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Predictive Values of Maternal Serum Levels of Procalcitonin, ESR, CRP, and WBC in the Diagnosis of Chorioamnionitis in Mothers with Preterm Premature Rupture of Membrane

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ABSTRACT

Background: Premature rupture of membrane (PROM) refers to the rupture of fetal membranes at least 1 hour before the onset of labor pain. We aimed to determine the predictive value of maternal serum level of procalcitonin in the early diagnosis of chorioamnionitis in mothers with preterm (PPROM).

Methods: In this prospective cohort study, 48 patients with PPROM were selected due to limited financial resources and in accordance with previous similar articles. The study was carried out in Kosar ward of Motahhari Hospital of Urmia, Iran. The inclusion criteria were leaking amniotic fluid, positive nitrazine and fern tests, gestational age of 28-33 weeks, and lack of fetal tachycardia. The exclusion criteria were chronic vascular and congenital heart diseases as well as the use of nonsteroidal anti-inflammatory drugs (NSAIDs). To analyze the data, we used descriptive statistics, Chi-square test (OR), independent t-test, and Pearson in SPSS, version 19.

***Results*:** The present study was conducted on 48 pregnant women and their neonates. About 39.6% of the mothers were pathologically infected with chorioamnionitis, while 60.4% of the patients were not infected with the disease. Moreover, 68.8% of the neonates had a five-minute Apgar score of ≥ 7. There was a significant correlation between the mothers' infection with histopathologic chorioamnionitis and neonatal hospitalization in neonatal intensive care unit (P<0.001).

Conclusion: According to the results, there was a significant correlation between the inflammatory indices of erythrocyte sedimentation rate, C-reactive protein, and white blood cell during the delivery time and histopathologic chorioamnionitis.

Keywords: Chorioamnionitis, Mother, Newborn, Preterm, Procalcitonin, PROM

Introduction

PROM denotes the premature rupture of membranes at least one hour before the onset of labor pain, which involves about 10% of pregnancies. One-third of PROM cases occur before week 37 of pregnancy, which are called PPROM (1). Nili and Ansari (2003) reported the incidence of PROM in Vali-e-Asr Hospital in Tehran, Iran, to be 7% (2). In a categorization, PPROM is divided into three groups, namely non-viable fetus (before week 23 of pregnancy), rupture of membranes from fetal viability to week 31 of pregnancy and from week 32 to 36 (3).

The exact cause of PROM has not yet been recognized (4); however, the important risk factors for PROM include gestational age, low maternal body mass index (BMI; <19.8), social and economic status of the mother, history of colonization of the uterine cervix, smoking, genital infections, excessive elongation of the membranes (due to polyhydramnios or multiple pregnancies), history of PPROM, nutritional factors (deficiency of copper or ascorbic acid), cervical incompetence,

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cervical cerclage and placental detachment (2nd and 3rd trimester bleeding) (5). The complications of PROM before the onset of labor pain comprise maternal infections (e.g., endometritis or sepsis), chorioamnionitis (9% in term PROM and 13-60% in PPROM), placental detachment, fetal infections, neonatal death, low Apgar score, umbilical cord compression and prolapse, pulmonary hypoplasia and low birth weight (6, 7). The infection with *Chlamydia trachomatis*, *Trichomonas vaginalis*, *Neisseria gonorrhea*, and Group B *Streptococcus* (GBS) cause PROM (5). The mean duration of hospitalization of PROM and PPROM neonates respectively increases by 20% and 25%. In comparison with other neonates, their imposed costs on the health system upsurge by 30.5% and 60%, respectively (8).

Chorioamnionitis is infectious inflammation of the uterine cavity, fetal membranes (amnion and chorion), and placenta with certain maternal and fetal complications (9, 10). Fever ≥ 38˚C (≥100.4˚F) along with rupture of membranes are the only reliable indicators of chorioamnionitis; nevertheless, maternal leukocytosis per se is not a reliable indicator. In anticipated treatment, it is necessary to monitor the patient for uterine tenderness, permanent maternal or fetal tachycardia, and foul-smelling vaginal discharge (11). However, a definitive diagnosis is established after microscopic observations (12).

Procalcitonin (PCT) is a 116-aminoacid-containing polypeptide, which is precursor of the hormone calcitonin and is processed to CT and one 32-aminoacid polypeptide via endopeptidase enzyme (13). The serum level of PCT increases within 2-6 hours after sepsis, but it decreases in the case of infection control (14, 15). Since chorioamnionitis is a bacterial infection causing sepsis and serum PCT increases in bacterial infections, it appears to be effective in the early diagnosis of chorioamnionitis, as well as early termination of pregnancy and fetal therapy. According to a study, the sensitivity and specificity of the maternal serum level of PCT for the diagnosis of histopathologic chorioamnionitis were 50% and 55.6%, respectively (16). Due to the limited number of studies in this area and significant effects of early diagnosis of chorioamnionitis on reducing maternal and neonatal complications, we sought to determine the predictive value of PCT in the early diagnosis of chorioamnionitis in pregnant mothers with PPROM in 2016, so as to increase the knowledge in this field and reduce the maternal and fetal complications of chorioamnionitis through proving the applicability of this biomarker in treatment interventions and patient managements.

Methods

The subjects of the present study included pregnant women with PPROM undergoing conventional therapy in Kosar ward of Motahhari Hospital, Urmia, Iran. They participated in the study as cohorts. Overall, 48 patients with PPROM were selected as the intended sample size due limited financial resources and in accordance with previous articles.

The intended variables were extracted through continuous rehearsal, a demographic checklist, lab test results, and histological examination. The demographic variables were recorded from the patient's dossier completed by themselves, and laboratory variables were derived from lab reports. The participants were the pregnant mothers hospitalized in the midwifery ward of Shahid Motahari Hospital due to rupture of membranes at the gestational age of 28 to 33 weeks.

Upon admission, these patients underwent blood sampling for screening erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), PCT, leukocytosis, fever, and non-stress test (NST) tape to diagnose fetal tachycardia. Afterwards, the patients underwent treatment in the hospital. Immediately after delivery (vaginal or cesarean), a blood sample was retaken to screen ESR, CRP, PCT and leukocytosis. The placenta of all the patients were transferred to a pathology laboratory for histological examination of chorioamnionitis by the advisor professor.

In the pathology lab, the sample preparation stages were as follows:

1. After isolating the samples fixed in formalin, the steps of tissue processing included: 1. additional fixation in formalin solution, 2. dehydration in 75, 85, and 96% alcohol and absolute alcohol, 3. clearing in xylene solution, and 4. impregnation in molten paraffin via a tissue processor;
2. Sample molding by paraffin and paraffin blocks;
3. Cutting the blocks at a thickness of 4 microns

by a micro-thermometer and transferring the tissues;
4. Paraffinizing the isolated tissues using dry heat or four ovens;
5. Hematoxylin and eosin staining as follows:

5.1. Hydrating tissues in 96, 85 and 75% alcohol
5.2. Washing with water
5.3. Staining with hematoxylin
5.4. Washing with water
5.5. De-staining (decoloring) in alcoholic acid
5.6. Washing with water
5.7. Alkalizing tissues by bicarbonates
5.8. Washing with water
5.9. Staining with eosin
5.10. Washing with water
5.11. Dehydrating with reverse alcohols
5.12. Clearing in xylene solution
5.13. Laminating with Entellan Merck

It should be noted that chorioamnionitis is pathologically characterized as leukocyte infiltration with neutrophilic priority and inflammatory infiltration on the fetal membranes (17). Finally, the patients were divided into three groups of a) pregnant mothers with clinical symptoms of chorioamnionitis, b) Pregnant mothers with histopathologic chorioamnionitis, and c) pregnant mothers with none of the above symptoms (clinical or histologic chorioamnionitis).

The patients underwent clinical examination for screening for fever and fetal tachycardia using NST tape 24 hours before the onset of labor. Antibiotic treatment was used to prevent neonatal sepsis in the patients.

Next, the mentioned inflammatory indices were compared in each group. The serum level of PCT higher than 0.06 ng/ml was considered as high level. This amount was selected with respect to the use of different cut-off points in the reviewed articles, population proximity of the neighboring country, that is, Turkey, with Iran, and the novelty of the present article (17). Cobas e411 analyzer and Roche diagnostic kit (Lot 187-424-02) were used to measure the level of PCT. The levels of CRP ≥ +1 and leukocytosis ≥ 15,000 were considered as positive criteria (18). The level of ESR ≥ 52 was positive in the present study.

There was a two-way blindness process between the histology group and the laboratory responsible for monitoring the maternal serum level of PCT. In order to evaluate the diagnostic value of PCT in diagnosing chorioamnionitis, it was respectively compared with clinical symptoms, histological results, specificity index, sensitivity index, positive and negative predictive values, and Yoden's index.

The inclusion criteria included proof of amniotic fluid leaking via speculum examination, positive nitrazine and fern tests, gestational age from week 28 to 33 that was proven to be less than week 20 by ultrasound, lack of fever, uterine contractions, abnormal vaginal discharge on the first day of hospitalization, absence of vaginal bleeding, and lack of fetal tachycardia. The exclusion criteria comprised of congenital heart disease, heart valve surgery, chronic vascular disease (nephritic syndrome, lupus), use of corticosteroids, and use of NSAIDs.

This study was approved by the Ethics Committee of Urmia University of Medical Sciences, with code No. 1394-01-32-2140. All the patients were thoroughly informed of the research process and the researcher did not intervene in the conventional process or the management and treatment of the patients. To analyze the data, descriptive statistics, independent t-test, and Pearson correlation coefficient were run in SPSS, version 19. P-value less than 0.05 was considered significant.

Result

We aimed to determine the predictive value of maternal serum level of PCT in the diagnosis of chorioamnionitis in 48 mothers with PPROM. The demographic characteristics of the 48 patients are shown in Table 1.

In the present study, the diagnosis of PPROM was positive in 23 patients (47.9%) due to the clear amniotic fluid leaking and in 25 patients (52.1%) due to nitrazine and fern tests. The gestational

Table 1. Demographic features of the intended mothers

Variable	Frequency	Percentage
G≤2	33	68.7
G≥3	15	31.3
PTL	1	2.1
PPROM	6	12.5
Abortion	6	12.5

PPROM: Preterm premature rupture of membranes
PTL: Preterm labor

Table 2. Minimum and maximum inflammatory indices upon hospitalization and delivery time

Variable	No.	Min.	Max.	Mean	SD
ESR upon hospitalization	48	20	74	38.93	11.62
ESR upon delivery time	48	34	104	59.12	16.97
WBC upon hospitalization	48	5000	16000	9664.6	2881.30
WBC upon delivery time	48	6200	18800	12204	3630.06
PCT upon hospitalization	48	0.02	0.10	0.041	0.017
PCT upon delivery time	48	0.03	0.95	0.104	0.175
The last measured index of amniotic fluid	48	0	38	19.42	9.91
Days of hospitalization until delivery	48	2	30	10.29	5.52

ESR: erythrocyte sedimentation rate
WBC: white blood cell
PCT: procalcitonin

age of 9 (18.8%) patients was evaluated using last menstrual period (LMP). Based on ultrasound, the gestational age of 34 (50%) patients were less than 12 weeks, and in 15 (39.9%) patients, it was less than 20 weeks. Amongst the 48 patients, the minimum gestational age at PROM was 28 weeks and 5 days, while the maximum gestational age at PROM was 33 weeks. The mean time of PPROM was 31w+6d±1w+2d. Moreover, the minimum gestational age at delivery was 29 weeks and 5 days, while the maximum gestational age at delivery was 34 weeks. The mean delivery time was 33w+2d±1w. In terms of 5-minute Apgar score, 3 (6.2%) neonates scored 4, 7 (14.6%) scored 5, 5 (10.4%) scored 6, and 33 (68.8%) neonates scored 7. In terms of birth weight (BW), the minimum birth weight was 1200 g, while the maximum BW was 2200 g. The mean BW was 1927.1±232.31 g. In terms of NICU hospitalization, only 12 (25%) neonates were hospitalized and the remaining 36 (75%) did not require NICU admission. Amongst the neonates hospitalized in NICU, 3 (25%) were discharged in a good condition, whereas 9 (75%) newborns died. The causes of neonatal death were reported to be pulmonary hemorrhage, acute respiratory distress syndrome (ARDS), cerebral hemorrhage, and sepsis.

According to Table 2, the minimum and maximum days of maternal care in hospital until delivery were 20 and 30 days, respectively, and the mean duration was 10.29±5.52 days. In terms of amniotic fluid index in the last ultrasound before delivery, the minimum and maximum indexes were 0 and 38 mm, respectively. The mean fluid index was 19.42±9.91 mm.

As presented in Table 3, in terms of ESR, the inflammatory index upon hospitalization

Table 3. Rate of maternal infection with pathologic chorioamnionitis based on WBC≥15000 upon hospitalization

Variable			Pathologic chorioamnionitis		Total
			Yes	No	
WBC≥15000 upon hospitalization	Positive	No.	1	1	2
		Percentage	50	50	100
	Negative	No.	18	28	46
		Percentage	39.1	60.9	100
	Total	No.	19	29	48
		Percentage	39.6	60.4	100
ESR>30 upon delivery time	Positive	No.	16	10	26
		Percentage	61.5	38.5	100
	Negative	No.	3	19	22
		Percentage	13.6	86.4	100
	Total	No.	19	29	48
		Percentage	39.6	60.4	100

ESR: erythrocyte sedimentation rate
WBC: white blood cell
PCT: procalcitonin

Table 4. Rate of maternal infection with pathologic chorioamnionitis based on WBC≥15000 upon delivery time

Variable			Pathologic chorioamnionitis		Total
			Yes	No	
WBC≥15000 upon delivery time	Positive	No.	13	3	16
		Percentage	81.2	18.8	100
	Negative	No.	6	26	32
		Percentage	18.8	81.2	100
	Total	No.	19	29	48
		Percentage	39.6	60.4	100
PCT>0.06 upon hospitalization	Positive	No.	2	0	2
		Percentage	100	0	100
	Negative	No.	17	29	46
		Percentage	37	63	100
	Total	No.	19	29	48
		Percentage	39.6	60.4	100

PCT: procalcitonin
WBC: white blood cell

the minimum and maximum values were 18 and 37, and the mean ESR was 24.98±5.05. On the other hand, the minimum and maximum ESR indexes at delivery time were 20 and 84, and the mean ESR index was 39.08±16.03. There was a significant correlation between ESR on admission and delivery time (R^2: 0.312, P<0.001). Regarding CRP inflammatory index upon hospitalization, the index of 39 (81.2%) patients was negative, in 8 (16.7%) patients it was +1, and in 1 (2.1%) patient it was +2. In terms. of CRP, the inflammatory index upon delivery time, the index of 18 (37.5%) patients were negative, in 16 (33.3%) patients it was +1, in 10 (20.8%) patients it was +2, and in 4 (8.3%) patients it was +3.

As presented in Table 4, in terms of WBC inflammatory index upon hospitalization, the minimum and maximum values were 5000 and 16000, respectively, and its mean index was 9664.6±2881.30. On the other hand, the minimum and maximum WBC indexes upon delivery were 6200 and 18800, respectively, and its mean index was 12204±3630.6. There was a significant correlation between WBC upon hospitalization and delivery time (R^2: 0.396, P<0.001). Considering, PCT inflammatory index upon hospitalization, the minimum and maximum values were 0.02 and 0.1, respectively, and its mean value was 0.041±0.017

On the other hand, the minimum and maximum PCT indexes upon delivery were 0.95 and 0.03, respectively, and its mean index was 0.104±0.175. There was not any statistically significant correlation between PCT upon hospitalization and delivery time (R^2: 0.04, P<0.176). The odds ratio of chorioamnionitis in mothers with increased ESR index upon delivery time was 19.28 (OR: 19.28). Amongst the mothers with positive WBC ≥ 15000 index upon hospitalization, 1 (50%) mother was infected with chorioamnionitis, while 1 (50%) patient was not. Moreover, amongst those with negative WBC index upon hospitalization, 18 (39.1%) had chorioamnionitis, whereas 28 (60.9%) were not infected. According to Chi-square test and Pearson correlation, there was not any significant correlation between WBC index upon hospitalization and infection with chorioamnionitis (P=0.761). Amongst mothers with positive WBC ≥ 15000 index upon delivery time, 13 (81.2%) mothers were infected with chorioamnionitis, while 3 (18.8%) were not. Moreover, amongst mothers with negative WBC index upon delivery time, 6 (18.8%) had chorioamnionitis, while 26 (81.2%) were not infected. According to Chi-square test and Pearson correlation, there was a significant correlation between WBC index upon delivery and infection with chorioamnionitis (P=0.001). The odds ratio of chorioamnionitis in mothers with elevated WBC index upon delivery time was 18.78 (OR: 17.78).

Table 5. Rate of neonatal hospitalization in neonatal intensive care unit with respect to maternal infection with chorioamnionitis

Variable			Pathologic chorioamnionitis		Total
			Yes	No	
Neonatal intensive care unit	Yes	No.	10	2	12
		Percentage	83.3	16.7	100
	No	No.	9	27	36
		Percentage	25	75	100
	Total	No.	19	29	48
		Percentage	39.6	60.4	100
PCT>0.06 upon delivery time	Positive	No.	16	8	24
		Percentage	66.7	33.3	100
	Negative	No.	3	21	24
		Percentage	12.5	87.5	100
	Total	No.	19	29	48
		Percentage	39.6	60.4	100

PCT: procalcitonin

According to Table 5, all the mothers with positive PCT ≥ 0.06 index upon hospitalization were infected with chorioamnionitis. Moreover, amongst the mothers with negative PCT index upon hospitalization, 17 (37%) had chorioamnionitis, whereas 29 (63%) were not infected. According to Chi-square test and Pearson correlation, there was not any significant correlation between PCT index upon hospitalization and infection with chorioamnionitis (P=0.077). Further, 16 (66.7%) mothers with positive PCT ≥ 0.06 index upon delivery time were infected with chorioamnionitis, while 8 (33.3%) were not. Moreover, amongst the mothers with negative PCT index upon delivery time, 3 (12.5%) had chorioamnionitis, while 21 (87.5%) were not infected. According to Chi-square test and Pearson correlation, there was a significant correlation between PCT index upon delivery and chorioamnionitis infection (P=0.001). The odds ratio of chorioamnionitis infection in mothers with increased PCT index upon delivery time was infinite (not defined) (OR: ∞). In addition, 10 (83.3%) neonates hospitalized in the NICU had infected mothers with pathologic chorioamnionitis, while 2 (16.7%) mothers were not infected. Moreover, amongst the neonates who were not hospitalized in NICU, 9 (25%) had infected mothers with chorioamnionitis, whereas 27 (75%) mothers were not infected. According to Chi-square test and Pearson correlation, there was a significant correlation between neonatal hospitalization in NICU and maternal infection with chorioamnionitis (P=0.001).

According to Table 6, the results of t-test

Table 6. Mean and standard deviation of inflammatory indices with respect to maternal infection with pathologic chorioamnionitis

Variable	Pathologic chorioamnionitis	No.	Mean	SD
ESR>30 upon hospitalization	Positive	19	28.16	5.12
	Negative	29	22.9	3.81
ESR>30 upon delivery time	Positive	19	53.21	15.99
	Negative	29	29.83	6.53
WBC≥15000 upon hospitalization	Positive	19	10116	2633.18
	Negative	29	9369	3041.27
WBC≥15000 upon delivery time	Positive	19	15189	2218.58
	Negative	29	10248	2990.89
PCT>0.06 upon hospitalization	Positive	19	0.045	0.021
	Negative	29	0.038	0.012
PCT>0.06 upon delivery time	Positive	19	0.18	0.265
	Negative	29	0.056	0.018

ESR: erythrocyte sedimentation rate
WBC: white blood cell
PCT: procalcitonin

Table 7. Results of Kendull Tau test for correlation between white blood cells and PCT

Variable			WBC upon delivery time	PCT upon delivery time
Kendull Tau Test	WBC upon delivery time	Correlation coefficient	1,000	0.148
		P-value	0.0	0.407
		No.	19	19
	PCT upon delivery time	Correlation coefficient	0.148	1,000
		P-value	0.407	0.0
		No.	19	19
Variable			PCT upon delivery time	ESR upon delivery time
Kendull Tau Test	PCT upon delivery time	Correlation coefficient	1,000	0.025
		P-value	0.0	0.886
		No.	19	19
	ESR upon delivery time	Correlation coefficient	0.025	1,000
		P-value	0.886	0.0
		No.	19	19

PCT**:** Procalcitonin
ESR: Erythrocyte sedimentation rate
WBC: White blood cell

indicated no significant correlation between maternal infection with pathologic chorioamnionitis and the mean values of WBC and PCT inflammatory indices upon hospitalization (P=0.386 and 0.191, respectively). On the contrary, based on the same test, there was a positive correlation between the mean value of ESR upon hospitalization and ESR, WBC and PCT upon delivery (P=0.001, P=0.001, P=0.407, and 0.148, respectively).

According to the results of the present study:

The sensitivity, specificity, as well as positive and negative predictive values of ESR inflammatory index were 94.73%, 62%, 63%, and 93%, respectively, for the diagnosis of histopathologic chorioamnionitis. The sensitivity, specificity, and positive and negative predictive values of CRP inflammatory index were 63.33%, 100%, 100%, and 62%, respectively, for the diagnosis of histopathologic chorioamnionitis.

The sensitivity, specificity, as well as positive and negative predictive values of WBC inflammatory index were 81.25%, 89.65%, 68.42%, and 89.65%, respectively, for the diagnosis of histopathologic chorioamnionitis.

The sensitivity, specificity, as well as positive and negative predictive values of PCT inflammatory index were 100%, 79%, 57.5%, and 100%, respectively, for the diagnosis of histopathologic chorioamnionitis.

According to Table 7, PCT did not have a normal distribution; therefore, Kendull Tau test was used instead of Pearson correlation to investigate the correlation between PCT and indices of WBC and ESR.

Discussion

Histologic chorioamnionitis (infection of fetal membranes and amniotic fluid) is commonly observed in mothers with PPROM, which may cause neonatal sepsis, preterm birth, pulmonary diseases, and neonatal brain injury. Thus, early diagnosis of chorioamnionitis is highly important (19, 20). PCT is a peptide precursor of calcitonin that is typically produced by monocytes and hepatocytes (21). The serum level of PCT rapidly increases in response to bacterial endotoxin within 3-4 hours and peaks within 18-24 hours and remains at the elevated serum level within at least 24-48 hours (21).

The results of the present study indicated a significant correlation between maternal infection with histologic chorioamnionitis and the inflammatory indices of WBC, CRP, ESR, and PCT upon delivery, while there was not any significant correlation between maternal infection with histologic chorioamnionitis and these indices, except for ESR upon hospitalization, indicating maternal infection and the reaction of maternal immune system during hospitalization. In a clinical study, it was found that the maternal serum level of PCT upon hospitalization of PPROM mothers (up to 4 hours after ROM) is not a reliable index to diagnose histologic chorioamnionitis, fetal infection, time interval between ROM and

delivery, and intrauterine infection. However, the maternal serum level of PCT in PPROM mothers was higher than that in non-PPROM mothers (22). A prospective study found that the increased maternal serum levels of CRP and PCT upon delivery were significantly correlated with histologic chorioamnionitis regardless of membrane status (23).

Oludaq et al. showed that the maternal serum level of PCT in PPROM mothers with histologic chorioamnionitis was significantly higher compared to that in PPROM mothers without chorioamnionitis. Moreover, the sensitivity and specificity of PCT were respectively 92.3% and 68.4% at 0.054 ng/ml serum level for the diagnosis of chorioamnionitis (17). In the present study, the sensitivity and specificity of PCT were respectively 57.57% and 100% at 0.06 ng/ml serum level.

Furthermore, a prospective study showed that the sensitivity and specificity of PCT were respectively 50% and 56% for the diagnosis of histologic chorioamnionitis that was considered as a poor predictive marker (16). Dulay reported that the maternal serum level of PCT was not useful for diagnosing chorioamnionitis in mothers. However, IL-6 and CPR increased in mothers infected with subclinical chorioamnionitis, which was higher in mothers with clinical symptoms (24). A cross-sectional study indicated that mothers infected with chorioamnionitis had higher levels of CRP, while it was not the case for PCT.

Furthermore, maternal chorioamnionitis had a significant correlation with higher levels of PCT and CRP in the umbilical cord (25). Ronzino-Dubost et al. found that the sensitivity, specificity, positive predictive value, and negative predictive value of PCT were respectively 54%, 79%, 60%, and 75% for diagnosing histologic chorioamnionitis; thus, the measurement of PCT serum level is not a reliable and useful index for diagnosing chorioamnionitis and changing or modifying the treatment process depending on its level (26). According to a prospective study, the serum levels of WBC, CRP, and cytokine IP-10 significantly increased in mothers with histologic chorioamnionitis in comparison to non-infected mothers (27). A retrospective study showed that the serum levels of CRP and WBC in mothers histologically infected with chorioamnionitis upon hospitalization were not significantly different from those in non-infected mothers. Another retrospective study reported a significantly higher level of CRP serum level in infected mothers upon delivery time (28).

Yoneda et al. found that the level of IL-8 in amniotic fluid and maternal body temperature were considered as the independent risk factors for chorioamnionitis. Moreover, the predictive values of IL-8 were equal to ≥9.9 ng/ml, ≥17.3, and ≥ 55.9, respectively, for different diagnostic stages of histologic chorioamnionitis, that is, stage 1 and above, stage 2 and above, and stage 3 (29). Popowski et al. stated that the sensitivity and specificity of CRP were respectively 56-86% and 55-82% for the diagnosis of clinical chorioamnionitis, while the level of WBC had a lower predictive value for diagnosing chorioamnionitis (30). Kidokoro et al. found that the measurement of neutrophilic elastase and lactate dehydrogenase levels in amniotic fluid was useful for the diagnosis and that neutrophilic elastase with a predictive value of 0.15 µg/ml had the highest sensitivity (88.9%) (31). Moreover, a prospective study showed that the elevated level of lactate dehydrogenase in the amniotic fluid of mothers with PPROM was significantly correlated with histologic chorioamnionitis (with a predictive value of 1029 IU/l), while the decreased level of glucose in the amniotic fluid did not have any correlation with chorioamnionitis (32).

According to the present study, the causes of neonatal death included pulmonary hemorrhage, acute respiratory distress syndrome (ARDS), and cerebral hemorrhage. An observational study found that cognitive disorders, neurodevelopmental disorders, and mortality were significantly more prevalent in neonates with a gestational age of ≤ 27 weeks born from mothers infected with chorioamnionitis than other neonates (33). According to a retrospective study, prenatal corticosteroid administration was associated with a significant reduction in neonatal mortality, ARDS, neonatal seizure, and cerebral hemorrhage in the neonates born from mothers infected with histologic chorioamnionitis (34). Another retrospective

study indicated that prenatal cortisone administration reduced the mortality rate before the age of three in children of mothers infected with histologic chorioamnionitis in comparison to children of non-infected mothers, while it did have any effects on the neurodevelopmental rate of children in both infected and non-infected groups. Therefore, corticosteroid prescription is recommended for mothers with chorioamnionitis (35).

According to a retrospective study on neonates with a BW of ≤ 1500 g born from mothers infected with chorioamnionitis, it was found that histologic chorioamnionitis was associated with an increased risk of chronic pulmonary disease and neonatal sepsis, while it did not correlate with cerebroventricular hemorrhage, periventricular leukomalacia, cerebral palsy, vision impairment, and neonatal death before discharge (36).

Recently, a new antibiotic regimen based on ceftriaxone, clarithromycin, and metronidazole has been used for the treatment of chorioamnionitis that has led to less maternal infection with histologic chorioamnionitis in comparison to ampicillin regimen with or without cephalosporin. Accordingly, the rates of cerebral palsy and ventricular hemorrhage were significantly lower in neonates treated with the new regimen than those receiving the previous regimen (37).

The limitations of the present study included high costs and limited financial resources to measure the serial serum level of PCT and to compare the studied patients with healthy non-PPROM pregnant mothers.

Conclusion

We found a significant correlation between PCT index at delivery time and histopathologic chorioamnionitis. Furthermore, there was a significant correlation between the inflammatory indices of ESR, CRP, and WBC at delivery time and histopathologic chorioamnionitis.

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Conflicts of interests

None.

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