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Factors associated with maternal serum C-reactive protein throughout pregnancy: A longitudinal study in women of Rio de Janeiro, Brazil

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ABSTRACT

Objectives: The aim of this study was to evaluate the longitudinal changes of C-reactive protein (CRP) concentrations during pregnancy and to assess whether socioeconomic, anthropometric, dietary, behavioral, and biochemical factors are associated with these changes.
Methods: This was a prospective cohort study of 115 adult pregnant women, followed at gestational weeks 5 to 13, 20 to 26, and 30 to 36. Serum concentrations of CRP (mg/L) were measured by the immunoturbidimetric method with ultrasensitive kits (sensitivity 0.05 mg/dL). The statistics included descriptive analysis (mean + SD) and longitudinal linear mixed-effects models, reporting the β coefficient and 95% confidence intervals (CI).
Results: Serum CRP concentrations progressively increased throughout pregnancy (β = 0.121; 95% CI, 0.071–0.171). Parity (β = 1.579; 95% CI, 0.731–2.427) and prepregnancy body mass index (BMI) (β = 0.316; 95% CI, 0.053–0.587) were positively associated and dietary glycemic load was negatively associated (β = −0.203; 95% CI, −0.380 to −0.026) with CRP concentrations in the multiple model. Prepregnancy obese women presented a more pronounced increase of CRP concentrations compared with normal weight women (β = 0.210; 95% CI, 0.059–0.360 versus 0.115, respectively; 95% CI, 0.049–0.181). A statistically significant interaction was observed between parity and gestational age (β = −0.045; 95% CI, −0.084 to −0.005), indicating that the variation of CRP throughout pregnancy differed according to parity categories.
Conclusion: CRP concentrations increased throughout pregnancy. Parity and prepregnancy BMI were positively associated and dietary glycemic load was negatively associated with concentrations of CRP.

Introduction

C-reactive protein (CRP) is an acute-phase biomarker that has been associated with the innate immune response [1]. Although CRP synthesis by pulmonary [2] and renal cells [3] has been demonstrated, most of it is produced by hepatocytes [4]. CRP's rate of synthesis is primarily stimulated by interleukin-6, interleukin-1β, and tumor necrosis factor-α as a reaction of tissues to infection or inflammation. It is suggested that concentrations of this cytokine are low and stable in healthy individuals [5].

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Different factors have been related to increased CRP concentrations, such as low socioeconomic status, advanced age, high parity, excessive body weight, excessive gestational weight gain, intake of low-quality carbohydrates, smoking, and excessive alcohol consumption [6–8]. Additionally, cardiovascular diseases were already associated with increased CRP concentrations [9–11].

One study found that CRP concentrations seemed to be higher during pregnancy. However, contradictory results about CRP concentrations throughout normal pregnancy have been found [12]. Some studies have shown no changes in CRP concentrations [12,13] but other studies have found an increase in early pregnancy and at the period near delivery, with constant values across rest of the pregnancy [14,15].

Considering the lack of consensus in the literature regarding the pattern of CRP concentrations throughout pregnancy, the present study aims to describe the longitudinal changes of maternal serum CRP concentrations and to evaluate the effect of socioeconomic, anthropometric, dietary, behavioral, and biochemical variables on the trends of this cytokine throughout healthy pregnancy.

Methods

This was a prospective cohort study (November 2009 to October 2011) with a sample composed of pregnant women who received prenatal care at a Municipal Health Center in Rio de Janeiro, Brazil, during the three trimesters of pregnancy (gestational weeks 5–13, 20–26, and 30–36).

In all, we recruited 299 pregnant women who were between 5 and 13 wk of gestation, between ages 20 and 40 y, and who did not have any noncommunicable chronic diseases (NCDs) other than obesity. After baseline clinical evaluation, women were excluded if they had a confirmed prepregnancy diagnosis of NCDs (n = 9), infectious or parasitic disease (n = 9), were expecting twins (n = 4), suffered a miscarriage before the first evaluation (n = 3), did not have blood samples collected before gestation week 13 (n = 13), did not have CRP measurements (n = 67), and reported use of anti-inflammatory drugs during pregnancy (n = 15). Additionally, women were excluded if they did not know their pregestational weight (n = 12) and if they showed differences between self-reported and measured weight until the 13th week of pregnancy outside the range of ±2 SDs in the Bland and Altman graph (n = 10). We further excluded women who had a positive result for urinary tract infection in the time period during which CRP was measured (weeks 5–13, n = 42; 20–26, n = 61; 30–36, n = 63). Therefore, the baseline sample consisted of 115 pregnant women who were followed at 20 to 26 (n = 96) and at 30 to 36 (n = 94) gestational weeks.

Blood samples were collected in all three trimesters of pregnancy after a 12-h fast. Serum and plasma were separated after 5 min of centrifugation (5000g) and stored at −196°C, initially in a liquid cryogen container. Subsequently, the samples were stored in an ultra-freezer at −80°C until analysis. Plasma with EDTA as anticoagulant was used for the determination of leptin, insulin, and adiponectin concentrations.

The CRP serum concentrations (mg/L) were measured by the immunoturbidimetric method with ultra-sensitive commercial kits (DiaSys Diagnostic Systems GmbH, Holzheim, Germany) with sensitivity of 0.05 mg/dL. Adiponectin (μg/mL), insulin (μU/mL), and leptin (ng/dL) plasma concentrations were determined using commercial enzyme-linked immunosorbent assay kits (Millipore, St. Charles, MO, USA) with sensitivities of 0.78 μg/mL, 2 μU/mL, and 0.5 ng/dL, respectively. Blood glucose was measured by the glucose oxidase-peroxidase enzymatic colorimetric method with a Wiener Lab kit (Rosario, Argentina).

Socioeconomic, demographic, reproductive, and lifestyle variables such as age (y), education (y), monthly per-capita family income (US$), marital status (married or living in union/single), self-reported skin color (white/brown and black), parity (number of parturition), smoking habit before pregnancy (no or yes) and alcohol consumption (no or yes) were obtained with structured questionnaires administered during the first follow-up visit (5–13 wk gestation).

The self-reported pregestational weight was obtained during the first follow-up visit. Maternal body weight was measured in all follow-up visits using a digital scale (Filizzola PL 150, Filizzola Ltda. Brazil), and height was measured only in the first wave of the follow-up using a portable stadiometer attached to the wall (Seca Ltda., Hamburg, Germany). Prepregnancy body mass index (BMI) was calculated based on self-reported pregestational weight and classified as normal weight (NW: 18.5–24.9 kg/m^2), overweight (OW: 25–29.9 kg/m^2), or obese (OB: ≥30 kg/m^2) according to the World Health Organization criteria [16].

Dietary variables were obtained through a semi-quantitative food frequency questionnaire during the first follow-up visit [17]. Food frequency questionnaire items were transformed into daily portion according to the daily frequency and portion size intake using a method previously described [18]. The Brazilian Food Composition Table [19] was used to determine the composition of foods, and the US Department of Agriculture nutrient database [20] was used for foods that were lacking information in the Brazilian source. These analyses were used to determine the dietary glycemic index (GI) and the glycemic load (GL). The GI was obtained considering values of the International Tables of GI and GL [21]. If a certain value was not available in this table, the GI was retrieved from the website www.glycemicindex.com of the University of Sydney [22]. The dietary GL was calculated multiplying the carbohydrate content of one serving by the GI, thus represents the quality and quantity of carbohydrates [23].

Gestational age was calculated based on data from the first ultrasonography performed (n = 95; 82.6%). The date of the last menstrual period (n = 20) was used if the first ultrasonography was not performed before week 24 of gestation.

Statistical analysis

Means and SD were used to describe the characteristics of the sample. Longitudinal linear mixed-effects (LME) models were used to assess the changes of CRP concentrations throughout pregnancy and to evaluate which variables were associated with the trend of change (reporting coefficients [β] and their 95% confidence interval [CI]).

LME regression coefficients provide a combined estimate of the effect between and within the participants, accommodate time-dependent and time-independent covariates, and allow unbalanced time intervals [24,25]. The models were fitted using the unstructured covariance matrix, and the gestational age (in weeks) was included in all LME models as both random and fixed effects to adjust for the overall and the individual variations in CRP concentrations over time. All other variables were considered as fixed-effects only.

Variables that yielded $P < 0.20$ in the longitudinal bivariate regression models were included in the full model. Subsequently, a backward selection from the full model was employed in which the variables included were removed one by one in decreasing order of significance so that only variables with $P < 0.05$ remained in the multiple model. The interaction between the variables that remained in the multiple model and the time variable (gestational age) was tested to evaluate if the effect of gestational age on CRP varied according to these variables.

Figures presenting the scatter and longitudinal linear prediction (predicted using LME models) of CRP concentrations were constructed to illustrate the variation of CRP during pregnancy for the total sample and were also stratified according to prepregnancy BMI categories (NW, OW, OB), parity (nulliparous × multiparous), and dietary GL (above or below the median).

Statistical analyses were performed using Stata Data Analysis and Statistical Software (STATA) version 12.0 (Stata Corp., College Station, TX, USA). P values <0.05 were considered statistically significant.

The study was approved by the Research Ethics Committees of the Municipal Secretariat of Health and Civil Defense of the State of Rio de Janeiro (IRB no. 0012.0.249.000-09, approved on August 13, 2009). All participants signed a two-way term of consent, which was obtained freely and spontaneously, after all necessary clarifications had been provided.

Results

The sample consisted of women with a mean age of 27 (5.6) y who had 8.9 (3) years of schooling and a pregestational BMI of 24.7 (4.5) kg/m^2. At the study baseline, the mean concentration of CRP was 5.7 (4.7) mg/L, adiponectin was 6 (4.4) μg/mL, insulin was 5.9 (3.7) U/mL, and leptin was 20.5 (14.5) ng/mL (Table 1).

We found an increase in CRP concentrations throughout pregnancy (β = 0.121; 95% CI, 0.071–0.170) for the overall sample (Fig. 1).

In the bivariate models, gestational age, parity, smoking habit (ex-smokers), body weight during pregnancy, and prepregnancy BMI were positively and significantly associated with CRP, whereas dietary GL was negatively associated (Table 2). These variables and the dietary GI ($P = 0.105$) were included in the full model.

In the multiple model, parity (β = 1.579; 95% CI, 0.731–2.427) and prepregnancy BMI (β = 0.316; 95% CI, 0.053–0.587) were positively and dietary GL was negatively (β = −0.203; 95% CI, −0.380 to −0.026) associated with serum concentrations of CRP. A statistically significant interaction was observed between parity and gestational age (β = −0.045; 95% CI, −0.084 to

Table 1
Baseline* characteristics of the pregnant women followed in a prenatal care center in Rio de Janeiro, Brazil

Variables†	Mean (SD)
Age (y)	27.0 (5.6)
Education (y)	8.9 (3.0)
Monthly per-capita family income (USD $)	326.9 (211.1)
Total caloric intake (kcal)	2340.9 (706.7)
Prepregnancy BMI (kg/m^2)	24.7 (4.5)
Height (cm)	159.7 (6.2)
Prepregnancy weight (kg)	64.0 (12.5)
CRP (mg/L)	5.7 (4.7)
Adiponectin (μg/mL)	6.0 (4.4)
Insulin (μU/mL)	5.9 (3.7)
Leptin (ng/dL)	20.5 (14.5)
Glucose (mg/dL)	83.7 (9.1)

BMI, body mass index; CRP, C-reactive protein
* Baseline was between gestational weeks 5 and 13.
† Number of observations = 115.

−0.005), indicating that the variation of CRP throughout pregnancy was different according to parity categories (Table 3).

CRP concentrations increased throughout gestation in all categories of prepregnancy BMI. The increase was more pronounced in prepregnancy OB women (β = 0.210; 95% CI, 0.059–0.361), intermediary for NW (β = 0.115; 95% CI, 0.049–0.181), and borderline in OW women (β = 0.096; 95% CI, −0.002 to 0.194). Parity was positively associated with CRP concentrations during pregnancy. Nulliparous women started pregnancy with lower concentrations of CRP, but had a greater increase in CRP concentrations (nulliparous: β = 0.192; 95% CI, 0.127–0.256 versus multiparous: β = 0.072; 95% CI, 0.002–0.142). There was an increase in CRP concentrations throughout pregnancy independent of the GL values (women with dietary GL values below the median: β = 0.114; 95% CI, 0.054–0.175; above the median: β = 0.120; 95% CI, 0.042–0.198). Women with lower dietary GL had higher CRP concentrations throughout the gestational period (Fig. 2).

Discussion

The present study had two main results. First, it confirmed the significant increase in serum CRP concentrations throughout pregnancy. Second, it demonstrated that prepregnancy BMI and parity were positively and dietary GL was negatively associated with CRP concentrations during pregnancy. We observed a more pronounced increase of CRP concentrations for prepregnancy obese women when compared with NW. The increase for OW women was not statistically significant.

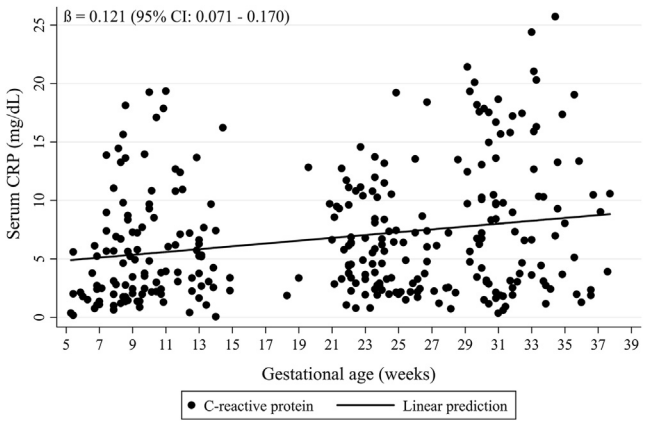

Fig. 1. Changes in serum CRP concentrations in pregnant women followed in a Prenatal Care Center in Rio de Janeiro, Brazil. Fitted values were predicted using a longitudinal linear regression model between CRP and gestational age (n = 305), β = 0.121; 95% CI, 0.071 to 0.170; $P < 0.001$. *P*-value refers to maximum likelihood estimator. N refers to total number of observations, i.e. the sum of observations for each trimester. β, longitudinal linear regression coefficient; CI, confidence interval; CRP, C-reactive protein; BMI, body mass index; GA, gestational age; GL, glycemic load.

Considering the longitudinal design of this study, a possible limitation is the loss of follow-up. Of the 115 women evaluated, 21 (18.3%) did not complete the follow-up. However, no differences were observed in relation to anthropometric and socioeconomic variables when we compared women who were lost to follow-up with those who reached the last follow-up visit, indicating a low probability of selective losses. Another potential limitation was the high number of excluded CRP values due to the occurrence of urinary tract infection (26.7% in the first trimester, 38.8% in the second, and 40.1% in the third). However, such exclusions were necessary because it is known that this condition alone can cause a change in the dynamics of CRP. A further limitation of the study was not having the information on the occurrence of periodontal diseases, gynecologic infections, or other infections in pregnant women.

The main strength of this study was the use of data analysis with repeated measures using the LME. This procedure improved the accuracy of estimates and required fewer experimental units, which reduced our limitation of the number of individuals in our sample. Furthermore, another strength was its originality; we did not find studies that explored longitudinal data analysis of factors associated with the evolution of CRP concentrations during pregnancy. Thus, comparisons between our data and the available literature are limited.

During pregnancy, the maternal immune system experiences changes aiming to prevent rejection of the fetus, including modifications of T-helper (Th) cells toward a relative increase in Th2 activity compared with type Th1 activity [26,27]. One study [28] showed that on a single-cell level, both CD4+ and CD8+ T cells produce less Th1 cytokines and more Th2 cytokines during normal human pregnancy than during nonpregnancy, due to the progressive increase of progesterone and estrogens during this period [29]. This may occur because Th1 cytokines can exert adverse effects on the fetus and placenta [30], and Th2 cells secrete anti-inflammatory cytokines. This suppression of specific maternal immunity to facilitate the maintenance of pregnancy is compensated by an increase in innate immunity, in which the monocyte rather than the lymphocyte assumes a central role in maternal immunologic adaptation [31]. The maternal innate system has a central role in maternal adaptation to pregnancy and helps protect the mother against infection [32]. This could explain the observed increase in CRP concentrations that has been associated with innate immune response [1,33].

Studies have consistently reported high levels of proinflammatory cytokines and immune factors, such as CRP, during pregnancy, although the pattern of changes documented by several authors is variable [12,14,15,34–37]. However, little is known about the patients' characteristics that may play a role in exacerbating the variation in CRP concentrations in pregnancy.

One study demonstrated that plasmatic CRP concentration was correlated with the activated macrophage and monocyte marker in pregnant women with transient hypertension and preeclampsia [38]. It has been shown that the CRP concentrations were related with alterations in inflammatory profile and associated with the risk for spontaneous preterm birth or spontaneous preterm labor [14]. Another study found higher risk for having detectable high-sensitivity CRP concentrations at the age of 12 y in boys born to women with prepregnancy BMI >66th

Table 2
Bivariate longitudinal regression model for c-reactive protein levels throughout pregnancy in pregnant women followed in a prenatal care center in Rio de Janeiro, Brazil

Variables	β*	95% CI	*P* value†
Gestational age (wk)	0.121	0.071–0.170	<0.001
Age (y)	0.046	−0.066 to 0.158	0.419
Education (y)	−0.054	−0.281 to 0.174	0.644
Monthly per-capita family income (USD $)	0.001	<−0.01 to <0.01	0.720
Marital status (married or living in union/single)‡	−0.347	−1.944 to 1.249	0.670
Self-reported skin color (white/other)‡	−0.224	−1.732 to 1.285	0.771
Parity (number of parturitions)	0.775	0.185–1.365	0.010
Previous smoking			
Ex-smoker/never smoked	2.408	0.786–4.030	0.004
Current smoker/never smoked	0.875	−1.852 to 3.603	0.529
Alcohol consumption (no/yes)‡	0.582	−0.758 to 1.921	0.395
Total caloric intake (kcal)	0.001	−0.001 to 0.001	0.517
Dietary glycemic index	0.124	−0.026 to 0.275	0.105
Dietary glycemic load	−0.197	−0.380 to −0.015	0.034
Maternal weight throughout pregnancy (kg)	0.095	0.042–0.148	<0.001
Prepregnancy BMI (kg/m^2)	0.322	0.174–0.470	<0.001
Insulin (μU/mL)	0.042	−0.026 to 0.110	0.224
Adiponectin (μg/mL)	−0.062	−0.191 to 0.067	0.349
Leptin (ng/dL)	0.012	−0.019 to 0.043	0.439
Fasting glucose (mg/dL)	−0.016	−0.072 to 0.039	0.568

BMI, body mass index; CRP, C-reactive protein
* β is the longitudinal linear regression coefficient for CRP.
† *P* values refer to maximum likelihood estimator.
‡ Categorical variables for which the first category is the reference and the second is the exposure.

percentile of a US representative sample compared with boys born to mothers who were classified below the 33rd percentile of the distribution [39].

To the best of our knowledge, there is only one previous study that has described the changes in CRP concentrations throughout pregnancy using a longitudinal regression model [14]. In that investigation, the researchers described an increase in CRP concentrations from early pregnancy up to ~20 wk, followed by a gradual decline until delivery. Methodologic differences may be the cause of the disagreement between these results and ours. For example, the researchers performed a study with four waves of follow-up, which possibly improved the sensitivity to capture the slight decrease that occurred at the end of pregnancy (gestational week 35).

Prepregnancy BMI was positively associated with CRP concentration during pregnancy. In the stratified analyses, it was possible to observe that the increase in CRP was more pronounced among women with prepregnancy obesity. The mean values of CRP over the first, second, and third trimesters of pregnancy among women with prepregnancy BMI <30 kg/m^2 versus ≥30 kg/m^2 have been described [40]. The authors observed a significant increase in CRP concentrations only in obese women at all time points, which corroborate our findings. Macrophages and adipocytes have common embryonic origins and are able, in special situations, to produce the same components, including inflammatory markers. Under normal conditions, adipocytes store lipids and regulate metabolic homeostasis, whereas macrophages are related to the inflammatory response. In obesity, there is an overlap of these metabolic and inflammatory pathways [41]. However, little is known in the context of pregnancy about the effects of being overweight or obese on the dynamics of the concentrations of inflammatory markers.

We did not find any studies reporting associations between CRP concentrations and parity in pregnant women. According to one study with healthy multiparous women, there is a systemic

Table 3
Multiple longitudinal regression model for c-reactive protein levels throughout pregnancy in pregnant women followed in a prenatal care center in Rio de Janeiro, Brazil

Fixed effects*	β†	95% CI	*P* value‡
Intercept	−3.008	−7.142 to 1.127	0.154
Gestational age (wk)	0.150	0.077–0.224	<0.001
Parity (number of parturition)	1.579	0.731–2.427	<0.001
Parity# gestational age§	−0.045	−0.084 to −0.005	0.027
Maternal weight throughout pregnancy (kg)	−0.004	−0.102 to 0.093	0.933
Dietary glycemic load	−0.203	−0.380 to −0.026	0.025
Prepregnancy BMI (kg/m^2)	0.316	0.053–0.587	0.018
Maximum likelihood estimator	−803.959		
Akaike information criterion	1629.917		
Random effects	**β (95% CI)**		
Intercept	4.836 (0.306–76.294)		
Gestational age	0.018 (0.004–0.088)		
Residual	9.201 (5.919–14.303)		

BMI, body mass index; CRP, C-reactive protein
* Number of observations = 305; Number of women = 115; Average of 2 observations of women.
† β = longitudinal linear regression coefficient for CRP.
‡ *P* values refer to maximum likelihood estimator.
§ Refers to interaction between parity and gestational age.

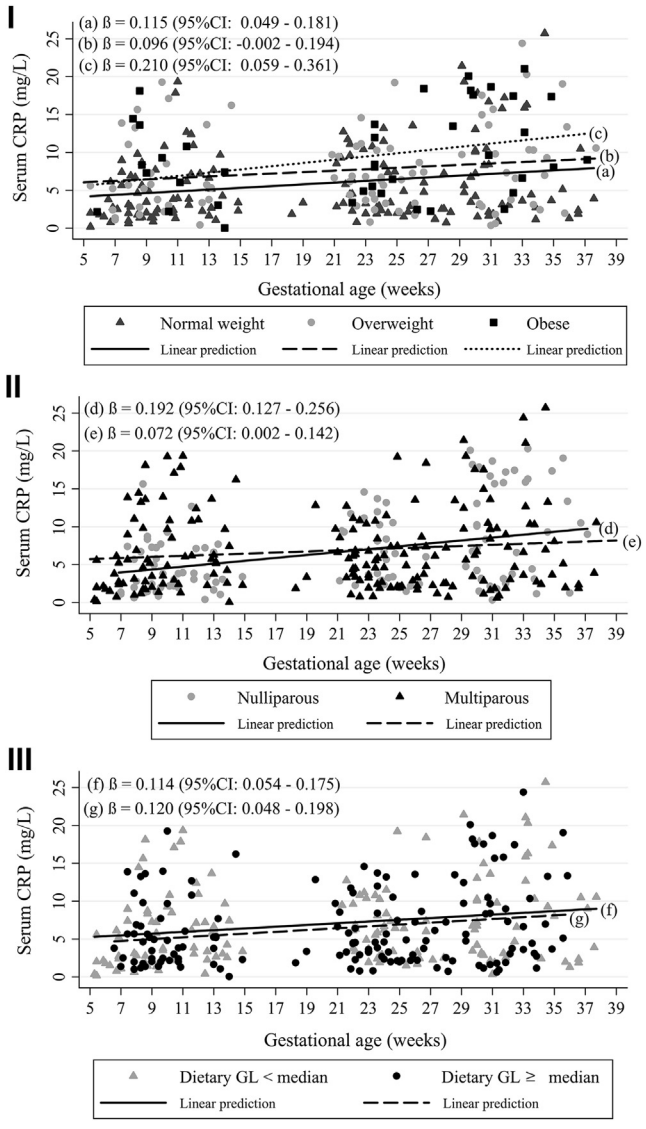

Fig. 2. Changes in serum CRP concentrations in pregnant women followed in a prenatal care center in Rio de Janeiro, Brazil, stratified for selected variables: (I) prepregnancy body mass index; (II) parity; (III) dietary glycemic load. Fitted values were predicted using a longitudinal linear regression model between CRP and gestational age for each category; β represents the gestational age coefficient of variation for women: (a) prepregnancy normal weight (n = 152; $P < 0.001$); (b) prepregnancy overweight (n = 87; $P = 0.059$); (c) prepregnancy obesity (n = 40; $P = 0.008$); (d) nulliparous (n = 115; $P < 0.001$); (e) multiparous (n = 180; $P = 0.045$); (f) with dietary glycemic load below median (n = 225; $P < 0.001$); (g) with dietary glycemic load at median or higher (n = 75; $P = 0.003$). *P* refers to maximum likelihood estimator; n refers to total number of observations (i.e., the sum of observations for each trimester). CRP, C-reactive protein; GL, glycemic load; β, longitudinal linear regression coefficients; CI, confidence interval.

inflammatory profile characterized by high concentrations of circulating proinflammatory cytokines [6]. The result of that study is in line with our findings showing that multiparous women enter pregnancy with higher CRP concentrations. However, despite the lower concentrations of CRP in nulliparous women during early pregnancy, these women had a more pronounced increase in this cytokine throughout pregnancy. This result is consistent with the negative association found when analyzing the interaction between parity and gestational age. A hypothesis that might explain this phenomenon is that those women who are experiencing their first pregnancy may have a greater increase in the concentrations of CRP as an immune response for the development of a fetus for the first time.

Dietary GL was negatively associated with serum concentrations of CRP. It is known that high CRP concentrations might indicate an inadequate diet [42] with a high amount of carbohydrates [43]. Based on these findings, we would expect a positive association between dietary GL and CRP concentrations. We could not find any previous studies evaluating this potential association during pregnancy. However, one study [44] already reported an inverse weak association between dietary GL and CRP concentrations ($\beta = -0.002$; $P = 0.04$) among obese individuals. Although we adjusted the analysis for potential confounders of the association of GL with CRP, it is still possible that other unknown factors may have biased our results.

Conclusion

We found a significant increase in CRP concentrations throughout pregnancy. Parity and prepregnancy BMI were positively associated, whereas dietary GL was negatively associated with concentrations of CRP. These results indicate that maternal factors can alter the dynamics of CRP in pregnancy.

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