ABSTRACT

Introduction: Chorioamnionitis that is associated with high rates of morbidity and mortality needs an early diagnosis for effective treatment. However, views are conflicting on the effectiveness of a clinical versus a histological diagnosis of the disease. The accuracy of clinical diagnoses should be evaluated by determining their correlation with histopathological data. Methods: A total of 696 placental records from single and multiple pregnancies between January 2011 and February 2018 were collected and reviewed to determine if chorioamnionitis was present. Results: Of the 696 records, 255 had histological data available, and of these, histological evidence for chorioamnionitis was recorded in 135 (52.9%). Clinical chorioamnionitis diagnosis was insensitive (26.7%; 95% confidence interval 19.43%–34.96%) and inaccurate (61.1%; 95% confidence interval 54.90%–67.19%). As well, 73.3% of histologically positive chorioamnionitis cases were missed using clinical indicators. Discussion: Clinical diagnosis for chorioamnionitis is inaccurate; in our study, most of the positive cases were not diagnosed using clinical indicators. However, of the clinical indicators examined, maternal and fetal tachycardia were the most reliable.

KEY WORDS: Chorioamnionitis, morbidity, pathology, placenta, pregnancy, reproducibility of results

INTRODUCTION

Chorioamnionitis is an infection of the chorionic and amniotic tissue (bacterial or viral) in the days leading up to and during delivery; the pathogens involved in this polymicrobial infection are primarily mycoplasmas, coliforms, and group B streptococci. It occurs most commonly as a result of the passage of pathogens from the cervix and vagina into the chorioamnion and/or umbilical cord, most often following membrane rupture, although it can occur with intact membranes.[1] Hematogenous infection and infection as a complication of amniocentesis or chorionic villous sampling are also possible, but less common.[1]

Chorioamnionitis is one of the most common forms of intrauterine infection and associated with premature labor and the delivery of infants who may be preterm or infected themselves.[2] The earlier the diagnosis of chorioamnionitis, the greater the likelihood of avoiding major associated complications, which for the mother include postpartum infections and sepsis, and for the fetus include perinatal death, asphyxia, early-onset neonatal sepsis, septic shock, pneumonia, intraventricular hemorrhage, cerebral white-matter damage, and long-term disability (e.g., cerebral palsy).[3,4]

Clinical chorioamnionitis occurs in 13%–60% of pregnant women who have premature rupture of membranes, and in 1% of women at term.[8] However, the incidence of chorioamnionitis diagnosed by histology is much higher than that of clinically diagnosed infection, suggesting that clinical methods for diagnosis may not be optimal and leading to the accepted view that histological analysis is the only effective way to diagnose this condition accurately.[7,8] Many cases diagnosed as chorioamnionitis may be misidentified. This poses a problem when performing studies that attempt to assess the accuracy of a specific indicator or the formation of wide-ranging conclusions. A recent study in Saudi Arabia showed increased risk of sepsis among neonates that had very low birth weights, depressed respiratory function at birth, or maternal risk factors.[9] However, no published reports from Saudi
Arabia have explored the correlation between clinical and histological diagnoses of chorioamnionitis.

Clinical diagnosis of chorioamnionitis can be made using several indicators, such as maternal fever,[10] maternal or fetal tachycardia, high maternal white blood cell count, uterine tenderness and foul/purulent amniotic fluid [Table 1].[11,12] In chorioamnionitis, the maternal heart rate is usually above 100 bpm, and the fetal heart rate is above 160 bpm.[1] Maternal leukocytosis is not necessarily indicative of chorioamnionitis. White blood cell count is generally increased during pregnancy as a result of physiologic stress induced by pregnancy itself: white blood cell counts during healthy pregnancy can vary from 6 × 10⁹ to 16 × 10⁹ cells/L, increasing further during labor and delivery.[13] However, maternal leukocytosis can be used as supportive evidence to increase the accuracy of clinical diagnosis.[13,14] Uterine fundal tenderness is another potential clinical sign of chorioamnionitis, but the use of epidural anesthesia during delivery may mask pain symptoms, making this clinical indicator less useful, particularly on its own.[15]

Chorioamnionitis can be observed histologically by examining the fetal membrane and chorionic plate. In early-stage infection, infiltration of scattered polymorphonuclear neutrophils of subchorionic fibrin would be expected, with or without membrane trophoblast. In intermediate-stage chorioamnionitis, it is common to observe diffuse-patchy polymorphonuclear neutrophils in the fibrous chorion, with or without amnion involvement. In advanced-stage chorioamnionitis, there is karyorrhexis of polymorphonuclear neutrophils and necrosis of amniocytes, with or without hypereosinophilia and thickening of the amnion basement membrane. Severe chorioamnionitis includes confluent polymorphonuclear neutrophils between the chorion and the decidua, in 3 foci or a continuous band.[6] Funisitis is defined as umbilical vasculitis with or without neutrophil infiltration of Wharton’s jelly. Figure 1 shows histopathological images of the different stages of chorioamnionitis.

Initiation of antibiotic therapy has been shown to reduce the maternal and fetal complications from clinical chorioamnionitis in premature rupture of membranes before term (but not in intact membranes). It is important to perform an early diagnosis to begin treatment and avoid the potential morbidity and mortality associated with this infection.[11,12] However, it is not uncommon for chorioamnionitis to go undiagnosed for several reasons, including delayed or late results, choosing not to investigate after delivery, and lack of interest in the placenta as “disposable” once the pregnancy is over. In this study, we reviewed hospital records to determine whether there was a correlation between clinical and histologic diagnoses of chorioamnionitis, assess the sensitivity and specificity of clinical diagnoses, and if possible, optimize the two methods for the early detection and treatment of chorioamnionitis.

**METHODS**

**Study design**

We conducted a retrospective chart review of data on clinical chorioamnionitis and histologic chorioamnionitis cases from January 2011 (the earliest date that electronic records were available at our center) to February 2018, from a single tertiary-care university hospital in Riyadh, Saudi Arabia. We selected this study type as a way of evaluating current practice and recommending changes to improve opportunities for the early diagnosis of chorioamnionitis.

**Ethical approval**

We obtained approval from the institutional review board of our institution to conduct this study. All personal details in patient charts were obscured to preserve confidentiality.

| Clinical indicator   | Abnormal value                        | Normal value                        |
|----------------------|---------------------------------------|-------------------------------------|
| Maternal fever       | >100.4°F or 38.0°C                    | <100.2°F or 37.8°C                  |
| Maternal tachycardia | >100 bpm                              | 60-100 bpm                          |
| Fetal tachycardia    | >160 bpm                              | 110-160 bpm                         |
| Vaginal discharge    | Purulent and foul odor                | Clear and no offensive smell        |
| Maternal leukocytosis| >15x10⁶ cells/L                       | 4-11x10⁶ cells/L                    |
| Uterine fundal tenderness | Present                      | Absent                               |

**Figure 1:** Stages of chorioamnionitis. (a) Early stage chorioamnionitis 40X. (b) Early stage chorioamnionitis 400X. (c) Intermediate stage chorioamnionitis 40X. (d) Intermediate stage chorioamnionitis 400X. (e) Advanced stage chorioamnionitis 40X. (f) Advanced stage chorioamnionitis 400X. (g) Funisitis 40X. (h) Funisitis 400X. All slides are formalin fixed, paraffin embedded, with subsequent hematoxylin and eosin staining.
Data collection
We included all complete records of single and multiple pregnancies, in which the maternal age was 18-46 years. We excluded cases in which the maternal age was <18 years or >46 years, or that had incomplete records. A single researcher evaluated clinical and histological information, consulting another pathologist for confirmation if needed.

We used a table to collect deidentified patient data, including maternal age, fetal gestational age, clinical indicators of chorioamnionitis (e.g., fever, maternal tachycardia, fetal tachycardia, vaginal discharge, and tender uterus), clinical diagnosis of chorioamnionitis, and histological diagnosis of chorioamnionitis, including grade and stage. In our center, amniotic fluid is not typically sent for microbiologic analysis; as a result, information about isolated organisms was not available.

Assessment
We reviewed the medical records for the presence of clinical indicators of chorioamnionitis [Table 1].

We collected samples previously analyzed by clinical pathologists (placentas) from the department of pathology at our institution. The review was conducted between March and August 2018. When samples were stored as glass slides, we reviewed the slides to confirm the histological diagnosis. Some were stored as paraffin blocks, in which case, we used the blocks to create new slides for histological evaluation. When our review of the samples confirmed an original diagnosis based on the samples, we entered that in our records. When we disagreed with the original diagnosis, we consulted another pathologist for confirmation.

We collected data from the electronic records and the histological samples using a standard form and recorded important information using a table. The patient’s information was de-identified, coded and stored in a password-protected file.

Statistical analysis
We analyzed descriptive statistics using mean ± standard deviation and percentages. For significance, we compared continuous variables using a two-tailed t-test and categorical variables using Fisher’s exact test. We evaluated the correlation between clinical and histologic chorioamnionitis using $\chi^2$ tests. All analyses were conducted using SPSS IBM SPSS, version 21, 2013 (SPSS, Inc, Chicago, IL, USA). For all tests, statistical significance was set at $P < 0.05$.

RESULTS

Data collection
A total of 696 women delivered during the study period, but only 255 (36.6%) had complete maternal and infant records and placental histologic examination.

Correlation between clinical and histological diagnoses of chorioamnionitis
Of the 255 cases for which we had complete medical records, we identified histologic evidence of chorioamnionitis in 135 cases (52.9%); of those, funisitis was present in 33 cases. The remaining 120 (47.1%) had no evidence of chorioamnionitis. Of the 135 cases later confirmed to be chorioamnionitis-positive via histological analysis, we found the following clinical indicators: fever in 12 (8.9%) cases, maternal tachycardia in 21 (15.6%), fetal tachycardia in 27 (20%), vaginal discharge in 39 (28.9%) and tender uterus in 12 (8.9%) [Table 2].

The analysis showed a significant correlation between histologic chorioamnionitis and clinical chorioamnionitis ($P = 0.00001$).

Sensitivity of chorioamnionitis diagnosis using clinical indicators
Diagnosis of chorioamnionitis using clinical indicators was highly specific (100%; 95% CI 96.97–100%), but insensitive (26.67%; 95% CI 19.43%–34.96%) and inaccurate (61.18%; 95% CI 54.90%–67.19%).

Most importantly, 73.3% of histologically positive chorioamnionitis was missed using clinical indicators.

DISCUSSION

Early diagnosis of chorioamnionitis is beneficial to both mother and fetus because it allows for the timely administration of proper medication to prevent complications from arising. However, because histological examination cannot be conducted during the perinatal stage when the disease may arise, finding ways to
ensure accurate diagnosis using clinical indicators is extremely important [Figure 2]. In many cases, the clinical diagnosis has proven ineffective due to a lack of symptoms (known as subclinical chorioamnionitis).\textsuperscript{[15,16]} Several studies have reported that acute chorioamnionitis has been missed in some patients, only diagnosed on autopsy.\textsuperscript{[16]} Therefore, it is imperative to investigate the effectiveness of clinical methods of diagnosis to reduce rates of failed detection of chorioamnionitis. Reports in the literature are contradictory about whether there is a correlation between clinical and histological chorioamnionitis. Several studies have reported that clinical manifestations of chorioamnionitis can be positively correlated with histological findings,\textsuperscript{[2]} but others have refuted this, showing that clinical chorioamnionitis was not associated with histological findings in a large number of cases.\textsuperscript{[17]} In recent years, efforts have been made to correct this discrepancy: some studies have found that clinical chorioamnionitis was correlated more strongly with histologic chorioamnionitis in the presence of one or more clinical indicators such as maternal fever and fetal tachycardia.\textsuperscript{[18]}

Some researchers have claimed that, aside from the objective measurements of maternal fever and fetal tachycardia, other clinical signs of chorioamnionitis are highly subjective; the presence of one (or even more than one) of these signs and symptoms does not necessarily indicate infection.\textsuperscript{[18]} We observed strong correlations between clinical indicators of chorioamnionitis and eventual histological diagnosis, but rates of diagnosis based on clinical findings were far lower, indicating that the current clinical methods of diagnosis in this hospital were inadequate. True clinical chorioamnionitis is difficult to diagnose. Different clinical management practices can alter the reliability of some of the diagnostic indicators, especially in preterm gestations.\textsuperscript{[19]}

Histologic chorioamnionitis identifies subclinical as well as clinical chorioamnionitis, so it is not surprising that overall histologic diagnoses are three times as frequent as clinical chorioamnionitis confirmed by amniotic fluid culture.\textsuperscript{[18]} In a study of clinical chorioamnionitis detection using cultivation and molecular techniques, microbiological methods missed histological chorioamnionitis in 29.2% of cases.\textsuperscript{[1]} The development and adoption of uniform pathologic guidelines for the investigation and diagnosis of chorioamnionitis would enhance our knowledge of the prevalence and manifestations of chorioamnionitis, and ultimately improve diagnosis and management.\textsuperscript{[20]}

**Limitations**

This study’s population represented only cases of clinical chorioamnionitis for which placental histology was obtained, so results might represent an optimistic assessment of histologic chorioamnionitis rates, as placentas might have been preferentially sent when an abnormality was expected.

This study was limited by the small sample size as a result of the many incomplete records at the hospital. To minimize this issue, we recommend that the hospital adopt an electronic record-keeping system instead of paper records which can be easily misplaced or misfiled. Another confounding factor was the occurrence of intrauterine fetal death, which inhibited our ability to acquire some clinical indicators, such as fetal tachycardia. For future studies, it is recommended that records be obtained from various institutions to minimize the risk of incomplete information and small sample sizes.

There are also limitations to a retrospective review analysis. Although unlikely, specific findings supportive of clinical diagnoses of chorioamnionitis might not have been recorded in medical records. Assuming that this was not the case, the absence of histologic confirmation of chorioamnionitis in 47.1% of cases shows a distinct lack of reliability of the clinical diagnostic methods.

**CONCLUSION**

This study proves that the methods used in one hospital for clinical diagnosis of chorioamnionitis were inaccurate, as most of the histologically positive cases were not diagnosed using clinical indicators. Among all the clinical indicators examined, maternal and fetal tachycardias were found to be the most reliable. These findings suggest that the clinical criteria for the diagnosis of chorioamnionitis currently used by our clinical colleagues are inadequate and there is a need
for a more accurate procedure. Therefore, it is recommended that the abortus status, maternal tachycardia, and fetal tachycardia be used as primary clinical indicators for better diagnosis and management of the disease until a more reliable and chorioamnionitis-specific method for diagnosis can be established. There is also a need for better understanding of the clinical manifestations of intraamniotic infection and associated placental histology to improve management for mothers and neonates.

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Conflicts of interest
There are no conflicts of interest.

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