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ORIGINAL PAPER

# Histological Chorioamnionitis – Experience from a Tertiary Care Center

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*ABSTRACT*

***Background and objectives:*** *Chorioamnionitis (CA) mostly represents the presence of intra-amniotic infection. The features of the disease can be detected during histopathological examination of the delivered fetal membranes. The current study aims to explore the features of all histological chorioamnionitis cases received in the Pathology Department of a university hospital over a period of five years.*

***Methods:*** *This retrospective cross-sectional study was conducted between January 2015 and December 2019 and used data from 78 women with histologically confirmed chorioamnionitis. All data were gathered from the hospital information system. The SPSS software's statistical methods were used to show and analyze descriptive and categorical data.*

***Results:*** *The selected patients had an average age of 36.18 ± 6.153 years (age range 21–50 years) and different stages of the disease: 29 (37.2%) in the first stage, 25 (32%) in the second stage and the remaining 24 (30.7%) subjects in the third stage. Nearly half of cases showed concomitant umbilical cord inflammation, whereas placental inflammation occurred much less frequently. The most common cause of chorioamnionitis was bacterial infection, where* Streptococcus agalactiae *was the most prevalent.*

***Conclusions:*** *This study showed that the majority of histological chorioamnionitis were of mild intensity (stage 1). Many cases were associated with umbilical cord and, to a lesser extent, with placental inflammation. Bacteria were the most typical cause of chorioamnionitis. The most common strain was* Streptococcus agalactiae.

**Keywords**: pregnancy, placentas, chorioamnionitis, histopathology.

## INTRODUCTION

Chorioamnionitis (CA) is an acute inflammation of the fetal membranes and chorion of the placenta due to an ascending polymicrobial bacterial infection, mostly following membrane rapture (1). The term clinical chorioamnionitis refers to the clinical syndrome associated with chorioamnionitis, whereas histologic chorioamnionitis refers to the microscopic examination of the placenta that comprises clinically unapparent (subclinical) chorioamnionitis as well as clinical chorioamnionitis (1, 2). As the amniotic fluid could be accessible during pregnancy, unlike the placenta, most studies correlate intra-amniotic infection with preterm labor rather than chorioamnionitis. Furthermore, intra-amniotic infections might not always be in agreement with the retrospective diagnosis of histological chorio-

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amnionitis (2). According to Amsterdam Placental Workshop Group, the severity of acute chorioamnionitis has been classified using a staging system where stage 1 shows neutrophilic infiltration restricted to the chorion. On the other hand, the neutrophils extend to the amniotic connective tissue in stage 2, whereas stage 3 shows additional necrosis (3).

Maternal complications of CA include wound infection, postpartum hemorrhage, endo-myometritis and preterm labor. Moreover, chorioamnionitis in one pregnancy could influence the risk of recurrence in future pregnancies, but the risk is low (2, 4). However, in neonates, CA could be associated with both short- and long-term complications. In premature birth, the risk of cerebral palsy, brain injury and necrotizing enterocolitis increases as a result of prematurity (1, 4).

Furthermore, there is a strong association between chorioamnionitis and the early onset of sepsis. Symptoms associated with chorioamnionitis determine the death rate (4). The clinical presentation of CA includes fever, uterine tenderness, maternal tachycardia (>100/min), fetal tachycardia (> 160/min) as well as foul purulent amniotic fluid (1, 4). Fever is manifested in 95–100% of cases. Maternal and fetal tachycardia are present in 50–80% and 40–70% of cases, respectively, whereas uterine tenderness and a foul odor to the amniotic fluid are reported in only 4–25% of CA cases. Therefore, maternal fever is the most important clinical sign (1, 2).

The diagnosis of CA is important to reduce the risk of maternal and neonatal morbidity and mortality. Histopathological changes detected in the fetal membranes can be useful to measure the accuracy of the diagnosis of clinical chorioamnionitis or early neonatal sepsis (4). A previous study, which was conducted in a single tertiary care university hospital, showed that the clinical chorioamnionitis diagnosis was insensitive and inaccurate as it was found that more than 70% of histologically confirmed chorioamnionitis cases were missed using clinical indicators (5). Overall, intravenous antibiotics is the treatment of choice for CA used to control the disease and prevent morbidity (4).

This study aims to explore the histopathological features of chorioamnionitis and the relationship with different clinicopathological parameters. It also hopes to improve knowledge and awareness about the disease among health care providers. ❑

## MATERIALS AND METHODS

### Study design

This was a retrospective cross-sectional study which was conducted over a period of five years (January 2015 to December 2019) in the Pathology Department of Sultan Qaboos University Hospital (SQUH) in Oman. All women with a histopathological diagnosis of chorioamnionitis were enrolled. Ethical approval was obtained from the Medical Research Ethics Committee (MREC) of the College of Medicine and Health Sciences (CoMHS), Sultan Qaboos University, in May 2022 (MREC # 2772).

### Data collection

Demographic data, clinical findings and histopathological features were collected from patients' medical records (TrakCare) stored by SQUH. The process started by collecting the medical records number (MRN) for the CA patients. Patients' records were searched for clinico-pathological variables, which included laboratory investigations such as complete blood count (CBC), white blood cell (WBC) and neutrophilic counts. The available microbiology results were also collected. Some other variables included the presence or absence premature rupture of membranes, meconium-stained amniotic fluid, fetal abnormalities and pregnancy outcome, previous procedures such as cerclage and persistent maternal infection such as bacterial vagi-nosis.

### Slide revision

For randomly selected cases representing each of the three CA histopathological stages, the archived H&E-stained slides were retrieved and blinded review was used to confirm the pathological diagnosis of CA. Criteria for evaluating the extent of CA (staging and grading) were used according to the recommendation of Amsterdam Placental Workshop Group (5). With regard to staging, stage 1 CA refers to lesions characterized by the existence of neutrophils in the chorion or subchorionic space, stage 2 to neutrophilic infiltration of the chorionic connective tissue and/or amnion, and stage 3 to additional necrotizing chorioamnionitis. Grading refers to the density of neutrophils, with grade 1 (mild to moderate)

meaning the presence of individual or small clusters of neutrophils whereas and grade 2 the occurrence of more dense confluent neutrophilic infiltration with formation of micro-abscesses. The inflammation of the umbilical cord (funisitis) and placental tissue were reported as present or absent.

### Statistical analysis

The Statistical Package for Social Science (SPSS version 26.0) and Excel applications were used to examine the data. Descriptive statistics of continuous variables (age, total WBC, and neutrophil) were presented with a mean and standard deviation (SD) in frequency tables, while categorized variables (chorioamnionitis staging, number of microorganisms, placenta, and cord inflammation) were presented with numbers and percentages in pie and bar charts. ❑

## RESULTS

### Demographic features

The current study investigated data collected from 78 cases with histopathological diagnosis of chorioamnionitis. Patients had an average age of 36.18 ± 6.153 years (age range 21 to 50 years) and all of them had Omani nationality.

### Distribution of stages of chorioamnionitis

Figure 1 shows the histopathological findings in the fetal membranes of the different stages of CA. We found the diagnosis of stage 1 CA in 37.2% of cases (n=29), followed by stage 2 CA in 32% (n=25) of subjects and stage 3 CA in 30.7% (n=24) of patients (Figure 2).

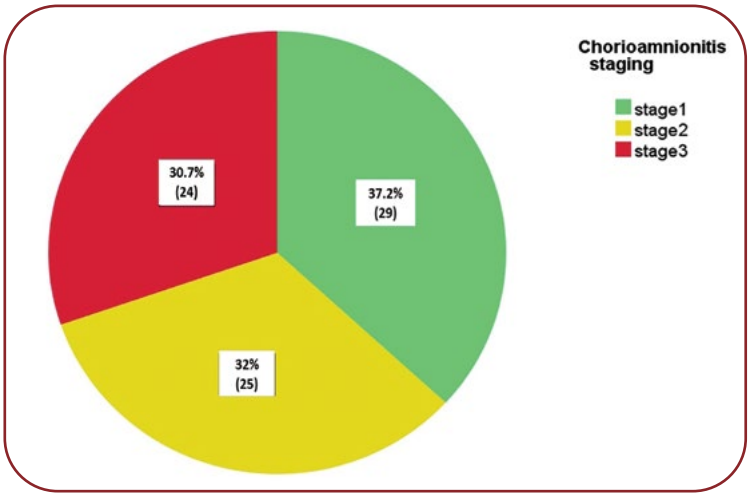


**FIGURE 2.** Histopathological findings in the fetal membranes

### Associations of chorioamnionitis with umbilical cord and placenta inflammation

The present study revealed that half of patients with CA showed concomitant inflammation in the umbilical cord (funisitis). Placental affection occurred to a lesser extent (12.8%) (Figure 3). There was no significant correlation between the stage of CA and the damage of either the umbilical cord or placenta. Examples of funisitis are illustrated in Figure 4.

### Microbiological findings

In this study, microbiological data were available for 59 cases. A total of 13 patients had no in-

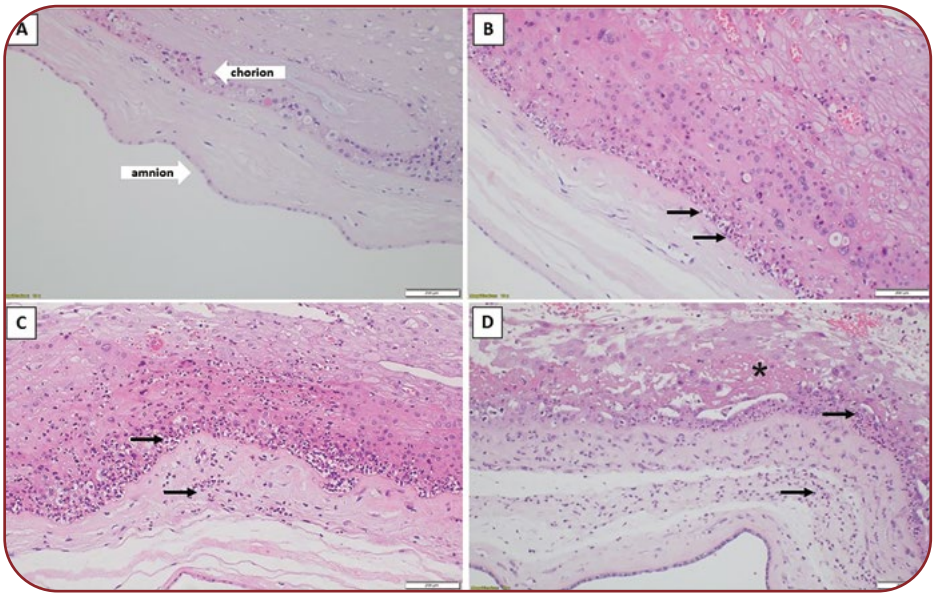


**FIGURE 1.** Stages of acute chorioamnionitis. A) normal chorion; B) Stage 1 "neutrophils are limited to the chorionic and sub-chorionic space (arrows)"; C) Stage 2 "neutrophilic migration into the amniotic connective tissue (arrows)"; and D) Stage 3 "showing additional necrosis (as-terisk)". H&E 200x

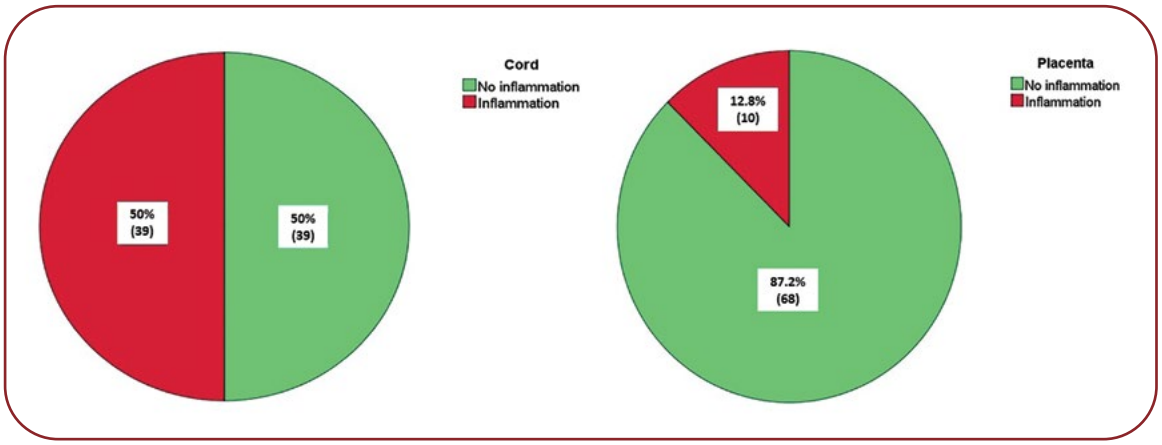


**FIGURE 3.** Histopathological findings in the umbilical cord and placenta in relation to chorioamnionitis

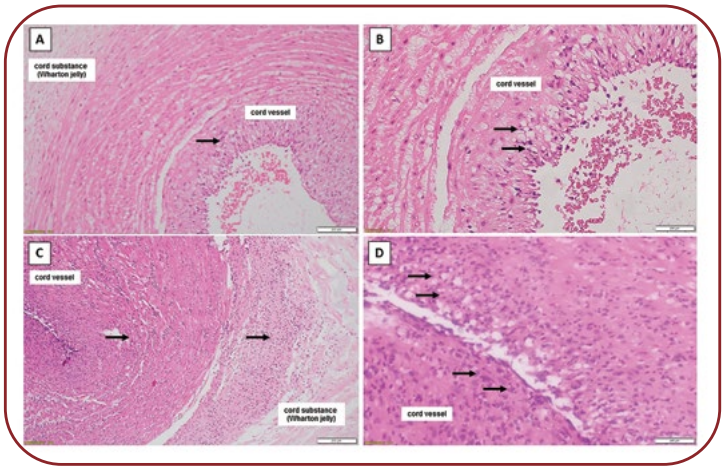


**FIGURE 4.** Various forms of umbilical cord involvement by inflammation (funisitis) during the course of chorioamnionitis. Neutrophilic inflammatory cellular infiltration (arrows) of the wall of umbilical vein alone (A and B) or, in addition, of the cord substance/Wharton jelly as well (C and D). H&E 40x (A and C) and 200x (B and D)

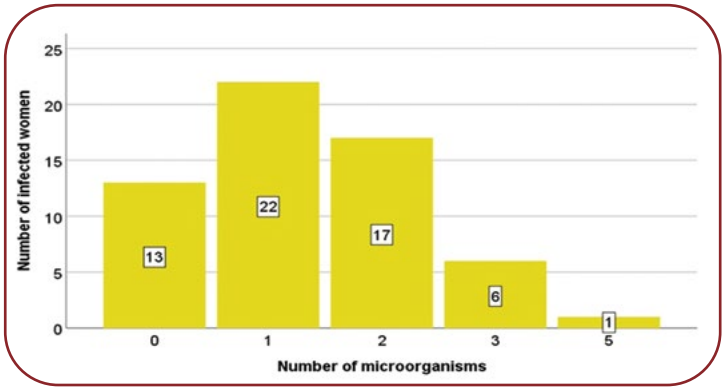


**FIGURE 5.** Microbiological findings in relation to chorioamnionitis

**TABLE 1.** Types of microorganisms causing chorioamnionitis in each study participant

| Agents | Number (n) | Percentage (%) |
|---|---|---|
| *Streptococcus agalactiae* | 14 | 21.3 |
| *Candida* species | 9 | 13.7 |
| *Escherichia coli* | 8 | 12.2 |
| *Enterococcus faecalis* | 5 | 7.6 |
| Fungus, unclassified | 4 | 6.2 |
| Gram positive cocci+ | 3 | 4.5 |
| *Staphylococcus caprae* | 2 | 3.0 |
| *Klebsiella pneumoniae* | 2 | 3.0 |
| Gram negative bacilli | 2 | 3.0 |
| Cytomegalovirus IgM | 2 | 3.0 |
| Rubella IgG equivocal | 2 | 3.0 |
| *Gardnerella vaginalis* | 1 | 1.5 |
| *Corynebacterium amycolatum* | 1 | 1.5 |
| *Streptococcus anginosus* | 1 | 1.5 |
| *Bacteroides fragilis* | 1 | 1.5 |
| *Pseudomonas aeruginosa* | 1 | 1.5 |
| *Veillonella parvula* | 1 | 1.5 |
| Hepatitis B surface antigen | 1 | 1.5 |
| *Serratia marcescens* | 1 | 1.5 |
| *Staphylococcus epidermidis* | 1 | 1.5 |
| *Dermabacter hominis* | 1 | 1.5 |
| *Streptococcus gallolyticus* | 1 | 1.5 |
| *Enterobacter cloacae* | 1 | 1.5 |
| *Citrobacter koseri* | 1 | 1.5 |
| **Total** | **66** | **100** |

fective agent, 22 had one infective agent, 17 had two infective agents, six had three infective agents and only one had five infective agents (Figure 5).

Table 1 shows the types of microorganisms isolated in CA patients. According to the current study, bacteria was the most common microorganism found by us, among which *Streptococcus agalactiae* (group B *Streptococcus*) was the most frequently identified pathogen (14 cases), fol-

**TABLE 2.** Total white blood cells and neutrophils in women with chorioamnionitis

| Parameters | Mean ($x10^9$/L) | Standard deviation ($x10^9$/L) | Minimum ($x10^9$/L) | Maximum ($x10^9$/L) |
|---|---|---|---|---|
| Total white blood cell count | 13.37 | 5.23 | 4.9 | 30.2 |
| Neutrophil count | 10.67 | 5.15 | 2.1 | 27.8 |

lowed by *Candida* species (nine cases for each of *C. albicans* and *C. orthospilosis*) and *Escherichia coli* (eight cases). There was no significant correlation between the stage of CA and the number or type of microorganism.

**Complete blood count parameters**

The results of the complete blood count (CBC) revealed that there was a significant increase in both total white blood cell (WBC) and neutrophil counts (Table 2). We found a mean total WBC of 13.37 x $10^9$/L and a mean neutrophil count of 10.67 x $10^9$/L. Of note, the normal ranges for WBC and neutrophils are 4.5 to 11.0 x $10^9$/L and 2.0 to 7.5 x$10^9$/L, respectively. There was no significant correlation of the stage of CA with blood count changes.

**Other clinicopathological parameters**

There were relatively deficient data for other originally sought variables, as shown in the previously described section of data collection. Therefore, these were not further analyzed. ❑

## DISCUSSION

The current study aimed to explore the histopathological features of CA among female patients examined in our Pathology Department in relation to the different clinicopathological parameters. The pregnant women diagnosed with CA who participated to our study had a mean age of 36.18 years (SD 6.15, age range 21 to 50 years), which was somehow different from the findings of Matulova *et al*'s study, where patients with CA had a median age of 31 years (6). Moreover, the median age of our patients was much above that reported by a previous study, which was about 28 years old (7). This variation could be explained by the differences in study populations and sample sizes.

In our study, 36.8% of women had histopathological stage 1 disease, 32.9% stage 2 disease and the remaining 30.3% stage 3 disease. Our data was in agreement with the recent study of Duan *et al*, who reported that stage 1 was the dominant one at the time of histopathological examination (8). In our institute, all pathology reports specify the stage, while a few also estimate the grade of disease. Most of our pathologists follow the concept that staging of CA is more important and reproducible than grading in evaluating the severity of inflammation (1).

Funisitis is an inflammation of the umbilical cord occurring as a fetal response to the inflammatory process associating chorioamnionitis. In half of patients with histological CA we found an association of the disease with funisitis, which was less frequently than previously observed by Zaidi *et al* (in about 70% of patients) (7), but nearly similar to the findings of Orsaria *et al* (about 48% of study participants) (9). Such variation could be attributed to differences in study populations and geographical locations as well as intensity, length and other aspects of infection.

The current study showed that the majority of cases (87.5%) were lacking evidence of placental inflammation. Similarly, the study of Orsaria *et al* found an association between pla-cental inflammation and histological CA in 12.84% of cases (9).

Our current work revealed that the most common microorganism detected microbiologically in CA patients was *Streptococcus agalactiae*, followed by *Candida* species and *Escherichia coli*. According to previously published research, infection by *Ureaplasma* species was the major infectious etiology for CA (1, 10). Some other organisms were also reported, although with less frequency than *Ureaplasma*, *Mycoplasma hominis* and *Fusobacterium* species (2). Less frequently, other bacteria such as *Gardnerella vaginalis*, *Escherichia coli* and group B *Streptococcus* were also isolated (2). In concordance with our findings, the role of *Streptococcus agalactiae* has been previously confirmed as an etiologic agent for intrauterine infections (11). This variation could be due to the population considered for the study, the period of time or the type of sample that had been taken (2, 10). These differences can be attributed to a variety of factors. One explanation is that various studies might choose women with various chorioamnionitis risk factors. For instance, some studies may include women with ruptured membranes, while others focus on those in preterm labor (6, 10, 12). The methods used for finding and classifying microorganisms are another contributor to variations in microbe percentages. For instance, some research may employ culturebased approaches, while others may use molecular methods like PCR (9, 12). In agreement with our data, the infection could be either mo-nomicrobial or poly-

microbial; however, we found that the polymicrobial infection occurred to a greater extent than the monomicrobial one (9).

Both the total WBC and neutrophil counts increased, according to the current study's CBC data. The neutrophils' mean was 10.67 x$10^9$/L and the mean total WBC 13.37 x$10^9$/L. This could cold be used as a parameter in predicting premature rupture of membranes (13). The increased WBC count could reflect the findings of previous works showing that the mean neutrophil percentage in the amniotic fluid was 70.3% among patients with CA *versus* 1.2% among those without the condition (1, 14).

Like any research work, the present study has some limitations. Given the retrospective nature of our study design, there was no sufficient information about some variables. Furthermore, the sample size was relatively small, which might be due to the fact that the study was carried out in only one hospital and did not include any cases from other healthcare centers over the same time period. Therefore, future studies should be performed on a national basis utilizing data for from multiple hospitals over longer periods of time. ❑

## CONCLUSIONS

The current study showed that histological chorioamnionitis mostly occurred as mild stage disease (stage 1) and it was often associated with umbilical cord inflammation. Microbial detection revealed that bacteria were the most typical cause of chorioamnionitis with associated in-crease in total WBC and neutrophil counts. ❑

*Ethics statement: The present study was approved by the ethical committee of Sultan Qaboos University Medical Research Ethics Committee (MREC), College of Medicine and Health Science (COMHS) (MERC # 2772). Formal written informed consent was not required with a waiver by the IRB.*

*Authos' contributions: conceptualization: MA; data collection: NQ; formal analysis: NQ; writing, review and editing: NQ and MA.*

*Conflicts of interest: none declared.*

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