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DOES C-REACTIVE PROTEIN PREDICT RECURRENT PREECLAMPSIA?

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Abstract

Objective—Evaluate association of the inflammatory marker C-reactive protein with recurrent preeclampsia.

Methods—Serum samples collected longitudinally in women with previous preeclampsia from the Maternal-Fetal Medicine Units Network trial of aspirin to prevent preeclampsia were assayed for CRP.

Results—Of 255 women studied, 50 developed recurrence. Baseline C-reactive protein concentration was similar between women who did and did not recur. After adjusting for confounders, neither elevated baseline C-reactive protein nor its change over gestation was associated with recurrence.

Conclusion—In this group of women with previous preeclampsia, neither baseline C-reactive protein concentration nor change in concentration over gestation was associated with recurrent preeclampsia.

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Conflicts of Interest/Disclosures
None

Keywords

Pregnancy; Preeclampsia; C-Reactive Protein; Inflammation; Acute-Phase Reaction

Introduction

Preeclampsia is a hypertensive disorder unique to pregnancy, characterized by maternal endothelial dysfunction and an excess inflammatory response.(1–3) The syndrome shares underlying pathophysiologic processes with cardiovascular disease and may portend its later development.(4, 5) Preeclampsia complicates approximately 5% of pregnancies and contributes significantly to maternal and perinatal morbidity and mortality. The specific pathogenesis of preeclampsia remains incompletely elucidated, though contributing factors have been identified, including abnormal placentation, oxidative stress, altered angiogenic factors, and inflammation.(6)

C-reactive protein (CRP) was identified in the 1930s as a plasma protein associated with acute inflammatory responses.(7) In the past decade, elevations in serum CRP have been associated with risk of cardiovascular disease(8), raising interest in the relationship of CRP with preeclampsia as a predictor of the syndrome and possible contributor to its pathogenesis. CRP concentrations are elevated in women with clinically evident preeclampsia. (9–17) However, the utility of CRP in the pre-clinical prediction of preeclampsia has been less consistent. (18–22)

Our objective was to assess the relationship between CRP in early pregnancy and the change in CRP during pregnancy with the subsequent development of preeclampsia in a population of women at high-risk for the syndrome. We sought to evaluate a possible predictive role of CRP for recurrent preeclampsia in women with a history of the disease in a prior pregnancy.

Methods

Study Design

We performed a secondary analysis of samples collected during the Maternal-Fetal Medicine Units Network multicenter randomized controlled trial: Low-Dose Aspirin to Prevent Preeclampsia in Women at High Risk.(23) This study investigated four groups of high-risk women: those with pre-gestational diabetes mellitus, chronic hypertension, multifetal gestation, and those with a history of preeclampsia in a previous pregnancy. For this study, we specifically investigated the subgroup of women with a prior history of preeclampsia (n = 606). At the time of enrollment in the clinical trial, a subset of women also agreed to participate in longitudinal collection of blood samples (n=262 for the prior preeclampsia subgroup). From these women, samples were drawn at three possible time points: 1) baseline (7–26 weeks of gestation), 2) 24–28 weeks of gestation, and 3) 34–38 weeks of gestation. Serum samples, continuously stored at −80 degrees Celsius since the original trial, were thawed for use in this study. Recurrent preeclampsia and gestational hypertension were defined according to criteria described in the primary study.(23) Briefly, gestational hypertension was defined as either systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg persistent over two measurements at least four hours apart. Preeclampsia was defined as gestational hypertension combined with either proteinuria (300mg protein in a 24-hour urine collection or 2 urinary dipsticks ≥ 2+, measured four hours apart and in the absence of infection), thrombocytopenia (platelet count < 100,000/mm^3), or pulmonary edema.

Institutional Review Board approval for the use of these stored samples was obtained at both the University of Pittsburgh and the George Washington University. Subjects had provided informed consent prior to enrolling in the initial study. Laboratory assessment was completed at Magee-Womens Research Institute, and data was subsequently linked and statistical assessment completed at the George Washington University Biostatistical Coordinating Center.

Laboratory methods

CRP was measured by high-sensitivity ELISA. Microplate wells were coated with a rabbit anti-human CRP antibody (Dako Corp. Denmark) overnight. Potential nonspecific binding sites in the microplate wells were blocked using a 2% BSA and 0.05% Tween 20 buffer. Serum samples and recombinant CRP standards were diluted in physiologic buffer that contained 2% BSA. Diluted standards and samples were incubated in the microplate wells for 1 hour at room temperature and then the unbound proteins were washed with a PBS, 0.05% Tween 20 wash buffer. The microplate wells were incubated with a diluted polyclonal rabbit anti-human CRP antibody (1:500) conjugated to horseradish peroxidase (HRP) (Dako Corp. Denmark) for 1 hour at room temperature. After incubation, the microplate wells were washed again and incubated with a substrate for HRP. The amount of CRP in the diluted samples was directly proportional to the amount of color that develops in each well and was compared to the values obtained from the standard curve. The standard curve was linear from 0.2 to 7.5ng/ml. The sensitivity is 0.2ng/ml and spike and recovery tests indicated 91 to 103% recovery. The intra-assay and inter-assay variability were 3.9% and 6.5%, respectively. Correlation with an established commercial laboratory (Quest Diagnostics) showed an r^2 of 0.97.

Statistical Methods

Continuous variables were compared using the Wilcoxon rank-sum test and categorical variables using the chi-square test. The Kruskal Wallis test was used to compare the CRP concentration for three outcome categories, normal, hypertensive and preeclamptic. Logistic regression with a pre-planned multivariable analysis was used to investigate associations of the recurrence of preeclampsia with 1) baseline CRP concentration, and 2) change in CRP concentration over gestation. Change in CRP was calculated by taking the difference of the CRP value at baseline and the CRP value closest to delivery and dividing by the number of weeks between the two sample collections. The multivariable analysis included body mass index (BMI, calculated from self-reported height and pre-pregnancy weight), gestational age at baseline sample collection, race, age, and smoking status. The logistic regression model for change in CRP concentration over gestation also included aspirin treatment and baseline CRP concentration.

We performed an *a priori* power analysis estimating that our study would have 80% power to detect a 30% difference in baseline CRP using a two-sided test with a significance level of 0.05, assuming a mean and standard deviation of CRP concentration in normal pregnancy of 0.3mg/dL and 0.2mg/dL, respectively.(24) Statistical analysis was performed using SAS version 8.2 (SAS Institute, Cary, NC).

Results

Of the 606 women with a history of preeclampsia in a prior pregnancy enrolled in the original trial, 262 had agreed to participate in the longitudinal collection of blood samples at the time of enrollment in the original trial. Of these, there were 259 for whom samples were available. Four women were excluded from the analysis; three women were missing a baseline serum sample, and one woman only had a baseline serum sample and was missing

subsequent samples resulting in 255 women in the final analysis. Demographic characteristics of the 255 women studied in this secondary analysis were compared with the 351 women enrolled in the original randomized trial and not included in this analysis. There were no differences between those studied and those not studied with respect to race, smoking status, age, or BMI. Fifty of these 255 women (20%) developed recurrent preeclampsia, which was similar to the preeclampsia rate seen among women enrolled in the original trial (16.5%, p=0.33). Of those subjects with recurrent preeclampsia, 16 (32%) met criteria (1) for severe disease. An additional 37 women (15% of the total population) developed isolated gestational hypertension and were included in the control group since CRP measures were similar among these women and controls. The demographic characteristics of the women according to outcome are shown in Table 1. While none of these baseline characteristics was different between the groups, there was a trend toward higher BMI among subjects who developed preeclampsia (mean BMI 30.2 versus 27.7 kg/m^2 for the control group, p=0.09).

The original trial of low dose aspirin in high-risk patients indicated no effect of aspirin on outcome, and in our subgroup, the incidence of preeclampsia was not significantly different in the aspirin and placebo treated groups (18% versus 21%, respectively, p=0.47). We found no effect of aspirin treatment on change in CRP concentration (p=0.31). We considered whether there was an interaction between aspirin treatment and CRP; in the regression model, neither the interaction between CRP and aspirin treatment nor between change in CRP and aspirin was significant. For these reasons, aspirin treated and placebo groups were combined for analysis in this study.

As shown in Table 1, the gestational age at baseline sample collection was similar for women with preeclampsia versus controls. There was no discernable relationship of baseline CRP concentration to gestational age.

Maternal serum CRP concentration was not different at the time of baseline sampling (7.6–26.9 weeks gestation) between subjects who later developed preeclampsia compared with women with previous preeclampsia who did not develop recurrence in the present pregnancy. The results of this comparison and the logistic regression analyses are shown in Table 2. There was no association of baseline CRP concentration or the change in CRP with the development of preeclampsia. In order to assess whether more extreme elevations in CRP were associated with recurrence, we performed a subanalysis dichotomizing baseline CRP using the 75th (1.7mg/dL) and 90th (2.3mg/dL) percentiles which were derived from the study population. There was no difference between those with recurrent preeclampsia and those without preeclampsia (26% vs. 24% for the 75^{th} percentile, and 8% vs. 10% for the 90^{th} percentile). In addition, there was no difference in CRP among women with preterm preeclampsia (n=16) compared with preterm controls (n=29) (data not shown).

In order to assess whether the variability in gestational age at baseline altered the association of baseline CRP with recurrent preeclampsia, we considered an interaction between CRP and gestational age at sample collection. In the regression model, this interaction was not significant (p=0.85).

Discussion

Interest regarding CRP and preeclampsia has been driven by the cardiovascular literature as well as by interest in whether CRP may contribute to the excess maternal inflammation evident in preeclampsia. This protein, long considered a marker of acute inflammation, has also been hypothesized to contribute mechanistically to the innate immune response and perhaps to disease states.(25, 26) The association of preeclampsia with later-life

cardiovascular disease(4, 5) has led to studies of whether CRP and other markers remain elevated postpartum in women with preeclampsia or eclampsia, and indeed, CRP concentrations measured much later in life are reported elevated in these subjects.(27) Surprisingly, however, such differences have not been observed in studies performed 1–6 years postpartum.(28, 29) Thus, some speculate that the association of measurable markers of cardiovascular risk with preeclampsia increases with age and is not apparent until years after delivery.(30)

We postulated, therefore, that a population of women with previous preeclampsia might show normal CRP concentrations between pregnancies but would constitute a population that was particularly likely to manifest increased CRP in a subsequent complicated pregnancy. Thus we investigated whether women with previous preeclampsia and destined to have recurrent preeclampsia would have elevated or rising CRP concentrations, but our results did not support this hypothesis.

Our results add to a complicated body of evidence regarding CRP alterations in preeclampsia. While CRP has been reported to be elevated in clinically-evident disease,(9–17) results have been inconsistent regarding CRP concentrations preceding the syndrome.(18–22)

In examining possible reasons for these inconsistencies, one notes that many studies have not accounted for BMI in the analyses. Further, in some studies, univariate differences in CRP were attenuated or negated by controlling for BMI.(9, 10, 13) Interestingly, Qui and colleagues performed a subset analysis noting that in lean women, CRP was predictive of subsequent preeclampsia, suggesting that it may have an effect but that the more dramatic influence of obesity superseded a smaller CRP-specific effect in their non-lean population.(20) In our study, the factor in our logistic regression model which came closest to statistical significance in predicting preeclampsia was BMI. However, our ability to comprehensively evaluate the relationship between adiposity, CRP, and preeclampsia was limited by lack of data on patient weight gain during gestation.

This mechanistic potential of CRP is particularly interesting in the context of obesity, as CRP is strongly correlated with BMI and is also influenced directly by endocrine function of adipose tissue. Benyo et al demonstrated that there is no difference in the expression of pro-inflammatory cytokines in the placentas of preeclamptic women compared with controls, suggesting that increases in maternal inflammatory markers in preeclampsia must derive from a non-placental source.(31) CRP is primarily produced by hepatocytes, under the influence of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Both of these pro-inflammatory cytokines are produced by adipose tissue.(32, 33) Interestingly, IL-6 and TNF-α are also elevated in clinically-manifest preeclampsia.(34) The link between obesity and preeclampsia is well-established. In a study aiming to quantify mechanisms by which obesity predisposes to preeclampsia, Bodnar and colleagues found that increased inflammation (as measured by CRP), in combination with hypertriglyceridemia, accounted for approximately one-third of this excess risk.(35)

In addition to the potential confounding effect of BMI differences on CRP concentrations, there are several other factors that may affect our findings. In order to detect slight alterations in CRP, influences on the baseline concentration, independent of the disease process in question, must be taken into account. Investigators have consistently found that there is an elevation in CRP in pregnancy relative to the non-pregnant state. Thus, general pregnancy-related factors directly influence baseline CRP concentrations, and any predictive value of CRP for preeclampsia must therefore represent an elevation above this new baseline. However, trends in CRP concentration relative to gestational age have not been

discernable.(24, 36–38) As mentioned, our data similarly showed no relationship between gestational age and baseline CRP concentration (data not shown). It may be that the CRP elevation associated with pregnancy masks any subtle changes that might represent an inflammatory tendency in some women. Along similar lines, other investigators have found that the consistent association of smoking with elevated CRP is not discernable in pregnancy.(38) The effect of pregnancy itself on CRP may limit its utility as a marker of preeclampsia risk in contrast to the association with cardiovascular disease in the nonpregnant state.

One other factor which may have led to generally higher concentrations of CRP in our population is the racial distribution. CRP has been shown to be slightly higher in African Americans compared to Caucasians,(39, 40) an effect which is more pronounced in pregnancy.(38) As three-quarters of our patient population were African American, this may have contributed to a baseline higher concentration of CRP, thus diminishing our discriminatory capacity for more subtle differences.

Additionally, of crucial importance in the assessment of the utility of CRP as a predictive marker for preeclampsia is the performance of the assay used for its quantification. Early assays for CRP were only able to quantify large increases in concentration, as is seen in acute inflammation (one thousand-fold elevations or more). More recently, as investigators have become interested in the elevation of CRP in the prediction of cardiovascular disease (two- to three-fold elevations), requisite assay sensitivity has increased dramatically. It has been suggested that for the purposes of research, a minimum sensitivity of 0.15mg/L is necessary.(41) As noted, our ELISA-based methodology resulted in an internally consistent assay with sensitivity below this recommended threshold. The serum samples assayed for this study had been stored at −80 degrees Celsius for several years. While freezing may theoretically alter CRP concentration, this effect is minimized by the fact that this was the first thaw of these samples. In addition, any effect of freezing would not be expected to differentially affect samples from subjects with recurrent preeclampsia compared with those without recurrence.

The strength of our investigation is in the large number of women studied and the ability to examine trends across gestation. Smaller studies cannot avoid being dramatically influenced by large inter-individual variation in CRP concentration. One potential limitation for our analysis is the variability of gestational ages at the time of baseline sample collection. However, the lack of relationship between baseline CRP and gestational age, the fact that gestational age at sample collection was controlled for in the multivariable analysis, the lack of a detectable interaction between gestational age and baseline CRP, and the use of a calculated trend parameter all limit the implication of this variability.

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References

1. Roberts JM, Taylor RN, Musci TJ, Rodgers GM, Hubel CA, McLaughlin MK. Preeclampsia: an endothelial cell disorder. Am J Obstet Gynecol. 1989; 161(5):1200–1204. [PubMed: 2589440]
2. Redman CW, Sacks GP, Sargent IL. Preeclampsia: an excessive maternal inflammatory response to pregnancy. Am J Obstet Gynecol. 1999; 180(2 Pt 1):499–506. [PubMed: 9988826]

3. Borzychowski AM, Sargent IL, Redman CWG. Inflammation and pre-eclampsia. Seminars in Fetal and Neonatal Medicine. 2006; 11(5):309–316. [PubMed: 16828580]
4. Funai EF, Friedlander Y, Paltiel O, Tiram E, Xue X, Deutsch L, et al. Long-term mortality after preeclampsia. Epidemiology. 2005; 16(2):206–15. [PubMed: 15703535]
5. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. Br Med J. 2001; 323(7323):1213–7. [PubMed: 11719411]
6. Roberts JM, Gammill HS. Preeclampsia: Recent Insights. Hypertension. 2005; 46(6):1243–1249. [PubMed: 16230510]
7. Tillet WSFT. Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. J Exp Med. 1930; 52:561. [PubMed: 19869788]
8. Pai JK, Pischon T, Ma J, Manson JE, Hankinson SE, Joshipura K, et al. Inflammatory Markers and the Risk of Coronary Heart Disease in Men and Women. N Engl J Med. 2004; 351(25):2599–2610. [PubMed: 15602020]
9. Wolf M, Kettyle E, Sandler L, Ecker JL, Roberts J, Thadhani R. Obesity and preeclampsia: the potential role of inflammation. Obstet Gynecol. 2001; 98(5 Part 1):757–762. [PubMed: 11704165]
10. Belo L, Santos-Silva A, Caslake M, Cooney J, Pereira-Leite L, Quintanilha A, et al. Neutrophil activation and C-reactive protein concentration in preeclampsia. Hypertension in Pregnancy. 2003; 22(2):129–141. [PubMed: 12908997]
11. Donker RB, Molema G, Faas MM, Kallenberg CGM, van Pampus MG, Timmer A, et al. Absence of In Vivo Generalized Pro-Inflammatory Endothelial Activation in Severe, Early-Onset Preeclampsia. J Soc Gynecol Investig. 2005; 12(7):518–528.
12. Ustun Y, Engin-Ustun Y, Kamaci M. Association of fibrinogen and C-reactive protein with severity of preeclampsia. European Journal of Obstetrics Gynecology and Reproductive Biology. 2005; 121(2):154–158.
13. Freeman DJ, McManus F, Brown EA, Cherry L, Norrie J, Ramsay JE, et al. Short- and Long-Term Changes in Plasma Inflammatory Markers Associated With Preeclampsia [Article]. Hypertension. 2004; 44(5):708–714. [PubMed: 15452036]
14. Teran E, Escudero C, Moya W, Flores M, Vallance P, Lopez-Jaramillo P. Elevated C-reactive protein and pro-inflammatory cytokines in Andean women with pre-eclampsia. International Journal of Gynecology & Obstetrics. 2001; 75(3):243–249. [PubMed: 11728484]
15. Paternoster DM, Fantinato S, Stella A, Nanhorngue KN, Milani M, Plebani M, et al. C-Reactive Protein in Hypertensive Disorders in Pregnancy. Clinical and Applied Thrombosis/Hemostasis. 2006; 12(3):330–337. [PubMed: 16959687]
16. Kumru S, Godekmerdan A, Kutlu S, Ozcan Z. Correlation of maternal serum high-sensitive C-reactive protein levels with biochemical and clinical parameters in preeclampsia. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2006; 124(2):164–167. [PubMed: 16054746]
17. Deveci K, Sogut E, Evliyaoglu O, Duras N. Pregnancy-associated plasma protein-A and C-reactive protein levels in pre-eclamptic and normotensive pregnant women at third trimester. J Obstet Gynaecol Res. 2009; 35(1):94–98. [PubMed: 19215554]
18. Tjoa ML, van Vugt JMG, Go ATJJ, Blankenstein MA, Oudejans CBM, van Wijk IJ. Elevated C-reactive protein levels during first trimester of pregnancy are indicative of preeclampsia and intrauterine growth restriction. J Reprod Immunol. 2003; 59(1):29–37. [PubMed: 12892901]
19. Savvidou MD, Lees CC, Parra M, Hingorani AD, Nicolaides KH. Levels of C-reactive protein in pregnant women who subsequently develop pre-eclampsia. BJOG: An International Journal of Obstetrics and Gynaecology. 2002; 109(3):297–301. [PubMed: 11950185]
20. Qiu C, Luthy DA, Zhang C, Walsh SW, Leisenring WM, Williams MA. A prospective study of maternal serum C-reactive protein concentrations and risk of preeclampsia. Am J Hypertens. 2004; 17(2):154–160. [PubMed: 14751658]
21. Garci'a RG, Celedon J, Sierra-Laguado J, Alarcon MA, Luengas C, Silva F, et al. Raised C-Reactive Protein and Impaired Flow-Mediated Vasodilation Precede the Development of Preeclampsia. Am J Hypertens. 2007; 20(1):98–103. [PubMed: 17198919]

22. Djurovic S, Clausen T, Wergeland R, Brosstad F, Berg K, Henriksen T. Absence of enhanced systemic inflammatory response at 18 weeks of gestation in women with subsequent pre-eclampsia. BJOG: An International Journal of Obstetrics and Gynaecology. 2002; 109(7):759–764. [PubMed: 12135211]

23. Caritis S, Sibai B, Hauth J, Lindheimer MD, Klebanoff M, Thom E, et al. Low-Dose Aspirin to Prevent Preeclampsia in Women at High Risk. N Engl J Med. 1998; 338(11):701–705. [PubMed: 9494145]

24. Teran E, Escudero C, Calle A. C-reactive protein during normal pregnancy and preeclampsia. International Journal of Gynecology & Obstetrics. 2005; 89(3):299–300. [PubMed: 15919407]

25. Black S, Kushner I, Samols D. C-reactive protein. Journal of Biological Chemistry. 2004; 279(47): 48487–48490. [PubMed: 15337754]

26. Marnell L, Mold C, Du Clos TW. C-reactive protein: Ligands, receptors and role in inflammation. Clinical Immunology. 2005; 117(2):104–111. [PubMed: 16214080]

27. Hubel CA, Powers RW, Snaedal S, Gammill HS, Ness RB, Roberts JM, et al. C-Reactive Protein Is Elevated 30 Years After Eclamptic Pregnancy. Hypertension. 2008; 51(6):1499–1505. [PubMed: 18413489]

28. Portelinha A, Belo Ls, Tejera E, Rebelo I. Adhesion molecules (VCAM-1 and ICAM-1) and C-reactive protein in women with history of preeclampsia. Acta Obstet Gynecol Scand. 2008; 87(9): 969– 971. [PubMed: 18720045]

29. Smith GN, Walker MC, Liu A, Wen SW, Swansburg M, Ramshaw H, et al. A history of preeclampsia identifies women who have underlying cardiovascular risk factors. Am J Obstet Gynecol. 2009; 200(1):58.e1–58.e8. [PubMed: 18691690]

30. Sattar N, Ramsay J, Crawford L, Cheyne H, Greer IA. Classic and Novel Risk Factor Parameters in Women With a History of Preeclampsia. Hypertension. 2003; 42(1):39–42. [PubMed: 12743016]

31. Benyo DF, Smarason A, Redman CW, Sims C, Conrad KP. Expression of inflammatory cytokines in placentas from women with preeclampsia. J Clin Endocrinol Metab. 2001; 86(6):2505–12. [PubMed: 11397847]

32. Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, et al. Subcutaneous Adipose Tissue Releases Interleukin-6, But Not Tumor Necrosis Factor-{alpha}, in Vivo. J Clin Endocrinol Metab. 1997; 82(12):4196–4200. [PubMed: 9398739]

33. Yudkin JS, Stehouwer CDA, Emeis JJ, Coppack SW. C-reactive protein in wealthy subjects: Associations with obesity, insulin resistance, and endothelial dysfunction - A potential role for cytokines originating from adipose tissue? Arteriosclerosis Thrombosis and Vascular Biology. 1999; 19(4):972–978.

34. Conrad KP, Miles TM, Benyo DF. Circulating levels of immunoreactive cytokines in women with preeclampsia. Am J Reprod Immunol. 1998; 40(2):102–111. [PubMed: 9764352]

35. Bodnar LM, Ness RB, Harger GF, Roberts JM. Inflammation and triglycerides partially mediate the effect of prepregnancy body mass index on the risk of preeclampsia. Am J Epidemiol. 2005; 162(12):1198–1206. [PubMed: 16269584]

36. Belo L, Santos-Silva A, Rocha S, Caslake M, Cooney J, Pereira-Leite L, et al. Fluctuations in C-reactive protein concentration and neutrophil activation during normal human pregnancy. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2005; 123(1):46–51. [PubMed: 16260340]

37. Bertran N, Camps J, Fernandez-Ballart J, Murphy MM, Arija V, Ferre N, et al. Evaluation of a high-sensitivity turbidimetric immunoassay for serum C-reactive protein: application to the study of longitudinal changes throughout normal pregnancy. Clin Chem Lab Med. 2005; 43(3):308–313. [PubMed: 15843237]

38. Picklesimer AH, Jared HL, Moss K, Offenbacher S, Beck JD, Boggess KA. Racial differences in C-reactive protein levels during normal pregnancy. Am J Obstet Gynecol. 2008; 199(5):523.e1–523.e6. [PubMed: 18539258]

39. Khera A, McGuire DK, Murphy SA, Stanek HG, Das SR, Vongpatanasin W, et al. Race and Gender Differences in C-Reactive Protein Levels. J Am Coll Cardiol. 2005; 46(3):464–469. [PubMed: 16053959]

40. Woloshin S, Schwartz LM. Distribution of C-Reactive Protein Values in the United States. N Engl J Med. 2005; 352(15):1611-a-1613. [PubMed: 15829550]

41. Ledue TB, Rifai N. Preanalytic and analytic sources of variations in C-reactive protein measurement: Implications for cardiovascular disease risk assessment. Clin Chem. 2003; 49(8): 1258–1271. [PubMed: 12881440]

Appendix

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Perspectives

In summary, our results suggest that the potential usefulness of CRP as a predictor of recurrence of preeclampsia is limited. This may be related to the larger effects of pregnancy, the significant inter-individual variation in CRP concentrations, the effect of racial differences in CRP, and the effects of adiposity, all of which can dramatically alter CRP concentrations and mask any discernable underlying predisposition toward inflammation. However, the inflammatory pathways that may be contributing to the syndrome (as evidenced by Qiu and others' residual effect in lean women and Bodnar and others' suggestion that inflammation is likely one of the major ways in which obesity predisposes to preeclampsia) remain incompletely elucidated and warrant further investigation.

Table 1

Historical and demographic descriptors of patients with recurrent preeclampsia and controls:

	Preeclampsia	**Controls**	**P-value**
	n=50	**n=205**	
Race			0.28
Caucasian, n (%)	13 (26%)	42 (20%)	
African American, n (%)	37 (74%)	155 (76%)	
Hispanic, n (%)	0 (0%)	8 (4%)	
Smoking, n (%)	9 (18%)	32 (16%)	0.68
Age (years)	25.1 ±5.6	24.6 ±5.4	0.38
BMI (kg/m^2)	30.2 ±9.2	27.7 ±7.7	0.09
Gestational age at baseline sample collection (weeks)	18.6 ±4.5	19.3 ±4.3	0.32

Data are presented as number of subjects (%) or mean ± standard deviation.

Table 2

Baseline CRP concentration and change in CRP are not associated with recurrence of preeclampsia

	Preeclampsia (n=50)	**Controls (n=205)**		
	Median (range)	**Median (range)**	**OR (95% CI) ##**	**Adjusted OR (95% CI) ##**
Baseline CRP (mg/dL)	1.17 (0.09, 5.72)	1.01 (0.01, 4.97)	1.000 (1.000, 1.000)	1.0 (1.000, 1.000) *
CRP closest to delivery (mg/dL)	0.71 (0.06, 2.94)	0.76 (0.01, 4.62)		
Change in CRP (mg/dL)	−0.02 (−0.22, 0.30)	−0.02 (−0.43, 0.05)	0.996 (0.992, 1.001)	0.993 (0.986, 1.000)#

*Controlling for BMI, gestational age at baseline sample collection, race, age, and smoking status.

#Controlling for BMI, gestational age at baseline sample collection, race, age, smoking status, baseline CRP concentration and aspirin treatment.

##Odds ratio represents an increase in odds for each μg/dl increase in CRP.