%)</td>
<td>53.5</td>
<td>46.7</td>
<td>33.3</td>
</tr>
<tr>
<td>Prepregnancy moderate or vigorous physical activity (%)</td>
<td>32.0</td>
<td>27.6</td>
<td>12.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.7 (6.6)</td>
<td>25.6 (5.9)</td>
<td>26.0 (6.8)</td>
</tr>
<tr>
<td>Waist circumference (cm)†</td>
<td>85.3 (15.5)</td>
<td>83.6 (10.5)</td>
<td>88.9 (17.1)</td>
</tr>
<tr>
<td>Family history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history preeclampsia or hypertension during pregnancy (%)</td>
<td>6.6</td>
<td>4.0</td>
<td>21.2</td>
</tr>
<tr>
<td>Mother was &lt;2,500 g at birth (%)‡</td>
<td>4.1</td>
<td>6.3</td>
<td>17.4</td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous (%)</td>
<td>60.5</td>
<td>48.7</td>
<td>57.6</td>
</tr>
<tr>
<td>Periconceptional multivitamin use (%)</td>
<td>45.6</td>
<td>48.7</td>
<td>24.2</td>
</tr>
<tr>
<td>Smoking during pregnancy (%)</td>
<td>30.7</td>
<td>36.8</td>
<td>39.4</td>
</tr>
<tr>
<td>Gestational age at sampling (weeks)</td>
<td>10.0 (3.8)</td>
<td>10.4 (4.0)</td>
<td>11.6 (4.6)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, standard deviation.
† Available for 212 women, adjusted for gestational age at sampling.
‡ Available for 281 women.

Early pregnancy inflammation, dyslipidemia, and spontaneous preterm birth

The presence of early pregnancy inflammation (C-reactive protein: ≥8 µg/ml) conferred a 2.6- to 2.8-fold increased risk of sPTB subtypes, after adjustment for race, body mass index, periconceptional multivitamin use, and gestational age at sampling (table 2). Moreover, we observed a dose-response relation between C-reactive protein concentrations and risk of sPTB subtypes. There was a positive linear relation between C-reactive protein and risk of sPTB at 34–<37 weeks (figure 3, part A). A 5-µg/ml increase in C-reactive protein was associated with a 1.4-fold (95 percent confidence interval (CI): 1.1, 2.0) increase in the risk of sPTB, independent of confounders. For sPTB at <34 weeks (figure 3, part B), the risk increased as C-reactive protein rose from 0 to 10 µg/ml. An increase of C-reactive protein from 5 to 8 µg/ml conferred a 70 percent increase in the risk of sPTB (adjusted odds ratio (OR) = 1.7, 95 percent CI: 1.1, 2.5). Beyond 10 µg/ml, precision was poor because of sparse data.

![FIGURE 2. Distribution of C-reactive protein (CRP) before 21 weeks' gestation, according to preterm birth status, Pregnancy Exposures and Preeclampsia Prevention Study, 1997–2001. The boxes represent the interquartile range (IQR) for each group (<34 weeks: IQR = 0.9–6.1 µg/ml; 34–<37 weeks: IQR = 0.9–7.1 µg/ml; ≥37 weeks: IQR = 1.0–5.3 µg/ml), and the square symbols represent values above the 95th percentile. The horizontal line in each box represents the median concentration of C-reactive protein (<34 weeks: 3.9 µg/ml; 34–<37 weeks: 2.8 µg/ml; ≥37 weeks: 2.4 µg/ml), and the asterisk represents the mean. Results were truncated at C-reactive protein concentrations of 24 µg/ml (three observations excluded).](image-url)
When early pregnancy inflammation and dyslipidemia were modeled jointly, inflammation alone conferred a 2.9-fold (95% CI: 1.1, 7.2) increase in risk of sPTB at 34–<37 weeks, adjusted for confounders. The risk increased 2.0-fold (95% CI: 1.0, 4.2) among women with early pregnancy dyslipidemia alone. The presence of both dyslipidemia and inflammation increased the risk of sPTB at 34–<37 weeks 4.0-fold (95% CI: 1.4, 11.8).

In contrast, the presence of early pregnancy dyslipidemia or inflammation alone was not associated with risk of preterm birth at <34 weeks. However, women with both conditions had a 6.4-fold increased risk for preterm birth at <34 weeks.

### TABLE 2. Inflammation and dyslipidemia before 21 weeks’ gestation according to preterm birth status, Pregnancy Exposures and Preclampia Prevention Study, 1997–2001

<table>
<thead>
<tr>
<th>Model</th>
<th>Unadjusted prevalence of spontaneous preterm births (%)</th>
<th>Adjusted odds ratio</th>
<th>95% confidence interval</th>
<th>Additional adjustment for body mass index§</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Inflammation (−)/dyslipidemia (−)</td>
<td>279</td>
<td>20.8</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Inflammation (+)/dyslipidemia (−)</td>
<td>58</td>
<td>31.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>Inflammation (−)/dyslipidemia (+)</td>
<td>211</td>
<td>16.5</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Inflammation (+)/dyslipidemia (+)</td>
<td>33</td>
<td>30.3</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Inflammation (−)/dyslipidemia (−)</td>
<td>68</td>
<td>27.9</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Inflammation (+)/dyslipidemia (+)</td>
<td>25</td>
<td>32.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* C-reactive protein (<8 µg/ml).
† Cholesterol (>230 mg/dl) or triglycerides (>140 mg/dl), adjusted for periconceptional vitamin use, gestational age at sampling, and body mass index.
‡ Additional adjustment for body mass index.
§ Additional adjustment for race, periconceptional vitamin use, and gestational age at sampling.

When early pregnancy inflammation and dyslipidemia were modeled jointly, inflammation alone conferred a 2.9-fold (95% CI: 1.1, 7.2) increase in risk of sPTB at 34–<37 weeks, adjusted for confounders. The risk increased 2.0-fold (95% CI: 1.0, 4.2) among women with early pregnancy dyslipidemia alone. The presence of both dyslipidemia and inflammation increased the risk of sPTB at 34–<37 weeks 4.0-fold (95% CI: 1.4, 11.8).

In contrast, the presence of early pregnancy dyslipidemia or inflammation alone was not associated with risk of preterm birth at <34 weeks. However, women with both conditions had a 6.4-fold increased risk for preterm birth at <34 weeks.

![FIGURE 3. Association between maternal serum C-reactive protein (CRP) concentration and spontaneous preterm birth at 34–<37 weeks (part A) and at <34 weeks (part B), Pregnancy Exposures and Preclampia Prevention Study, 1997–2001. Curves were estimated by calculating predicted probabilities based on unadjusted logistic regression models. C-reactive protein was modeled as a continuous, linear variable for preterm birth at 34–<37 weeks (p = 0.02) and as a restricted quadratic spline for preterm birth at <34 weeks (C-reactive protein: p = 0.01; C-reactive protein spline term: p = 0.06). The solid line represents the point estimate, and the dashed lines represent 95% confidence intervals. Results were truncated at C-reactive protein concentrations of 24 µg/ml (three observations excluded).](image-url)
(95 percent CI: 1.7, 24.1). With formal testing, there was no evidence of interaction between inflammation and dyslipidemia when the variables were categorized (p = 0.16). However, there was support of an interaction when evaluated with C-reactive protein modeled as a spline (which likely represents the best specification of this variable and provides the most power) (p = 0.06).

There was evidence that body mass index negatively confounded the relation between early inflammation and risk of spontaneous preterm birth, although there was no evidence of effect measure modification. In addition, each two-unit increase in body mass index without early pregnancy inflammation or dyslipidemia was associated with about a 10 percent reduction in the risk of sPTB (34–<37 weeks: OR = 0.90, 95 percent CI: 0.81, 0.99; <34 weeks: OR = 0.91, 95 percent CI: 0.79, 1.05).

Inflammation measured early and late in pregnancy

Of the 48 women with early pregnancy inflammation, 22 (46 percent) also had late pregnancy inflammation (C-reactive protein: ≥12 μg/ml). In contrast, 67 percent of the women with late inflammation did not have inflammation early in pregnancy (44/66). After adjustment for race, body mass index, periconceptional vitamin use, dyslipidemia at <21 weeks, and gestational age at sampling, early inflammation (OR = 3.8, 95 percent CI: 1.1, 13.4) or late inflammation (OR = 3.1, 95 percent CI: 1.1, 8.7) each independently increased the risk of preterm birth at <34 weeks. There was no evidence of interaction between these factors (p = 0.9); thus, women with inflammation at both times during pregnancy had about a 12-fold increased risk of preterm birth at <34 weeks. The relation of early (OR = 1.8, 95 percent CI: 0.7, 4.3) or late (OR = 1.4, 95 percent CI: 0.6, 2.8) inflammation on the risk of sPTB at 34–<37 weeks was more modest.

DISCUSSION

Inflammation and dyslipidemia early in pregnancy were independently associated with increased risk of sPTB at 34–<37 weeks. Our data suggested that the risk may have been particularly elevated for sPTB at <34 weeks when both conditions were present before 21 weeks’ gestation. In addition, inflammation early or late in pregnancy was independently associated with increased risk of sPTB at <34 weeks.

Our results relating elevated C-reactive protein to sPTB risk are generally consistent with those of previous studies, although they provide novel evidence of a dose response such that even modest increases in C-reactive protein were associated with increased risk. Hviilsom et al. (8) detected elevated C-reactive protein concentrations at 17 weeks’ gestation among 84 women with idiopathic preterm birth at <37 weeks compared with 400 controls and detected a two-fold increased risk for sPTB in women with elevated C-reactive protein using a threshold similar to ours. Pitiphat et al. (9) reported a 4.64-fold (95 percent CI: 0.94, 22.96) increase in risk of sPTB at <37 weeks among women with C-reactive protein at or above 8 μg/ml before 20 weeks’ gestation. Although this estimate was higher than our results, our estimates were more precise as our study included twice as many cases of sPTB. In addition, Pitiphat et al. reported median concentrations of C-reactive protein among women with preterm birth at <34 weeks that were higher than those in our study, but the majority of these were from women with indicated preterm birth. C-reactive protein concentrations early in pregnancy among women who go on to develop preeclampsia, the leading cause of indicated preterm birth, are similarly high (18, 19). Our results suggest that early pregnancy elevations in C-reactive protein among women with sPTB are intermediary between those of women with uncomplicated term births and the more severe elevations found among women with preeclampsia.

Among nonpregnant adults, inflammation and infection induce many changes in blood lipid levels, including increases in triglycerides that are thought to be an integral part of innate immunity (20). There is also recent longitudinal evidence that elevated inflammatory plasma proteins induce hypercholesterolemia among individuals with previously normal cholesterol concentrations (21). In addition, lipid-lowering statin therapy also has antiinflammatory effects that appear to be independent of its effects on lipids (22, 23). Taken together, this evidence supports the possibility that dyslipidemia and inflammation are biologically related but may operate via distinct but perhaps synergistic pathways. Although the role of these pathways to influence pregnancy outcome is unexplored, our results suggest that elevated C-reactive protein, hypercholesterolemia, and hypertriglyceridemia may converge in women with idiopathic preterm birth. Mechanisms can only be speculated, but it is possible that these factors may disrupt normal placentation. Evidence linking metabolic syndrome characteristics to oxidative stress support this possibility (24–26), but this warrants further study in the setting of pregnancy.

Evidence relating high body mass index with sPTB is conflicting, with most (27, 28) but not all (29) studies reporting a protective effect. In our data, there was evidence that body mass index negatively confounded the relation between elevated C-reactive protein early in pregnancy and sPTB. Indeed, although high body mass index was correlated with higher C-reactive protein in our study and others (30), increasing body mass index without early pregnancy inflammation or dyslipidemia was associated with reduced risk of sPTB. Prepregnancy obesity is associated with first trimester markers of reduced placental function in otherwise uncomplicated pregnancies (31). Obesity is also associated with increased risk of spontaneous abortion (32). Thus, placentation may be impaired among obese women, perhaps when accompanied by excess inflammation. It is possible that a portion of these poorly implanted pregnancies, perhaps when exposed to other factors, could result in sPTB.

Elevated C-reactive protein early or late in pregnancy was associated with increased sPTB risk in our study, and elevations at both times appeared to be related to particularly elevated risk. These results are consistent with the possibility of an inflammatory phenotype, defined as those with elevated C-reactive protein at both measurement times,
which may be related to sPTB risk. This possibility is supported by evidence that preterm birth aggregates in families (33), as well as by emerging evidence that proinflammatory cytokine polymorphisms are related to risk of sPTB (34, 35). Future research is needed to determine if elevated C-reactive protein concentrations persist postpartum in this group and perhaps even antedate pregnancy.

Our results should be considered in light of several limitations. We did not have fasting serum available and, although we have no reason to believe that the time since the last meal would differ systematically based on factors associated with sPTB risk, our lipid results should be replicated in fasting serum. Nonfasting specimens also precluded our ability to evaluate evidence of insulin resistance, which is related to hyperlipidemia and inflammation. In addition, future studies should relate other markers of inflammation early in pregnancy, such as interleukin 6 or tumor necrosis factor α, to spontaneous preterm birth risk. We were missing a late pregnancy specimen for 42 women and, therefore, may have underestimated the relation of late pregnancy C-reactive protein to sPTB risk. In addition, small sample sizes limited the precision of our estimates. Although we were able to consider a variety of socioeconomic factors related to sPTB risk, residual confounding due to unmeasured factors cannot be ruled out. The large number of sPTB cases may have underestimated the relation of late pregnancy C-reactive protein concentrations to sPTB risk, perhaps in combination with inflammation, may be related to sPTB risk in women. Additional research is needed to determine if these factors persist postpartum.

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REFERENCES


