





Original Research

Comparison of Histological Chorioamnionitis Findings Between Term and Preterm Deliveries

Ahmet Ilker Eryilmaz^{1,*}, Durmus Onder¹, Meryem Busra Birsen¹, Hasan Ali Inal¹,
Gulsah Inal², Metin Kaba¹

¹Department of Obstetrics and Gynecology, Antalya Training and Research Hospital, Health Science University, 07100 Antalya, Turkey

²Department of Pathology, Antalya Training and Research Hospital, Health Science University, 07100 Antalya, Turkey

*Correspondence: aiker_eryilmaz@hotmail.com (Ahmet Ilker Eryilmaz)

Academic Editor: George Daskalakis

Submitted: 6 February 2025 Revised: 1 April 2025 Accepted: 27 April 2025 Published: 18 June 2025

Abstract

Background: This study aimed to determine the findings of histological chorioamnionitis (HCA) that may lead to preterm labor. **Methods:** A total of 126 women who underwent cesarean delivery at our hospital's obstetrics clinic between May 1 and December 31, 2022, were prospectively included in the study (Group 1, Term labor, n = 63, Group 2, Preterm labor, n = 63). Participants' sociodemographic characteristics, laboratory results, and histopathological findings were documented and compared between the groups. Placentas were examined for the diagnosis of HCA by a senior pathologist. **Results:** Significant differences were observed between Group 1 and Group 2 in gestational age at delivery (38.6 ± 1.3 vs 33.6 ± 1.6 weeks, respectively; $p < 0.001$), Apgar scores at the first minute (8.8 ± 0.6 vs 8.1 ± 1.8 ; $p < 0.001$), and neonatal intensive care unit (NICU) admission (9.5% vs 42.9%; $p < 0.001$). Although hemoglobin (Hb) levels, mean platelet volume (MPV), mean corpuscular volume (MCV), and lymphocyte, neutrophil, monocyte, platelet counts, as well as the pan-inflammatory value at admission, were comparable between groups ($p > 0.05$), leukocyte counts ($10,382.54 \pm 2020.58$ vs $12,133.33 \pm 4936.01$, respectively; $p = 0.011$), neutrophil-lymphocyte ratio (4.21 ± 1.60 vs 5.46 ± 1.48 ; $p = 0.040$), and C-reactive protein (CRP) values (6.46 ± 5.56 vs 15.90 ± 9.27 g/dL; $p = 0.027$) differed significantly between the two groups. The incidence of acute (7.9% vs 49.2%), mild (33.3% vs 49.2%), and moderate (3.2% vs 14.3%) chorioamnionitis was statistically significantly higher in the preterm labor group ($p < 0.05$). **Conclusions:** The study findings show that the prevalence of HCA is notably higher in pregnant women with preterm deliveries, and that both the neutrophil-to-lymphocyte ratio and CRP levels are higher in preterm compared to term deliveries. Further studies with larger cohorts are warranted to elucidate these associations.

Keywords: chorioamnionitis; C-reactive protein; premature birth

1. Introduction

Births occurring between 20 and 36.6 weeks of gestation are classified as preterm. The prevalence is 15–20% in developing countries and 5–10% in developed countries; however, it is unfortunately increasing, partly as a result of the growing use of assisted reproductive techniques [1]. Although the exact etiopathogenesis remains unknown, proposed mechanisms include infections, uterine distension, cervical insufficiency, and chorioamnionitis [2]. Maternal and fetal stress, along with inflammatory reactions in the fetal membranes and decidua, have been shown to induce prostaglandin synthesis and trigger myometrial contractions [3,4]. Factors associated with preterm labor include a history of preterm birth, smoking, alcohol use, adolescent pregnancy, maternal age over 35 years of age, Black race, low body mass index (BMI), previous cervical surgery, cervical length less than 25 mm, an interpregnancy interval of less than 18 months, uterine anomalies, depression, anxiety, stress, multiple pregnancies, antenatal bleeding, infections, and fetal anomalies [5–7].

The American College of Obstetricians and Gynecology (ACOG) defines preterm labor as the presence of

at least two or more contractions in 20 minutes, each lasting at least 30 seconds and with an amplitude of 50 mmHg, accompanied by cervical effusion and dilation [8]. Preterm birth can cause severe morbidity, such as respiratory distress syndrome, temporary tachypnea of the newborn, bronchopulmonary dysplasia, retinopathy of prematurity, periventricular leukomalacia, cerebral palsy, necrotizing enterocolitis, sepsis, behavioral problems resulting from adverse effects on neuropsychiatric development in childhood, and cognitive in social intelligence and cognitive development, as well as imposing a socioeconomic burden [9]. In addition to medical treatments for preterm labor, such as cervical pessary, progesterone therapy, cyclooxygenase inhibitors, calcium channel blockers, beta-agonists, oxytocin receptor antagonists, magnesium sulfate, and nitric oxide donors, surgical interventions like cervical cerclage are also utilized [6,10].

Prolonged rupture of membranes, prolonged labor, meconium-stained amniotic fluid, and smoking are among the risk factors for histological chorioamnionitis (HCA), which is defined as inflammation of the amniotic fluid, membranes, and decidua [11]. HCA is an infection caused



by bacterial, fungal, and viral pathogens, typically originating in the lower genital tract and ascending to infect the amniotic fluid and membranes. Although rare, HCA can also develop via the hematogenous route and may lead to postpartum uterine atony or rupture, increased need for blood transfusion, increased postoperative wound infection, endometritis, pelvic abscess, septic pelvic thrombophlebitis, prolonged hospitalization, extended neonatal intensive care unit (NICU) stays, and increased neonatal mortality [9,10].

HCA is diagnosed immunohistochemically based on the presence of neutrophil infiltration and microabscesses in the decidua, with treatment most commonly involving ampicillin or cefoxitin [6]. HCA can cause placental inflammation and may lead to growth restriction by disrupting perfusion and reducing blood flow. It can also contribute to neuronal damage in the brain through the action of various cytokines and to bronchopulmonary dysplasia by causing capillary endothelial damage in the fetal lung [9]. Untreated chorioamnionitis triggers a systemic fetal response known as fetal inflammatory response (FIR) syndrome, which can cause neonatal sepsis, hemodynamics disruption, and multi-organ failure [12]. The purpose of this prospective study was to compare the findings of HCA between term and preterm deliveries.

2. Materials and Methods

2.1 Study Design

A total of 126 women were included in the study between May 1 and December 31, 2022: 63 women who underwent an elective cesarean section (Group 1) in the obstetric outpatient clinic, and 63 included in the preterm labor group (Group 2) admitted to the obstetrics emergency department with diagnoses of preterm labor. Approval for the study was granted by the Ethics Committee of Health Science University, Antalya Training and Research Hospital, Turkey (reference no: 2022-4/25). The study was conducted in accordance with the Declaration of Helsinki.

Pregnant women aged 18–40 years who underwent cesarean sections between 37 and 40 + 0 weeks of gestation, according to the last menstrual cycle, were enrolled in Group 1. Women aged 18–40 years with gestational ages between 24 and 36 + 6 weeks, according to the last menstrual cycle, who presented to the emergency department with complaints such as pain, bleeding, or fluid leakage, and who were admitted to the delivery room due to active membrane rupture, cervical dilation, uterine contractions detected by cardiotocography, or indications such as previous painful or repeated cesarean section, were included in Group 2.

Preterm labor was defined as the presence of cervical changes (dilatation and/or effacement) accompanied by increased uterine activity, according to the ACOG 2016 criteria [4]. Increased uterine activity was defined as the presence of strong uterine contractions (45–50 mmHg) detected by cardiotocography, occurring regularly at least

twice within 20 minutes, and lasting a minimum of 30 seconds each.

The collected data included sociodemographic characteristics (maternal age, BMI, smoking status, gravidity, parity, miscarriage history) clinical parameters (presence of meconium in amniotic fluid, gestational age at delivery, Apgar scores at the first and fifth minute gestational age at delivery, and NICU admissions), laboratory and ultrasound findings at the time of admission (hemoglobin [Hb] levels, mean corpuscular volume [MCV], lymphocyte, neutrophil, monocyte, and platelet counts, leukocyte counts, neutrophil-to-lymphocyte ratio, and C-reactive protein [CRP] levels, and pan-inflammatory value), as well as histopathological findings (acute, subacute, mild, moderate, and severe chorioamnionitis).

After delivery, placentas from both groups were fixed in 10% formaldehyde solution for histopathological evaluation and sent to the pathology department for immunohistochemical analysis by a specialist pathologist. Following fixation, the placenta was weighed, and the size, length, and diameter of the umbilical cord were measured. In cases where macroscopic pathological areas were detected in the placenta or umbilical cord, sampling was performed from these areas. The placenta was sliced at 1 cm intervals, and the cross-sectional surfaces were examined. Umbilical cord sampling was performed with one section from the insertion site and four additional sections from different areas. The placenta was sampled into two sections from the fetal surface, two from the maternal surface, and one from the central region. Additionally, two blocks were taken from the placental membranes. Following tissue processing, sections 3- μ m-thick sections were obtained using a microtome. These were then stained with hematoxylin and eosin, and examined under a light microscope. Cases with predominant inflammatory infiltration by polymorphonuclear leukocytes in the placenta and placental membrane structures upon microscopic examination were classified as acute HCA, whereas those with predominant inflammatory infiltration were considered representative of chronic HCA. Cases with acute HCA were divided into mild, moderate, and severe groups according to the degree of inflammatory infiltration. Cases with inflammatory infiltration limited to focal areas of the placental membranes and decidua were classified as mild; cases in which inflammatory infiltration was detected with abscess formations, necrotizing changes, widespread villitis, and/or funisitis were considered severe; and those falling between these two extremes were defined as moderate.

2.2 Statistical Analysis

A minimum of at least 60 participants for group was necessary to detect a 10% difference with $\alpha = 0.05$ and $\beta = 0.20$, as calculated using the Research Sample Size Calculation Program. This difference of 10% was predicted both from a pilot study and from our clinical trials.

Data were analyzed by SPSS version 24.0 (IBM Corp., Chicago, IL, USA) statistical software. The Kolmogorov-Smirnov test was used to determine the normality of data distribution. The Student's *t*-test was used to compare normally distributed parametric variables between groups. Nonnormally distributed metric data were compared by the Mann-Whitney U test, as appropriate. Categorical variables were presented as percentages. The Chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate. Continuous measurement data were represented as mean \pm standard deviation (SD), and nominal data were expressed as numbers of cases and percentages. A *p*-value < 0.05 was considered significant.

3. Results

39 of the 165 patients initially evaluated between 1 May and 31 December, 2022, were excluded due to ineligibility. The remaining 126 were consecutively divided into two groups: term delivery (Group 1, *n* = 63) and preterm delivery (Group 2, *n* = 63). All 126 were included in the final analysis, as shown in Fig. 1.

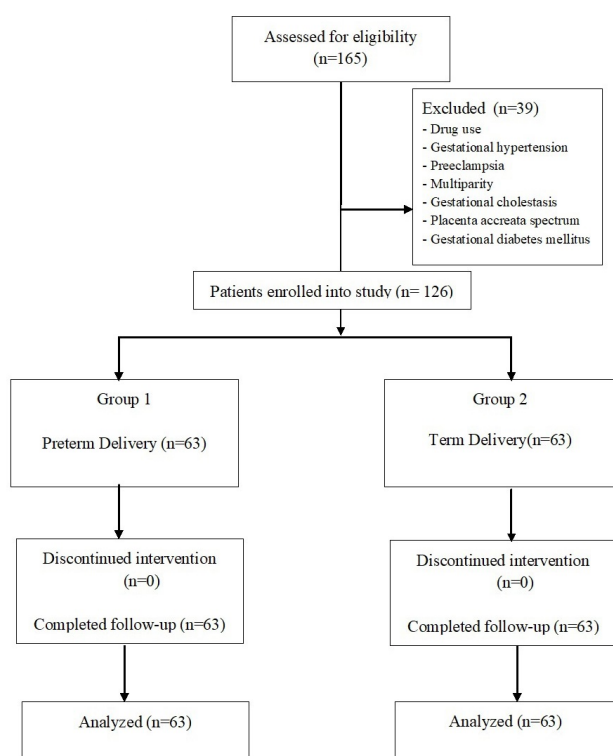


Fig. 1. Flowchart of participant enrollment and allocation in the study.

The sociodemographic and obstetric characteristics of the participants are presented in Table 1.

No significant differences were found between the groups in terms of maternal age, BMI, smoking status, history of miscarriages, presence of meconium in amniotic fluid, gravity, and Apgar scores at the fifth minute (*p* >

0.05). However, significant differences were observed in terms of parity (2.0 [1.0–2.0] vs 1.0 [0–2.0] in Groups 1 and 2, respectively; *p* = 0.008), gestational age at delivery (38.6 \pm 1.3 vs 33.6 \pm 1.6 in Groups 1 and 2, respectively; *p* < 0.001), Apgar scores at the first minute (8.8 \pm 0.6 vs 8.1 \pm 1.8 in Groups 1 and 2, respectively; *p* < 0.001), and NICU admissions (9.5% vs 42.9% in Groups 1 and 2, respectively; *p* < 0.001).

The laboratory outcomes of the participants are summarized in Table 2. Although Hb levels, MCV, and lymphocyte, neutrophil, monocyte, platelet counts, and pan-inflammatory values on admission were similar between Groups 1 and 2 (*p* > 0.05), leukocyte counts (10,382.54 \pm 2020.58 vs 12,133.33 \pm 4936.01; *p* = 0.011), neutrophil-lymphocyte ratios (4.21 \pm 1.60 vs 5.46 \pm 1.48; *p* = 0.040), and CRP values (6.46 \pm 5.56 vs 15.90 \pm 9.27 g/dL; *p* = 0.027) differed significantly.

Table 3 lists the histopathological findings of the participants. Funisitis and vasculitis were observed in 4 (6.3%) pregnancies and villitis in 5 (7.9%) in the preterm delivery group. Acute chorioamnionitis was observed in 7.9% and 49.2% of the women in Groups 1 and 2, respectively. Subacute chorioamnionitis occurred in 15.9% and 14.3%, chronic chorioamnionitis in 12.7% and 4.8%, mild chorioamnionitis in 33.3% and 49.2%, moderate chorioamnionitis in 3.2% and 14.3%, and severe chorioamnionitis in 0% and 4.8%.

4. Discussion

This study compared the laboratory parameters and findings of HCA among patients who underwent cesarean sections at term and preterm. A significant difference was observed between the two groups in terms of parity, gestational age at delivery, first-minute Apgar scores, and NICU admission rates. Leukocyte counts, neutrophil-to-lymphocyte ratios, and CRP levels also differed, and acute and severe HCA were more frequent in preterm deliveries. While subacute chorioamnionitis were comparable between the groups, chronic chorioamnionitis was detected at a higher rate in term pregnancies. Neonatal morbidity and mortality in preterm labor remain a major health concern, and research aimed at predicting preterm labor is ongoing.

Survival rates among premature infants have improved greatly in recent years due to advances in medical science and technology. However, despite improved survival rates, these infants may experience a wide range of long-term complications, as well as experiencing prolonged neonatal unit stays. Early childhood can be marked by neurodevelopmental deficiencies and recurrent health problems. Such infants may also encounter hidden challenges later in life, such as learning difficulties and behavioral problems. Saigal and Doyle [13] found that gestational age and morbidity were inversely proportional, with NICU

Table 1. Sociodemographic and obstetric characteristics of the participants.

	Term labor (n = 63)	Preterm labor (n = 63)	<i>p</i> -value
Age (years)	30.70 ± 5.65	29.49 ± 6.55	0.271
BMI (kg/m ²)	30.56 ± 4.70	29.13 ± 4.87	0.107
Smoking status (n, %)	6.00 (9.5%)	9.00 (14.3%)	0.584
Meconium in amniotic fluid (n, %)	4.00 (6.3%)	7.00 (11.1%)	0.530
Gravity	3.00 (2.0–4.0)	2.00 (1.0–2.0)	0.088
Parity	2.00 (1.0–2.0)	1.00 (0–2.0)	0.008*
Miscarriage History	0.00 (0–1)	0.00 (0–0)	0.551
Gestational age at delivery (weeks)	38.60 ± 1.30	33.60 ± 1.60	<0.001*
Apgar score			
1st minute	8.80 ± 0.60	8.10 ± 1.80	<0.001*
5th minute	9.84 ± 0.60	9.51 ± 1.41	0.089
NICU admission rate (%)	6.00 (9.5%)	27.00 (42.9%)	<0.001*

BMI, body mass index; NICU, neonatal intensive care unit.

* Statistically significant.

Table 2. Participants' laboratory results.

	Term labor (n = 63)	Preterm labor (n = 63)	<i>p</i> -value
Hb (g/dL)	11.46 ± 1.23	11.41 ± 1.43	0.826
Leukocyte count	10,382.54 ± 2020.58	12,133.33 ± 4936.01	0.011*
Neutrophil count	8692.70 ± 2884.26	9255.56 ± 4764.12	0.658
Lymphocyte count	1918.41 ± 475.07	2023.81 ± 719.92	0.334
Monocyte count	699.05 ± 188.15	722.22 ± 301.84	0.606
Neutrophil/Lymphocyte ratio	4.21 ± 1.60	5.46 ± 1.48	0.040*
MPV	10.93 ± 1.03	11.11 ± 0.85	0.283
MCV	86.25 ± 7.14	84.50 ± 4.72	0.109
Platelet count	236.62 ± 68.33	250.05 ± 91.48	0.352
PIV	603.51 (428.53–911.94)	653.58 (443.00–1075.80)	0.352
CRP	6.46 ± 5.56	15.90 ± 9.27	0.027*

Hb, hemoglobin; MPV, mean platelet volume; MCV, mean corpuscular volume; PIV, pan-inflammatory value; CRP, C-reactive protein.

* Statistically significant.

Table 3. Participants' histopathological findings.

	Term labor (n = 63)	Preterm labor (n = 63)	<i>p</i> -value
Funisitis	0	4 (6.3%)	0.119
Villitis	0	5 (7.9%)	0.058
Vasculitis	0	4 (6.3%)	0.119
Duration of inflammation			
Acute chorioamnionitis	5 (7.9%)	31 (49.2%)	
Subacute chorioamnionitis	10 (15.9%)	9 (14.3%)	<0.001*
Chronic chorioamnionitis	8 (12.7%)	3 (4.8%)	
Degree of inflammation			
Mild chorioamnionitis	21 (33.3%)	31 (49.2%)	
Moderate chorioamnionitis	2 (3.2%)	9 (14.3%)	0.161
Severe chorioamnionitis	0	3 (4.8%)	

* Statistically significant.

hospitalization rates also decreasing as gestational age increased. In the present study, a statistically significant association was also observed between gestational age and NICU admissions.

In a study of 802,119 pregnant women, 30,237 deliveries occurred before 37 weeks, and subgroup analyses showed that nulliparity increased the risk of preterm birth 1.95 times. The authors concluded that first pregnancy and a history of previous preterm delivery are important risk

factors for preterm labor [14]. In the present research, the number of births in the preterm birth group was lower than that in the term birth group, a finding consistent with the aforementioned study.

In a study by Ko *et al.* [15] involving 21,000 pregnant women, maternal smoking was associated with preterm birth, particularly when mothers smoked >20 cigarettes per day, regardless of the stage of pregnancy. Hamadneh S and Hamadneh J [16] reported lower gestational ages at birth among pregnant women who smoked actively, although no significant association was found with direct preterm labor. The birth weights of infants born to actively smoking mothers were significantly lower than those born to passive smokers and non-smoker. In the present study, although proportion of pregnant women who smoked was higher in the preterm labor group, this difference was not statistically significant.

The Apgar score is a widely accepted and commonly used method to determine the condition of the newborn immediately after birth and to evaluate the need for resuscitation. However, Apgar scores alone cannot predict the presence of asphyxia or long-term neurological outcomes. In particular, extremely preterm infants (<28 weeks of gestation) and very premature infants (between 28 and 31 weeks of gestation) may receive a low score due to an immature respiratory reflex and low muscle tone. Although the Apgar score can be used to evaluate the condition of preterm infants, it may also reflect biological immaturity in this group. In addition, Cnattingius *et al.* [17] reported that a low first-minute Apgar score at all gestational ages was associated with a significantly increased risk of neonatal death. In the present study, first-minute Apgar scores were significantly associated with the frequency of preterm labor. Cnattingius *et al.* [17] also showed that fifth-minute Apgar scores are more predictive of neonatal survival. In the current study, although fifth-minute Apgar scores were higher in the term pregnancy group, the difference between the two groups was not statistically significant. This may be due to early and appropriate interventions for preterm births in our hospital, a tertiary care institution.

Asgharnia *et al.* [18] observed that the frequency of preterm birth increases directly with the number of pregnancies and inversely proportionally to the interval between pregnancies. Those authors found that each additional pregnancy raised the risk of preterm birth by 1.45-fold. However, we found no statistically significant relationship between the number of pregnancies and preterm birth.

Intrauterine inflammation is thought to contribute to the triggering of preterm labor. The markers of intrauterine inflammation are classified as placental inflammatory response, umbilical cord inflammatory response, maternal inflammatory response (MIR), and FIR [19]. MIR occurs when inflammation spreads to the chorion, amnion, or decidua, while FIR is caused by the infiltration of inflammation into the chorionic structure, umbilical cord, and fe-

tal vessels [20]. Activation of the natural immune system causes an increase in the number of white blood cells. Instead of relying on invasive procedures such as amniocentesis and chorionic villous sampling, there is a growing need for less invasive and inexpensive laboratory markers to detect inflammation associated with the onset of preterm labor. In their retrospective evaluation of 483 preterm deliveries, Kim *et al.* [21] compared serum leukocyte and CRP levels, neutrophil-lymphocyte ratio (NLR), and HCA frequencies with those of term pregnancies, and found that all these parameters were significantly higher in the preterm delivery group. In the present study, serum leukocyte and CRP values, NLR, and HCA were also higher in the preterm delivery group compared to the term delivery group.

In the meta-analysis by Rahmati *et al.* [22], which consisted of 18 studies including approximately 932,000 pregnant women, a significant association was observed between maternal anemia and preterm birth during the first trimester, but not in the second and third trimesters. While maternal anemia increased the risk of preterm delivery 1.65 times (95% confidence interval [CI]: 1.25–1.95) in the first trimester, the values for the second and third trimesters were statistically insignificant. All pregnant women participating in the present study were in the second and third trimesters, and no significant difference was found between the groups regarding Hb values.

The placenta is the most important organ for fetal development and survival. Pathological changes in the placenta affect the normal fetal organ development and associated with prematurity. Amniotic fluid infection associated with placental inflammation is classified as chorioamniotic membrane inflammation (chorioamnionitis) or umbilical cord inflammation (funisitis).

Lee *et al.* [23] graded the inflammatory response in the umbilical cord and chorioamniotic membranes histologically in 339 preterm deliveries, at or before 34 weeks of gestation, and compared these retrospectively with neonatal outcomes. The authors reported that respiratory distress syndrome (RDS), bronchopulmonary dysplasia, intraventricular hemorrhage, and retinopathy of prematurity increased with the severity of inflammation, whereas the frequency of periventricular leukomalacia and necrotizing enterocolitis remained unchanged. They concluded that acute HCA increases neonatal morbidity in preterm deliveries [23]. Although there was no significant difference in umbilical cord inflammation between the term and preterm groups in the present study, no funisitis was observed in the term group. Umbilical cord inflammation was observed in 6.3% of the preterm labor group, chorionic villi inflammation in 7.9%, and vasculitis in 6.3%.

Goldenberg *et al.* [24] showed that low BMI before pregnancy increases the risk of preterm birth compared to obesity. Although the difference was not statistically significant, maternal BMI was lower in the preterm group compared to the term group in the present study.

In the review by Vogel *et al.* [8], they reported that although the risk of preterm birth increased in adolescents under 18 years and women over 35, no consistent relationship was found between maternal age and delivery outcomes. Similarly, no significant difference in maternal age was observed between the term and preterm delivery group in the present study.

It is now recognized that intrauterine infection causes a significant proportion of spontaneous preterm births [20]. This may cause asymptomatic infection, HCA, or clinical chorioamnionitis. Diagnosis is made by sampling amniotic fluid, fetal cord blood, or placental tissue exhibiting HCA. In a study of infants born to mothers with gestational ages at birth of less than 29 weeks, 197 (51%) of the 384 infants were born to mothers with evidence of HCA [22]. In the present study, HCA rates were 68.3% in the preterm group and 36.5% in the term group; however, the difference was not statistically significant.

Acute inflammatory lesions of the placenta include acute chorioamnionitis, funisitis, and chorionic vasculitis, and presence of chemotactic agents in the amniotic cavity indicate maternal or fetal response, as previously described. Acute chorioamnionitis constitutes evidence of the maternal host response, while funisitis and chorionic vasculitis demonstrate the FIR. Intra-amniotic infection is generally accepted as the cause of acute chorioamnionitis and funisitis, while sterile intra-amniotic inflammation in the absence of microorganisms, has also been found to be triggered by “danger signals” and is associated with these lesions [20].

In their study including 392 singleton pregnancies, Torricelli *et al.* [25] divided HCA into three groups (mild, moderate, and severe) and observed that the rate of HCA increased as gestational weeks decreased. In other words, there is a negative correlation between gestational week and HCA severity [25]. In the present study, mild and moderate chorioamnionitis were significantly more frequent in preterm deliveries than in term deliveries.

Conti *et al.* [26] reported that while the rate of HCA was 20% in term pregnancies, it approached 50% in preterm pregnancies. Although HCA is less symptomatic in term pregnancies, it exhibits distinct clinical signs in preterm pregnancies [2]. Consistent with that research, the rate of chronic chorioamnionitis was significantly higher in term deliveries, while the rate of acute chorioamnionitis was higher in preterm deliveries in the present study. This suggests that chronic chorioamnionitis is not a cause of preterm labor, whereas acute chorioamnionitis triggers preterm labor and produces clinical manifestations.

Fahmi *et al.* [27] compared 98 term, 71 late preterm, and 65 early preterm deliveries, reporting frequencies of HCA of 26.7% in late preterm deliveries and 38.5% in early preterm deliveries. When classifying HCA as low- or high-grade, they found that low-grade HCA was more common in term deliveries, while high-grade HCA was more frequent in preterm deliveries, occurring 2.17 times more

frequently in preterm than in term deliveries [28]. In the present study, severe HCA was not found in any patients in the term group but was seen in 3% in the preterm group; however, the difference was not statistically significant.

Amniocentesis is the accepted “gold standard” test for detecting maternal and fetal intra-amniotic infection, but it has clinical limitations. Similarly, fetal inflammatory response syndrome (FIRS) can be assessed by measuring interleukin (IL)-6 levels via cordocentesis; however, this method is clinically impractical for prospective diagnosis of fetal infection and carries significant risk. Imaging techniques (e.g., ultrasound and magnetic resonance imaging) especially of the placenta, have the potential to prospectively detect chorioamnionitis without posing significant risk to the fetus or mother. Currently, clinicians must balance the risks and benefits to both mother and fetus when deciding whether to prolong gestation in the presence of undiagnosed intrauterine infection. It is unlikely that a single predictive diagnostic test will soon be available to determine diagnosis, timing of delivery, and prognosis. However, combining imaging techniques with established biological markers currently hold the greatest promise [28,29].

While the limitations of this study include its single-center setting and being conducted in a tertiary institution, its strength lies in its prospective design.

5. Conclusions

Acute chorioamnionitis, an inflammatory response affecting the placenta and its appendages, is an important risk factor for preterm birth. Its prevalence is inversely proportional to the gestational week and is associated with adverse neonatal outcomes. In addition, elevated leukocyte counts, NLR, and CRP parameters can be helpful in the diagnosis of chorioamnionitis. Timely administration of appropriate antibiotic therapy and corticosteroid use may improve neonatal outcomes.

Availability of Data and Materials

Data are available with the permission of the corresponding author (E-mail: ailker_eryilmaz@hotmail.com).

Author Contributions

AIE, DO, MBB, HAI, GI, and MK were responsible for the study design, data collection, statistical analyses, and manuscript writing. AIE and HAI analyzed the samples and reviewed the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study was carried out in accordance with the guidelines of the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Health Sci-

ence University, Antalya Training and Research Hospital (approval number: 2022-4/25). All patients or their families/legal guardians gave their informed consent for inclusion before they participated in the study.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

- [1] Frey HA, Klebanoff MA. The epidemiology, etiology, and costs of preterm birth. *Seminars in Fetal & Neonatal Medicine*. 2016; 21: 68–73. <https://doi.org/10.1016/j.siny.2015.12.011>.
- [2] Sharma A, Davis A, Shekhawat PS. Hypoglycemia in the preterm neonate: etiopathogenesis, diagnosis, management and long-term outcomes. *Translational Pediatrics*. 2017; 6: 335–348. <https://doi.org/10.21037/tp.2017.10.06>.
- [3] Helmo FR, Alves EAR, Moreira RADA, Severino VO, Rocha LP, Monteiro MLGDR, *et al*. Intrauterine infection, immune system and premature birth. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2018; 31: 1227–1233. <https://doi.org/10.1080/14767058.2017.1311318>.
- [4] Mitrogiannis I, Evangelou E, Efthymiou A, Kanavos T, Birbas E, Makrydimas G, *et al*. Risk factors for preterm birth: an umbrella review of meta-analyses of observational studies. *BMC Medicine*. 2023; 21: 494. <https://doi.org/10.1186/s12916-023-03171-4>.
- [5] Ye CX, Chen SB, Wang TT, Zhang SM, Qin JB, Chen LZ. Risk factors for preterm birth: a prospective cohort study. *Chinese Journal Of Contemporary Pediatrics*. 2021; 23: 1242–1249. <http://doi.org/10.7499/j.issn.1008-8830.2108015>.
- [6] Shennan A, Story L, Jacobsson B, Grobman WA. FIGO good practice recommendations on cervical cerclage for prevention of preterm birth. *International Journal of Gynecology & Obstetrics*. 2021; 155: 19–22. <https://doi.org/10.1002/ijgo.13835>.
- [7] Inal ZO, Inal HA, Kucukkendirci H, Oruc AS. Investigation of cesarean sections at Konya Training and research hospital obstetrics and gynecology department between 2010 and 2015. *Ginekologia Polska*. 2017; 88: 185–190. <https://doi.org/10.5603/GP.a2017.0036>.
- [8] Vogel JP, Chawanpaiboon S, Moller A, Watananirun K, Bonet M, Lumbiganon P. The global epidemiology of preterm birth. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2018; 52: 3–12. <https://doi.org/10.1016/j.bpobgyn.2018.04.003>.
- [9] Inal HA, Inal ZO. Comparison of Perinatal Outcomes between syrian refugees and turkish women in the middle anatolia region of Turkey. *Maternal and Child Health Journal*. 2023; 27: 2139–2146. <https://doi.org/10.1007/s10995-023-03748-8>.
- [10] Saccone G, Maruotti GM, Giudicepietro A, Martinelli P. Effect of cervical pessary on spontaneous preterm birth in women with singleton pregnancies and short cervical length. *JAMA*. 2017; 318: 2317. <https://doi.org/10.1001/jama.2017.18956>.
- [11] Rallis D, Lithoxopoulou M, Pervana S, Karagianni P, Hatzioannidis I, Soubasi V, *et al*. Clinical chorioamnionitis and histologic placental inflammation: association with early-neonatal sepsis. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2022; 35: 8090–8096. <https://doi.org/10.1001/1080/14767058.2021.1961727>.
- [12] Catov JM, Scifres CM, Caritis SN, Bertolet M, Larkin J, Parks WT. Neonatal outcomes following preterm birth classified according to placental features. *American Journal of Obstetrics and Gynecology*. 2017; 216: 411.e1–411.e14. <https://doi.org/10.1016/j.ajog.2016.12.022>.
- [13] Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *The Lancet*. 2008; 371: 261–269. [https://doi.org/10.1016/S0140-6736\(08\)60136-1](https://doi.org/10.1016/S0140-6736(08)60136-1).
- [14] Koullali B, van Zijl MD, Kazemier BM, Oudijk MA, Mol BWJ, Pajkrt E, *et al*. The association between parity and spontaneous preterm birth: a population based study. *BMC Pregnancy and Childbirth*. 2020; 20: 233. <https://doi.org/10.1186/s12884-020-02940-w>.
- [15] Ko T, Tsai L, Chu L, Yeh S, Leung C, Chen C, *et al*. Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. *Pediatrics & Neonatology*. 2014; 55: 20–27. <https://doi.org/10.1016/j.pedneo.2013.05.005>.
- [16] Hamadneh S, Hamadneh J. Active and passive maternal smoking during pregnancy and birth outcomes: a study from a developing country. *Annals of Global Health*. 2021; 87: 122. <https://doi.org/10.1136/10.5334/aogh.3384>.
- [17] Cnattingius S, Johansson S, Razaz N. Apgar score and risk of neonatal death among preterm infants. *New England Journal of Medicine*. 2020; 383: 49–57. <https://doi.org/10.1056/NEJMoa1915075>.
- [18] Asgharnia M, Varasteh T, Pourmarzi D. Inter-pregnancy interval and the incidence of preterm birth. *Journal of Family Reproductive Health*. 2020; 14: 52–56.
- [19] Wong YP, Khong TY. Changing laboratory practice for early detection of a fetal inflammatory response: a contemporary approach. *diagnostics*. 2023; 13: 487. <https://doi.org/10.3390/diagnostics13030487>.
- [20] Gomez-Lopez N, Galaz J, Miller D, Farias-Jofre M, Liu Z, Arenas-Hernandez M, *et al*. The immunobiology of preterm labor and birth: intra-amniotic inflammation or breakdown of maternal–fetal homeostasis. *Reproduction*. 2022; 164: R11–R45. <https://doi.org/10.1530/REP-22-0046>.
- [21] Kim MA, Lee YS, Seo K. Assessment of predictive markers for placental inflammatory response in preterm births. *PLoS ONE*. 2014; 9: e107880. <https://doi.org/10.1371/journal.pone.0107880>.
- [22] Rahmati S, Azami M, Badfar G, Parizad N, Sayehmiri K. The relationship between maternal anemia during pregnancy with preterm birth: a systematic review and meta-analysis. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2020; 33: 2679–2689. <https://doi.org/10.1080/14767058.2018.1555811>.
- [23] Lee Y, Kim H, Choi S, Oh S, Kim J, Roh C, *et al*. Is there a stepwise increase in neonatal morbidities according to histological stage (or grade) of acute chorioamnionitis and funisitis?: effect of gestational age at delivery. *Journal of Perinatal Medicine*. 2015; 43: 259–267. <https://doi.org/10.1515/jpm-2014-0035>.
- [24] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *The Lancet*. 2008; 371: 75–84. [https://doi.org/10.1016/S0140-6736\(08\)60074-4](https://doi.org/10.1016/S0140-6736(08)60074-4).
- [25] Torricelli M, Voltolini C, Toti P, Vellucci FL, Conti N, Cannoni A, *et al*. Histologic chorioamnionitis: different histologic features at different gestational ages. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2014; 27: 910–913. <https://doi.org/10.3109/14767058.2013.846313>.
- [26] Conti N, Torricelli M, Voltolini C, Vannuccini S, Clifton VL, Bloise E, *et al*. Term histologic chorioamnionitis: a heterogeneous condition. *European Journal of Obstetrics & Gynecology*

and Reproductive Biology. 2015; 188: 34–38. <https://doi.org/10.1016/j.ejogrb.2015.02.034>.

- [27] Fahmi S, Papadogiannakis N, Nasiell J. High-but not low-grade histologic chorioamnionitis is associated with spontaneous preterm birth in a Swedish cohort. *The Journal of Maternal-Fetal & Neonatal Medicine*. 2018; 31: 2265–2270. <https://doi.org/10.1080/14767058.2017.1340447>.
- [28] Hall M, Hutter J, Suff N, Avena Zampieri C, Tribe RM, Shennan A, *et al.* Antenatal diagnosis of chorioamnionitis: a review of the potential role of fetal and placental imaging. *Prenatal Diagnosis*. 2022; 42: 1049–1058. <https://doi.org/10.1002/pd.6188>.
- [29] Svigos JM. The fetal inflammatory response syndrome and cerebral palsy: yet another challenge and dilemma for the obstetrician. *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 2001; 41: 170–176. <https://doi.org/10.1111/j.1479-828x.2001.tb01203.x>.