Histologic Chorioamnionitis and Preterm Delivery

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Inconsistent findings linking placental histologic chorioamnionitis (HCA) and preterm delivery may result from variations in HCA definition, population studied, and exclusion criteria. This analysis from the 1998–2004 Pregnancy Outcomes and Community Health Study (five Michigan communities) includes the first 1,053 subcohort women (239 preterm, 814 term) with completed placental assessments. Multiple HCA definitions were constructed by 1) varying polymorphonuclear leukocytes/high-powered field thresholds and placenta components included and 2) using polymorphonuclear leukocyte characteristics to assign low/high maternal, fetal inflammation stage and grade. In African Americans, HCA was associated with preterm delivery before 35 weeks. The effect size was modest for polymorphonuclear leukocytes/high-powered field thresholds of greater than 10 and greater than 30 (odds ratios (ORs) = 0.8 and 2.0); larger for greater than 100 (OR = 3.2, 95% confidence interval (CI): 1.4, 7.1); strengthened after excluding medically indicated preterm deliveries (OR = 4.9, 95% CI: 2.0, 11.8); and strongest for high maternal/high fetal HCA (OR = 5.6, 95% CI: 1.4, 22.1). These latter HCA criteria also produced the largest effect size in Whites/others (OR = 2.7, 95% CI: 0.3, 26.9). Among preterm deliveries before 35 weeks excluding those medically indicated, 12% of Whites/others and 55% of African Americans had high maternal HCA. The authors conclude that HCA definition, exclusion criteria, and race/ethnicity influence the HCA-preterm delivery association and that HCA contributes to preterm delivery-related ethnic disparity.

The link between infection and preterm delivery disparities is supported through a series of related observations. Race/ethnic disparity is greatest for earlier preterm delivery (e.g., <35 weeks) (14), and these early deliveries are more often accompanied by premature rupture of membranes and/or evidence of infection (21–26). Bacterial vaginosis, a polymicrobial overgrowth associated with preterm delivery (27), is more prevalent in disadvantaged (28, 29) and African-American women (30, 31).

The placenta is a key tissue for understanding infection and/or inflammation pathways leading to preterm delivery, but the strength of association between histologic chorioamnionitis (HCA) and preterm delivery has been inconsistent.
Some studies have examined only preterm placentas (26, 32, 33), and others have included preterm and term placentas assessed for clinical indications (34, 35) with the potential for selection bias. In studies comparing term and preterm placentas, odds ratios for HCA have ranged from 0.8 to 5.9 (23, 34, 36–43). This wide range may be due, in part, to differences in maternal characteristics, excluded subgroups (e.g., hypertensives, medically indicated deliveries), preterm category (e.g., early vs. all preterm), and HCA definition.

Throughout the preterm delivery literature, HCA case definitions have differed markedly. Most studies can be grouped into one of two categories: those that have used inflammatory cell thresholds (i.e., polymorphonuclear leukocytes/high-powered field) (24, 38, 43–48) and those that have incorporated a complex HCA grading and/or staging approach (49–51). Within the first category, HCA criteria have varied with respect to 1) the tissue components included, for example, placental disc, extraplacental membranes, and cord (33, 42, 47, 52), disc only (24, 25, 38, 40, 53), or extraplacental membranes only (41, 43, 44, 48); 2) threshold, for example, “any inflammation” (25, 33, 34, 42, 52, 53), greater than five polymorphonuclear leukocytes/high-powered field (24, 38, 47), and greater than 10 polymorphonuclear leukocytes/high-powered field (43, 45, 46, 48); and 3) number of high-powered fields that must exceed the threshold (43, 46, 48). In the second category, the detailed systems of staging/grading have also varied. Typically these protocols document polymorphonuclear leukocyte location, density, and degeneration to estimate intensity and progression (i.e., grade and stage) (49–51) and, in some instances, to distinguish fetal from maternal inflammatory response (50). Differences across studies in HCA definition, population, and exclusion criteria make it difficult to disentangle the influences of specific variations on study results.

In the community-based, prospective Pregnancy Outcomes and Community Health Study, delivered placentas from a subset of women (subcohort) were assessed by a study pathologist using a detailed descriptive rather than diagnostic approach. This protocol permitted construction of several commonly used HCA definitions within a single sample to determine how these definitions affect associations between HCA and preterm delivery. In addition, it provided an opportunity to examine modification of the HCA-preterm delivery association by factors such as preterm subgroup, exclusion criteria, and race/ethnicity.

**MATERIALS AND METHODS**

**Study population**

The Pregnancy Outcomes and Community Health (or “POUCH”) Study recruited pregnant women from August 1998 to June 2004 from 52 clinics in five Michigan communities. Women were enrolled in gestational weeks 15 through 27 (87 percent before week 25). Inclusion criteria were singleton pregnancy with no known congenital anomaly, maternal age of 15 or more years, maternal serum alpha-fetoprotein screen in gestational weeks 15–22, no prepregnancy diabetes mellitus, and proficiency in English. The study received approval from institutional review boards at Michigan State University, Michigan Department of Community Health, and nine community hospitals. Women were invited to participate at the time of prenatal screening. The study included all interested women with unexplained maternal serum alpha-fetoprotein levels greater than two multiples of the median (7 percent of cohort) and a stratified sample (ethnic-specific strata) of women with normal maternal serum alpha-fetoprotein levels. Of the 3,038 women enrolled, 19 were lost to follow-up, leaving a cohort of 3,019. At enrollment, cohort women were interviewed and had biologic samples collected and stored.

In a subcohort (n = 1,371), assays were performed on stored biologic samples, prenatal and labor and delivery records were abstracted, and delivered placentas were examined by a study placental pathologist. The subcohort included all women who delivered preterm (<37 weeks), all women with elevated maternal serum alpha-fetoprotein (>2 multiples of the median) and term deliveries, and a sample of women with normal maternal serum alpha-fetoprotein levels and term deliveries (i.e., 72 percent of African-American and 23 percent of White/other women in this category). The sampling scheme was designed to optimize available resources and maximize statistical power for studying at-risk subgroups (i.e., African Americans and women with high maternal serum alpha-fetoprotein). Placentas were retrieved for 1,213 (88 percent) subcohort women, and this analysis included the first 1,053 (239 preterm, 814 term) with completed placenta assessments.

**Placenta examination protocol**

Placentas were formalin fixed and received gross examination using standard protocols. Nine tissue samples were embedded in paraffin blocks for microscopic assessment: two extraplacental membrane (membrane roll) samples; two umbilical cord samples (one proximal and one distal to disc insertion); and five full-thickness disc samples, one at the cord insertion, one in central tissue that appeared normal on gross examination, two from central tissue, and one at the margin, these latter three representative of grossly visible abnormalities if present. Microscopic findings were recorded in a descriptive, computer-based instrument adapted from a prototype by Dr. Caroline Salafia. The microscopic description included details, such as the highest number of cells/high-powered field for each leukocyte type in each placenta tissue compartment (e.g., intervillous space, subchorion, chorion and amnion of plate and extraplacental membranes, chorionic vessels, and umbilical cord). While performing microscopic examinations, the study pathologist was blinded to gestational age at delivery, all clinical data, and gross examination findings.

**Definitions of histologic chorioamnionitis**

HCA definitions were constructed to parallel those found in the literature on HCA and preterm delivery. One set of definitions incorporated variations in placental tissue components (i.e., cord, plate, and extraplacental membrane; extraplacental membrane only) and polymorphonuclear leukocyte threshold (i.e., at least one high-powered field.
with a polymorphonuclear leukocyte inflammatory pattern; >10 polymorphonuclear leukocytes; >30 polymorphonuclear leukocytes; and >100 polymorphonuclear leukocytes). A staging and grading system was adapted from an approach described by Redline et al. (50). “Maternal stages” 1–3 were assigned as follows: stage 1—at least one high-powered field with greater than 10 polymorphonuclear leukocytes in subchorionic fibrin but not in chorion or amnion; stage 2—polymorphonuclear leukocyte inflammatory pattern in chorionic plate or extraplacental membrane chorion plus or minus amnion but no polymorphonuclear leukocyte karyorrhexis or necrotizing inflammation; and stage 3—polymorphonuclear leukocyte inflammatory pattern in chorionic plate and/or extraplacental membrane chorion and amnion, plus karyorrhexis and/or necrotizing inflammation. “Fetal stages” 1–3 were assigned as follows: stage 1—at least one high-powered field with a polymorphonuclear leukocyte inflammatory pattern in fetal chorionic plate vessels but not in umbilical vessels; stage 2—polymorphonuclear leukocyte inflammatory pattern in umbilical vessels, confined to the vessel wall; and stage 3—polymorphonuclear leukocyte inflammatory pattern in umbilical vessels extending into Wharton’s jelly. Maternal grade and fetal grade were based on maximum polymorphonuclear leukocytes/high-powered field, that is, grade 1 (1–10 polymorphonuclear leukocytes). A staging and grading system was adapted from an approach described by Redline et al. (50). “Maternal stages” 1–3 were assigned as follows: stage 1—at least one high-powered field with greater than 10 polymorphonuclear leukocytes in subchorionic fibrin but not in chorion or amnion; stage 2—polymorphonuclear leukocyte inflammatory pattern in chorionic plate or extraplacental membrane chorion plus or minus amnion but no polymorphonuclear leukocyte karyorrhexis or necrotizing inflammation; and stage 3—polymorphonuclear leukocyte inflammatory pattern in chorionic plate and/or extraplacental membrane chorion and amnion, plus karyorrhexis and/or necrotizing inflammation. “Fetal stages” 1–3 were assigned as follows: stage 1—at least one high-powered field with a polymorphonuclear leukocyte inflammatory pattern in fetal chorionic plate vessels but not in umbilical vessels; stage 2—polymorphonuclear leukocyte inflammatory pattern in umbilical vessels, confined to the vessel wall; and stage 3—polymorphonuclear leukocyte inflammatory pattern in umbilical vessels extending into Wharton’s jelly. Maternal grade and fetal grade were based on maximum polymorphonuclear leukocytes/high-powered field, that is, grade 1 (1–10 polymorphonuclear leukocytes), grade 2 (11–30 polymorphonuclear leukocytes), grade 3 (31–100 polymorphonuclear leukocytes), and grade 4 (>100 polymorphonuclear leukocytes).

**Pregnancy outcome**

Gestational age at delivery was calculated by use of the date of the last menstrual period or gestational age estimate from ultrasound if the last menstrual period and ultrasound estimate differed by more than 2 weeks. The last menstrual period-based estimate was similar (within 2 weeks) to the ultrasound-based estimate at less than or equal to 20 weeks in 64 percent of the cohort and to the ultrasound-based estimate at 21–25 weeks in an additional 12 percent of the cohort. Ultrasound-based estimates were used for 18 percent of the cohort with absent or conflicting last menstrual period-based estimates. In the remaining 6 percent, only the last menstrual period-based estimates were available. Two abstractors, a physician and a study labor-and-delivery nurse, independently reviewed subcohort prenatal and labor and delivery records to identify medically indicated preterm deliveries. Disagreements were resolved through reexamination of medical records. Medically indicated preterm delivery was defined as delivery before 37 weeks that begins by induction or cesarean section in the absence of spontaneous labor (cervix dilated ≥2 cm and regular contractions) or rupture of membrane as an initiating event.

**Analytical approach**

Prevalence of HCA and its association with preterm delivery was calculated using SAS Survey Freq and Survey Logistic procedures, respectively (54). Weights were applied to reflect oversampling of high maternal serum alphafetoprotein into the cohort and the subcohort sampling scheme. Odds of HCA in term deliveries were compared with those in preterm deliveries at 35–36 weeks and before 35 weeks by use of various HCA definitions in race/ethnic-specific models. Analyses were repeated after removing all medically indicated preterm deliveries, a group delivered early most often because of maternal vascular disease and rarely HCA. These models were constructed to examine variation in effect size for the association between HCA and preterm delivery in relation to factors that are inconsistent across studies, that is, HCA definition, race/ethnicity, gestational weeks of the preterm delivery, and inclusion/exclusion of medically indicated preterm delivery.

For both maternal and fetal inflammatory responses, stages 1–3 and grades 1–4 were dichotomized into “low” (i.e., one or two) and “high” (i.e., three or more), and a five-level “HCA severity” variable was created: no HCA (referent); low grade/low stage; low grade/high stage; high grade/low stage; and high grade/high stage. The two five-level variables representing maternal and fetal inflammatory responses were each incorporated into separate models to assess their association with preterm delivery. In a final model, maternal and fetal inflammatory responses were combined into a single HCA severity variable. The cutpoints for dichotomizing low and high responses were based on associations with preterm delivery in the maternal-specific and fetal-specific models. The maternal “high” inflammatory response was stage 3 or higher and any grade, and “low” was stage 1 or 2 and any grade. The fetal “high” inflammatory response was stage and grade 3 or higher, and “low” was stage or grades 1–2. The new five-level variable for maternal/fetal inflammation was as follows: no HCA (referent); low maternal/low fetal; low maternal/high fetal; high maternal/low fetal; and high maternal/high fetal.

**RESULTS**

The maternal characteristics of this subcohort sample are presented in table 1 without sampling weights; therefore, the overall prevalences and differences between term and preterm in this table do not reflect those in the entire cohort. In this subcohort sample, 54 percent were insured by Medicaid, 38 percent were African Americans, and a small percentage was other ethnic minorities. In the following analyses, sampling weights were used, and the “other” ethnic group was combined with Whites because HCA prevalence in the “other” group more closely paralleled that in Whites than that in African Americans.

HCA prevalence in term deliveries ranged from 85 percent down to 7 percent and in preterm delivery from 63 percent down to 4 percent, depending on the polymorphonuclear leukocytes/high-powered field threshold used to define HCA (figure 1). Overall, the prevalence dramatically decreased as the threshold increased, and for most thresholds, the HCA prevalence was lower when based on examination of extraplacental membranes only versus examination of all placental tissue compartments (figure 1). In term and preterm deliveries, the HCA prevalence was higher in African Americans compared with that in Whites/other, and these race/ethnic differences increased as the polymorphonuclear
leukocytes/high-powered field threshold increased (figure 1). When cord, plate, and extraplacental membrane were examined and a polymorphonuclear leukocytes/high-powered field threshold of greater than 30 was used to define HCA, the prevalence of HCA in African Americans versus Whites/others was 37 percent versus 25 percent in term deliveries, 23 percent versus 14 percent in preterm deliveries at 35–36 weeks, and 46 percent versus 6 percent in preterm deliveries before 35 weeks.

In race/ethnic-specific logistic regression models, HCA defined by any of the polymorphonuclear leukocytes/high-powered field thresholds was not associated with preterm delivery at 35–36 weeks (table 2). HCA was significantly related to preterm delivery before 35 weeks but only in African Americans, and only when the polymorphonuclear leukocytes/high-powered field threshold for HCA was greater than 100 (odds ratio [OR] = 3.2, 95 percent confidence interval [CI]: 1.4, 7.1). After removal of the medically indicated preterm deliveries, this association was further strengthened (OR = 4.9, 95 percent CI: 2.0, 11.8), and even HCA defined by lower thresholds (e.g., >30 polymorphonuclear leukocytes/high-powered field) appeared related to preterm delivery before 35 weeks in African Americans (table 2).

By use of a staging and grading system for maternal and fetal inflammatory response (HCA) and excluding medically indicated preterm deliveries, the association between high maternal/high fetal inflammatory response and preterm delivery before 37 weeks was weak and statistically nonsignificant among Whites/others (OR = 1.9, 95 percent CI: 0.4, 8.1) and, again, more pronounced in African Americans (OR = 3.2, 95 percent CI: 1.2, 8.3) (table 3). The same analytical models were repeated but this time comparing HCA in term with that in preterm deliveries before 35 weeks (table 4). The odds ratio estimate for high maternal/high fetal inflammatory response increased slightly in Whites/others (OR = 2.7, 95 percent CI: 0.3, 26.9), but the confidence interval was wider because of the smaller sample size after excluding 35- to 36-week preterm deliveries. In African Americans, preterm delivery before 35 weeks was associated with high maternal/low fetal response (OR = 3.6, 95 percent CI: 1.0, 13.4) and with high maternal/high fetal response (OR = 5.6, 95 percent CI: 1.4, 22.1).

### DISCUSSION

In this study, the HCA-preterm delivery relation was strongly influenced by HCA definition, inclusion/exclusion of preterm delivery at 35–36 weeks and medically indicated preterm delivery, and the race/ethnic group studied. Surprisingly, there has been little discussion regarding variations in HCA definition across studies. Within studies, kappas for interrater reliability have ranged from 0.15 to 0.83, with less agreement for mild HCA or severity of HCA and greater agreement for the presence of any HCA (55–57). However, in most reliability studies, the HCA definition and protocol were standardized. Across studies, two approaches for assessing HCA predominate, one using polymorphonuclear leukocytes/high-powered field thresholds and the other using a complex staging and/or grading scheme, with each approach having its own set of varied definitions. Blanc (49) first proposed three stages based on maternal polymorphonuclear leukocyte movement from subchorion to chorion to amnion overlaying the placental plate. Later classification schemes, for example, those reported by Salafia et al. (51) and Redline et al. (50), incorporated location, density, and characteristics of polymorphonuclear leukocyte infiltrates.

Applying the polymorphonuclear leukocytes/high-powered field approach with low thresholds (i.e., >0 or >10 polymorphonuclear leukocytes/high-powered field) in the cord, extraplacental membranes, plate, or subchorion, we observed that 54–76 percent of White/other term placentas and 64–85 percent of African-American term placentas met...
these HCA criteria. Other studies examining term placentas have reported HCA prevalences ranging from 4 percent to 79 percent (23, 34, 36–43, 51). These findings underscore the need to compare inflammatory cells/patterns in preterm placentas with those in term placentas to arrive at meaningful relations between HCA and preterm delivery. Previous studies have often focused solely on HCA in preterm placentas (21, 26, 33, 45, 52), and many studies have used a low polymorphonuclear leukocytes/high-powered field threshold to define HCA (24, 38, 47), which would have an attenuating effect on the HCA-preterm delivery association. The high prevalence of low intensity HCA in term placentas may mark the beginning of a maternal response to microbial ascent during labor. In addition, infection may precipitate delivery at any point along the gestational continuum, and a less fulminating inflammation may adequately trigger delivery in late gestational tissues already primed. We observed high stage/high grade fetal inflammation in 3 percent of White/other and 10 percent of African-American term placentas, evidence that this problem is not confined to preterm delivery and that ethnic disparities persist at term.

For each polymorphonuclear leukocytes/high-powered field threshold in our analyses, assessment of cord, plate, and extraplacental membranes tended to produce a higher HCA prevalence than that found in extraplacental membranes alone. One explanation could be empirical; the more tissue locations sampled, the greater the likelihood of finding a locus with a high number of polymorphonuclear leukocytes/high-powered field. However, these results highlight the challenges of comparing HCA results across studies that include only extraplacental membranes (23, 41, 43, 48), only disc (24, 25, 38, 40, 53), or both (26, 34, 36, 46).

In our HCA stage/grade analyses that excluded medically indicated preterm deliveries, all but one placenta delivered before 35 weeks with high fetal response also had high maternal response. However, among term placentas with high fetal response, a substantial proportion (10 of 16 White/others, 14 of 33 African American) had a low maternal response. This may reflect the ability of a more mature fetus to mount a robust immune response earlier in the process of exposure to infection and possibly discordance in maternal and fetal immune responsiveness.

We also observed a higher prevalence of HCA in African Americans compared with that in Whites/others within term, preterm delivery at 35–36 weeks, and preterm delivery before 35 weeks. In deliveries before 35 weeks that were not

![FIGURE 1. Prevalence of histologic chorioamnionitis (HCA) by race/ethnicity and gestational week at delivery, Pregnancy Outcomes and Community Health (POUCH) Study, 1998–2004. A–D compare different criteria used to define HCA: A and C, polymorphonuclear leukocytes evaluated in plate, cord, and extraplacental membranes in Whites/others and African Americans, respectively; B and D, polymorphonuclear leukocytes evaluated in extraplacental membranes only in Whites/others and African Americans, respectively. Prevalences are weighted to account for the subcohort sampling design. HCA was considered present if the highest number of polymorphonuclear leukocytes/high-powered field (PMNL/hpf) observed in any tissue component was equal to or greater than the defined cutoff (threshold). The lowest threshold was greater than zero PMNL/hpf and an inflammatory pattern.](https://academic.oup.com/aje/article/166/7/786/95559)
medically indicated. Twelve percent of White/other placentas and 55 percent of African-American placentas showed evidence of a high maternal inflammatory response. The largest HCA odds ratio for very preterm delivery was 5.6 in African Americans but only 2.7 and not statistically significant in Whites/others. These results are in agreement with many (21, 58–60), but not all (40), previous studies showing that HCA is a key element in race/ethnic disparity in early preterm delivery. The findings also suggest that the importance of an HCA pathway to preterm delivery could vary considerably with the population studied. Often reports on HCA and preterm delivery come from inner-city teaching hospitals with large proportions of minority populations and urban poor (38, 59, 60).

Among the African-American deliveries in our study, three factors increased the effect size of the association between HCA and preterm delivery: 1) higher polymorphonuclear leukocytes/high-powered field threshold or more advanced maternal and fetal inflammatory response; 2) restricting the outcome to preterm delivery before 35 weeks; and 3) exclusion of medically indicated preterm delivery. Thus, even studies with similar populations may be expected to produce different results if these factors are not consistent. Our findings are in agreement with previous research showing that inflammation/infection plays a larger role in the earliest preterm delivery (21–26) and in preterm delivery that begins with spontaneous labor or rupture of membranes (21, 32, 33) as compared with medically indicated preterm delivery.

One study limitation was sample size. We had 26 White/other and 22 African-American deliveries before 35 weeks after excluding medically indicated preterm deliveries. Based on the low prevalence of high maternal/fetal inflammatory response in the White/other placentas, one would need at least 324 nonmedically indicated preterm deliveries before 35 weeks in Whites/others to have 80 percent power to detect an odds ratio of 2.0. We also had too few extreme preterm deliveries, that is, before 33 weeks, to separately examine this subgroup. The importance of HCA may be more similar across race/ethnic groups in the before-33-week deliveries compared with the marked race/ethnic disparities that we observed in the before-35-week deliveries. Another limitation is one inherent in much of the literature on HCA. We used the location of polymorphonuclear leukocytes to infer an inflammatory infiltrate and direction of chemotaxis, and we had no additional immunohistologic staining or RNA microarray evidence that these polymorphonuclear leukocytes were recruited as part of an inflammatory process.

Despite these limitations, this study also had multiple strengths. The sample was socioeconomically diverse, and participants were recruited from a large number of prenatal clinics that serve urban, suburban, and rural women with low- and high-risk pregnancies, thereby improving the generalizability of findings. During gross and histologic examinations, the pathologist was unaware of the gestational week at delivery, pregnancy complications, delivery circumstances, and race/ethnicity associated with each placenta.
### TABLE 3. Associations between maternal and fetal inflammatory responses and preterm delivery (<37 weeks), excluding medically indicated preterm delivery, Pregnancy Outcomes and Community Health Study,* 1998–2004†

<table>
<thead>
<tr>
<th>Maternal inflammation</th>
<th>Fetal inflammation</th>
<th>Maternal-fetal combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCA† severity</td>
<td>No. of preterm deliveries</td>
<td>No. of term deliveries</td>
</tr>
<tr>
<td>Whites/others</td>
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<td></td>
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<tr>
<td>No HCA (referent)</td>
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<td>183</td>
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<tr>
<td>Low stage/low grade</td>
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<td>213</td>
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<tr>
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<td>25</td>
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<tr>
<td>Total</td>
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</tr>
<tr>
<td>African Americans</td>
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<tr>
<td>No HCA (referent)</td>
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<td>Low stage/low grade</td>
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</tr>
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<tr>
<td>High stage/high grade</td>
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<td>48</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>335</td>
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* Referred to as the “POUCH” Study.
† All odds ratios and 95% confidence intervals incorporate cohort/subcohort sampling weights as applicable.
‡ HCA, histologic chorioamnionitis.

### TABLE 4. Associations between maternal and fetal inflammatory responses and preterm delivery (<35 weeks), excluding medically indicated preterm delivery, Pregnancy Outcomes and Community Health Study,* 1998–2004†

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<tr>
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information that could influence pathologists' impressions. Placental assessment followed a strict protocol and incorporated considerable detail to permit construction of multiple HCA definitions; this combination of rigor and flexibility was a unique feature of this study. We were able to assess the effects of HCA definition, race/ethnicity, and preterm delivery subtypes within a single study, whereas comparisons across studies are often confounded by other salient factors such as variations in study samples and methodologies. In summary, after noting large inconsistencies in results from studies linking HCA and preterm delivery, we hypothesized that factors such as HCA definition, exclusion of medically indicated preterm deliveries, gestational weeks of the preterm deliveries, and race/ethnicity might explain some of the heterogeneity. Our results supported these hypotheses and offered further evidence that HCA may be a powerful contributor to ethnic differences in preterm delivery risk.

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Conflict of interest: none declared.

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