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Prenatal *Chlamydia trachomatis* infection increases the risk of preeclampsia

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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 a first prenatal visit (mean 14.2 weeks) and at delivery. Prenatal infections were identified as IgG/IgM seroconversion or a four-fold 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).

Keywords

Chlamydia trachomatis; *Chlamydia pneumoniae*; cytomegalovirus; herpes simplex virus; preeclampsia

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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.

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 (2 or more measurements of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg for the first time after 24 weeks of gestation) and proteinuria (2 random urine dipsticks of 1+ protein or one dipstick of 2+ protein), with postpartum return to normal. In the intrapartum period, the first 5 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 total¹⁸ and IgM¹⁹ 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 four-fold 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 characteristics, such as a higher smoking rate. Second, the DNBC is a Danish, largely homogenous population whereas the CPP is ethnically diverse. Despite differences, findings were remarkably similar, supporting the robustness of the association. Our findings are consistent with several cross-sectional studies linking several bacterial and viral infections to preeclampsia.^{9;21;22} A handful of additional studies have demonstrated that women who were seronegative for HSV-2,^{8;23} CMV,^{8;23} and Epstein Barr virus in early pregnancy,⁸ and thus hypothesized to be at risk prenatal infection, were more likely to develop preeclampsia. However, these studies are limited by the fact that reinfection, reactivation, or infection with a different strain is possible among seropositive women. In our study, we had the ability to directly measure prenatal infection by considering seroconversion or four-fold increase in IgG between two time-points in pregnancy.

The null relationships between *C. pneumoniae*, HSV-2, CMV, and preeclampsia found in our study are consistent with other longitudinal,²⁴ case-control,¹⁴ and metaanalysis²⁵ studies, although literature is conflicting.^{8;9;13;16;23} The reason for these discrepancies is not entirely clear, but it is possible that bacterial and viral infections are not universally associated with preeclampsia. As *C. trachomatis* but not *C. pneumoniae* was associated with preeclampsia in our study, it is possible that the effects of infection are local rather than systemic. Indeed, as *C. trachomatis* infection is mucosal in nature, systemic effects are likely minimal.

Our study has a number of strengths including the large sample size, prospectively collected data, and assessment of antibodies early in pregnancy through postpartum. Our study suggests that *C. trachomatis* infection may trigger preeclampsia, although prenatal infection was infrequent among this general pregnant population. Studies in populations at greater risk for sexually transmitted infections are needed to further explore these relationships.

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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	15.1 ± 2.9	13.9 ± 3.5	p < 0.0001
Race			
Non-Black	121	270	64.0
Black	84	152	36.0
			1.2 (0.9 – 1.7)
Maternal Age			
11–20	130	223	52.7%
21–25	62	148	35.0%
26+	13	52	12.3%
			0.4 (0.2 – 0.8)
BMI			
< 25	157	356	92.2%
>=25	31	30	7.8%
			2.3 (1.4 – 4.0)
Smoking			
Non-smoker	140	242	57.2%
Smoker	65	181	42.8%
			0.6 (0.4 – 0.9)
Small for gestational age	30	36	8.7%
			1.9 (1.1 – 3.1)
Preterm Birth <37 weeks	33	53	12.5%
			1.3 (0.8 – 2.1)

Table 2

Serological associations between *Chlamydia trachomatis*, *Chlamydia pneumoniae*, HSV, and CMV prenatal infections and preeclampsia

	Preeclampsia (N=205) n %	Normotensive Controls (N=423) n %	RR (95% CI)	ADJ. RR (95% CI)
<i>C. trachomatis</i>	5 (2.6)	4 (1.0)	2.7 (0.7 – 10.3)	7.2 (1.3 – 39.7)
<i>C. pneumoniae</i>	1 (0.5)	11 (2.7)	0.2 (0.02 – 1.5)	0.3 (0.03 – 2.2)
HSV	2 (1.1)	4 (1.0)	1.1 (0.2 – 6.0)	1.5 (0.3 – 8.3)
CMV	4 (2.2)	13 (3.3)	0.7 (0.2 – 2.0)	0.7 (0.2 – 2.4)

Identified as IgG/IgM seroconversion or a four-fold rise in IgG antibody titers

Adjusted for maternal age, BMI, smoking status, race, and time between blood sampling