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Prenatal *Chlamydia trachomatis* infection increases the risk of preeclampsia

Catherine L. Haggerty [a,b,*], Mark A. Klebanoff [c], Inge Panum [d], Soren A. Uldum [d], Debra C. Bass [a], Jorn Olsen [e], James M. Roberts [a,b,f], Roberta B. Ness [g]

[a] Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, United States
[b] Magee-Womens Research Institute, Pittsburgh, PA, United States
[c] The Research Institute at Nationwide Children's Hospital, The Ohio State University College of Medicine, Columbus, Ohio
[d] Statens Serum Institut, Copenhagen, Denmark
[e] University of Aarhus, Denmark School of Public Health, Danish Epidemiology Science Centre, Aarhus, Denmark
[f] Department of Obstetrics, Gynecology & Reproductive Sciences, University of Pittsburgh, Pittsburgh, PA, United States
[g] University of Texas School of Public Health, Houston, TX, United States

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ABSTRACT

The relationship between *Chlamydia trachomatis* (CT) and preeclampsia was examined longitudinally among 205 cases and 423 normotensive controls nested within the Collaborative Perinatal Project. Antibodies were analyzed at the first prenatal visit (mean 14.2 weeks) and at delivery. Prenatal infections were identified as IgG/IgM seroconversion or a fourfold rise in IgG antibody titers. Although serological evidence of incident prenatal CT infection was uncommon ($n = 9$, 1.4%) in this general pregnant population, infected women were more likely to develop preeclampsia, after adjustment for maternal age, body mass index, smoking status, race and time between blood draws (OR_{adj} 7.2, 95% CI 1.3–39.7).

Introduction

Preeclampsia is a leading cause of maternal morbidity and perinatal morbidity and mortality worldwide. Although the etiology is not completely understood, a central pathophysiologic feature is endothelial dysfunction, hypothesized to be activated by the generalized inflammatory response to pregnancy, exaggerated in cases of preeclampsia [1]. Cross-sectional third trimester studies have shown that normal pregnancy is associated with leukocyte activation, increased neutrophil production of reactive oxygen species, and increased cytokine production [2,3] and these differences are even more striking among preeclamptic women [2,3]. There are several hypothesized causes of the exaggerated inflammatory response to pregnancy among preeclamptic women, including increased trophoblast debris released by a dysfunctional placenta [4], placental ischemia [5], or bacterial and viral infections, known to elicit an overall upregulation of immune mediators and oxidative stress [1,2,6–17]. As the causes of inflammation seen in preeclampsia are not clear, we performed a nested case-control study examining the relationships between primary infection with *Chlamydia trachomatis*, *Chlamydia pneumoniae*, cytomegalovirus (CMV), herpes simplex virus (HSV), and preeclampsia, within the Collaborative Perinatal Project (CPP) of 55,908 pregnancies.

* Corresponding author. Address: Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, 516B Parran Hall, Pittsburgh, PA 15261, United States. Tel.: +1 412 624 7377; fax: +1 412 624 7397.
E-mail address: haggerty@pitt.edu (C.L. Haggerty).

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Methods

Study population

The CPP is a completed longitudinal study of 55,908 pregnancies among women enrolled when attending prenatal care at 12 university-affiliated medical centers (Baltimore, MD; Boston, MA; Buffalo, NY; Memphis, TN; Minneapolis, MN; New Orleans, LA; New York, NY; Philadelphia, PA; Portland, OR; Providence, RI; and Richmond, VA) between 1959 and 1965. We analyzed antibodies to *C. trachomatis*, *C. pneumoniae*, HSV 1/2, and CMV among a subset of 205 single gestation primiparous preeclamptic and 423 normotensive pregnancies with a first serum sample collected between 5 and 19 weeks of gestation (mean 14.2 ± 3.3) and a recorded delivery between 25 and 44 weeks of gestation. The study was approved by the University of Pittsburgh Institutional Review Board.

Preeclampsia definition

Preeclampsia was based on chart abstraction of blood pressure and protein levels and defined as gestational hypertension (two or more measurements of systolic blood pressure $\geqslant$140 mmHg and/or diastolic blood pressure $\geqslant$90 mmHg for the first time after 24 weeks of gestation) and proteinuria (two random urine dipsticks of 1+ protein or one dipstick of 2+ protein), with postpartum return to normal. In the intrapartum period, the first five pressures obtained after hospital admission for delivery were averaged.

Measurement of antibodies

Antibodies to *C. trachomatis*, *C. pneumoniae*, HSV 1/2, and CMV were measured in sera obtained at a first prenatal visit and postpartum. Briefly, IgG and IgM antibodies to *C. pneumoniae* and to *C. trachomatis* were measured using the *Chlamydia* micro-immunofluorescent antibody (MIF) assay (Focus Technologies) which utilized purified elementary bodies (EB) as antigens (substrate) [6]. In-house assays were used to measure total [18] and IgM [19] antibodies to CMV. HSV-1 and HSV-2 antibodies were measured using the Focus Technologies HerpeSelect™ 1 ELISA IgG assay [6]. Measurement of IgG and IgM antibodies from archived samples has shown to be highly stable, even after long term storage [20].

Statistical analysis

Maternal characteristics were compared between cases and controls. Prenatal infections were identified as IgG/IgM seroconversion or a fourfold rise in IgG antibody titers. Multiple regressions were used to determine the relative risks and 95% confidence intervals, adjusting for maternal age, BMI, smoking status, race and time between blood draws.

Results and discussion

Women with preeclampsia were more likely to be overweight or obese pre-pregnancy, were less likely to report current cigarette smoking at enrollment, and were more likely to deliver a small for gestational age infant or deliver preterm (Table 1). *C. trachomatis* infection was associated with an increased risk of preeclampsia, both before (Table 2), (RR 2.7, 95% CI 0.7–10.3) and after adjustment for confounders (RR_{adj} 7.2, 95% CI 1.3–39.7). *C. pneumoniae*, HSV, and CMV were not associated with preeclampsia. Our findings parallel those we previously reported from the contemporary Danish National Birth Cohort (DNBC) study (1996–2003) in which *C. trachomatis* infection was associated with preeclampsia (OR_{adj} 1.6, 95% CI 0.7, 3.6), severe preeclampsia (OR_{adj} 1.8, 95% CI 0.6, 5.3), and preeclampsia resulting in preterm birth (OR_{adj} 1.7, 95% CI 0.6–4.9) or birth of a small for gestational age infant (OR_{adj} 2.1, 95% CI 0.6, 7.5), whereas *C. pneumoniae*, HSV, and CMV were not [6]. These two prospective pregnancy cohort studies are similar in design but do differ in a number of ways. First, CPP is an older cohort with different underlying

Table 1
Demographic, clinical, and behavioral characteristics, and pregnancy outcomes of primiparous preeclamptic cases and normotensive controls.

	Preeclampsia (N = 205)	Normotensive controls (N = 423)	OR (95% CI) or p-value
Gestational age at first sample (weeks)	15.1 ± 2.9	13.9 ± 3.5	$p < 0.0001$
Race			
Non-Black	121 59.0	270 64.0	1.0
Black	84 41.0	152 36.0	1.2 (0.9–1.7)
Maternal age			
11–20	130 63.4%	223 52.7%	1.0
21–25	62 30.2%	148 35.0%	0.7 (0.5–1.0)
26+	13 6.3%	52 12.3%	0.4 (0.2–0.8)
BMI			
<25	157 83.5%	356 92.2%	1.0
$\geqslant$25	31 16.5%	30 7.8%	2.3 (1.4–4.0)
Smoking			
Non-smoker	140 68.3%	242 57.2%	1.0
Smoker	65 31.7%	181 42.8%	0.6 (0.4–0.9)
Small for gestational age	30 15.0%	36 8.7%	1.9 (1.1–3.1)
Preterm birth <37 weeks	33 16.1%	53 12.5%	1.3 (0.8–2.1)