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Maternal Serum C-Reactive Protein Concentrations in Early Pregnancy and Subsequent Risk of Preterm Delivery

Vitool Lohsoonthorn, MDMS^{1,2}, Chunfang Qiu, MDMS³, and Michelle A. Williams ScD^{2,3}

¹Department of Preventive and Social Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand ²Department of Epidemiology, Multidisciplinary International Research Training Program, University of Washington School of Public Health and Community Medicine ³Center for Perinatal Studies, Swedish Medical Center, Seattle, Washington, USA.

Abstract

Objective—To examine the relation between maternal early pregnancy serum C-reactive protein (CRP) and preterm delivery (PTD).

Design and Methods—Women were recruited before 20 weeks gestation and were followed up until delivery. Maternal serum CRP was measured by competitive immunoassay. Logistic regression procedures were used to calculate adjusted odds ratio (OR) and 95% confidence intervals (95%CI).

Results—Elevations in CRP concentrations were associated with the risk of PTD overall. After adjusting for confounding, the OR for highest quartile (≥ 7.5 vs. < 2.0 mg/l) of CRP was 2.04 (95% CI: 1.13–3.69). Stratified analyses indicated that elevated CRP was associated with an increased risk of spontaneous preterm labour (OR=2.15, 95%CI: 0.85–5.42), medically indicated preterm delivery (OR=3.29, 95%CI: 0.98–11.02), and very preterm delivery (OR=20.6, 95%CI: 2.53–168.03), but not with preterm premature rupture of membranes (OR=1.48, 95%CI: 0.56–3.86)

Conclusions—Elevated CRP concentrations in early pregnancy are associated with an increased risk of PTD, particularly medically indicated PTD and very PTD

Keywords

C-reactive protein; preterm delivery

Introduction

Preterm delivery, defined as delivery prior to the completion of 37 weeks gestation and which is an important determinant of neonatal and infant morbidity and mortality, complicated some 11.9% of pregnancies in the United States in 2001 and has been steadily increasing for the past two decades (1). Although the pathophysiology of preterm delivery remains unknown, accumulating evidence suggests that subclinical infections and chronic inflammation may account for a majority of preterm deliveries. Importantly, some investigators have indicated that infections are major causes of preterm deliveries (PTD), responsible for somewhere

Corresponding Author: Dr. Vitool Lohsoonthorn, University of Washington, MIRT Program, Department of Epidemiology (Box 357236), 1959 NE Pacific Street (HSB, F-263), Seattle, WA 98195 USA. Phone (206) 543-7559, Fax (206) 543-8525, E-mail: vitool@u.washington.edu

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between 30% and 50% of all cases (2,3). Available evidence suggest that bacterial infection of the chorioamnion, or extraplacental membrane, may lead to chorioamnionitis, a condition strongly associated with premature rupture of membranes and preterm delivery (4,5). Intrauterine infections are also known to play an important etiologic role in preterm birth (6, 7). Moreover there is increasing evidence which suggests that other infectious processes occurring elsewhere in the body may contribute to preterm delivery (8-10).

C-reactive protein (CRP) is a sensitive marker of inflammation that remains stable in serum (11). Elevated concentrations of CRP in peripheral circulation has been associated with the presence of intrauterine infection (12,13). Additionally, investigators have noted elevated amniotic fluid CRP concentrations among women with intrauterine infections as compared with controls (14,15). Hvilsum et al, in 2002, were among the first group of investigators to report that elevated concentrations of CRP in maternal serum during early pregnancy ($\geq 85^{\text{th}}$ percentile vs. $<85^{\text{th}}$ percentile) were associated with a 2-fold increased risk of preterm delivery (OR=2.0, 95%CI: 1.2-3.5) (16). This early finding has been corroborated by some (17,18), though not all (14) investigators. Because of the conflicting reports, we assessed the relation between maternal serum CRP concentrations in early pregnancy and the risk of subsequent preterm delivery among a cohort of singleton pregnant women. We also completed stratified analyses in attempts to account for the possible heterogeneity in the aetiology of preterm delivery (19-22).

Methods

The Omega Study

The population for the present analysis was drawn from the participants of the Omega Study, a prospective cohort study of maternal dietary and other risk factors of adverse pregnancy outcomes including preeclampsia, gestational diabetes mellitus and other adverse outcomes of pregnancy. Women participating in the study attended prenatal care clinics affiliated with Swedish Medical Center (Seattle) and Tacoma General Hospital (Tacoma), in Washington State between December 1996 and September 2002. Women eligible for inclusion were those who initiated prenatal care prior to 20 weeks gestation, were 18 years of age or older, could speak and read English, planned to carry the pregnancy to term, and to deliver at either of the two study hospitals. In the first 18 months of the Omega Study, only nulliparous women were approached and enrolled. Eligibility criteria were later expanded to include multiparous women.

Enrolled participants were asked to take part in an hour-long interview in which trained research personnel used a structured questionnaire to elicit information regarding maternal socio-demographic and anthropometric characteristics, lifestyle habits, and medical and reproductive histories. Participants also provided non-fasting blood and urine samples. Pregnancy outcome information was ascertained by reviewing participants' hospital labour and delivery medical records and clinic records after delivery. The procedures used in this study were approved by the Institutional Review Boards of Swedish Medical Center and Tacoma General Hospital. All participants provided written informed consent.

Analytical population

During the study period, 2,381 eligible women were approached, and 2,000 (84%) agreed to participate. One hundred and twenty-one women who were lost to follow-up (delivery outcome unknown or medical record not found) were excluded from this analysis. Also excluded were women who experienced an abortion or fetal demise prior to 28 weeks of gestation (n=49), and those with multi-fetal pregnancies (n=61). A cohort of 1,769 women remained for analysis.

Pregnancy Outcome

The diagnosis of preterm delivery was made using American College of Obstetricians and Gynaecologists (ACOG) guidelines (23). Gestational age was based on the last menstrual period and confirmed by ultrasound examination, conducted prior to 20 weeks gestation. If both last menstrual period and ultrasound dating were available and the two agreed within 14 days, we used the former to assign gestational age. If the two dates differed by more than 14 days, we used the ultrasound date. A total of 146 preterm delivery cases were identified; of these 8 were subsequently excluded along with 70 term deliveries because serum samples were not available for determining maternal serum CRP concentrations. Using the detailed information collected from medical records, we categorized preterm delivery cases according to the three pathophysiological groups previously described (i.e., spontaneous preterm labour and delivery, preterm premature rupture of membranes, and medically indicated preterm delivery) (19-22). We also categorized preterm delivery cases according to gestational age at delivery (i.e., very preterm delivery, defined as delivery prior to the completion of 34 weeks gestation; and moderate preterm delivery, defined as delivery between 34 and 36 weeks gestation).

Other Covariates

Using a structured questionnaire, interviewers collected information on maternal socio-demographic, behavioural, and medical characteristics. Covariate information included maternal age, reproductive and medical histories. We also collected information on maternal educational attainment, annual household income, occupation, and smoking and alcohol consumption during pregnancy. Maternal age at the time of interview was expressed in years. Parity was reported as the number of previous pregnancies lasting beyond 20 weeks gestation.

Maternal non-fasting blood samples, collected in 10 ml vacutainer tubes at 13 weeks gestation, on average, were protected from ultraviolet light, kept on wet ice and processed within 20 minutes of phlebotomy. Serum decanted into cryovials was frozen at -80°C until analysis. Serum CRP concentrations were measured by an ultra-sensitive competitive immunoassay (Dade Behring, Deerfield, Illinois) with the intra- and inter-assay coefficients of variation both $<10\%$ (24). All assays were performed without knowledge of pregnancy outcome.

Statistical Analysis

The distribution of maternal socio-demographic characteristics, medical and reproductive histories according to preterm and term delivery status was examined. To estimate the relative association between varying concentrations of CRP and risk of preterm delivery, we categorized each subject according to quartiles determined by the distribution of serum CRP concentrations among the term deliveries. This procedure for determining exposure categories for continuous covariates has been previously described by Hsieh and colleagues (25). Using the lowest quartile as the referent group, odds ratios (OR) and their attendant 95% confidence intervals (95%CI) were estimated. Logistic regression procedures were used to calculate maximum likelihood estimates of odds ratios and 95% confidence intervals, adjusted for potential confounding factors (26,27). Confounders were defined as those factors which altered unadjusted odds ratios by at least 10%. Maternal marital status, ethnicity, gestational age at sample collection, physical activities during pregnancy, and whether women worked during pregnancy were found not to be confounders. In multiple logistic regression models, significance for monotonic trends in risk between preterm delivery and serum CRP concentrations were assessed by treating the four quartiles as a continuous variable after assigning a score as its value (27). These analytical procedures were used in stratified analyses designed to assess risk of sub-types of PTD (i.e., spontaneous preterm labour, preterm premature rupture of membrane, medically indicated preterm delivery, very preterm delivery and moderate preterm delivery). All reported p values are two sided.

Results

Approximately 8.3 % of the women (146 of 1769) in this cohort delivered preterm. Among preterm deliveries, 32.9 % were preceded by spontaneous preterm labour. Approximately 37.0 % and 30.1 % were classified as preterm premature rupture of membrane and medically indicated preterm delivery, respectively.

Maternal socio-demographic, medical and reproductive characteristics of those who delivered preterm and those who delivered at term are presented in Table 1. Overall, preterm delivery cases and term controls were similar with regards to maternal age, race/ethnicity, education, smoking status, participation in physical activity during pregnancy, and gestational age at blood collection. Preterm delivery cases, however, were heavier, were more likely to report using periconceptional multivitamins, and reported lower annual household income than controls. The median concentrations of serum CRP in preterm cases was higher than those in controls who had term deliveries (4.44 vs. 3.92 mg/l, $p=0.053$).

Since reference values for maternal serum CRP concentrations in early pregnancy are not available, we calculated odds ratios for preterm delivery for different quartiles of CRP concentrations based on the distribution noted in the term deliveries (25). As seen in Table 2, women in the highest quartile as compared with women in the lowest quartile, experienced a 1.88-fold increased risk of preterm delivery overall (OR=1.88, 95% CI: 1.15-3.09). Adjustment for possible confounding by maternal age, race/ethnicity, parity, pre-pregnancy body mass index and gestational age at blood collection did not result in a material difference in the association (adjusted OR=2.04, 95% CI: 1.13-3.69). In these analyses, there was evidence of a linear increase in risk of preterm delivery associated with increasing maternal serum CRP concentrations (P for Trend = 0.033).

Because results from prior studies suggest that there may be some heterogeneity in the epidemiology of preterm delivery according to gestational age of delivery and pathophysiology (19-22), we repeated analyses allowing for this possibility. As can be seen in Table 3, there was no clear evidence of a positive association between maternal serum CRP and risk of preterm premature rupture of membrane. For spontaneous preterm labour, or medically indicated preterm delivery, however, we noted that the corresponding ORs for highest quartile were 2.15 (95% CI: 0.85-5.42), and 3.29 (95% CI: 0.98-11.02), respectively.

As can be seen in Table 4, there appeared to be no association between maternal serum CRP concentrations and subsequent risk of moderate preterm delivery (delivery between 34 and 36 weeks gestation). There was, however, some evidence supporting an association between highest quartile of serum CRP (≥ 7.5 mg/l) and risk of very preterm delivery (delivery prior to the completion of 34 weeks gestation) (OR=20.60, 95% CI: 2.53-168.03). Inferences from these analyses, however, are hindered because of the small sample size and extremely wide 95% confidence intervals.

Discussion

C-reactive protein is an acute-phase reactant protein synthesized primarily by liver cells in response to the proinflammatory cytokines including interleukin-6 and TNF- α (28,29). CRP concentrations in peripheral circulation are also known to be associated with high body mass index (BMI) and other markers of adiposity (30,31). The proportion of obesity (pre-pregnancy BMI ≥ 30.0 kg/m²) among preterm cases (18.8%) was significantly higher than those of controls (8.8%) in this study. Thus pre-pregnancy BMI was one of crucial confounders that was entered into logistic regression model. C-reactive protein in maternal peripheral circulation is associated with the presence of intrauterine infection (13). Endothelial dysfunction has been postulated to be part of an exaggerated maternal inflammatory response to pregnancy (32). In

addition, cross-sectional analyses indicate that CRP is strongly correlated with markers of endothelial activation and dysfunction (33). Collectively, these findings, suggest that C-reactive protein, a marker of systemic inflammation, may be involved in the pathogenesis of preterm delivery.

In the present study, we found that elevations in maternal serum CRP concentrations in early pregnancy are positively associated with preterm delivery risk. We observed a 2.04-fold increased risk of preterm delivery among women with CRP concentrations ≥ 7.5 mg/l as compared with women whose concentrations were < 2.0 mg/l (OR=2.04, 95%CI: 1.13-3.69). The association between elevated CRP and medically indicated preterm delivery was particularly strong. No clear evidence was noted for a specific association between elevated CRP and risk of preterm premature rupture of membranes. We noted little evidence of an association between maternal serum CRP concentrations and risk of delivery between 34 and 36 weeks gestation (i.e., moderate preterm delivery). However, elevated CRP concentrations were associated with an increased risk of delivery prior to the completion of 34 weeks gestation (i.e., very preterm delivery).

Our results are consistent with some (16,17), though not all (14) previously published studies of CRP concentrations (measure in early pregnancy) and subsequent risk of preterm delivery. Our results are largely consistent with reports by Hvilsom et al. In their prospective nested case-control study of cohort of 84 singleton preterm cases and 400 term controls, the authors reported that women with CRP concentrations the $\geq 85^{\text{th}}$ percentile (i.e., ≥ 7.6 mg/l) experienced a 2-fold increased risk of preterm delivery (OR=2.0, 95%CI: 1.2-3.5) compared with women who had lower CRP concentrations (16). However, the authors did not assess risk of different sub-types of preterm delivery in relation to varying concentrations of CRP. Pitiphat et al also examined the association between CRP concentrations and preterm delivery risk in a nested case-control study. Subjects were 117 women who delivered preterm (< 37 weeks' gestation) and 117 controls (term deliveries). Median concentrations of CRP were 3.2 mg/l in cases versus 2.4 mg/l in controls. The authors reported that CRP concentrations ≥ 8 mg/l were associated with a more than doubling in risk of preterm delivery (OR=2.55, 95%CI: 1.05, 6.02) (17). Our results and those of Hvilsom et al (16) and Pitiphat et al (17), however, are discordant with reports by Ghezzi et al (14), who observed no association between maternal blood CRP concentrations and risk of moderate preterm delivery (34-36 weeks) or very preterm delivery (< 34 weeks).

In subgroup analyses of PTD, we noted that elevated CRP concentrations (≥ 7.5 mg/l) were associated with a 2.15-fold increased risk of spontaneous preterm labour (95%CI: 0.85-5.42), and 3.29-fold increased risk of medically indicated preterm delivery (95%CI: 0.98-11.02), but not with increased risk of premature rupture of membrane preceding preterm delivery (OR=1.48, 95%CI: 0.56-3.86). Our results are inconsistent with findings reported by Pitichat et al (17) who reported that the association was stronger among cases who experienced spontaneous preterm delivery (OR=4.64, 95%CI: 0.94-22.96) than medically-indicated preterm deliveries (OR=1.42, 95%CI: 0.44-4.61).

Differences in study design, the timing of blood collection, the underlying characteristics study populations, and incomplete or no control for confounding may account for the variability in results across studies. For instance, investigators have noted that serum CRP concentrations measured in the third trimester (28 weeks gestation) is more strongly associated with preterm delivery, while concentrations measured in serum collected upon entry to prenatal care (first and early second trimesters) appear to be less strongly associated with preterm delivery. Variations in prevalence of subclinical infections across diverse populations studied to date may also account for the variability in results across studies.

Our present study has several strengths. First, determination of CRP status using serum collected in early pregnancy served to clarify the temporal relationship between elevated maternal serum CRP concentrations and subsequent risk of preterm delivery. Second, we worked toward identifying etiologically homogenous grouping of preterm delivery by subgroup analysis of spontaneous preterm labour, preterm premature rupture of membranes, and medically indicated preterm delivery. However, our study also has some limitations. First, a single measurement of serum CRP is not likely to provide a time-integrated measure of maternal inflammation status during the index pregnancy. Second, the relatively small number of subjects available for subgroup analyses resulted in imprecise measures of associations as reflected by the very wide 95% confidence intervals.

In conclusion, elevated CRP concentrations in early pregnancy are associated with an increased risk of PTD, particularly nearly 3-fold increased risk of medically indicated PTD and nearly 21-fold increased risk of very PTD. These results are consistent with some previous reports, and further underscore the potential for heterogeneity in the aetiology of preterm delivery.

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Table 1

Characteristics of study members according to preterm case and control status, Seattle and Tacoma, WA, 1996-2002.

Characteristic	Control (n = 1,623) *		Preterm cases (n = 146) *		p-value
	n	%	n	%	
Maternal age (Yrs)					0.326
<20	13	0.8	2	1.4	
20-34	1118	70.6	91	65.0	
≥35	452	28.6	47	33.6	
Mean ± SE	32.07 ± 0.11		32.21 ± 0.46		0.758
Maternal ethnicity					0.417
White	1337	84.6	118	84.3	
African American	31	2.0	5	3.6	
Other	212	13.4	17	12.1	
Unmarried	160	10.1	15	10.7	0.822
≤ 12 Years education	75	4.8	9	6.5	0.389
Nulliparity	1051	66.4	99	70.7	0.298
Smoked during pregnancy	98	6.0	13	8.9	0.171
Pre-pregnancy body mass index (kg/m ²)					<0.001
<20.0	312	19.9	16	11.6	
20.0-24.9	882	56.2	81	58.7	
25.0-29.9	237	15.1	15	10.9	
≥ 30.0	139	8.8	26	18.8	
Mean ± SE	23.41 ± 0.12		25.01 ± 0.51		0.003
Annual household income (\$)					0.021
<30,000	68	4.4	8	5.9	
30,000-69,999	379	24.6	47	34.6	
≥ 70,000	1092	71.0	81	59.6	
Work during pregnancy	1308	82.8	112	80.0	0.378
Physical activities during pregnancy	1311	82.8	116	82.9	0.990
Gestational weeks at blood collection Mean ± SE	14.58 ± 0.10		14.02 ± 0.30		0.262
C-reactive protein Median ± IQR	3.92 ± 5.52		4.44 ± 6.76		0.053

* Number may not be added up to the total number due to missing data

SE: standard error; IQR: inter-quartile range

Odds ratio and 95% CI of preterm delivery according to maternal serum C-reactive protein concentrations measured in early pregnancy, Seattle and Tacoma, WA, 1996-2002

Table 2

C-Reactive Protein (mg/l)	Control (n = 1,623)		Preterm cases (n = 146)		Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
	n	%	n	%		
Quartile 1 (<2.0)	388	23.9	26	17.8	1.00	Reference
Quartile 2 (2.0-3.9)	385	23.7	35	24.0	1.36	(0.82-2.53)
Quartile 3 (4.0-7.4)	391	24.1	28	19.2	1.07	1.44 (0.72-2.32)
Quartile 4 (≥ 7.5)	389	24.0	49	33.6	1.88	1.29 (1.13-3.69)
Missing	70	4.3	8	5.5		
Trend test p-value					0.027	0.033

* Adjusted for maternal age, race, parity, pre-pregnancy body mass index and gestational age at blood collection 70 controls and 8 cases were not included in the analysis of CRP because of missing data.

Odds ratio and 95% CI of preterm subgroups according to maternal serum C - reactive protein concentrations measured in early pregnancy, Seattle and Tacoma, WA, 1996-2002.

Table 3

C-Reactive Protein (mg/l)	Controls (n=1,623)		Spontaneous preterm delivery (n=48)		Preterm premature rupture of membrane (n=54)		Medically indicated preterm delivery (n=44)	
	n		n	OR*	(95%CI)	n	OR*	(95%CI)
Quartile 1 (<2.0)	388		10	1.00	Reference	11	1.00	Reference
Quartile 2 (2.0-3.9)	385		13	1.29	(0.52-3.17)	18	1.89	(0.85-4.23)
Quartile 3 (4.0-7.4)	391		7	0.88	(0.32-2.43)	10	1.03	(0.40-2.63)
Quartile 4 (≥ 7.5)	389		16	2.15	(0.85-5.42)	14	1.48	(0.56-3.86)
Missing	70		2			1		
Trend test p-value				0.198			0.736	
								0.012

* Adjusted for maternal age, race, parity, pre-pregnancy body mass index and gestational age at blood collection 70 controls and 8 cases were not included in the analysis of CRP because of missing data.

Table 4

Odds ratio and 95% CI of moderate preterm delivery (PTD) (34-36 wks' gestation) and very PTD (<34 wks' gestation) according to maternal serum C-reactive protein concentrations measured in early pregnancy, Seattle and Tacoma, WA, 1996-2002.

C-Reactive Protein (mg/l)	Controls (n=1,623)		Moderate PTD (34-36wks) (n=123)		Very PTD (<34wks) (n=23)	
	n		n	OR* (95%CI)	n	OR* (95%CI)
Quartile 1 (<2.0)	388		25	1.00 Reference	1	1.00 Reference
Quartile 2 (2.0-3.9)	385		32	1.36 (0.76-2.43)	3	3.21 (0.33-31.31)
Quartile 3 (4.0-7.4)	391		25	1.17 (0.63-2.16)	3	3.58 (0.36-35.21)
Quartile 4 (7.5)	389		35	1.35 (0.71-2.58)	14	20.60 (2.53-168.03)
Missing	70		6		2	
Trend test p-value				0.475		<0.001

* Adjusted for maternal age, race, parity, pre-pregnancy body mass index and gestational age at blood collection 70 controls and 8 cases were not included in the analysis of CRP because of missing data