OBSTETRICS

C-reactive protein levels in early pregnancy, fetal growth patterns, and the risk for neonatal complications: the Generation R Study

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OBJECTIVE: We sought to examine the associations of maternal C-reactive protein (CRP) levels with fetal growth and the risks of neonatal complications.

STUDY DESIGN: CRP levels were measured in early pregnancy in 6016 women. Main outcome measures were fetal growth in each trimester and neonatal complications.

RESULTS: As compared to the reference group (CRP levels <5 mg/L), elevated maternal CRP levels (≥25 mg/L) were associated with lower estimated fetal weight in third trimester and lower weight at birth (differences: −29 g, 95% confidence interval [CI], −58 to 0 and −128 g, 95% CI, −195 to −60, respectively). Elevated maternal CRP levels were also associated with an increased risk of a small size for gestational age in the offspring (adjusted odds ratio, 2.94; 95% CI, 1.61–5.36).

CONCLUSION: Maternal CRP levels in early pregnancy are associated with fetal growth restriction and increased risks of neonatal complications.

Key words: cohort studies, C-reactive protein, fetal growth, inflammation, neonatal complications, pregnancy

Cite this article as: Ernst GDS, de Jonge LL, Hofman A, et al. C-reactive protein levels in early pregnancy, fetal growth patterns, and the risk for neonatal complications: the Generation R Study. Am J Obstet Gynecol 2011;205:132.e1-8.

C-reactive protein (CRP) is an acute-phase reactant and a frequently used marker of low-grade systemic inflammation. Its levels increase in response to both infectious and noninfectious exposures.[1] Elevated CRP levels are associated with increased risks of common diseases such as cardiovascular disease and type 2 diabetes.[2,3] However, it is still not clear whether these associations reflect causal pathways.[4,5] Elevated CRP levels during pregnancy, as a marker of low-grade inflammation, have also been suggested to be associated with increased risks of fetal growth restriction and neonatal complications, such as preterm birth, low birthweight, and small size for gestational age (SGA).[6-8] Low-grade inflammation is associated with endothelial dysfunction, leading to vascular dysfunction and suboptimal placental development. Maternal systemic inflammation might also be a response to ischemia of the placenta, due to suboptimal placentation.[9,10] Subsequently, suboptimal placental development might predispose mothers to increased risks for various pregnancy complications.[11,12] Although the association of elevated CRP levels with preterm birth has been shown in several studies, results from studies relating CRP levels with fetal growth measures or neonatal complications are not consistent.[7,8,13,14] Differences in results might be due to differences in study designs and populations. It is not known whether and in which trimester CRP levels affect fetal growth measures.

In a population-based prospective cohort study among 6016 pregnant

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Presented as a poster at the 34th Annual Conference of Werkgroep Epidemiologisch Onderzoek Nederland, Nijmegen, The Netherlands, June 10-11, 2010, and as a poster at the Fifth Conference of Epidemiological Longitudinal Studies in Europe, Paphos, Cyprus, Oct. 13-15, 2010.

Received Nov. 22, 2010; revised Feb. 23, 2011; accepted March 29, 2011.

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The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and the Faculty of Social Sciences at the Erasmus University, Rotterdam; the Municipal Health Service, Rotterdam area; and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond (Star-MDC), Rotterdam.

The general design of the Generation R Study was made possible by financial support from the Erasmus Medical Center, Rotterdam; Erasmus University, Rotterdam; the Dutch Ministry of Health, Welfare and Sport; and The Netherlands Organization for Health Research and Development (ZonMw). Further support for the present study was obtained from the Dutch Heart Foundation (2008B114) and Abbott Diagnostics B.V., Hoofddorp, The Netherlands. Dr Jaddoe received additional grants from The Netherlands Organization for Health Research and Development (ZonMw 90700303, 916.10159).

0002-9378/$36.00 • • doi: 10.1016/j.ajog.2011.03.049

women, we examined the associations of maternal CRP levels, as marker of low-grade inflammation in early pregnancy, with fetal growth characteristics in different trimesters of pregnancy and the risks of neonatal complications.

MATERIALS AND METHODS

Design and population

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onward in the city of Rotterdam, The Netherlands.[15] Enrollment was aimed in early pregnancy but was allowed until birth of the child. All mothers were enrolled from 2001 through 2005. Response rate was 61%.[15] The study was approved by the Medical Ethical Committee of the Erasmus MC, Rotterdam. Written informed consent was obtained from all participants.

Of the total of 8880 mothers who were enrolled during pregnancy, 76% (n = 6748) were enrolled before a gestational age of 18 weeks.[15] Of these mothers, blood plasma samples were collected in 95% (n = 6398) and CRP was successfully measured in 90% (n = 6091). Mothers with extremely high CRP levels (>100 mg/L) (n = 6), and mothers with twin pregnancies (n = 69) were excluded, leaving 6016 mothers with singleton live births for analysis (Supplementary Figure S1).

High-sensitivity CRP levels

Maternal venous blood samples were collected in early pregnancy (median, 13.2; 95% range, 9.6–17.6 weeks) and transported to the regional laboratory (Star-MDC, Rotterdam, The Netherlands) for processing and storage.[16] Blood samples were stored at −80°C. CRP concentrations were measured in EDTA plasma samples at the Department of Clinical Chemistry of the Erasmus MC in 2009. We measured high-sensitivity CRP since traditional clinically used CRP methods lack the sensitivity in low ranges needed for predicting future risk of events in apparently healthy individuals.[17] CRP levels were analyzed using an immunoturbidimetric assay on the Architect System (Abbot Diagnostics B.V., Hoofddorp, The Netherlands). The within run precision for CRP was 1.3% at 12.9 mg/L and 1.2% at 39.9 mg/L. The lowest level of detection was 0.2 mg/L. We created 6 categories of CRP levels (<5.0, 5.0-9.9, 10.0-14.9, 15.0-19.9, 20.0-24.9, and ≥25 mg/L). Levels <5.0 mg/L and ≥25 mg/L were considered as low (reference) and elevated levels, respectively.

Fetal growth characteristics

Fetal ultrasound examinations were performed in 1 of the 2 dedicated research centers in each trimester of pregnancy. Median gestational age for first, second, and third trimester visits were 12.4 weeks (95% range, 10.7–14.5), 20.5 weeks (95% range, 18.7–23.1), and 30.4 weeks (95% range, 28.6–32.8), respectively. In the second and third trimester of pregnancy, we measured fetal head circumference, abdominal circumference, and femur length to the nearest millimeter using standardized ultrasound procedures.[18] Estimated fetal weight was calculated using the formula by Hadlock et al.[19] Longitudinal growth curves and gestational age-adjusted SD scores (SDS) were constructed for all fetal growth measurements.[20]

Information about offspring sex, gestational age, weight, length, and head circumference at birth was obtained from medical records and registries. Since head circumference and length at birth were not routinely measured at birth, missing birth measures were completed with data from the first-month visit at the routine child health center. Preterm birth was defined as a gestational age of <37 weeks at delivery, low birthweight was defined as birthweight <2500 g, and SGA at birth was defined as a sex-specific gestational age-adjusted birthweight below the fifth percentile in the study cohort (SDS ≤1.81 for boys and ≤1.78 for girls).

Covariates

Information about maternal educational level, ethnicity and parity was obtained by a questionnaire at enrollment in the study. Maternal smoking and alcohol consumption habits were assessed by questionnaires in each trimester. Maternal anthropometrics, including height and weight, were measured without shoes and heavy clothing and body mass index (BMI) was calculated (weight/height^2 [kg/m^2]) at enrollment.[21] Maternal systolic and diastolic blood pressure were measured at intake, using standardized methods. For each participant, the mean value of 2 blood pressure readings over a 60-second interval was documented.[22] Folate levels were analyzed from venous samples drawn in the first trimester of pregnancy. Maternal age was registered at enrollment.

Statistical analysis

We assessed the associations of maternal characteristics with CRP levels as outcome levels using multivariate linear regression models. Since CRP levels were not normally distributed, we applied a logarithmic transformation for these analyses. Results are presented as geometric means (95% range) per determinant category and an overall *P* for trend based on these regression models. Associations of CRP levels with fetal growth characteristics were assessed using linear regression models. These models were adjusted for gestational age at the measurement, fetal sex, and maternal age, BMI, education, ethnicity, parity, smoking, alcohol consumption. BMI is known to be highly correlated with levels of CRP,[23] and with birthweight,[21,24] and therefore expected to be our main confounder. Further variables were included in these models based on their association with both the CRP levels and pregnancy outcomes, or a 10% change in the effect estimate. Next, we assessed the associations of CRP level with the risks of neonatal complications (preterm birth, low birthweight, and SGA). These models were adjusted for maternal age, BMI, education, ethnicity, parity, smoking, alcohol consumption and folic acid level at intake. Tests for trends were performed using CRP as continuous variable in multivariate linear and logistic regression analyses. The percentages of missing values within the population for analysis were <1% for continuous data and <13% for the categorical data. We applied multiple imputation for covariates.[25] Since there were no major differences in the observed results between analyses with imputed missing data or