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Original Research Article

Study of C-reactive protein and procalcitonin in detecting subclinical intrauterine infections in preterm prelabour rupture of membrane

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ABSTRACT

Background: Chorioamnionitis or intrauterine infection contributes to approximately 40–50% of preterm deliveries. Clinical signs appear late and are subjective, while conventional investigations such as leukocyte count and cultures are either unreliable or time consuming. Histopathological examination of the placenta confirms the diagnosis only after delivery. This study assessed C-reactive protein (CRP) and procalcitonin (PCT) in detecting subclinical intrauterine infection in women with preterm prelabour rupture of membranes (PPROM).
Methods: This cross-sectional study included 40 women with singleton pregnancies complicated by PPROM between 28 and 36+6 weeks of gestation at Hindu Rao Hospital over one year. Women with leaking per vaginum for more than12 hours were enrolled. CRP and PCT levels were measured at admission and delivery. Their association with clinical and histopathological chorioamnionitis was analyzed using SPSS version 25.0, and ROC curves determining optimal cut-off values.
Results: The mean age was 25.12±3.7 years, and mean gestational age was 34.98±1.38 weeks. Clinical chorioamnionitis occurred in 80% and histopathological chorioamnionitis in 55% of cases, with risk increasing significantly as leaking duration per vaginum prolonged. CRP was found to be a better predictor than PCT. CRP at termination predicted clinical chorioamnionitis at a cut-off >15.6 mg/l (AUC 0.805), whereas CRP on admission predicted histopathological chorioamnionitis at a cut-off >12 mg/l (AUC 0.941).
Conclusions: CRP and PCT are valuable biomarkers for early intrauterine infection detection in PPROM, enabling timely treatment and improving maternal-neonatal outcomes.

Keywords: C-Reactive protein, Intrauterine infection, Preterm premature rupture of membranes, Procalcitonin

INTRODUCTION

Preterm prelabour rupture of membranes (PPROM) which is defined as spontaneous membrane rupture before 37 completed weeks is responsible for 30% of preterm deliveries and contributes around 10% of perinatal mortality.[1,2] The incidence of PPROM is variable between 2-4.5% of all deliveries. Neonates born in the early-preterm period make up the smallest proportion of births, but these infants experience disproportionately higher rates of prematurity-related complications, including death.[3]

PPROM results from a multifactorial aetiology, with intrauterine infection, oxidative stress- induced DNA

damage, and premature cellular senescence as major predisposing events.[3] The physiological weakening of membranes, coupled with the mechanical stress exerted by uterine contractions, further predisposes to membrane rupture. Removal of barrier to ascending infection dramatically increases the likelihood of infection of the chorion, the amnion or amniotic fluid and thus the development of chorioamnionitis.[4] Chorioamnionitis or intrauterine infection may contribute to 40-50 percent of all preterm births.[5]

Chorioamnionitis is diagnosed clinically in accordance with the signs: fever (≥38°C orally), vaginal discharge, maternal tachycardia (>100 beats per minute), fetal tachycardia (>160 beats per minute), abdominal pain, uterine tenderness, and leukocytosis. The presence of at least three signs has been shown to indicate a strong probability of chorioamnionitis, but they appear very late once the disease is clinically established and they are subjective and unreliable for early diagnosis of subclinical intrauterine infection.[6]

There are other indicators of infections which can be used for diagnosing chorioamniotic infection. C-reactive protein is one such indicator which is acute phase protein synthesized in the liver during infection. Production of C-reactive protein is due to release of pro inflammatory cytokines including interleukin-1, interleukin-6, interferon-alpha and other acute phase reactants. C-reactive protein accompanies both acute and chronic inflammatory disorder. Elevated concentration of C reactive protein is seen both in peripheral circulation and in amniotic fluid in patient with intrauterine infection.[7] C-reactive protein level may increase non-specifically in presence of bacterial infections, viral infections other microbial infection, autoimmune disease and cancer.

Procalcitonin (PCT), an acute phase reactant and a marker of monocyte activity have also been widely used as a predictor of infection.[8] It is a peptide precursor of calcitonin, synthesized by the parafollicular C cells of the thyroid. Procalcitonin levels significantly elevate in response to severe bacterial infections; they remain low in viral infections and nonspecific inflammatory conditions. However, measured PCT levels do not reliably predict the onset of overt or subclinical chorioamnionitis following premature rupture of membranes.[9,10]

Histologic chorioamnionitis, which includes both subclinical and clinical cases, is up to three times more prevalent than clinical chorioamnionitis confirmed by amniotic fluid culture. This discrepancy is partly due to the low sensitivity of genital mycoplasma cultures, which are among the most commonly associated organisms. Additionally, subclinical chorioamnionitis and non-infectious inflammation contribute to this variation. The pathological diagnostic criteria of chorioamnionitis includes leukocytosis of chorionic plate and amnion and demonstrates diffuse aggregation and infiltration, with ≥5 neutrophils per view under a light microscope on the highest magnification.[11] The pathological confirmatory diagnosis can be made only after delivery.

An expectant management for PPROM is an accepted modality of treatment. But PPROM can cause an intrauterine infection and lead to morbidity of both mother and fetus if untreated. Management of PPROM is based on creating a balance between reducing the maternal/neonatal complications and maximizing the gestational age in order to minimize the complications associated with prematurity.[12] The delay between the diagnosis and treatment of chorioamnionitis and the clinical development of infection is associated with an increased risk of maternal and neonatal morbidity due to sepsis. Chorioamnionitis/intrauterine infection remains a strong predictor of impaired cognitive and neurodevelopmental outcomes.[13,14]

So, it is necessary to have a rapid, cost effective and accurate test for early diagnosis of any intrauterine infection after preterm prelabour rupture of membranes as clinical sign and symptoms appear late after an infection and laboratory indicators like total leucocyte count, differential leucocyte count for prediction of infection is unreliable while urine and vaginal culture are time consuming. When amniotic fluid cultures are performed, chorioamnionitis is detected in 36% of women with PPROM. There is limited evidence supporting the use of blood cultures for diagnosis, and high vaginal swabs have not been shown to provide significant benefits in diagnosing or managing the condition.[15]

Studies have shown that both C-reactive protein and procalcitonin have high sensitivity and specificity in PPROM associated with intrauterine infections and can be used to predict asymptomatic intrauterine infection.[11] So the present study was proposed to determine the role of biomarkers C-reactive protein and procalcitonin for early detection of subclinical intrauterine infection in pregnant women with preterm prelabour rupture of membranes and to correlate these biomarkers with histopathology examination of placenta.

METHODS

The present cross-sectional study was conducted on 40 pregnant women with PPROM attending OPD of Obstetrics and Gynaecology department or admitted in Labour Room or maternity ward of Hindu Rao hospital, Delhi from Jan 2024 onwards for one year. Patients with singleton pregnancy who had leaking per vaginum within 12 hours and had gestation age >28 weeks but <36+6 weeks were enrolled in the study.

Based on previous study by Baker R Z et al[16] where mean 1 = 59.63, mean 2 = 8.87, standard deviation 1 = 73.99 and standard deviation 2 = 9.12 and using formula:

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 (SD_1^2 + SD_2^2)}{(\bar{x}_1 - \bar{x}_2)^2}$$

A sample size of 17 in each group was calculated and hence a sample size 40 was taken. Pregnant females with: Pre- eclampsia, HELLP, acute fatty liver of pregnancy, multifetal gestation, or any other comorbid medical disorders in pregnancy like diabetes, acute or chronic liver or kidney or heart disease or any respiratory, urinary tract infection, chorioamnionitis or any longstanding diseases such as rheumatoid arthritis, alcohol or drug addictions were excluded. Patients with fetal anomalies or fetal distress or any indication suggestive of immediate delivery were also excluded from the study. Clearance was obtained from the scientific and the ethics committee of our hospital. The study methodology was explained to the patient and details were recorded in a pre-structured performa after obtaining a written informed consent.

The diagnosis of PPROM was based on the combination of patient's history and physical examination by a sterile speculum with direct visualization of fluid in the posterior fornix or clear fluid flowing from the cervical canal and cervical dilation or effacement.[3] History of number of contractions felt, fetal movement, time of possible rupture of membrane, amount of fluid, color and odor of fluid, vaginal bleeding, pain, recent sexual encounters, recent trauma, and recent physical activity was taken. Diagnosis of clinical chorioamnionitis was made on the basis of history, physical and systemic examination after taking in consideration any clinical feature of chorioamnionitis (fever, abdominal pain, vaginal discharge, tachycardia, uterine tenderness) during conservative management.

All routine investigations were sent along with blood sample for C-reactive protein and procalcitonin at the time of admission and another sample at delivery from antecubital vein (5 ml). Samples were kept at room temperature for 10 min and then centrifuged at 3,000 rpm for 10 min. The serum was then collected for determining procalcitonin and C-reactive protein levels which were measured by fully automatic Biochemistry analyser 'DiaSys' with reagent kits provided by DiaSys. Particle enhanced immunoturbidimetric test principle was used for determination of level of the biomarkers. Sample for total leukocyte count was also measured.

In the study, C-reactive protein values more than 6 mg/L and procalcitonin more than 0.01ng/ml were considered abnormal.[17,18] All patients were managed as per hospital protocol. After delivery placenta was sent for histopathology examination. The pathological confirmatory diagnostic criteria of chorioamnionitis was considered when leukocytosis of chorionic plate and amnion was demonstrated with diffuse aggregation and infiltration, by ≥5 neutrophils per view under a light microscope on the highest magnification.[11]

Patients were followed till delivery and they were divided into two groups: one (with chorioamnionitis) and another (without chorioamnionitis) on the basis of leukocytosis of chorion or amnion (histopathological) and clinical signs and symptoms. Association of clinical chorioamnionitis and histopathological chorioamnionitis was established with other variables and biomarkers. Association of chorioamnionitis with leukocytosis in blood was also determined.

Statistical analysis

The presentation of the Categorical variables was done in the form of number and percentage (%) and on the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The association of the variables which were qualitative in nature were analyzed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used. The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0. For statistical significance, p value of less than 0.05 was considered statistically significant. Receiver operating characteristic curve was used to assess cut off of C-reactive protein and procalcitonin for predicting clinical chorioamnionitis and histopathological chorioamnionitis.

RESULTS

Table 1 shows the distribution of patients according to complaints, vitals and leucocyte count. Maximum number of cases were multipara (55%) and primipara were 45%. Table 2 gives the distribution of C reactive protein and procalcitonin levels on admission and at termination of pregnancy. Mean CRP on admission and at termination were 13.6±6.84 mg/l and 15.49±7.56 mg/l respectively. Mean of Procalcitonin levels on admission was 0.1±0.08 ng/l and at termination was 0.2±0.18 ng/l. Based on presence of any suggestive clinical signs or symptoms (fever, abdominal pain, vaginal discharge, tachycardia, uterine tenderness) clinical chorioamnionitis was seen in 80.00% cases. Histopathological chorioamnionitis was seen in 55.00% cases (37.50% cases showed 5 to 15 neutrophils and 17.50% cases had >15 neutrophils per hpf placenta respectively) while 45.00% cases did not have histopathological chorioamnionitis (histopathology of placenta showed ≤5 leukocytosis per high power field). Association of various maternal parameters and level of biomarkers with clinical and histopathological chorioamnionitis respectively is shown in Table 6. There was statistically significant association of maternal tachycardia, temperature and total leukocyte count with clinical as well as histopathological chorioamnionitis. Table 7 show the receiver operating characteristic curve of CRP and procalcitonin on admission and termination for predicting clinical and histopathological chorioamnionitis respectively.

Table 1: Profile of cases according to history and vitals.

Profile	Mean±SD	Median (25th-75th percentile)	Range
Age (years)	25.12±3.7	25 (22.75-28)	19-34
Period of gestation (weeks)	34.98±1.38	35.2 (34.15-36.125)	29.6-36.6
Duration of leaking P/V (hours)	16.1±3.46	16 (12.75-19.25)	12-22
Temperature (^{O}C)	37.96±0.96	37.5 (37.2-39)	36-39.5
Pulse rate on admission (/minute)	88.45±5.46	88 (86-90)	90-102
Pulse rate on termination (/minute)	96.25±7.31	78-106	82-112
Total leucocyte count (µL)	15108.75±4894.32	15500 (10725-16900)	8200-36000

Table: 2 Distribution of C reactive protein and procalcitonin levels on admission and at termination of pregnancy.

Biomarker	On admission (n=40)	At termination (n=40)
CRP (mg/l)		
Mean±SD	13.6±6.84	15.49±7.56
Median (25th -75th percentile)	12.2 (8.8-18)	14.5 (10.675-20)
Range	5-35.7	3-42.1
Procalcitonin (ng/ml)		
Mean±SD	0.1±0.08	0.2±0.18
Median (25th -75th percentile)	0.1(0.04-0.152)	0.12(0.05-0.325)
Range	0.01-0.4	0.02-0.6

Table 3: Association of period of gestation at diagnosis with chorioamnionitis.

Gestation at diagnosis	Clinical chorioamnionitis		Histopathological chorioamnionitis	
	Yes (n=32), N (%)	No (n=8), N (%)	Yes (n=22), N (%)	No (n=18), N (%)
28 to 32 weeks (n=1)	1 (100)	0 (0)	1 (100)	0 (0)
32 weeks +1 day to 34 weeks (n=9)	6 (66.67)	3 (33.33)	4 (44.44)	5 (55.56)
34 weeks + 1 day to 37 weeks (n=30)	25 (83.33)	5 (16.67)	17 (56.67)	13 (43.33)
P value	0.484*		0.838*	

Fisher's exact test.

Table 4: Association of presence of leaking per vagina with chorioamnionitis.

Leaking per vagina	Clinical chorioamnionitis		Histopathological chorioamnionitis	
	Yes (n=32), N (%)	No (n=8), N (%)	Yes (n=22), N (%)	No (n=18), N (%)
12 to 18 hours (n=25)	17 (68)	8 (32)	9 (36)	16 (64)
18 to 24 hours (n=15)	15 (100)	0 (0)	13 (86.67)	2 (13.33)
P value	0.016*		0.003*	
Mean±SD	16.72±3.57	13.62±1.3	18.14±2.88	13.61±2.3
Median (25th -75th percentile)	16.5 (13.5-20)	14 (12.75-14)	18.5 (16-20)	12.5 (12-14)
Range	12-22	12-16	12-22	12-20
P value	0.0004‡		<0.0001‡	

‡Independent t test, *Fisher's exact test

Table 5: Association of clinical chorioamnionitis with histopathological chorioamnionitis.

Clinical chorioamnionitis	Histopathological chorioamnionitis		P value
	No (n=18), N (%)	Yes (n=22), N (%)	
No (n=8)	7 (17.50)	1 (2.50)	0.014*
Yes (n=32)	11 (27.50)	21 (52.50)	

*Fisher's exact test

Table 6: Association of maternal parameters and levels of biomarkers with clinical chorioamnionitis and with histopathological chorioamnionitis.

Parameters	Clinical chorioamnionitis, N (%)		P value	Sensitivity (%)	Specificity (%)	AUC	Positive predictive value (%)	Negative predictive value (%)	Diagnostic accuracy (%)
	Yes (n=32)	No (n=8)							
Maternal tachycardia (>100 bpm)									
≤100	17 (68)	8 (32)	0.016*	46.88	100.00	0.764	100	32.00	57.50
>100	15 (100)	0 (0)							
Maternal temperature (≥ 38 ºC)									
<38	17 (70.83)	7 (29.17)	0.029*	48.48	100	0.805	100	29.17	57.5
≥38	16 (100)	0 (0)							
TLC (≥ 13,000/µL)									
<13000	7 (53.85)	6 (46.15)	0.008*	78.12	75.00	0.77	92.59	46.15	77.5
≥13000	25 (92.59)	2 (7.41)							
CRP (>6 mg/L) on admission									
≤6	1 (33.33)	2 (66.67)	0.096*	96.87	25.00	0.61	83.78	66.67	82.50
>6	31 (83.78)	6 (16.22)							
Procalcitonin (>0.1 ng/mL) on admission									
≤0.1	21 (77.78)	6 (22.22)	1*	34.38	75.00	0.55	84.62	22.22	42.50
>0.1	11 (84.62)	2 (15.38)							
CRP (>6 mg/L) on termination									
≤6	1 (33.33)	2 (66.67)	0.096*	96.87	25.00	0.61	83.78	66.67	82.50
>6	31 (83.78)	6 (16.22)							
Procalcitonin (>0.1 ng/mL) on termination									
≤0.1	15 (78.95)	4 (21.05)	1*	53.13	50.00	0.52	80.95	21.05	52.5
>0.1	17 (80.95)	4 (19.05)							
Parameters	**Histopathological chorioamnionitis**		**P value**	**Sensitivity (%)**	**Specificity (%)**	**AUC**	**Positive predictive value (%)**	**Negative predictive value (%)**	**Diagnostic accuracy (%)**
	Yes (n=22)	**No (n=18)**							
Maternal tachycardia (> 100 bpm)									
≤100	10 (40)	15 (60)	0.022*	54.55	83.33	0.69	80.00	60.00	0.675
>100	12 (80)	3 (20)							
Maternal temperature (≥ 38 ºC)									
<38	10 (41.66)	14 (58.33)	.05†	54.55	77.78	0.736	75	58.33	0.65
≥38	12 (75)	4 (25)							
TLC (≥ 13,000/µL)									
<13000	4 (30.7)	9 (69.2)	0.05†	77.27	44.44	0.758	66.67	69.23	0.675
≥13000	18 (66.66)	9 (33.3)							
CRP (>6 mg/L) on admission									
≤6	0 (0)	3 (100)	0.04*	81.8200	16.67	0.58	59.46	100.00	0.625
>6	22 (59.46)	15 (40.54)							
Procalcitonin (>0.1 ng/mL) on admission									
≤0.1	13 (48.15)	14 (51.85)	0.312*	40.91	77.78	0.59	69.23	51.85	0.575
>0.1	9 (69.23)	4 (30.77)							
CRP (>6 mg/L) on termination									
≤6	0 (0)	3 (100)	0.083*	100.00	16.67	0.58	59.46	100.00	0.625
>6	22 (59.46)	15 (40.54)							
Procalcitonin (>0.1 ng/mL) on termination									
≤0.1	9 (47.37)	10 (52.63)	0.356†	59.09	55.56	0.57	61.90	52.63	0.575
>0.1	13 (61.90)	8 (38.10)							

*Fisher's exact test, †Chi square test

Table 7: Receiver operating characteristic curve of CRP and procalcitonin for predicting clinical chorioamnionitis and predicting histopathological chorioamnionitis.

Variables	Predicting clinical chorioamnionitis				Predicting histopathological chorioamnionitis			
	CRP on admission	Procalcito-nin on admission	CRP at termi-nation	Procalci-tonin at termination	CRP on admis-sion	Procalci-tonin on admission	CRP at termi nation	Procalci-tonin at termination
Area under the ROC curve (AUC)	0.773	0.541	0.805	0.529	0.941	0.559	0.894	0.593
P value	0.0006	0.6459	0.0001	0.7954	<0.000 1	0.5308	<0.00 01	0.3139
Cut off	>12.6mg/l	≤0.05ng/ml	>15.6 mg/l	≤0.04ng/dl	>12 mg/l	>0.15ng/l	>14 mg/l	>0.09ng/l
Sensitivity (95% CI)	53.13	43.75	53.13	18.75	86.36	36.36	81.82	77.27
Specificity (95% CI)	100	87.5	100	100	94.44	88.89	88.89	44.44
PPV (95% CI)	100	93.3	100	100	95	80	90	63
NPV (95% CI)	34.8	28	34.8	23.5	85	53.3	80	61.5
Diagnostic accuracy, (%)	62.50	52.50	62.50	35.00	90.00	60.00	85.00	62.50

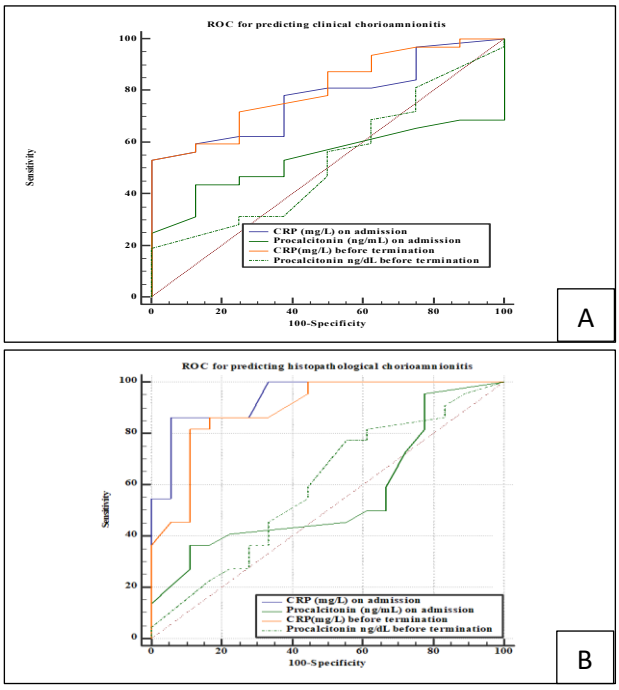

Figure 1: Receiver operating characteristic curve of procalcitonin at termination. A) For predicting clinical chorioamnionitis, B) For predicting Histopathological chorioamnionitis.

DISCUSSION

Majority of women with PPROM (Preterm Premature Rupture of Membranes) are asymptomatic at the beginning. So ACOG (American College of Obstetricians and Gynecologists) recommends expectant management in the absence of maternal or fetal complication for such patients.[19] Expectant management reduces severe neonatal complications. However, it may increase certain feto-maternal risks, such as infection, placental abruption and fetal distress leading to increased fetomaternal morbidity.

The present study was undertaken to examine the inflammatory markers CRP (C-reactive protein) and PCT (Procalcitonin) in blood to predict chorioamnionitis. Additionally, the study aimed to correlate these markers with leukocytosis of placenta on histopathological examination (HPE), which is the definitive diagnostic method for chorioamnionitis. But HPE can only be done after delivery. The study was done to find out whether CRP and PCT could indicate chorioamnionitis before the onset of clinical symptoms and histopathological involvement of placenta so that expectant management of PPROM could be continued and development of chorioamnionitis is avoided at same time.

The study included 40 PPROM diagnosed antenatal women with gestational age between 28 weeks to 37 weeks. As far as profile of patients is concerned as shown in table 1, the mean age of cases was 25.12±3.7 years with median 25 years. This corelates with the study conducted by Aggarwal et al where mean age of study group was 23.42±3.25 years.[20] Maximum number of patients were either nulliparous or primipara (45% each) which corelates with the study conducted by Aggarwal et al where maximum number of patients were primigravida (40%).[20] In our study mean period of gestational age was 34.98±1.38 weeks and it corelates with the study conducted by Aggarwal et al where mean gestational age was 33.4±2.109 weeks.[20] But Bakar et al study shows

mean gestational age as 28.33± 2.97 weeks.[16] Asadi et al study shows mean gestational age 24.3±1.8 weeks.[21]

Mean value of TLC in our study was 15108.75±4894.32/µl. Asadi et al found mean value of TLC as 11198.3±3585.1/µl in their study.[21] Our study shows that mean CRP levels on admission were 13.6±6.84 mg/L and at termination was 15.49±7.56mg/l (Table 2). Mean of procalcitonin levels on admission was 0.1±0.08 ng/l and at termination was 0.2±0.18 ng/l. Bakar et al have shown similar CRP level on admission with mean 15.±22.36 mg/l but different CRP levels at termination with mean 59.63±73.99mg/l.[16] Mean of CRP levels at termination was high in their study as there was delay in termination of pregnancy. Mean of Procalcitonin levels on admission was 0.05±0.03(ng/l) in their study which is not similar to our study while mean at termination was 0.2±0.18(ng/l) which is similar to our study. Asadi et al found mean of CRP level on admission 16.4±14.8 mg/l which is similar to our study but CRP levels mean at termination was 20.7±15.6 mg/l which is higher than our study.[21] Mean of Procalcitonin levels on admission was 0.09±1.1ng/l which is similar to our study and mean at termination was 0.9±1.1 ng/l which is not similar to our study. They also managed the patient conservatively for longer duration.

80% patients in our study were diagnosed to have clinical chorioamnionitis. They had any one of the clinical signs: fever, abdominal pain, vaginal discharge, tachycardia, uterine tenderness. Asadi et al study shows that 45.3% patient were diagnosed to have clinical chorioamnionitis which is not similar to our study.[21] Our study included any one out of five signs while Asadi et al included presence of at least three clinical signs so it was less.[21] In our study, 35% of neonates required NICU admission, whereas Aggarwal et al (2018) reported a higher NICU admission rate of 40%.[15] The perinatal mortality rate in our study was 15%, compared to 33.33% reported in neonates weighing <2 kg in Aggarwal et al.[20]

In our study, 55% cases had >5 neutrophils per hpf of placenta on histopathological examination while 17.5% had >15 neutrophils per hpf (moderate to severe chorioamnionitis). Asadi et al study shows that 55% of the cases had histopathological chorioamnionitis which is similar to our study.[21] Aggarwal et al found histopathological chorioamnionitis in 36% cases out of which 10% cases had moderate to severe chorioamnionitis.[20]

All cases with gestational age of 28 to 32 weeks had clinical as well as histopathological chorioamnionitis. Among those between 32 weeks + 1 day and 34 weeks, 66.67% had the condition, while 83.33% of cases between 34 weeks + 1 day and 37 weeks were affected (p-value as 0.484 statistically not significant). Thus, gestational age does not have a significant effect on chorioamnionitis. Bakar et al and Asadi et al also reported similar results (p value of 0.054 and 0.25 respectively, not significant).[16,21]

As shown in Table 4, patients who had leaking per vaginum for 18-24 hour had 100% clinical chorioamnionitis while 86.67% had histopathological chorioamnionitis (p value 0.016 and p value 0.003 for clinical and histopathological chorioamnionitis respectively, statistically significant). As duration of leaking increased the risk of chorioamnionitis increased. Table 5 shows that out of 32 patients with clinical chorioamnionitis, 52.50% showed histopathological chorioamnionitis (p value=0.014). Though histopathological chorioamnionitis was significantly associated with clinical chorioamnionitis in our study but pathologic findings are more confirmatory and diagnostic and clinical diagnosis may exaggerate the number. Aggarwal et al found histopathological chorioamnionitis in 36% of the patient with PROM.[20]

As far as maternal parameters are concerned, all cases with pulse >100 bpm had clinical chorioamnionitis (p value=0.016) and 80% had histopathological chorioamnionitis with p value=0.022. All the patients who had temperature ≥38 ºC had clinical chorioamnionitis (pvalue=0.029) and 75% had histopathological chorioamnionitis (p value=0.05). Aggarwal et al also found that all who had clinical chorioamnionitis had temperature >38ºC which is similar to our study.[20] 92% cases with TLC >13,000/µl had clinical chorioamnionitis and it was a statistically significant association (p value=0.008). Study conducted by Aggarwal et al shows 50% clinical chorioamnionitis with TLC >11000/µl.[20] Values are different as cut off for TLC count was different in our study. 66.6% with TLC >130000/µL had histopathological chorioamnionitis and it was a statistically significant association (p=0.05). Aggarwal et al[20] found that 22.22% with temperature ≥38 ºC and 22.22% with TLC >11000/µl had histopathological chorioamnionitis.

Table 6 show sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of biomarkers at the advocated cut off values for chorioamnionitis at admission and termination of pregnancy. 83.78% cases with CRP >6 mg/l and 80.95% cases with PCT >0.1 ng/ml on termination of pregnancy had clinical chorioamnionitis but it was not statistically significant (p value = 0.096 and p value=1). Also 59.46% cases with CRP >6 mg/l and 61.9% cases with PCT >0.1 ng/ml on termination of pregnancy had histopathological chorioamnionitis but it was not statistically significant (p value = 0.083 and p value=0.356). At the advocated cut off values for both the biomarkers the association with chorioamnionitis was not statistically significant. This could be because of small sample size.

Diagnostic performance of maternal temperature, maternal tachycardia, total leucocyte count and CRP at advocated cut off for predicting clinical and histopathological chorioamnionitis from our study and its comparison with other study is shown in Table 8.

As shown in Table 7, 8 and Figure 1A, 1B the ROC curves of CRP and procalcitonin above the diagonal lines are considered to have reasonable discriminating ability to predict clinical and histopathological chorioamnionitis. Discriminatory power of CRP at cut off 15.6 mg/L before termination was excellent (AUC 0.805) and on admission was acceptable (AUC 0.773). On the other hand, discriminatory power of procalcitonin at cut off 0.05 ng/ml on admission (AUC 0.541) and at cut off 0.04 ng/ml at termination (AUC 0.529) was non-significant. Among all the parameters, CRP at termination was the best predictor of clinical chorioamnionitis at cut off point of >15.6 mg/l for correctly predicting clinical chorioamnionitis. As far as histopathological chorioamnionitis is concerned the interpretation of ROC curve showed that the performance of CRP on admission was outstanding (AUC 0.941) and at termination was excellent (AUC 0.894). On the other hand, discriminatory power of procalcitonin on admission (AUC 0.559) and at termination (AUC 0.593) was non-significant. Among all the parameters, CRP on admission was the best predictor of histopathological chorioamnionitis at cut off point of >12 mg/l for correctly predicting histopathological chorioamnionitis.

At termination, our CRP cut-off (15.6 mg/dl) showed similar AUC (0.805) to Asadi et al (16 mg/dl, AUC 0.8), with both studies demonstrating high specificity.[21] Bakar et al and Wang et al reported lower CRP cut-offs with moderate diagnostic accuracy.[16,23] Our study highlights the high specificity of CRP and Procalcitonin in diagnosing clinical chorioamnionitis, though sensitivity varies across studies. CRP had higher sensitivity and specificity than Asadi et al, with an AUC of 0.941 on admission and 0.894 at termination, indicating strong diagnostic accuracy for histopathological chorioamnionitis (Table 7).[21] Procalcitonin had lower sensitivity on admission but improved at termination (77.27%), though specificity was lower but AUC for procalcitonin in our study is similar to study by Asadi et al.[21] Overall, CRP proved to be a more reliable marker for diagnosing histopathological chorioamnionitis in our study.

CONCLUSION

CRP and Procalcitonin are reliable and good inflammatory marker for predicting clinical and histopathological chorioamnionitis in PPROM. If CRP levels are < 6 mg/dl the patient of PPROM can be managed conservatively, till the foetus is matured enough and complication of prematurity in foetus avoided. Pregnancy with PPROM can be well monitored and managed with help of C-Reactive protein and procalcitonin levels by creating a balance between reducing the maternal and neonatal complication and maximizing the gestation age so that complication associated with prematurity are avoided. CRP and PCT levels can serve as effective screening tools for chorioamnionitis and assist the clinicians in determining the appropriate management approach, including antibiotic therapy, delivery timing, and maternal-fetal monitoring.

Recommendations

Further studies with high quality randomized controlled trial with large sample are necessary to determine whether the diagnostic values of procalcitonin and C reactive protein for intra uterine infection are well correlated.

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