C-Reactive Protein and Preterm Delivery: Clues From Placental Findings and Maternal Weight

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Bertha L. Bullen, PhD¹, Nicole M. Jones, PhD², Claudia B. Holzman, DVM, MPH, PhD¹, Yan Tian, MS¹, Patricia K. Senagore, MD³, Poul Thorsen, MD, PhD⁴, Kristin Skogstrand, MSc, PhD⁵, David M. Hougaard, MD, DSc⁵, and Alla Sikorskii, PhD⁶

Abstract

To study the association between maternal C-reactive protein (CRP) and preterm delivery (PTD) pathways, CRP was measured in maternal plasma collected at mid-pregnancy ($n = 1310$). PTD was subdivided into spontaneous (sPTD) or medically indicated (MI-PTD). Histologic chorioamnionitis (HCA) was determined by placental histopathology ($n = 1076$). Adjusted CRP levels were elevated for sPTD ($5.5 \mu\text{g/mL}$) versus term deliveries ($4.8 \mu\text{g/mL}$) and higher in sPTD with HCA ($6.3 \mu\text{g/mL}$). After removing HCA, an interaction between body mass index (BMI) and sPTD in relation to CRP was noted. In BMI-stratified models, an association between CRP and sPTD among women with prepregnancy BMI ≥ 25 ($8.9 \mu\text{g/mL}$ for sPTD; $7.2 \mu\text{g/mL}$ for term) was absent among women with lower BMI. We propose that this remaining association in overweight/obese women suggests that CRP may mark an obesity/inflammation PTD pathway that is distinct from the pathway indicated by HCA.

Keywords

preterm birth, C-reactive protein, prepregnancy body mass index, placentas, chorioamnionitis

Introduction

Preterm delivery (PTD) is the leading cause of death in US infants¹ and is associated with long-term neurodevelopmental and behavioral consequences for the preterm survivor.² Among proposed pathways leading to PTD³⁻⁵ an inflammation/infection pathway⁶ and a maternal vascular disease pathway⁷ have accumulated significant evidence. Reliable biomarkers for these pathways would help identify women at increased risk of PTD and provide insights into the underlying biologic mechanisms.^{5,8-10}

C-reactive protein (CRP), an acute phase reactant in the innate immune response, is a nonspecific biomarker of inflammation. In acute inflammation, CRP levels increase rapidly and dramatically, exceeding normal levels ($<1.0 \mu\text{g/mL}$) within 6 hours of infection/injury and peaking around 48 hours at levels exceeding $500 \mu\text{g/mL}$.¹¹ Although CRP's causal role in inflammation and cardiovascular disease remains controversial,¹² modest and sustained elevations (3.0 - $10.0 \mu\text{g/mL}$) have been associated with a large number of medical conditions,¹³ obesity,¹⁴⁻¹⁶ and normal pregnancy.¹⁷

Levels of maternal CRP have been positively associated with PTD in at least 6 studies,¹⁸⁻²³ with at least 2 studies suggesting a dose-response relationship between CRP levels and PTD risk.^{19,21} However, associations between CRP and PTD have not been clearly related to PTD pathways. In a study of CRP measured at 13 weeks' gestation, levels were not linked

to the subsequent development of histologic chorioamnionitis (HCA),²⁴ an indicator of an infection/inflammation pathway, but findings have been mixed in the prospective studies of preeclampsia (PE) and gestational hypertension (GH),^{25,26} indicators of a maternal vascular disease pathway. CRP levels are strongly associated with body mass index (BMI),^{11,14,27,28} which may be related to extrahepatic production of CRP by adipocytes.^{29,30} However, previous works have varied in their approach to adjusting for BMI. Although higher BMI is associated with various pregnancy, birth, and neonatal

¹ Department of Epidemiology and Biostatistics, Michigan State University, East Lansing, MI, USA

² Biomedical Research and Informatics Core, Michigan State University, East Lansing, MI, USA

³ Department of Physiology, Michigan State University, East Lansing, MI, USA

⁴ Department of Gynecology and Obstetrics, Lillebaelt Hospital, Kolding, Denmark

⁵ Department of Clinical Biochemistry and Immunology, Statens Serum Institut, Copenhagen, Denmark

⁶ Department of Statistics and Probability, Michigan State University, East Lansing, MI, USA

Corresponding Author:

Claudia B. Holzman, Department of Epidemiology and Biostatistics, Michigan State University, West Fee Hall, 909 Fee Road, Room B601, East Lansing, MI 48824, USA.

Email: holzman@msu.edu

complications,^{31,32} the relation between BMI and PTD appears to be U-shaped, with both lower BMI (underweight) women³³ and higher BMI (overweight/obese) women^{22,31} at higher risk of PTD.

Here, we explore mid-pregnancy maternal CRP as a potential biomarker for PTD pathways. We test the association between CRP levels and selected indicators of infection/inflammatory and maternal vascular disease/inflammatory pathways and further examine the possible influence of maternal BMI/inflammation on the association between CRP and spontaneous PTD (sPTD).

Materials and Methods

Study Design

The Pregnancy Outcomes and Community Health (POUCH) study was designed to investigate pathways to PTD as well as other adverse pregnancy outcomes. The study received institutional review board approval at Michigan State University, Michigan Department of Community Health, and 9 community hospitals. Women in community clinics who met eligibility criteria and expressed interest constituted the sampling frame. A random, stratified sampling scheme was used to sample women from the sampling frame for the POUCH study cohort and subcohort (described below). Certain groups of interest were oversampled, a technique frequently employed in national surveys such as the National Health and Nutrition Examination Survey.³⁴ Oversampling of specific strata improves the precision of risk estimates for the oversampled strata when the total sample size is limited by available resources. In analyses of the entire sample, sampling weights are used and individuals in oversampled strata are assigned lower sampling weights so that, among the whole, each stratum represents its original proportion in the sampling frame (described further in the Analytic Strategy section).

The POUCH Study Cohort

Eligibility criteria for the POUCH study cohort included a singleton pregnancy at 16 to 27 weeks of gestation with no known chromosomal abnormality or birth defect, maternal serum α -fetoprotein (MSAFP) screening, prenatal care at 1 of 52 clinics in 5 Michigan communities between September 8, 1998 and June 15, 2004, maternal age of at least 15 years, no prepregnancy diabetes mellitus, and proficiency in English. Women who met the eligibility criteria and expressed interest in the study constituted the sampling frame. Those who had normal MSAFP levels were stratified by race/ethnicity and randomly sampled into the cohort. In addition, all interested women with unexplained high MSAFP levels of ≥ 2 multiples of the median were invited to participate because this prenatal screening biomarker has been consistently linked to risk of PTD and was of particular interest in the POUCH study.⁴ Of the 3038 women recruited into the cohort, 3019 were followed (99%) through delivery. Overall, 7% of the cohort had high

MSAFP levels compared to the typical 3% to 5% in the screened population. However, in cohort analyses where sampling weights are applied, women with elevated MSAFP account for only 3% to 5% of the cohort, typical of any unselected pregnancy cohort. Thus, the POUCH study cohort can be thought of as a survey sample intended to represent the original sampling frame. A comparison of the maternal characteristics between POUCH study participants and all mothers delivering within the 5 study communities during the same period (data from birth certificates) showed there was little difference, with the exception that older African American mothers were slightly underrepresented in the POUCH study. The weighted percentage of PTD in the POUCH study cohort was 10.7%, similar to that found in the community populations.

At enrollment (16–27 weeks of gestation) cohort women met with a study nurse, signed consent forms, completed in person interviews and self-administered questionnaires, and had biological samples collected. Questionnaire data included the participant's self-report of race/ethnicity, educational attainment, Medicaid insurance status, obstetric history, height, and prepregnancy weight. Plasma was obtained by standard protocol from the blood collected by venipuncture into Vacutainer EDTA blood collection tubes (Becton, Dickinson & Company, Franklin Lakes, New Jersey) and stored at -80°C for later assay. Gestational age was calculated from the last menstrual period (LMP) or from early ultrasound (≤ 25 weeks of gestation) when this estimate differed from the LMP-based estimate by more than 2 weeks. PTD was defined as any delivery occurring before 37 weeks of gestation.

The POUCH Study Subcohort

In order to conserve resources, some costly data elements (eg, placental examinations, medical record abstraction, and assays in stored biologic samples) were obtained from only a subsample of POUCH study participants, referred to as the subcohort. The subcohort of 1371 women was assembled using a random stratified sampling design, sampling from among the cohort, and again oversampling from certain strata. There were 8 sampling strata defined by race/ethnicity (African American, non-African American), MSAFP levels (high, normal), and pregnancy outcome (preterm, term). The subcohort included 100% of the cohort women who delivered preterm ($n = 335$) and 100% of the women who delivered at term with high MSAFP ($n = 165$). In the remaining strata of women with normal MSAFP and term deliveries, the study sampled 72% of the African Americans ($n = 422$) and 23% of the non-African Americans ($n = 449$). In all subcohort analyses, sampling weights were used to account for the oversampling of women with high MSAFP into the cohort and the oversampling of particular maternal characteristics (ie, high MSAFP, PTD, and African Americans with term deliveries) into the subcohort. Each subcohort woman is assigned a sampling weight that reflects her representation of similar

women in the original sampling frame (described further in the Analytic Strategy section).

In the present study, 1310 participants (96% of the subcohort) had plasma available for bioassay. Of these, 1076 (82%) had placental histopathology results available from the examinations completed to date. These subgroups did not differ significantly from each other or from the subcohort with respect to maternal age, education, race/ethnicity, gestational age at blood draw, Medicaid insurance status, parity, or BMI.

Covariates

Stored plasma was shipped frozen to the analytic laboratory (Statens Serum Institut, Copenhagen, Denmark) that was blinded to all clinical information, including gestational age at delivery. CRP was measured using a previously described sandwich enzyme-linked immunosorbent assay.³⁵ Coefficients of variation were 5.3% (intraassay) and 15.6% (interassay), with a limit of quantitation (LOQ) of 0.005 $\mu\text{g/mL}$. In all, 4 participants (0.3% of those assayed) with values below the LOQ were assigned an assay value of 0.0025 $\mu\text{g/mL}$ (one-half of LOQ) to avoid truncating the distribution.³⁶

Delivery circumstances (medically indicated [MI-PTD] or sPTD) were determined through independent reviews of medical records by 2 abstractors, a physician, and a labor and delivery nurse, with disagreements resolved through reexamination of the medical records by an expert team. MI-PTD was defined as delivery before 37 weeks of gestation initiated by either labor induction or C-section in the absence of spontaneous labor or membrane rupture. sPTD was defined as delivery before 37 weeks of gestation initiated by either spontaneous labor (onset of regular contractions resulting in cervical dilation of at least 2 cm) or preterm premature rupture of membranes (PPROMs; membrane rupture occurring before or simultaneously with the onset of labor). Gestational hypertension was considered present in women with an explicit diagnosis of GH in the prenatal record or with documented diastolic blood pressure ≥ 90 mmHg and/or systolic blood pressure ≥ 140 mmHg on at least 2 different calendar days beginning after 20 weeks of gestation. Preeclampsia was considered present in women with an explicit diagnosis of PE in the prenatal record or with otherwise unexplained proteinuria in the presence of GH.

HCA and placental maternal vascular findings were determined as described elsewhere.^{37,38} Detailed examinations of the placentas were completed by the study's sole placental pathologist (P.K.S.) who was blinded to all clinical information, including gestational age at delivery. HCA was considered present if (1) the fetal response included a polymorphonuclear cell (PMNL) inflammatory pattern in the umbilical vessels extending into Wharton jelly and >30 PMNLs/high-power field or (2) the maternal response included a PMNL inflammatory pattern in the chorionic plate and/or extraplacental membrane chorion and amnion, and karyorrhexis and/or necrotizing inflammation. This definition for the presence of HCA was derived from the POUCH study data which show a threshold effect with sPTD.³⁷ Placental

maternal vascular findings were considered "high" if there was a high score in any 1 of the 3 maternal vascular groupings described by Kelly et al.³⁸ Those groupings were (1) obstructive, which included findings of major placental infarcts and decidual vessel atherosclerosis, (2) disruption of integrity, which included findings of retroplacental hemorrhage and bleeding in the decidua, and (3) developmental, which included findings of decreased remodeling of maternal spiral arteries. For the analyses reported here, maternal vascular complications (MVCs), defined as high placental maternal vascular score, PE, or GH, was dichotomized as present or absent.

Analytic Strategy

As noted above, the POUCH study cohort and subcohort were constructed by probability sampling from the original sampling frame. Sampling weights were used in all the analyses to produce results that are generalizable to the sampling frame and maintain estimators with correct standard errors for hypothesis testing and confidence intervals (CIs). According to the principles of survey design and analysis,³⁹ each woman included in the analyses is statistically representative of a certain number of similar women in the sampling frame. Women in a particular sampling stratum receive a sampling weight so that as a group these women reflect the proportion of that stratum in the original sampling frame. For example, African American women who delivered a preterm infant and had elevated MSAFP constituted 0.33% of the sampling frame. Due to oversampling, this group of women (stratum) accounts for over 0.33% in the subcohort according to raw numbers, but after applying sampling weights the contribution of these women returns to the original percentage (ie, 0.33%). Using the sampling weights, we remove bias in the risk estimates that would be due to oversampling of certain risk groups.

The CRP values were log transformed for analyses to better approximate a normal distribution. Prepregnancy BMI was dichotomized into low/normal ($\text{BMI} < 25 \text{ kg/m}^2$) or overweight/obese ($\text{BMI} \geq 25 \text{ kg/m}^2$) consistent with Centers for Disease Control and Prevention guidelines.⁴⁰ The same cut points were used to group women by BMI at enrollment as there are currently no equivalent guidelines for categorizing women based on mid-pregnancy BMI. Weighted linear regression models (Proc Surveyreg in SAS 9.2, SAS Institute, Inc., Cary, North Carolina) were used to examine the associations between CRP levels and maternal characteristics as well as pregnancy outcome (PTD vs term). The least squares means of the log value were output from these models. Least square means were then retransformed to the original scale ($\mu\text{g/mL}$) for reporting and are referred to as the least squares geometric mean (GMean) of CRP levels.

Maternal characteristics that were significantly associated with CRP levels in unadjusted models (maternal age, gestational age at blood draw, parity, and maternal BMI) or that have been consistently associated with CRP in previous studies (race) were included in the multivariable models. Analyses

examined associations between CRP and pregnancy outcomes modeled in 5 ways (1) a 2-level outcome of term and PTD that was then stratified on maternal BMI, (2) a 3-level outcome of term, MI-PTD, and sPTD; (3) a 4-level outcome of term with and without HCA and sPTD with and without HCA; (4) a 4-level outcome of term with and without MVC and sPTD with and without MVC; and (5) a 2-level outcome of term and sPTD after excluding HCA or MVC that was then stratified on maternal BMI. In models 3 to 5, the MI-PTD was removed because CRP was unrelated to MI-PTD in the 3-level model.

Results

Unadjusted comparisons of the CRP levels by maternal characteristics and pregnancy outcome are summarized in Table 1. Higher CRP levels were found in women aged 20 to 29 years, in women with a history of previous live birth and in women with higher prepregnancy BMI or higher BMI at enrollment (≥ 25 kg/m²). Lower CRP levels were noted with gestational ages at blood draw in the second and fifth quintiles (20.3- < 21.8 weeks and ≥ 24.5 weeks). No difference in CRP level was found with respect to maternal education, race/ethnicity, Medicaid insurance status, or pregnancy outcome. However, when stratified on maternal BMI (data not shown), higher CRP levels in women delivering preterm as compared to those delivering at term reached statistical significance only in women with higher BMI at enrollment (7.5 μ g/mL vs 6.6 μ g/mL; $P < .05$).

In unadjusted models, no statistically significant associations were found between CRP and MI-PTD or CRP and sPTD (Table 2). However, in multivariable models, the GMean CRP level was significantly higher ($P = .02$) in sPTD (5.5 μ g/mL; 95% CI: 5.0-6.1) versus term (4.8 μ g/mL; 95% CI: 4.5-5.2).

To examine whether the association between CRP and sPTD could be explained by pregnancy complications related to either HCA or MVC, we compared women with or without HCA or MVC. Adjusted GMean CRP was significantly higher ($P = .01$) in sPTD with HCA (6.3 μ g/mL; 95% CI: 5.1-7.9) as compared to term deliveries with no HCA (4.7 μ g/mL; 95% CI: 4.3-5.2; Table 3). Similar analyses grouping term and sPTD by MVC status revealed no significant elevations of CRP across groups as compared to term deliveries with no MVC.

After removing women whose placentas showed evidence of HCA, a significant interaction ($P = .03$) between BMI and sPTD in relation to CRP was noted for BMI at enrollment, and a trend ($P = .06$) toward a similar interaction was noted for prepregnancy BMI. Different variances for CRP among BMI categories further suggested that covariance adjustment for BMI was not appropriate, so models stratified on maternal BMI were used.

In BMI-stratified models, CRP was not significantly associated with sPTD among women with a prepregnancy BMI <25 and among women with a BMI at enrollment of <25 (Table 4). In contrast, adjusted GMean CRP was significantly higher in association with sPTD among women with higher BMIs. For example, in those with a prepregnancy

Table 1. Unadjusted Comparisons of CRP Levels by Maternal Characteristics and Pregnancy Outcome (N = 1310).

	CRP ^{a,b} (μ g/mL)		
	Overall		
	N	GMean	(95% CI)
All women	1310	5.4	(5.0-5.7)
Maternal age (years)			
<20 (reference)	231	4.2	(3.6-4.8)
20-29	743	6.0 ^c	(5.5-6.5)
≥ 30	336	4.8	(4.2-5.6)
Maternal education (years)			
<12 (reference)	301	5.3	(4.6-6.1)
12	381	5.3	(4.6-6.2)
>12	628	5.4	(5.0-5.8)
Race/Ethnicity			
White (reference)	667	5.4	(4.9-5.9)
African American	546	5.2	(4.7-5.7)
Others	97	5.5	(4.4-6.9)
Gestational age at blood draw			
Quintile 1: <20.3 weeks (reference)	260	6.2	(5.5-6.9)
Quintile 2: 20.3 to <21.8 weeks	265	4.9 ^c	(4.3-5.7)
Quintile 3: 21.8 to <23.1 weeks	263	5.6	(4.9-6.4)
Quintile 4: 23.1 to <24.5 weeks	260	5.4	(4.7-6.3)
Quintile 5: ≥ 24.5 weeks	262	4.8 ^c	(4.0-5.7)
Medicaid insured ^d			
Never	564	5.0	(4.6-5.5)
Ever	744	5.7	(5.2-6.3)
Parity			
No previous live birth (reference)	548	4.5	(4.0-5.0)
Previous live birth term delivery	696	6.1 ^c	(5.6-6.7)
Previous live birth preterm delivery	66	5.3	(4.2-6.7)
Prepregnancy BMI			
<25 (low/normal)	642	3.6	(3.2-4.0)
≥ 25 (overweight/obese)	668	8.0 ^c	(7.5-8.6)
BMI at enrollment			
<25	384	3.1	(2.8-3.5)
≥ 25	926	6.7 ^c	(6.2-7.1)
Preterm delivery			
Term (≥ 37 weeks of gestation)	992	5.3	(4.9-5.7)
Preterm (< 37 weeks of gestation)	318	5.8	(5.3-6.4)

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; GMean, geometric mean.

^a Geometric mean of the log value, retransformed to the original scale.

^b Weighted for the subcohort sampling scheme.

^c $P < .05$ for comparison test within each maternal characteristic.

^d Medicaid insurance status missing for 2 participants.

BMI ≥ 25 , the adjusted GMean CRP was 8.9 μ g/mL for sPTD (95% CI: 7.6-10.3) and 7.2 μ g/mL for term deliveries (95% CI: 6.5-8.0; $P = .01$). An analysis removing both HCA and MVC yielded similar results, with the association between CRP and sPTD persisting only in women with higher BMI (data not shown). Results were similar to those reported in Table 4 in analyses that also removed women with PPROM (data not shown), with the difference in CRP levels slightly attenuated in all comparisons, but remaining significant ($P = .05$) in higher BMI women for the comparison of sPTD to term.

Table 2. Associations Between CRP Levels and PTD by Clinical Circumstance (N = 1310).

	N	CRP ^{a,b} (μg/mL) Unadjusted			CRP ^{a,b} (μg/mL) Adjusted		
		GMean	(95% CI)	P Value	GMean	(95% CI)	P Value
PTD ^c							
Term (reference)	992	5.3	(4.9-5.7)		4.8	(4.5-5.2)	
MI-PTD	99	6.0	(5.0-7.1)	.22	5.1	(4.4-6.0)	.44
sPTD	219	5.7	(5.1-6.4)	.31	5.5	(5.0-6.1)	.02

Abbreviations: CI, confidence interval; CRP, C-reactive protein; GMean, geometric mean; PTD, preterm delivery; MI-PTD, medically indicated preterm delivery; sPTD, spontaneous preterm delivery.

^a Geometric mean of the log value, retransformed to the original scale.

^b Weighted for the subcohort sampling scheme.

^c Adjusted for race, gestational age at blood draw, maternal age, parity, and body mass index at enrollment.

Table 3. Associations of CRP Levels and sPTD Using Information on HCA and MVC (N = 989 of the 1076 With Placenta Data).^a

	CRP ^{b,c} (μg/mL)			
	N	GMean	(95% CI)	P Value
sPTD ^d				
Term without HCA (reference)	701	4.7	(4.3-5.2)	
Term with HCA	93	4.9	(3.9-6.1)	.76
sPTD without HCA	158	5.3	(4.7-6.0)	.08
sPTD with HCA	37	6.3	(5.1-7.9)	.01
sPTD ^d				
Term without MVC (reference)	483	5.0	(4.5-5.5)	
Term with MVC	311	4.5	(3.9-5.1)	.16
sPTD without MVC	101	5.7	(4.9-6.6)	.10
sPTD with MVC	94	5.3	(4.6-6.2)	.40

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HCA, histologic chorioamnionitis; GMean, geometric mean; MVC, maternal vascular complications; PTD, preterm delivery; sPTD, spontaneous preterm delivery.

^a Women with medically indicated preterm delivery were removed from these analyses.

^b Geometric mean of the log value, retransformed to the original scale.

^c Weighted for the subcohort sampling scheme.

^d Adjusted for race, gestational age at blood draw, maternal age, parity, and body mass index at enrollment.

Discussion

We report a positive association between maternal CRP levels and sPTD, a finding consistent with some^{19,21} but not all²² previous reports. Within the sPTD group, elevated mid-pregnancy CRP levels were partially explained by HCA. In BMI-stratified analyses, the association between CRP and sPTD in the absence of HCA was significant only in higher BMI women. Removal of women with evidence of MVC did not eliminate the positive CRP-sPTD relation among women with high BMIs. We hypothesize that, in addition to its association with HCA-related pathways, elevated mid-pregnancy CRP may mark, and potentially participate in, the activation of distinct pathways to PTD in overweight/obese women.

Previous studies examining maternal CRP-chorioamnionitis relations often measured CRP after PPROM, and reviews of such studies suggest that CRP is not a useful marker for HCA.^{41,42} One nested case-control study (n = 72) found no association between CRP measured at 13 weeks of gestation and HCA at delivery.²⁴ In contrast, we report a significant elevation in CRP at mid-pregnancy in women delivering

preterm with HCA. Although sample size, study population, and chorioamnionitis definition may explain inconsistent results across the studies, it is also possible that our later measurement of CRP captured the progression of HCA with advancing gestational age.

Our finding that the association between CRP and sPTD without HCA was significant only in higher BMI women suggests that elevated CRP may have a different meaning in overweight/obese women than in low/normal weight women. The attenuation of the CRP-sPTD association in multivariable models as compared to BMI-stratified models may partially explain conclusions that associations between maternal CRP and sPTD are weak.⁴³

Elucidation of pathways to PTD in overweight/obese women is beyond the scope of this study. However, obesity (BMI >30 kg/m²) was the number one risk factor for elevated CRP in a large US sample,⁴⁴ and positive CRP-BMI associations have been reported in uncomplicated pregnancies.⁴⁵ Thus, the association between CRP and sPTD in higher BMI women may indicate an adipokine-mediated chronic proinflammatory state of obesity,¹⁴ whereas in normal

Table 4. Associations of CRP Levels and sPTD After Removing Women With HCA (N = 859).^a

	CRP ^{b,c} (μg/mL)			P Value
	N	GMean	(95% CI)	
sPTD ^d				
Term without HCA (reference)	701	4.7	(4.3-5.2)	
sPTD without HCA	158	5.3	(4.7-6.0)	.08
Prepregnancy BMI <25 ^e				
Term without HCA (reference)	335	3.2	(2.8-3.7)	
sPTD without HCA	91	3.4	(2.8-4.2)	.50
Prepregnancy BMI ≥25 ^e				
Term without HCA (reference)	366	7.2	(6.5-8.0)	
sPTD without HCA	67	8.9	(7.6-10.3)	.01
BMI at enrollment <25 ^e				
Term without HCA (reference)	203	3.1	(2.7-3.6)	
sPTD without HCA	64	3.0	(2.4-3.7)	.78
BMI at enrollment ≥25 ^e				
Term without HCA (reference)	498	5.8	(5.2-6.5)	
sPTD without HCA	94	7.3	(6.2-8.6)	.01

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive Protein; GMean, geometric mean; HCA, histologic chorioamnionitis; sPTD, spontaneous preterm delivery.

^a Women with medically indicated preterm delivery were removed from these analyses.

^b Geometric mean of the log value, retransformed to the original scale.

^c Weighted for the subcohort sampling scheme.

^d Adjusted for race, gestational age at blood draw, maternal age, parity, and body mass index at enrollment.

^e Adjusted for race, gestational age at blood draw, maternal age, and parity.

weight women an elevated single measure of CRP may reflect a more transient response to infection, injury, or other acute insult. We further hypothesize that chronically elevated CRP levels in higher BMI women may amplify inflammatory responses to acute insults, which could explain some obesity-related health risks as well as the prognostic value of CRP among those already diagnosed with medical conditions.¹³

Results were similar for prepregnancy BMI and BMI at enrollment. In the former, height and prepregnancy weight were self-reported while BMI at enrollment was based on a mid-pregnancy weight measured at study enrollment. Since women tend to overestimate height and underestimate weight, with overweight/obese women underestimating weight to a greater degree than low/normal weight women,⁴⁶ our prepregnancy BMI may have included some misclassification, which would attenuate observed differences between the high and the low BMI categories.

Strengths of this study are its large generalizable sample, mid-pregnancy measurement of CRP, inclusion of well-defined placental histopathology findings, and detailed interview and medical record data. Limitations include reliance on self-reported height for BMI calculations, availability of only 1 CRP measure during pregnancy, and lack of a baseline prepregnancy CRP measure for assessing genetic variations in CRP expression that could modify the magnitude of the response.⁴⁷⁻⁴⁹

In summary, we find that plasma CRP measured at mid-pregnancy is associated with sPTD and that the presence

of HCA at delivery accounts for much of this association. However, a significant association between CRP and sPTD in the absence of HCA remains in higher BMI women, suggesting that CRP in overweight/obese women may mark activation of pathways to PTD that are distinct from pathways related to HCA. Future research to describe these pathways will contribute to our understanding of the role of inflammation in pregnancy as well as the nature of obesity-related risk.

Declaration of Conflicting Interests

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