OBSTETRICS

Prenatal inflammation is associated with adverse neonatal outcomes

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OBJECTIVE: The purpose of this study was to determine whether prenatal inflammation (as assessed by clinical chorioamnionitis, maternal temperature >38°C, or histologic chorioamnionitis) is associated with a composite adverse neonatal outcome.

STUDY DESIGN: We performed a prospective cohort study of women at 22 weeks to 33 weeks 6 days' gestation with symptoms of labor (April 2009 to March 2012). Relevant maternal and neonatal exposures and outcomes were recorded. Multivariable logistic regression was performed to determine the association between prenatal inflammation and neonatal outcomes that were controlled for potential confounders.

RESULTS: We analyzed 871 mother-infant pairs. The preterm birth rate was 42.0%. When we controlled for infant sex and modified the data by gestational age at delivery, prenatal inflammation remains a significant risk factor for adverse neonatal outcomes, despite advancing gestational age: clinical chorioamnionitis at 32 weeks' gestation (odds ratio [OR], 3.12; 95% confidence interval [CI], 1.02—9.52], at 36 weeks' gestation (OR, 8.88; 95% CI, 4.32—18.25), and at 40 weeks' gestation (OR, 25.30; 95% CI, 9.25—69.19); maternal temperature >38°C at 32 weeks' gestation (OR, 3.18; 95% CI, 0.66—15.42), at 36 weeks gestation (OR, 8.40; 95% CI, 3.60—19.61), and at 40 weeks gestation (OR, 22.19; 95% CI, 8.15—60.44); histologic chorioamnionitis at 32 weeks gestation (OR, 1.25; 95% CI, 0.64—2.46), at 36 weeks gestation (OR, 2.56; 95% CI, 1.54—4.23), and at 40 weeks gestation (OR, 5.23; 95% CI, 1.95—13.99).

CONCLUSION: The protective association with advancing gestational age is diminished when prenatal inflammation is present.

Key words: adverse neonatal outcome, chorioamnionitis, placenta, prenatal inflammation, preterm birth

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Over the last 20 years, evidence has emerged to suggest that prenatal inflammation and/or intrauterine infection leads to the activation of localized inflammatory pathways, plays a critical role in at least 25-40% of spontaneous preterm births,[1-6] and is a significant contributor to the development of adverse neonatal outcomes.[7-9] Prenatal inflammation that predisposes to spontaneous preterm birth and adverse neonatal outcomes may occur in the form of either histologic (HCA)[10-13] and/or acute clinical[14-22] chorioamnionitis (CCA).

The association between acute CCA or perinatal infection[23] and adverse neonatal outcomes (which includes sepsis,[24-27] respiratory compromise,[20,25,27-31] necrotizing enterocolitis,[20,31-33] intraventricular hemorrhage,[20,25,27,34,35] and long-term outcomes such as cerebral palsy[21,36-45] and neonatal death[18,25]) has been well-established. However, most of these studies have been small and retrospective and have focused on the prevalence of adverse neonatal outcomes in cohorts of preterm infants. As a result, many investigators attribute the risk of adversity to gestational age at delivery rather than prenatal inflammation.[46] Furthermore, studies that have examined the risks of inflammation to term neonates have concluded that inflammation poses only minimal risk.[47,48] As a result, the relative contributions of preterm birth and prenatal inflammation to adverse neonatal outcomes are yet to be determined.

To that end, our primary objective was to determine whether prenatal inflammation that is assessed by acute CCA, maternal temperature >38°C in the 24 hours preceding delivery, or postpartum diagnosis of HCA was associated with a composite adverse neonatal outcome variable (COMP). Secondary objectives were to determine the association between prenatal inflammation and the individual adverse neonatal outcomes sepsis and respiratory compromise. Our hypotheses were that, for all outcomes, prenatal inflammation would be associated with an increased risk for neonatal adversity and that these associations

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TABLE 1
Association between demographic variables and prenatal inflammation (n = 871)

Demographic characteristics	Exposure		*P* value[a]
	Present	Not present	
Clinical chorioamnionitis[b]			
Preterm birth <37 wk, n (%)	28 (49)	338 (42)	.26
Gestational age at delivery, wk[c]	34.93 ± 5.48	36.60 ± 3.38	.34
Race, n (%)			.29
Black	47 (82)	668 (82)	
White	4 (7)	94 (12)	
Asian	4 (7)	24 (3)	
Other	2 (4)	28 (3)	
Infant male sex, n (%)	33 (58)	436 (54)	.53
Corticosteroids, n (%)	27 (47)	269 (33)	.03
Maternal age, y[c]	24.97 ± 6.08	25.62 ± 6.08	.48
Gestational age at enrollment, wk[c]	29.35 ± 3.24	30.36 ± 3.66	.03
Temperature >38°C[d]			
Preterm birth <37 wk, n (%)	15 (31)	351 (43)	.10
Gestational age at delivery, wk[c]	37.41 ± 3.89	36.44 ± 3.55	.003
Race, n (%)			.60
Black	40 (82)	675 (82)	
White	4 (8)	94 (11)	
Asian	3 (6)	25 (3)	
Other	2 (4)	28 (3)	
Infant male sex, n (%)	32 (65)	437 (53)	.10
Corticosteroids, n (%)	12 (24)	284 (35)	.15
Maternal age, y[c]	24.37 ± 5.84	25.65 ± 6.09	.12
Gestational age at enrollment, wk[c]	30.12 ± 3.19	30.31 ± 3.67	.50
Histologic chorioamnionitis[e]			
Preterm birth <37 wk, n (%)	160 (72)	206 (32)	< .001
Gestational age at delivery, wk[c]	33.75 ± 4.72	37.44 ± 2.47	< .001
Race, n (%)			.16
Black	192 (86)	523 (81)	
White	16 (7)	82 (13)	
Asian	8 (4)	20 (3)	
Other	7 (3)	23 (4)	
Infant male sex, n (%)	121 (54)	348 (54)	.89
Corticosteroids, n (%)	125 (56)	171 (26)	< .001
Maternal age, y[c]	25.62 ± 6.18	25.57 ± 6.05	.93
Gestational age at enrollment, wk[c]	29.86 ± 3.77	30.45 ± 3.59	.04

[a] Determined by χ^2 test (categoric data) and Kruskal-Wallis rank test (continuous data); [b] Present, 57; not present, 814; [c] Data presented as mean ± SD; [d] Present, 49; not present, 822; [e] Present, 223; not present, 648.

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would persist when adjustment was made for gestational age at delivery.

Materials and Methods

We performed a prospective cohort study at a single, urban tertiary care center. The cohort consisted of women with singleton pregnancies at 22 weeks to 33 week 6 days' gestational age who came to the labor and delivery triage unit with complaints concerning preterm labor. Patients were excluded for multiple-gestation, major fetal anomaly, intrauterine fetal death, severe preeclampsia before enrollment, chronic steroid or immunosuppressive drug use, active immunologic disease, acute systemic febrile illness, and/or pregestational diabetes mellitus. Patients who either were not delivered at our institution or whose infants were transferred to a different hospital for care were also excluded from these analyses.

Patients were enrolled in the study by trained clinical research coordinators who obtained informed consent at the time of enrollment. Once a patient was enrolled in the study, all treatment decisions were made by the treating physician according to the standard of care at our institution. Women were enrolled from April 2009 through March 2012.

At our institution, maternal fever is diagnosed as a temperature >38°C. Maternal temperature is recorded on laboring patients every 4 hours while membranes are intact and hourly after membranes are ruptured. A diagnosis of temperature >38°C was obtained from review of the electronic nursing records in the 24 hours preceding each patient's delivery. Acute CCA is diagnosed in the setting of maternal temperature >38°C and at least 1 of the following occurrences: maternal tachycardia (≥100 beats per minute), fetal tachycardia (>160 beats per minute), and/or fundal tenderness. Patients who receive a diagnosis of acute CCA who are not in spontaneous labor are induced at the time this diagnosis is made. HCA is a diagnosis that is made by the pathologist after microscopic examination of the placenta and is defined as the presence of neutrophils in the chorion or amnion.