### Title

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### Authors

Palmsten, Kristin
Nelson, Katharine K
Laurent, Louise C
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# Subclinical and clinical chorioamnionitis, fetal vasculitis, and risk for preterm birth: A cohort study

Kristin Palmsten[a,b,*], Katharine K. Nelson[c,d], Louise C. Laurent[d,e], Soojin Park[d,e], Christina D. Chambers[b,f], Mana M. Parast[c,d]

[a] HealthPartners Institute, Mail Stop: 23301A, P.O. Box 1524, Minneapolis, MN, 55440, United States
[b] Department of Pediatrics, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA, 92093, United States
[c] Department of Pathology, University of California San Diego, La Jolla, 9500 Gilman Drive, La Jolla, CA, 92093, United States
[d] Sanford Consortium for Regenerative Medicine, University of California San Diego, La Jolla, CA, 92093, United States
[e] Department of Obstetrics, Gynecology, and Reproductive Sciences, University of California San Diego, 9500 Gilman Drive, La Jolla, CA, 92093, United States
[f] Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, 9500 Gilman Drive, La Jolla, CA, 92093, United States

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ABSTRACT

*Objective:* To evaluate the association between subclinical and clinical chorioamnionitis and risk of preterm birth (PTB).

*Methods:* Demographic and clinical characteristics were abstracted from medical records and placental examinations performed (N = 1371 pregnancies including spontaneous and medically-indicated PTBs). Pregnancies were classified as having clinical chorioamnionitis (with or without histologic chorioamnionitis), subclinical chorioamnionitis (histologic, but not clinical, chorioamnionitis), or no chorioamnionitis; pregnancies with histologic chorioamnionitis were further evaluated for fetal vasculitis. Relative risks for PTB, early and late PTB, and PTB ± premature rupture of membranes (PROM) were adjusted for maternal characteristics.

*Results:* Clinical (4.3%) and subclinical (24.5%) chorioamnionitis were not associated with PTB overall. In pregnancies without clinical or subclinical chorioamnionitis, the risk of PTB with PROM and early PTB was 2.2% and 8.6%, respectively. In comparison, clinical chorioamnionitis was associated with an increased risk of PTB with PROM (aRR: 3.42 (95%CI: 1.07, 10.98), whereas subclinical chorioamnionitis was associated with increased risk of PTB with PROM (aRR: 3.92 (95% CI: 2.15, 7.12)) and early PTB (aRR: 1.77 (95% CI: 1.18, 2.64)). Histologic chorioamnionitis with fetal vasculitis was associated with increased risk of PTB with PROM (aRR: 7.44 (95% CI: 3.68, 15.05)) and early PTB (aRR: 2.94 (95% CI: 1.78, 4.87)), whereas histologic chorioamnionitis without fetal vasculitis was associated with increased risk of PTB with PROM only (aRR: 2.64, 95% CI: 1.27, 5.50).

*Conclusions:* Subclinical chorioamnionitis and histologic chorioamnionitis with fetal vasculitis were associated with early PTB and PTB with PROM but not with PTB overall, likely due to inclusion of indicated PTBs.

## 1. Introduction

Chorioamnionitis, acute inflammation of the amnion and chorion, is a marker of intra-amniotic infection, although it can occur in the absence of detectable infection [1]. Histologic chorioamnionitis, identified through pathologic examination of the placenta, can be present in the absence of clinical chorioamnionitis [1], which is diagnosed primarily by maternal fever [2]. Such subclinical cases represent 40–90% of histologic chorioamnionitis cases, with factors, including variations in the definitions of clinical chorioamnionitis used in different studies, contributing to the variability [3–9]. Additionally, intra-amniotic infection can lead to a fetal inflammatory response, which is identified histologically by fetal vasculitis, i.e., inflammation of the fetal vessels of the chorionic plate or umbilical cord [1,10].

Preterm birth (PTB) has multifactorial and heterogeneous etiologies and can be subdivided by gestational age at delivery or by clinical presentation (spontaneous preterm labor, preterm premature rupture of membranes (PPROM), and medically indicated) [11–13]. Intra-uterine infection and associated inflammation is believed to be an important cause of PTB [13], and histologic chorioamnionitis is associated with PTB [1,7,14–16] and lower gestational age at delivery among PTBs [1,4,17]. Previous studies have reported a 2.5–8-fold increased odds of

* Corresponding author. Mail Stop: 23301A, P.O. Box 1524, Minneapolis, MN, 55440-1524, United States.
*E-mail address:* kristin.k.palmsten@healthpartners.com (K. Palmsten).

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PTB among women with histologic chorioamnionitis [7,14,16]. However, the impact of subclinical chorioamnionitis, specifically, on PTB risk has not been described. Furthermore, some studies of histologic chorioamnionitis and risk of PTB have adjusted for potential confounding factors, such as age, race, and preeclampsia [14,16]. However, the same studies simultaneously adjusted for potential intermediate variables, including premature rupture of membranes (PROM), fever, and time from rupture until delivery [14,16], which precludes estimation of the total effect of histologic chorioamnionitis on PTB [18]. Finally, data regarding the impact of histologic chorioamnionitis with fetal vasculitis on PTB [15,19] and fetal tachycardia, presumably due to infection [8,20,21], are sparse.

The aims of our study were: 1) to quantify the relationship between subclinical and clinical chorioamnionitis and PTB, while adjusting for confounders but not intermediates of these associations; and 2) to evaluate the association between histologic chorioamnionitis with and without fetal vasculitis and PTB and fetal tachycardia.

## 2. Materials and methods

### 2.1. Study population

As part of the Perinatal Biorepository at UC San Diego, we enrolled women with singleton pregnancies. We targeted women at high risk of pregnancy/perinatal complications, including women with abnormal maternal serum analytes (i.e., human chorionic gonadotropin, pregnancy associated plasma protein A, alpha-fetoprotein, inhibin, unconjugated estriol), prior or current pregnancy complications (i.e. preeclampsia or gestational diabetes), or chronic comorbidities (i.e. hypertension or diabetes), but we also enrolled low risk women (i.e. those without the above findings). Both clinical data from electronic medical records (EMR) and biospecimens, including placental tissue, were collected.

All pregnancies among women with completed placental pathology who delivered between February 2011 and December 2015 were eligible for the current study (n = 1433; Supplemental Figure). Pregnancies that could not be linked with EMR delivery records were excluded (n = 62), yielding 1371 pregnancies available for the primary analysis. There were 12 women with > 1 pregnancy included in the study. Additionally, pregnancies that could not be linked with prenatal care information in the electronic medication record, including pregnancies with prenatal care outside of UC San Diego Health, were excluded from an analysis of factors linked with infection that utilized outpatient lab data (n = 160). The study was approved by the University of California Human Research Protections Program Committee.

### 2.2. Participant data

Information regarding participants' demographics, comorbidities, and intrapartum characteristics, including gestational age at delivery, lab values, and medications, were abstracted from the EMR.

Gross and histologic placental examinations were performed by a single board-certified anatomic pathologist (MMP) according to standard protocols. Placentas were sectioned and examined histologically as follows: one section each of umbilical cord and membrane roll; any disc lesions; and two full-thickness sections of grossly-normal placental disc [22]. All sections were processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin [22].

Histologic chorioamnionitis was defined as the presence of either acute or mixed (acute and chronic) inflammatory infiltrate in the subchorionic space and/or fetal membranes, excluding cases with chronic inflammatory cells (chronic chorioamnionitis) only. Subclinical chorioamnionitis was defined as histologic chorioamnionitis in the absence of a maternal fever > 101.4 °F during the delivery hospitalization. Clinical chorioamnionitis was defined as the presence of maternal fever > 101.4 °F during the delivery hospitalization, with or without histologic chorioamnionitis. Fetal vasculitis was defined as the presence of acute or mixed inflammatory infiltrate around large fetal vessels in the placenta, including chorionic plate and/or umbilical cord vessels.

PTB was defined as gestational age at delivery < 37 weeks; early PTB was defined as < 34 weeks, and late PTB was defined as between 34 and < 37 weeks. PTB was also classified according to the presence or absence of PROM.

### 2.3. Statistical analysis

We used modified Poisson regression to estimate relative risks (RR) and 95% confidence intervals (CI) of binary outcomes [23]. Including a correlation structure to account for non-independence among women with more than one pregnancy [24] did not change CIs appreciably; therefore, the correlation structures were removed from all analyses. For nominal outcomes (i.e., type of PTB), we used multinomial regression to estimate RRs and 95% CIs. All models were adjusted for maternal age, race, ethnicity, parity, diabetes or gestational diabetes, and hypertension or preeclampsia.

First, we compared the risk for PTB according to whether pregnancies had subclinical chorioamnionitis, clinical chorioamnionitis, clinical chorioamnionitis with histologic confirmation (a subset of clinical chorioamnionitis), or neither subclinical nor clinical chorioamnionitis (reference group). Also, regardless of clinical chorioamnionitis, we compared the risk for PTB according to whether pregnancies had histologic chorioamnionitis with fetal vasculitis, histologic chorioamnionitis without fetal vasculitis, or no histologic chorioamnionitis (reference), excluding 11 pregnancies with fetal vasculitis but without histologic chorioamnionitis (and also without clinical chorioamnionitis). Second, using the same comparison groups, except for the subgroup of clinical chorioamnionitis with histologic chorioamnionitis due to small numbers, we assessed the risks for early PTB, late PTB, and PTB with and without PROM. To explore whether medically indicated delivery could be more likely among PTBs with PROM, we reported the n and % with hypertension or preeclampsia, diabetes or gestational diabetes, cesarean delivery and the median gestational age at delivery and interquartile range according to PTB PROM status. Third, we compared the risk for fetal tachycardia according to the fetal vasculitis/histologic chorioamnionitis groups described above. Finally, to explore whether clinical or subclinical chorioamnionitis was associated with possible intrauterine infection prior to rupture of membranes, we assessed the association between subclinical and clinical chorioamnionitis and any and each of the following: white blood cell count > 13,000 $mm^3$ during delivery admission and before rupture of membranes, at least one IV antibiotic during the delivery admission and before rupture of membranes, or positive Group B strep culture between gestational week 20 and before rupture of membranes.

## 3. Results

### 3.1. Study population characteristics

Approximately half of the study population was white and more than half was non-Hispanic (Table 1). Hypertension and diabetes were common: more than one-third had hypertension or preeclampsia and more than one-third had diabetes or gestational diabetes. Women with subclinical or clinical chorioamnionitis had diabetes or hypertension less frequently than women without subclinical or clinical chorioamnionitis.

In this study population, 336 (24.5%) pregnancies had subclinical chorioamnionitis and 59 (4.3%) pregnancies had clinical chorioamnionitis. There were 14 (1.0%) cases of clinical chorioamnionitis without histologic confirmation and 45 (3.3%) cases with histologic confirmation. Furthermore, 155 (11.3%) pregnancies had histologic chorioamnionitis with fetal vasculitis and 226 (16.5%) pregnancies had histologic chorioamnionitis without fetal vasculitis. Overall, 135 (9.8%)

**Table 1**
Characteristics of study cohort by chorioamnionitis exposure groups.

| Characteristic, n (%) | Subclinical Chorioamnionitis n = 336 | Clinical Chorioamnionitis[a] n = 59 | No Clinical or Subclinical Chorioamnionitis n = 976 |
|---|---|---|---|
| Maternal Age (years) | | | |
| 18 to < 30 | 134 (39.9) | 25 (42.4) | 376 (38.5) |
| 30 to < 35 | 97 (28.9) | 21 (35.6) | 321 (32.9) |
| > 35 | 105 (31.3) | 13 (22.0) | 279 (28.6) |
| Race[b] | | | |
| White | 167 (49.7) | 27 (45.8) | 470 (48.2) |
| Asian or Pacific Islander | 32 (9.5) | 8 (13.6) | 93 (9.5) |
| Black | 10 (3.0) | – | 58 (5.9) |
| More than 1 Race or Other | 122 (36.3) | 22 (37.3) | 344 (35.2) |
| Ethnicity[c] | | | |
| Hispanic | 156 (46.4) | 19 (32.2) | 464 (47.5) |
| Non-Hispanic | 179 (53.3) | 40 (67.8) | 510 (52.3) |
| Multiparous | 145 (43.2) | 11 (18.6) | 588 (60.2) |
| Hypertension or pree-clampsia | 94 (28.0) | 20 (33.9) | 382 (39.1) |
| Diabetes or gestational diabetes | 113 (33.6) | 13 (22.0) | 364 (37.3) |

[a] With or without histologic chorioamnionitis.
[b] Missing for 17 (1.2%) pregnancies.
[c] Missing for < 5 pregnancies.

had early PTB and 154 (11.2%) had late PTB; 54 (3.9%) had PTB with PROM and 235 (17.1%) had PTB without PROM.

### 3.2. PTB

The risk of PTB overall was highest in pregnancies without subclinical or clinical chorioamnionitis (22.2%; Table 2). Compared with this group, neither subclinical chorioamnionitis (adjusted (a) RR: 0.92 (95% CI: 0.71, 1.20)), clinical chorioamnionitis (aRR: 0.81 (95% CI: 0.44, 1.50)), nor the subset of clinical chorioamnionitis with histologic chorioamnionitis (aRR: 0.82 (95% CI: 0.40, 1.69) were associated with an altered risk for PTB overall.

Among pregnancies without histologic chorioamnionitis (with or without clinical chorioamnionitis), the risk of PTB overall was 22.4%. Compared with this group, neither histologic chorioamnionitis with fetal vasculitis (aRR: 1.17 (95% CI: 0.84, 1.64) nor histologic chorioamnionitis without fetal vasculitis (aRR: 0.73 (95% CI: 0.52, 1.03) were associated with an altered risk for PTB overall.

### 3.3. Early and late PTB

The risks of early and late PTB were 8.6% and 13.6%, respectively, among pregnancies without subclinical or clinical chorioamnionitis (Table 3). Compared to these groups, subclinical chorioamnionitis was associated with an increased risk of early PTB (aRR: 1.77 (95% CI: 1.18, 2.64) and a decreased risk of late PTB (aRR: 0.35 (95%: 0.20, 0.61)), whereas clinical chorioamnionitis was not associated with either early or late PTB.

Among pregnancies without histologic chorioamnionitis, the risk of early PTB was 8.6%. Compared with this group, histologic chorioamnionitis with fetal vasculitis was associated with an increased risk of early PTB (aRR: 2.94 (95% CI: 1.78, 4.87)), but histologic chorioamnionitis without fetal vasculitis was not.

### 3.4. PTB with and without PROM

The risks of PTB with or without PROM among pregnancies without clinical or subclinical chorioamnionitis were 2.2% or 20.1%, respectively (Table 4). Among pregnancies with subclinical chorioamnionitis, the risk for PTB with PROM was increased (aRR: 3.93 (95%: 2.15, 7.12)), and PTB without PROM was reduced (aRR: 0.51 (95%: 0.34, 0.78)). Clinical chorioamnionitis followed a similar pattern, although the decreased risk for PTB without PROM was not statistically significant.

Among pregnancies without histologic chorioamnionitis, the risks of PTB with or without PROM were 2.0% or 20.3%, respectively. Compared with these groups, histologic chorioamnionitis with fetal vasculitis was associated with a statistically increased risk of PTB with PROM (aRR: 7.44 (95% CI: 3.68, 15.05)) and trended toward a decreased risk for PTB without PROM that was not statistically significant (aRR: 0.57 (95% CI: 0.32, 1.02)). Histologic chorioamnionitis without fetal vasculitis was also associated with an increased risk of PTB with PROM (aRR: 2.64, 95% CI: 1.27, 5.50)) and a complementary decreased risk of PTB without PROM (aRR: 0.43 (95% CI: 0.43 (0.26, 0.72)).

We also examined the relationships between clinical characteristics potentially associated with medically indicated PTB and PPROM status (Supplemental Table 1). To summarize, women with PTB without PROM had hypertension or preeclampsia (71.1%), diabetes or gestational diabetes (46.0%), and cesarean delivery (62.6%) more often than PTB patients with PROM.

### 3.5. Fetal tachycardia

The risk of fetal tachycardia was 8.8% in pregnancies without histologic chorioamnionitis (Table 5). Compared with this group, pregnancies with histologic chorioamnionitis with fetal vasculitis had an increased risk of fetal tachycardia (aRR: 2.90, (95% CI: 2.07, 4.05)). Histologic chorioamnionitis without fetal vasculitis was not associated with a significant increased risk of fetal tachycardia (aRR: 1.46 (95% CI: 0.98, 2.17).

**Table 2**
Risk and relative risk of preterm birth by chorioamnionitis and fetal vasculitis exposure groups.

| Exposure Group | N | Preterm Birth, n (%) | Unadjusted RR & 95% CI | Adjusted[a] RR & 95% CI |
|---|---|---|---|---|
| Subclinical Chorioamnionitis | 336 | 62 (18.5) | 0.83 (0.64, 1.07) | 0.92 (0.71, 1.20) |
| Clinical Chorioamnionitis[b] | 59 | 10 (17.0) | 0.76 (0.43, 1.36) | 0.81 (0.44, 1.50) |
| Clinical Chorioamnionitis with Histologic Confirmation | 45 | 7 (15.6) | 0.70 (0.35, 1.40) | 0.82 (0.40, 1.69) |
| No Clinical or Subclinical Chorioamnionitis (Reference) | 976 | 217 (22.2) | – | – |
| Histologic Chorioamnionitis with Fetal Vasculitis | 155 | 36 (23.2) | 1.04 (0.76, 1.41) | 1.17 (0.84, 1.64) |
| Histologic Chorioamnionitis without Fetal Vasculitis | 226 | 33 (14.6) | 0.65 (0.47, 0.91) | 0.73 (0.52, 1.03) |
| No Histologic Chorioamnionitis (Reference) | 979 | 219 (22.4) | – | – |

Abbreviations: RR, relative risk; CI, confidence interval.
[a] Adjusted for maternal age, race, ethnicity, parity, diabetes or gestational diabetes, hypertension or preeclampsia.
[b] With or without histologic chorioamnionitis.

**Table 3**
Risk and relative risk of early and late preterm birth by chorioamnionitis and fetal vasculitis exposure groups.

| Exposure Group | N | Early Preterm Birth (< 34 gestational weeks) | | | Late Preterm Birth (34 to < 37 gestational weeks) | | |
|---|---|---|---|---|---|---|---|
| | | n (%) | Unadjusted RR & 95% CI | Adjusted[a] RR & 95% CI | n (%) | Unadjusted RR & 95% CI | Adjusted[a] RR & 95% CI |
| Subclinical Chorioamnionitis | 336 | 47 (14.0) | 1.55 (1.06, 2.27) | 1.77 (1.18, 2.64) | 15 (4.5) | 0.31 (0.18, 0.54) | 0.35 (0.20, 0.61) |
| Clinical Chorioamnionitis[b] | 59 | 4 (6.8) | 0.74 (0.26, 2.10) | 0.85 (0.29, 2.48) | 6 (10.2) | 0.70 (0.29, 1.66) | 0.69 (0.28, 1.71) |
| No Clinical or Subclinical Chorioamnionitis (Reference) | 976 | 84 (8.6) | – | – | 133 (13.6) | – | – |
| Histologic Chorioamnionitis with Fetal Vasculitis | 155 | 30 (19.4) | 2.28 (1.44, 3.61) | 2.94 (1.78, 4.87) | 6 (3.9) | 0.28 (0.12, 0.66) | 0.32 (0.13, 0.75) |
| Histologic Chorioamnionitis without Fetal Vasculitis | 226 | 20 (8.8) | 0.94 (0.56, 1.57) | 1.05 (0.62, 1.78) | 13 (5.8) | 0.38 (0.21, 0.68) | 0.42 (0.23, 0.77) |
| No Histologic Chorioamnionitis (Reference) | 979 | 84 (8.6) | – | – | 135 (13.8) | – | – |

Abbreviations: RR, relative risk; CI, confidence interval.
[a] Adjusted for maternal age, race, ethnicity, parity, diabetes or gestational diabetes, and hypertension or preeclampsia.
[b] With or without histologic chorioamnionitis.

**Table 4**
Risk and relative risk of preterm birth with and without premature rupture of membranes by chorioamnionitis and fetal vasculitis exposure groups.

| Exposure Group | N | Preterm Birth with PROM | | | Preterm Birth without PROM | | |
|---|---|---|---|---|---|---|---|
| | | n (%) | Unadjusted RR & 95% CI | Adjusted[a] RR & 95% CI | n (%) | Unadjusted RR & 95% CI | Adjusted[a] RR & 95% CI |
| Subclinical Chorioamnionitis | 336 | 29 (8.6) | 3.83 (2.15, 6.82) | 3.92 (2.15, 7.15) | 33 (9.8) | 0.47 (0.31, 0.69) | 0.51 (0.34, 0.78) |
| Clinical Chorioamnionitis[b] | 59 | 4 (6.8) | 2.95 (0.97, 8.93) | 3.42 (1.07, 10.98) | 6 (10.2) | 0.47 (0.20, 1.12) | 0.47 (0.19, 1.16) |
| No Clinical or Subclinical Chorioamnionitis (Reference) | 976 | 21 (2.2) | – | – | 196 (20.1) | – | – |
| Histologic Chorioamnionitis with Fetal Vasculitis | 155 | 20 (12.9) | 6.39 (3.34, 12.22) | 7.44 (3.68, 15.05) | 16 (10.3) | 0.51 (0.30, 0.89) | 0.57 (0.32, 1.02) |
| Histologic Chorioamnionitis without Fetal Vasculitis | 226 | 13 (5.8) | 2.56 (1.25, 5.24) | 2.64 (1.27, 5.50) | 20 (8.8) | 0.40 (0.24, 0.64) | 0.43 (0.26, 0.72) |
| No Histologic Chorioamnionitis (Reference) | 979 | 20 (2.0) | – | – | 199 (20.3) | – | – |

Abbreviations: PROM, premature rupture of membranes; RR, relative risk; CI, confidence interval.
[a] Adjusted for maternal age, race, ethnicity, parity, diabetes or gestational diabetes, and hypertension or preeclampsia.
[b] With or without histologic chorioamnionitis.

### *3.6. Factors linked to infection*

Among pregnancies without clinical or subclinical chorioamnionitis, 24.2% had factors linked to infection besides fever (i.e., elevated white blood cell count, IV antibiotics, and/or positive rectovaginal or urine group B strep culture) prior to rupture of membranes (Table 6). Compared with this group, subclinical, but not clinical, chorioamnionitis was associated with an increased risk of these factors prior to rupture of membranes (aRR: 1.27 (95% CI: 1.02, 1.58). Although subclinical chorioamnionitis was positively associated with each factor individually, only increased risk of elevated white blood cell count was statistically significant (aRR: 1.71 (95% CI: 1.19, 2.44).

## 4. Discussion

In this cohort, which was enriched with high risk pregnancies, including spontaneous and medically indicated PTBs and pregnancies with elevated risks of these outcomes, neither subclinical nor clinical chorioamnionitis was associated with PTB overall. Subclinical chorioamnionitis was widespread, affecting one quarter of all pregnancies and representing the majority of cases of histologic chorioamnionitis. Subclinical chorioamnionitis was associated with a nearly 2-fold increased risk of early PTB and a nearly 4-fold increased risk of PTB with PROM. Clinical chorioamnionitis occurred in fewer than 5% of pregnancies and was associated with an increased risk of PTB with PROM only. Histologic chorioamnionitis with fetal vasculitis was associated with a nearly 3-fold increased risk of early PTB and fetal tachycardia and a more than 7-fold increased risk for PTB with PROM. In contrast, histologic chorioamnionitis without fetal vasculitis was not associated with early PTB or fetal tachycardia and trended toward being less strongly associated with PTB with PROM.

Unlike previous studies reporting an association between histologic chorioamnionitis and PTB [1,7,14–16], in our cohort, subclinical chorioamnionitis, clinical chorioamnionitis, and fetal vasculitis were not associated with PTB overall. However, the magnitude of the associations between subclinical chorioamnionitis and early PTB and of PTB

**Table 5**
Association between fetal vasculitis and fetal tachycardia.

| Exposure Group | N | Fetal Tachycardia n (%) | Unadjusted RR & 95% CI | Adjusted[a] RR & 95% CI |
|---|---|---|---|---|
| Histologic Chorioamnionitis with Fetal Vasculitis | 155 | 46 (29.7) | 3.38 (2.46, 4.63) | 2.90 (2.07, 4.05) |
| Histologic Chorioamnionitis without Fetal Vasculitis | 226 | 31 (13.7) | 1.56 (1.06, 2.29) | 1.46 (0.98, 2.17) |
| No Histologic Chorioamnionitis (Reference) | 979 | 86 (8.8) | – | – |

Abbreviations: RR, relative risk; CI, confidence interval.
[a] Adjusted for maternal age, race, ethnicity, parity, diabetes or gestational diabetes, and hypertension or preeclampsia.

**Table 6**
Association between subclinical chorioamnionitis and factors linked to infection other than fever before membrane rupture (ROM), restricted to women with both delivery records and prenatal care records (N = 1211).

| Exposure Group | N | Factors Linked to Infection Before Rupture of Membranes[a] | | | White Blood Cell Count > 13,000 mm^3[b] | | | Group B Strep Positive[c] | | | IV Antibiotic[d] | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n.(%) | RR.& 95% CI | Adjusted[e] RR.& 95% CI | n.(%) | RR.& 95% CI | Adjusted[e] RR & 95% CI | N.(%) | RR.& 95% CI | Adjusted[e] RR.& 95% CI | n.(%) | RR.& 95% CI | Adjusted[e] RR & 95% CI |
| Subclinical Chorioamnionitis | 280 | 87 (31.1) | 1.28.(1.04, 1.58) | 1.27.(1.02, 1.58) | 42 (15.0) | 1.71.(1.21, 2.43) | 1.71.(1.19, 2.44) | 52 (18.6) | 1.26.(0.94, 1.68) | 1.45.(0.64, 3.28) | 8 (2.9) | 1.26.(0.56, 2.82) | 1.27.(0.94, 1.71) |
| Clinical Chorioamnionitis[f] | 51 | 14 (27.5) | 1.13.(0.72, 1.80) | 1.04.(0.65, 1.66) | 5 (9.8) | 1.12.(0.47, 2.65) | 1.05.(0.44, 2.47) | 9 (17.7) | 1.19.(0.65, 2.20) | 1.51.(0.37, 6.12) | 2 (3.9) | 1.73.(0.41, 7.18) | 1.21.(0.65, 2.27) |
| No Clinical or Subclinical Chorioamnionitis (Reference) | 880 | 213 (24.2) | – | – | 77 (8.8) | – | – | 130 (14.8) | – | – | 20 (2.3) | – | – |

[a] At least one of the other three factors (i.e., elevated white blood cell count, group B strep positive, IV antibiotics).
[b] White blood cell count > 13,000 mm^3 during delivery admission and before rupture of membranes.
[c] Positive group B strep culture between gestational week 20 and before rupture of membranes; 1 missing.
[d] At least one antibiotic during the delivery admission and before rupture of membranes.
[e] Adjusted for maternal age, race, ethnicity, parity, diabetes or gestational diabetes, hypertension or preeclampsia.
[f] Regardless of histologic confirmation.

with PROM was in line with previously reported associations between histologic chorioamnionitis and PTB overall [7,14,16]. The likely high proportion of medically indicated PTB in our cohort may have contributed to the lack of association between subclinical and clinical chorioamnionitis and PTB overall observed in our study, as medically indicated PTB may have frequently preceded the opportunity for ascending infection that otherwise could have led to PTB. Consistent with this possibility, the previous studies reporting the strongest associations between histologic chorioamnionitis and PTB excluded indicated PTBs [7] or women with risk factors for indicated PTB including hypertension [14]. Although we did not have complete information on the clinical presentation of patients with PTB, more women with PTB without PROM had hypertension and diabetes than women with PTB with PROM, suggesting that indicated PTBs were common in the PTB without PROM group. Moreover, subclinical chorioamnionitis was inversely associated with PTB without PROM, suggesting that medically-indicated PTB was an important competing risk for infection-related PTB [25]. Similarly, a previous study including only preterm deliveries reported that histologic chorioamnionitis was associated with an increased risk of PROM and preterm labor and a strong decreased risk of indicated delivery [5].

Fetal vasculitis is associated with higher risk of neonatal morbidity, including infection, than histologic chorioamnionitis alone in some studies [19,26]. We demonstrated that fetal vasculitis is also associated with a higher risk of early PTB and a higher, although not significantly higher, risk of PTB with PROM than histologic chorioamnionitis alone. In a study of term pregnancies, Curtin et al. demonstrated that histologic chorioamnionitis and fetal inflammatory response were associated with a nearly 3-fold increase risk of fetal tachycardia [8]. Building upon this study, we found that fetal tachycardia was associated with a nearly 3-fold increased risk when histologic chorioamnionitis was accompanied by fetal vasculitis, but not in the latter's absence.

Taken together, these results suggest that intrauterine infection, as indicated by histologic chorioamnionitis (particularly in the presence of fetal vasculitis, and even in the absence of clinical signs of chorioamnionitis), is strongly associated with early PTB and PTB with PPROM. Furthermore, the previous literature indicates that histologic chorioamnionitis can be used to predict the risk of neonatal infection and associated complications [5,19,26,27].

Our study could not determine the primary causal pathway underlying the association between subclinical chorioamnionitis and early PTB or PTB with PROM, including subclinical chorioamnionitis triggering spontaneous preterm labor or PPROM causing ascending infection leading to both subclinical chorioamnionitis and PTB. However, we found evidence supportive of both pathways contributing to the association in this cohort. The strong positive association between subclinical chorioamnionitis and PTB with PROM suggests ascending infection after rupture of membrane. Infection before rupture may have contributed to PTB as well, as there was a modest positive association between subclinical chorioamnionitis and factors linked to infection during the delivery hospitalization before membrane rupture.

The major limitation of our study was the lack of sufficient information regarding the onset of labor to allow us to definitively classify PTBs, aside from PPROM, as either spontaneous or medically indicated. This information would have allowed us to evaluate the impact of subclinical infection on each type of PTB and to explore our hypothesis of competing medically indicated causes of PTB as an explanation of the null finding between subclinical chorioamnionitis and PTB observed in our study. Additionally, we did not have the information available to restrict our analyses to women with cesarean delivery before membrane rupture, in order to distinguish between subclinical infection as a cause of PTB vs. the result of PPROM. Furthermore, we defined clinical chorioamnionitis based on fever as recorded in the EMR during the delivery hospitalization as opposed to using additional clinical criteria. Although this approach was intended to be sensitive, nearly one-quarter of women classified as having

clinical chorioamnionitis did not have histologic chorioamnionitis, and the definition may have included patients who were not considered to have clinical chorioamnionitis by their providers. Finally, we do not know how accurately fever was captured in the EMR data, and under-recording of fever could contribute to the disparity between the prevalence of clinical and subclinical chorioamnionitis.

Our study population was racially and ethnically diverse, which may increase the generalizability of the results. However, the prevalence of women with comorbidities was high, and the findings may not be generalizable to populations with lower risks of pregnancy complications, especially if our hypothesis regarding the competing cause of medically indicated PTB holds true.

Nevertheless, the major strength of the study is the availability of information on both histologic chorioamnionitis and fetal vasculitis, unlike previous studies that primarily focused on histologic chorioamnionitis [7,14,16]. The large study size and high incidence of PTB allowed for adequate statistical power to evaluate the impact of subclinical chorioamnionitis on PTB subtypes. Unlike previous studies which provided unadjusted risk estimates or odds ratios adjusted for both potential confounders and downstream consequences of chorioamnionitis [1,7,14–16], our study provided relative risk estimates adjusted only for potential confounders.

Our study quantifies the association between subclinical chorioamnionitis, as well as histologic chorioamnionitis with and without fetal vasculitis, and early PTB and PTB with PROM in a cohort enriched with high risk pregnancies. While there was no association between subclinical or clinical chorioamnionitis and PTB overall, subclinical chorioamnionitis and histologic chorioamnionitis with fetal vasculitis were strongly associated with early PTB and PTB with PROM, demonstrating the importance of considering subtypes when studying PTB. Given the strong association between subclinical chorioamnionitis and early PTB and PTB with PROM, and that only 12% of histologic chorioamnionitis was clinically apparent, our study further highlights the crucial role of a complete placental pathologic examination in the setting of PTB.

## Contributions

Kristin Palmsten: I declare that I participated in the study conception and design, analysis and interpretation of results, drafting of the manuscript, and critical revision of the manuscript and that I have seen and approved the final version. I have the following conflicts of interest: none to declare.

Katharine K Nelson: I declare that I participated in the acquisition of the data and critical revision of the manuscript and that I have seen and approved the final version. I have the following conflicts of interest: none to declare.

Louise L Laurent: I declare that I participated in the study conception and design, interpretation of results, and critical revision of the manuscript and that I have seen and approved the final version. I have the following conflicts of interest: none to declare.

Soojin Park: I declare that I participated in the acquisition of the data and critical revision of the manuscript and that I have seen and approved the final version. I have the following conflicts of interest: none to declare.

Christina D Chambers: I declare that I participated in the study conception and design, interpretation of results, and critical revision of the manuscript and that I have seen and approved the final version. I have the following conflicts of interest: none to declare.

Mana Parast: I declare that I participated in the study conception and design, acquisition of data, interpretation of results, and critical revision of the manuscript and that I have seen and approved the final version. I have the following conflicts of interest: none to declare.

## Data statement

The data are confidential and are not available for open access.

## Declarations of competing interests

None to report.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.placenta.2018.06.001.

## References

[1] C.J. Kim, R. Romero, P. Chaemsaithong, N. Chaiyasit, B.H. Yoon, Y.M. Kim, Acute chorioamnionitis and funisitis: definition, pathologic features, and clinical significance, Am. J. Obstet. Gynecol. 213 (4 Suppl) (2015) S29–S52.
[2] A.T. Tita, W.W. Andrews, Diagnosis and management of clinical chorioamnionitis, Clin. Perinatol. 37 (2) (2010) 339–354.
[3] R.M. Viscardi, C.K. Muhumuza, A. Rodriguez, et al., Inflammatory markers in intrauterine and fetal blood and cerebrospinal fluid compartments are associated with adverse pulmonary and neurologic outcomes in preterm infants, Pediatr. Res. 55 (6) (2004) 1009–1017.
[4] M. Gupta, K.K. Mestan, C.R. Martin, et al., Impact of clinical and histologic correlates of maternal and fetal inflammatory response on gestational age in preterm births, J. Matern. Fetal Neonatal Med. 20 (1) (2007) 39–46.
[5] D. Ogunyemi, M. Murillo, U. Jackson, N. Hunter, B. Alperson, The relationship between placental histopathology findings and perinatal outcome in preterm infants, J. Matern. Fetal Neonatal Med. 13 (2) (2003) 102–109.
[6] J. Armstrong-Wells, M.D. Post, M. Donnelly, M.J. Manco-Johnson, B.M. Fisher, V.D. Winn, Patterns of placental pathology in preterm premature rupture of membranes, J Dev Orig Health Dis. 4 (3) (2013) 249–255.
[7] B. Horvath, F. Lakatos, C. Toth, T. Bodecs, J. Bodis, Silent chorioamnionitis and associated pregnancy outcomes: a review of clinical data gathered over a 16-year period, J. Perinat. Med. 42 (4) (2014) 441–447.
[8] W.M. Curtin, P.J. Katzman, H. Florescue, L.A. Metlay, Accuracy of signs of clinical chorioamnionitis in the term parturient, J. Perinatol. 33 (6) (2013) 422–428.
[9] M.S. Doty, C. Salafia, S. Shen-Schwarz, E. Guzman, G.R. Saade, S.P. Chauhan, Histologic funisitis and likelihood of intrauterine inflammation or infection: a case-control study, Am. J. Perinatol. (2018), http://dx.doi.org/10.1055/s-0037-1620232.
[10] R.W. Redline, Classification of placental lesions, Am. J. Obstet. Gynecol. 213 (4 Suppl) (2015) S21–S28.
[11] M.S. Kramer, A. Papageorghiou, J. Culhane, et al., Challenges in defining and classifying the preterm birth syndrome, Am. J. Obstet. Gynecol. 206 (2) (2012) 108–112.
[12] J. Villar, A.T. Papageorghiou, H.E. Knight, et al., The preterm birth syndrome: a prototype phenotypic classification, Am. J. Obstet. Gynecol. 206 (2) (2012) 119–123.
[13] R.L. Goldenberg, J.F. Culhane, J.D. Iams, R. Romero, Epidemiology and causes of preterm birth, Lancet 371 (9606) (2008) 75–84.
[14] S.L. Hillier, J. Martius, M. Krohn, N. Kiviat, K.K. Holmes, D.A. Eschenbach, A case-control study of chorioamnionic infection and histologic chorioamnionitis in prematurity, N. Engl. J. Med. 319 (15) (1988) 972–978.
[15] C. Ustun, I. Kocak, S. Baris, A. Uzel, F. Saltik, Subclinical chorioamnionitis as an etiologic factor in preterm deliveries, Int. J. Gynaecol. Obstet. 72 (2) (2001) 109–115.
[16] D.S. Guzick, K. Winn, The association of chorioamnionitis with preterm delivery, Obstet. Gynecol. 65 (1) (1985) 11–16.
[17] M.M. Lahra, P.J. Beeby, H.E. Jeffery, Maternal versus fetal inflammation and respiratory distress syndrome: a 10-year hospital cohort study, Arch. Dis. Child. Fetal Neonatal Ed. 94 (1) (2009) F13–F16.
[18] E.F. Schisterman, S.R. Cole, R.W. Platt, Overadjustment bias and unnecessary adjustment in epidemiologic studies, Epidemiology 20 (4) (2009) 488–495.
[19] J. Lau, F. Magee, Z. Qiu, J. Hoube, P. Von Dadelszen, S.K. Lee, Chorioamnionitis with a fetal inflammatory response is associated with higher neonatal mortality, morbidity, and resource use than chorioamnionitis displaying a maternal

inflammatory response only, Am. J. Obstet. Gynecol. 193 (3 Pt 1) (2005) 708–713.
[20] C.M. Salafia, A. Ghidini, D.M. Sherer, J.C. Pezzullo, Abnormalities of the fetal heart rate in preterm deliveries are associated with acute intra-amniotic infection, J. Soc. Gynecol. Invest. 5 (4) (1998) 188–191.
[21] H. Kyozuka, S. Yasuda, T. Hiraiwa, M. Ishibashi, K. Kato, K. Fujimori, Histological chorioamnionitis as a risk factor for preterm birth without disturbing fetal heart rate: a case-control study, Tohoku J. Exp. Med. 243 (4) (2017) 289–295.
[22] S.M. Leon-Garcia, H.A. Roeder, K.K. Nelson, et al., Maternal obesity and sex-specific differences in placental pathology, Placenta 38 (2016) 33–40.
[23] G. Zou, A modified Poisson regression approach to prospective studies with binary data, Am. J. Epidemiol. 159 (7) (2004) 702–706.
[24] G.Y. Zou, A. Donner, Extension of the modified Poisson regression model to prospective studies with correlated binary data, Stat. Meth. Med. Res. 22 (6) (2013) 661–670.
[25] K.S. Joseph, Early and later gestation outcomes: competing risks across the pregnancy continuum, Paediatr. Perinat. Epidemiol. 31 (1) (2017) 64–66.
[26] H. Du, E. Liu, C. Xu, S. Zhao, H. Xiang, Z. Li, Prognostic value of funisitis and/or chorionic vasculitis compared to histologic chorioamnionitis in full-term infants, J. Matern. Fetal Neonatal Med. 30 (2) (2017) 169–173.
[27] K.M. Chisholm, A. Heerema-McKenney, L. Tian, et al., Correlation of preterm infant illness severity with placental histology, Placenta 39 (2016) 61–69.