Correlation of histologic chorioamnionitis and intra-partum leukocytosis

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Article

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Abstract

**Background** Histologic chorioamnionitis (HCA) is the most common placental lesion measuring maternal/fetal responses to intraamniotic bacterial infection.

**Study design** We reviewed 1400 placentas referred for placental examination and explored the relationship of HCA with clinical information and with total white cells (WBC), differentials, and whether maternal admission WBC and differentials predict HCA.

**Results** The frequency of HCA of the 1400 placentas was 38.8% (543 of 1400), and funisitis 16.9% (237 of 1400). Abnormal white blood count (total WBC >10.3) within this population was 41.1% with abnormal neutrophil differential of 39.1% and lymphopenia of 33.9%. There is an association between HCA and elevated WBC, neutrophil differentials, and preterm delivery 32 weeks or earlier. The predictive value of WBC, differentials and gestational age was 59% using ROC analysis.

**Conclusion** Prediction of HCA using WBC and differential is suboptimal. Molecular solution to HCA is required to identify patients at risk for maternal/fetal complications.

Introduction

Acute chorioamnionitis with ascending bacterial infection in pregnancy is the most common pregnancy complication with significant maternal and neonatal morbidities [1]. Suspected chorioamnionitis (intraamniotic infection) is defined clinically as maternal fever with fetal tachycardia associated with one of the clinical risk factors, and the presence of these signs and symptoms is generally accepted as clinical criteria for intraamniotic bacterial infection leading to intrapartum antibiotic treatment [2]. However, these clinical signs and symptoms of bacterial infection demonstrate low sensitivity and low specificity in clinical setting, and a large percentage of patients with histologic evidence of acute chorioamnionitis shows no clinical signs and symptoms [3]. These patients without clinical manifestation of intraamniotic infection (acute chorioamnionitis) are undetected and untreated despite the increased risks of neonatal bacterial infection and other pregnancy related complications. Histologic chorioamnionitis graded and staged using elaborate scheme of anatomic locations of acute infection (neutrophils) within the placenta correlate poorly with clinical manifestation of bacterial infection, and the diagnosis of histologic chorioamnionitis occurs after delivery [4-6]. It is therefore impossible to use this histologic information for clinical management of maternal or fetal infection intrapartum. However, similar to clinical chorioamnionitis, histologic chorioamnionitis poses risks to other pregnancy complications including pre-term birth, abnormal fetal heart tracing and maternal and fetal bacterial infections intrapartum and postpartum. The knowledge gap between the clinical manifestation and subsequent histologic features of acute chorioamnionitis lead to lapse of treatment of meaningful bacterial infection before or during delivery, and identification of patients with chorioamnionitis using clinically relevant lab tests is needed in stratifying the patient population for appropriate management. Complete blood counts (CBC) with differentials have been used for many decades as lab indications for
clinical infections, and the predictive value of these lab tests in pregnancy is somewhat dampened due to the physiologic changes during pregnancy. We sought to revisit this topic in our current study. In an era of microbiome, specific bacterial infection is associated with changes of diversity of microbiome in the genital tract (dysbiosis) which is in turn affected by many other physiologic or pathologic conditions such as diet, genetic susceptibility and antibiotic usage. The presence of histologic chorioamnionitis represents a complex host biochemical response (including maternal and/or fetal) to environmental (microbiome) changes at physiological levels during pregnancy, and these host responses at the molecular levels may represent a new direction of clinical diagnostics for bacterial infection.

**Material And Methods**

The study was approved by the hospital Institutional Review Board (IRB). A total 1400 placentas were routinely submitted for pathology examination from March to October 2020. Placental submission for pathology examination in our institution is based on the maternal, fetal and placental criteria [7].

Histologic examination of placentas was carried out according to the Amsterdam guideline using the routine hematoxylin & Eosin staining methods [4]. The study population consisted of all grades and stages of acute chorioamnionitis including acute subchorionitis. Acute funisitis was recorded separately when the vessels of the umbilical cord were involved. The pathologic features and relevant clinical information of all the placentas were recorded in an Excel spreadsheet from the medical records at the time of examination, and these data was analyzed by using various programs of R-package (http://statistics4everyone.blogspot.com/2018/01/fathers-data-visualization.html). The clinical information includes antenatal, prenatal maternal history and clinical presentation at the time of hospital admission for delivery including body temperature and body mass index (BMI). Results of the routine admission tests including complete blood count with differentials (CBC) were collected at the time of hospital admission. Blood testing data after delivery were excluded.

**Result**

1. Frequency of histologic chorioamnionitis in the studied population:

A total 1400 placentas were examined during the seven months period from March to October 2020. Histologic chorioamnionitis was found in 543 placentas (38.8%), and acute funisitis was found in 237 placentas, representing less than half of those with acute chorioamnionitis (16.9%) (Table 1). The presence of acute chorioamnionitis was associated positively with chronic deciduitis (p=0.000), category 2 fetal heart tracing (p=0.001), and negatively with preeclampsia/ pregnancy induced hypertension (PIH) (p<0.000), maternal vasculopathy (p<0.000), gestational diabetes (GDM2)(p<0.001) and intrauterine fetal growth restriction (IUGR) (p<0.001). There is no association between the presence of acute chorioamnionitis and pre-term delivery at 36 weeks or earlier and other pregnancy related clinical and placental complications (Table1). However, there is clear association between histologic chorioamnionitis
and pre-term delivery 32 weeks or earlier (p=0.022). The Odds ratio of acute chorioamnionitis associated with or without a variety of placental and clinical conditions are listed in Figure 1.

A total 943 placentas with CBC data and 936 CBC with differential counts were available for correlation study. Abnormally elevated white blood cell count (leukocytosis, WBC >10.3, upper limit of normal range) was found in 41.4% of the study population and abnormal neutrophil differentials (left shift, >75.6%, upper limit of neutrophil differentials) in 39.1%. Lymphopenia (lymphocyte differential less than 15.5%, lower limit of normal range) was found in 33.9%. CBC with differentials demonstrated close positive correlation with acute chorioamnionitis. Leukocytosis, left shift and lymphopenia all showed significant changes in the presence of acute chorioamnionitis. Body temperature at the time of admission and BMI were not significantly changed in acute chorioamnionitis (Table 1).

2. Correlation of white blood cell count and differentials with histologic chorioamnionitis:

Acute chorioamnionitis is known to be associated with elevated white blood cells (leukocytosis) with or without left shift (increased neutrophil differentials). However, in pregnancy, the normal range of white cell counts appears widened due to the physiological changes of pregnancy, and clinical diagnostic value of white counts and differentials is somewhat altered. We examined the ranges of white blood counts and neutrophils and lymphocytes differentials in normal pregnancy and in conditions with histopathologic chorioamnionitis. We divided the white blood counts (WBC) into four groups, group 1 (normal, less than or equal to 10.3, upper limit of normal range), group 2 (10.4 to 12), Group 3 (greater than >12), and group 4 (greater than >15) (Table 2). There is a clear association between the increased WBC and incidence of acute chorioamnionitis and acute funisitis (p = 0.000 respectively) (Table 1 and Table 2). The mean of WBC, neutrophilic and lymphocytic differentials with or without chorioamnionitis were shown in Figure 2. When WBC was greater than 15 (group 4), the frequency of acute chorioamnionitis increased to 64.1%, a significant increase in comparison to that of marginal increase (group 2, 41.0%). There is also a clear association of increased WBC with increased rate of vaginal delivery (p = 0.031). Using the gestational age, WBC and neutrophil differentials as predictive values, the ROC curve for acute chorioamnionitis is less than 60% (Figure 3).

3. Pre-term delivery, acute chorioamnionitis and white blood counts

There were 151 placentas of pre-term deliveries associated with a variety of clinical and placental pathologic features (Table 3). Understandably, pre-term delivery was positively associated with preeclampsia, infarcts, abruption, IUFD and twin pregnancy, but negatively associated with meconium
staining of fetal membrane, chronic villitis, and umbilical cord coiling. Pre-term delivery was also associated with lower placental weight (p = 0.000). Importantly, pre-term delivery at 36 weeks or earlier was not statistically associated with acute chorioamnionitis, chronic deciduitis or acute funisitis (p=0.732). However, pre-term birth at 32 weeks or earlier showed a clear association with acute chorioamnionitis (p=0.022) (Table 1 and 3). Furthermore, pre-term deliveries before 36 weeks or before 32 weeks were not statistically associated with maternal leukocytosis, elevated neutrophil differentials (left shift) or lymphopenia (Figure 2). The Odds ratio of pre-term delivery associated with other clinical and placental pathological findings is shown in Figure 4.

4. Chronic inflammatory changes (deciduitis, villitis) and white blood cells

There were 525 placentas with histologic chronic deciduitis and 331 placentas with chronic villitis. Chronic deciduitis was found to be associated with acute chorioamnionitis (Table 1) (p = 0.000), and chronic villitis was not (p = 0.191). Neither of them were associated with leukocytosis, left shift or lymphopenia. Chronic villitis was noted to be associated with fetal vascular malperfusion (avascular villi) (p=0.000) (data not shown).

Discussion

Identifying patient population using appropriate clinical lab tests and administering proper antibiotics to the right patients becomes an urgent need in the healthcare system [8, 9]. On the one hand, proper usage of antibiotics will prevent from over-usage /over-prescribing, thus eliminating the challenge of antibiotic resistance. On the other hand, proper usage of antibiotics for the right patients will prevent specific pathogen -induced infection and complications. Also, correctly identifying patients with chorioamnionitis allows the appropriate triage of neoantes to the NICU if necessary and initiation of antibiotics if they are at risk of sepsis [10]. Histologic chorioamnionitis with inflammatory cell infiltrates within the placental tissues represents cellular immune response of the mother to invading bacterial pathogens, similar to physiological or pathological responses such as fever (elevated body temperature) or tachycardia. However, histologic chorioamnionitis can only be rendered after delivery of placentas and neonates, and proper management of patients (both mothers and neonates) in a timely manner cannot be based on the presence of histologic changes post-partum. Development of new diagnostic tools for prompt prenatal diagnosis of clinical chorioamnionitis (intraamniotic infection) is clearly needed [11, 12].

Our current data showed that 38.8% placentas in the studied population were affected with acute chorioamnionitis and 16.9% with acute funisitis. Meanwhile, 41.4% mothers showed leukocytosis and 39.1% with left shift. These results demonstrated that on the one hand, maternal WBC with differentials could represent earliest indication of maternal bacterial infection, and the value and utility of intrapartum WBCs are currently underestimated in the clinical setting. On the other hand, the predictive value of these
routine lab tests is suboptimal (less than 60%) by ROC curve analysis. Even in the higher range group (WBC >15), the diagnostic value of histologic chorioamnionitis was only 64.1%. These data indicate the complexity of chorioamnionitis in terms of variable host responses to various invading bacterial pathogens, and some of the significant pathogens were known for not eliciting host responses [13, 14]. These results are similar to those of previous studies, and reinforce the previous association between histologic chorioamnionitis and other clinically important complications, such as category 2 fetal heart tracing, similar to those previously reported [15-18]. Pathogen specific molecular tests such as PCR for group B streptococcus are widely available but those tests are limited to single pathogen detection, and clinically a spectrum of microorganisms are known to be the causing agents of chorioamnionitis and preterm delivery [19-23]. Based on the clinical and histologic features of chorioamnionitis and patients’ individual susceptibility, a combination of identification of host response and pathogenic bacteria will likely be useful, similar to the algorithmic method using microbiomic, genomics and transcriptomics previously described for clinical sepsis [24-27].

Our current data showed that preterm delivery at 32 weeks or earlier is statistically associated with histologic chorioamnionitis or abnormal levels of CBCs. Our clinical experience is that most of the preterm deliveries between 20-30 weeks are likely due to bacterial infection (acute chorioamnionitis) [23, 28, 29]. Preterm delivery was previously attributed to two major pathogenic etiologies, decidual vasculopathy and bacterial infection [28, 30], and our current data support the close association between the maternal vasculopathy and preeclampsia. It is important to note that our data didn’t separate preterm deliveries from those premature rupture of membrane, and prolonged premature rupture of membrane provides opportunity for bacterial invasion with ascending bacterial infection. There was no antibiotic treatment data in our study population before admission to labor and delivery for current pregnancy and no neonatal follow-up data in the study.

**Declarations**

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**Competing interest statement:**

The authors disclose no conflict of interests or competing interest.

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**Tables**

Tables 1-3 are available in the Supplementary Files