Effect of gestational age at first delivery and interpregnancy interval on the recurrence of clinical chorioamnionitis

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BACKGROUND: There is an increased odds of having a recurrence of clinical chorioamnionitis in patients with a diagnosis of clinical chorioamnionitis compared with those without clinical chorioamnionitis in a previous pregnancy. However, it is unclear how gestational age at delivery of the first pregnancy or interpregnancy interval may contribute to this increased risk.

OBJECTIVE: This study aimed to evaluate how gestational age of delivery in a first pregnancy and interpregnancy interval affect the odds of recurrent clinical chorioamnionitis.

STUDY DESIGN: Using maternally linked birth record files, Nulliparous patients from California with at least 2 consecutive deliveries between the gestational ages of 20 and 44 weeks from 2007 to 2012 were identified. The rates of clinical chorioamnionitis in the second pregnancy for patients with clinical chorioamnionitis vs those without clinical chorioamnionitis in the first pregnancy, stratified by the gestational age at delivery of the first pregnancy were determined. As a secondary analysis, the analysis by interpregnancy interval (<18 months vs ≥18 months) was stratified. Corresponding crude and adjusted odds ratios for each stratum were calculated to assess the association of clinical chorioamnionitis in the first and second pregnancies.

RESULTS: Among 31,571 nulliparous patients with clinical chorioamnionitis in the first pregnancy, the frequency of clinical chorioamnionitis in the next pregnancy was 4.0% (1257 cases). This was in comparison with the 1.0% (9177 of 896,154) of nulliparous patients without clinical chorioamnionitis in the first pregnancy who were diagnosed with clinical chorioamnionitis in the next pregnancy (adjusted odds ratio, 2.78; 95% confidence interval, 2.61−2.96). The absolute frequency of recurrence was the highest (54 cases [8.2%]) in those who delivered at 20 to 24 weeks of gestation in the first pregnancy with the diagnosis of clinical chorioamnionitis (adjusted odds ratio, 1.76; 95% confidence interval, 1.25−2.48). For pregnancies delivered at term in the first pregnancy, the frequency of clinical chorioamnionitis in the next pregnancy was higher in those diagnosed with clinical chorioamnionitis in the first pregnancy than in those without clinical chorioamnionitis in the first pregnancy (4.0% vs 1.0%; adjusted odds ratio, 2.85; 95% confidence interval, 2.66−3.05). An interpregnancy interval of <18 months was not associated with increased odds of recurrent clinical chorioamnionitis.

CONCLUSION: The odds of recurrence of clinical chorioamnionitis were the strongest when a patient delivered in the term to postterm period in the first pregnancy, with the absolute risk being the highest when the first pregnancy was delivered in the perivable period (20−24 weeks of gestation). The interpregnancy interval did not seem to modify the risk of recurrent clinical chorioamnionitis.

Key words: chorioamnionitis, intra-amniotic infection, maternal fever, maternal infection

Clinical chorioamnionitis (CC), or intraamniotic infection, is suspected when an intrapartum fever is noted along with maternal leukocytosis, purulent cervical drainage, or fetal tachycardia.1 It is estimated to affect approximately 2% to 5% of term pregnancies and complicates up to 40% to 70% of preterm deliveries presenting with preterm premature rupture of membranes (PPROM).1–3 Chorioamnionitis leads to an increased risk of cesarean delivery.

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Why was this study conducted?
Clinical chorioamnionitis (CC) is more likely to occur in patients with a history of the disease, but little is known about what contributes to this recurrence. This study investigated how gestational age of delivery in the first pregnancy and interpregnancy interval (IPI) affected the odds of recurrence.

Key findings
The recurrence of CC was most significant when a patient delivered in the term to postterm period in the first pregnancy (37–42 weeks of gestation), but the absolute risk was the highest when the first pregnancy was delivered in the perivable period (20–24 weeks of gestation). IPI did not contribute significantly to the risk of recurrent CC.

What does this add to what is known?
Gestational age of delivery in the first pregnancy has been found to be a significant risk factor for the recurrence of CC in a subsequent pregnancy.

Materials and Methods
This prospective cohort study used a previously linked database from California’s Office of Statewide Health Planning and Development. The database contains linked birth and fetal death certificates and maternal and infant hospitalization discharge records for births in the state between 2007 and 2012, including across a patient’s pregnancies if they had more than one. The Stanford Institutional Review Board approved the study (IRB protocol: 14746). Ethics approval for this study was obtained from the State of California Committee for the Protection of Human Subjects and the Stanford University Research Compliance Office.

We included patients who had at least 2 deliveries at ≥20 weeks of gestation between the years 2007 and 2012 and who were nulliparous at the time of their first delivery during this period. If a patient had >2 deliveries during this period, only the first 2 deliveries were included in the analysis. Only singleton pregnancies between the gestational ages of 20 to 44 weeks who had labored were included. Patients were considered to have labored if vaginal delivery was noted or if there was an indication for a CD after labor, such as a failed trial of labor after CD, arrest of dilation, arrest of descent, or nonreassuring fetal status. Because of their very low risk of CC, we excluded patients who had a scheduled CD in either delivery. A CD was considered scheduled if it did not have the following conditions: fetal distress, cephalopelvic disproportion, induction of labor, prolonged labor, failed operative vaginal delivery, uterine rupture, and/or attempt at vaginal delivery (ie, arrest of dilation or arrest of descent). Other exclusion criteria included records that were missing information on covariates that were used in the multivariate analysis and maternal hospitalizations not linked to birth certificate data.

CC was identified through International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM) codes (658.4, 658.41, 658.42, 659.3, and 762.7) or if the patient was coded for “chorioamnionitis” or “CC” diagnosed during labor or maternal temperature ≥38°C (100.4°F) on their birth certificate for either of the 2 pregnancies.

We first compared the characteristics of patients who did and did not develop CC in their first delivery. Moreover, we compared the characteristics of those diagnosed with CC in their second pregnancy by their CC status in their first pregnancy to understand if those who were diagnosed with CC twice were distinct from those who were only diagnosed once. Differences between these groups were assessed with chi-square testing.

Next, we calculated the rate of CC in the first pregnancy. Furthermore, we calculated the rates of CC in the second pregnancy, stratified by those with and without CC in the first pregnancy. Crude odds ratios (ORs) and adjusted ORs (aORs) were calculated to evaluate the association between having CC in the first pregnancy and having CC in the second pregnancy. The covariates used to calculate the aORs were measures from the first pregnancy (education and type of insurance) and second pregnancy (maternal age, prolonged rupture of membranes, prolonged labor [defined as ≥20 hours in labor], epidural, and group B streptococcus (GBS) colonization). We further adjusted for the mode of delivery in both the first and second deliveries (vaginal delivery-CD, CD-CD, and CD-vaginal delivery).

In addition, we replicated these analyses stratified by gestational age of delivery in the first pregnancy: 20–24, 25–32, 33–36, 37–41, and 42–44 weeks. As a
Results
There were 927,725 patients with a singleton delivery at ≥20 gestational weeks in their first delivery. Of these patients, 31,571 (3.4%) were diagnosed with CC in their first pregnancy, and 896,154 (96.6%) did not have CC (Figure 1). In examining the second pregnancy, 10,434 patients (1.1%) were diagnosed with CC. Of the 31,571 patients with CC in the first pregnancy, 1,257 (4.0%) were diagnosed with CC in the second pregnancy. This was in contrast with the 9,177 patients (1.0%) who did not have CC in their first pregnancy but were diagnosed with CC in their second pregnancy.

Table 1 shows the characteristics of those with CC vs those without CC in their first pregnancy. Patients diagnosed with CC were more likely to have a CD (22.4% vs 7.1%), be GBS carriers (33.9% vs 22.5%), and have an epidural in labor (30.0% vs 14.8%). Furthermore, patients with CC were more likely to have meconium-stained amniotic fluid, prolonged rupture of membranes, PPROM, stillbirth, and postpartum hemorrhage.

Table 2 shows the characteristics of patients with CC in the second pregnancy, stratified by whether the patient had CC in the first pregnancy. Patients with CC in both the first and second pregnancies were more likely to experience prolonged rupture of membranes, PPROM, postpartum hemorrhage, meconium-stained amniotic fluid, and stillbirth than patients only diagnosed with CC in the second pregnancy and not the first pregnancy. Furthermore, they were more likely to deliver between 20 and 32 weeks of gestation (7.0% vs 1.5%) and had higher frequencies of primary CD (19.6% vs 6.8%) and operative vaginal delivery (7.8% vs 4.3%).

Table 3 shows the frequency of CC in the second pregnancy overall and stratified by gestational age of delivery in the first pregnancy. Those with CC in the first pregnancy had significantly higher odds of being diagnosed with CC in a second pregnancy (aOR, 2.78; 95% confidence interval [CI], 2.61–2.96). The absolute frequency of CC was the highest in those with CC in the first pregnancy with delivery at 20 to 24 weeks of gestation at 8.2% (aOR, 1.76; 95% CI, 1.25–2.48). However, the OR for the association between a history of CC and occurrence in the second pregnancy was the highest in the full-term strata: 37 to 41 weeks of gestation (aOR, 2.85; 95% CI, 2.66–3.05) and 42 to 44 weeks of gestation (aOR, 2.50; 95% CI, 1.93–3.22).

Table 4 shows the frequency of CC in the second pregnancy, comparing those with CC vs those without CC in the first pregnancy, stratified by shorter (<18 months) vs longer (≥18 months) IPI.

Discussion
Principal findings
We found that the absolute frequency of recurrent CC was the highest when the first pregnancy was delivered in the periviable period (20 to 24 weeks of gestation), but that the highest OR occurred when the first pregnancy was delivered in the term to postterm period. In addition, we found that the duration of IPI did not affect the recurrence risk of CC, as the odds were increased when a short IPI and a long IPI were analyzed.

Results in the context of what is known
The first investigation into the recurrence of CC did not show an increased risk of diagnosis in a subsequent pregnancy. However, this study was limited by a small sample size of 76 patients and may not have been large enough to detect a difference. More recent studies have shown an approximate 2- to 3-fold increased odds of being diagnosed with recurrent CC, which is congruent with our results. However, these studies were also limited in the absolute number of patients who had a recurrence of CC at 131 and 138 patients, respectively. Given that we had 1257 patients who were diagnosed with CC twice, we were able to further investigate gestational age and IPI as risk factors for recurrence.

As expected, the absolute frequency of CC at earlier gestations was higher than at term, as this diagnosis is oftentimes the indication for preterm delivery. However, of those who delivered in the periviable period with CC in the first pregnancy, more than 8% of these patients were diagnosed with CC in a subsequent pregnancy, regardless of the gestational age they delivered in a subsequent pregnancy. It is unclear why such increased risk is conferred, but this could potentially be due to dysbiosis of the vaginal flora or a persistent
infectious or inflammatory environment, as infection-induced inflammatory pathways involved with bacterial vaginosis or other ascending pathogens have shown an association with preterm delivery. This was further supported by the higher number of patients in our cohort who were colonized with GBS and ended up being diagnosed with recurrent CC.

The strongest association with recurrent CC occurred when the first delivery was at term or in the postterm period. There has been a noted association with an increased relative risk of chorioamnionitis after 40 weeks of gestation. However, it is unclear why patients who have a diagnosis of CC in the term or postterm period in their first pregnancy have higher odds of recurrence in a subsequent pregnancy than patients with a recurrence of CC who have delivered in the preterm period in their first pregnancy. However, some of these occurrences could be related to intrapartum variables in those who labor at term, such as the number of internal examinations or misoprostol use as an induction agent, which could lead to an intrapartum fever and potential overdiagnosis of chorioamnionitis.

In addition, a short IPI is associated with multiple adverse outcomes, including preterm delivery, with increased cytokines present in those with the diagnosis of CC. The biochemistry regarding the etiology of a preterm birth is complicated, and multiple pathways can lead to alterations in triggering of inflammation or anti-inflammation, up-regulation of oxytocin receptors, and down-regulation of progesterone receptors, with studies showing a decrease in anti-inflammatory cytokines in those who are affected. Given that CC in the periviable period conferred such a large absolute risk of developing CC in a subsequent pregnancy, we hypothesized that a short IPI would confer a larger risk of developing a recurrence because of a potential state of chronic infection or inflammation. However, we found no significant association between the length of IPI and the recurrence of CC. It is possible that we were underpowered

| Characteristic | CC (n=31,571), n (%) | No CC (n=896,154), n (%) | P valuea |
|---------------|---------------------|-------------------------|---------|
| Maternal age (y) | <.001 |
| ≤18 | 3159 (10.0) 134,626 (15) |
| 19−30 | 19,997 (63.3) 581,011 (64.8) |
| 31−35 | 6634 (21.0) 145,356 (16.2) |
| 36−40 | 1690 (5.4) 33,515 (3.7) |
| ≥41 | 91 (0.3) 1626 (0.2) |
| Maternal race and ethnicity | <.001 |
| American Indian or Alaskan Native | 111 (0.4) 4209 (0.5) |
| Asian | 5101 (16.2) 106,581 (11.9) |
| Black | 1997 (6.3) 51,702 (5.8) |
| Latina | 11,493 (36.5) 340,098 (38.0) |
| Pacific Islander | 2263 (7.2) 33,669 (3.8) |
| White | 10,527 (33.4) 357,655 (40.0) |
| Other | 23 (0.1) 491 (0.1) |
| Refused to answer or unknown | 56 (0.002) 1749 (0.002) |
| Gestational age at delivery (wk) | <.001 |
| 20−24 | 657 (2.1) 2822 (0.3) |
| 25−32 | 981 (3.1) 10,208 (1.1) |
| 33−36 | 1791 (5.7) 59,127 (6.6) |
| 37−41 | 26,344 (83.4) 772,511 (86.2) |
| 42−44 | 1798 (5.7) 51,486 (5.7) |
| Mode of delivery | <.001 |
| Spontaneous vaginal | 19,215 (60.9) 721,565 (80.5) |
| Cesarean | 7079 (22.4) 63,929 (7.1) |
| Operative vaginal | 5277 (16.7) 110,660 (12.3) |
| Gestational diabetes mellitus | 1704 (5.4) 32,270 (3.6) <.001 |
| Pregestational diabetes mellitus | 559 (1.8) 11,929 (1.3) <.001 |
| Chronic hypertension | 333 (1.1) 6255 (0.7) <.001 |
| Cigarette use in pregnancy | 606 (1.9) 17,019 (1.9) .794 |
| Epidural | 9484 (30.0) 132,701 (14.8) <.001 |
| Group B streptococcus positive | 10,705 (33.9) 201,636 (22.5) <.001 |
| Meconium | 3141 (9.9) 43,083 (4.8) <.001 |
| Prolonged rupture of membranes | 1899 (6.0) 15,352 (1.7) <.001 |
| Preterm prelabor rupture of membranes | 2494 (7.9) 40,742 (4.5) <.001 |
| Stillbirth | 513 (1.62) 4184 (0.47) <.001 |
| Postpartum hemorrhage | 2115 (6.7) 26,968 (3.0) <.001 |

CC, clinical chorioamnionitis.

a All comparisons had P values of <.001.

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### TABLE 2
Characteristics of patients diagnosed with CC vs patients without CC in the first pregnancy among those who had CC in their second pregnancy

| Characteristic                      | CC in the first pregnancy (n=1257), n (%) | No CC in the first pregnancy (n=30,314), n (%) | P value |
|-------------------------------------|------------------------------------------|-----------------------------------------------|---------|
| Maternal age (y)                   |                                          |                                               | .09     |
| ≤18                                 | 11 (0.9)                                 | 510 (1.7)                                      |         |
| 19–30                               | 650 (51.7)                               | 16,168 (53.3)                                 |         |
| 31–35                               | 382 (30.4)                               | 8873 (29.3)                                   |         |
| 36–40                               | 183 (14.6)                               | 4171 (13.8)                                   |         |
| ≥41                                 | 31 (2.5)                                 | 592 (2.0)                                     |         |
| Maternal race and ethnicity         |                                          |                                               | <.001   |
| American Indian                     | 3 (0.2)                                  | 94 (0.3)                                      |         |
| Asian                               | 205 (16.7)                               | 4840 (16.2)                                   |         |
| Black                               | 113 (9.2)                                | 1842 (6.2)                                    |         |
| Latina                              | 444 (36.1)                               | 10,956 (36.7)                                 |         |
| Pacific Islander                    | 150 (12.2)                               | 2080 (7.0)                                    |         |
| White                               | 316 (25.7)                               | 10,062 (33.7)                                 |         |
| Gestational age at second delivery (wk) |                                          |                                               | <.001   |
| 20–24                               | 26 (2.1)                                 | 89 (0.3)                                      |         |
| 25–32                               | 61 (4.9)                                 | 352 (1.2)                                     |         |
| 33–36                               | 77 (6.1)                                 | 1758 (5.8)                                    |         |
| 37–41                               | 1057 (84.1)                              | 27,266 (89.9)                                 |         |
| 42–44                               | 36 (2.9)                                 | 849 (2.8)                                     |         |
| Mode of delivery                    |                                          |                                               | <.001   |
| Vaginal delivery                    | 698 (55.5)                               | 22,540 (74.4)                                 |         |
| CD, primary                         | 246 (19.6)                               | 2060 (6.8)                                    |         |
| CD, repeat                          | 214 (17.0)                               | 4411 (14.6)                                   |         |
| Operative vaginal birth             | 99 (7.8)                                 | 1303 (4.3)                                    |         |
| Vaginal birth after CD              | 110 (8.8)                                | 930 (3.1)                                     |         |
| Gestational diabetes mellitus       | 135 (10.7)                               | 2573 (8.5)                                    | .005    |
| Pregestational diabetes mellitus    | 25 (2.0)                                 | 582 (1.9)                                     | .86     |
| Chronic hypertension                | 28 (2.2)                                 | 393 (1.3)                                     | <.001   |
| Cigarette use during pregnancy      | 24 (1.9)                                 | 509 (1.7)                                     | .53     |
| Epidural                            | 667 (53.1)                               | 12,697 (41.9)                                 | <.001   |
| Group B streptococcus positive      | 697 (55.4)                               | 14,757 (48.7)                                 | <.001   |
| Meconium                            | 119 (9.5)                                | 1383 (4.6)                                    | <.001   |
| Prolonged rupture of membranes      | 47 (3.7)                                 | 265 (0.9)                                     | <.001   |
| Preterm prelabor rupture of membranes | 110 (8.8)                              | 1210 (4.0)                                    | <.001   |
| Stillbirth                          | 14 (1.11)                                | 93 (0.31)                                     | <.001   |
| Postpartum hemorrhage               | 101 (8.0)                                | 1113 (3.7)                                    | <.001   |

CC, clinical chorioamnionitis; CD, cesarean delivery.

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to detect an association between extremely short IPIs (ie, IPI of <6 months) and recurrent CC.

**Clinical implications**
The diagnosis of CC is a risk factor for multiple adverse pregnancy and neonatal outcomes. In a subsequent pregnancy, patients may be interested in knowing how a previous infection may affect their odds of recurrence. Although previous evidence would suggest a 2- to 3-fold increased odds of a recurrence of CC,7,8 our study provided a more granular information about the probability of recurrence based on the gestational age of delivery in the first pregnancy. Furthermore, it may lead to a more timely diagnosis by the care team in recognizing this increased risk for this particular group of patients.

**Research implications**
Research implications of our work are potentially important in identifying the causes of the high absolute recurrence rate when the index case of CC occurs in the periviable period. For example, if persistent vaginal dysbiosis or persistent infection or inflammation is identified, then interventions might be tested to prevent a recurrence.

**Strengths and limitations**
The main strength of this study was its longitudinal data can be collected to be powered to detect an association between even shorter IPIs (ie, IPI of <6 months), and this would be another area for further research once more longitudinal data can be collected to be powered to evaluate this outcome.

In addition, although we studied IPI as a risk factor for recurrent CC, we used a cutoff for a short IPI of <18 months. We were potentially underpowered to detect an association between even shorter IPIs (ie, <6 months), and this would be another area for further research once more longitudinal data can be collected to be powered to evaluate this outcome.

**Conclusions**
We found that the highest absolute odds of recurrent CC was associated with delivery during the periviable period of

| Gestational age at delivery in the first pregnancy (wk) | With CC in the first pregnancy | Without CC in the first pregnancy | OR (95% CI) | Adjusted OR (95% CI)* |
|--------------------------------------------------------|-------------------------------|----------------------------------|-------------|-----------------------|
| 20–24                                                  | 54 (8.2)                      | 119 (4.2)                        | 2.03 (1.46–2.84) | 1.76 (1.25–2.48)     |
| 25–32                                                  | 26 (2.7)                      | 204 (2.0)                        | 1.34 (0.88–2.02) | 1.18 (0.78–1.79)     |
| 33–36                                                  | 59 (3.3)                      | 762 (1.3)                        | 2.58 (1.98–3.36) | 2.16 (1.65–2.84)     |
| 37–41                                                  | 1042 (4.0)                    | 7493 (1.0)                       | 4.21 (3.94–4.99) | 2.85 (2.66–3.05)     |
| 42–44                                                  | 76 (4.2)                      | 599 (1.2)                        | 3.75 (2.94–4.79) | 2.50 (1.93–3.22)     |
| Total                                                  | 1257 (4.0)                    | 9177 (1.0)                       | 4.00 (3.77–4.26) | 2.78 (2.61–2.96)     |

CC, clinical chorioamnionitis; CI, confidence interval; OR, odds ratio.

* Adjusted for education level and insurance type in the first pregnancy and for maternal age, prolonged rupture of membranes, gestational age, prolonged labor, epidural, and group B streptococcus carrier status in the second pregnancy. Adjusted for mode of delivery in the first and second pregnancies.

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**TABLE 4**
The frequency of CC in the second pregnancy by IP of <18 months vs ≥18 months

| IPI         | With CC in the first pregnancy | Without CC in the first pregnancy | OR (95% CI) | Adjusted OR (95% CI)* |
|-------------|--------------------------------|----------------------------------|-------------|-----------------------|
| <18 mo      | 459 (3.9)                      | 2577 (0.8)                       | 3.66 (3.39–3.95) | 2.55 (2.35–2.76)     |
| ≥18 mo      | 795 (4.0)                      | 6550 (1.1)                       | 3.71 (3.45–4.00) | 2.59 (2.39–2.80)     |

CC, clinical chorioamnionitis; CI, confidence interval; IP, interpregnancy interval; OR, odds ratio.

* Adjusted for education level and insurance type in the first pregnancy and for maternal age, prolonged rupture of membranes, gestational age, prolonged labor, epidural, and group B streptococcus carrier status in the second pregnancy. Adjusted for mode of delivery in the first and second pregnancies.

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20 to 24 weeks of gestation in the first pregnancy. These patients would benefit from extensive counseling regarding the increased odds of recurrence and its implications, and providers should ensure that patients receive adequate contraception counseling if the patient does not accept these risks.

In addition, the odds of experiencing a recurrence of CC was the strongest when a patient delivered in the term to post-term period in their first pregnancy. This information may aid in the identification of CC and lead to a more timely diagnosis and treatment of recurrent infection.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.xagr.2022.100116.

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