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Comparison of maternal CRP with WBC count in predicting intra-amniotic infection in premature rupture of membranes

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Abstract
Background: To evaluate the usefulness of maternal CRP and WBC count in diagnosing intra-amniontic infection in the preclinical stage in women with prelabor rupture of membranes.
Methods: This prospective study was conducted in the department of obstetrics & gynaecology at CSSH, Meerut over a period of two years (2014-2016). 100 women were included in the study as subjects, of which 50 had ruptured membranes before labor and 50 were gestational age matched controls with intact membranes. After informed consent, maternal blood and serum for White blood cells (WBC) Count and CRP evaluation was obtained in subjects with evident leaking of amniotic fluid vaginally and also in subjects acting as control group. Intra-amniotic infection was confirmed by obtaining amniotic fluid vaginally and subjecting it for aerobic and anaerobic culture.
Results: The sensitivity and specificity of maternal CRP was 83.33% and 80.76% respectively. The sensitivity and specificity of WBC count in predicting intra-amniotic infection was 64.86% and 58.73% respectively.
Conclusion: Present study concluded that CRP is a reliable diagnostic marker than WBC count for predicting intra-amniotic infection in pregnancies complicated with rupture of membranes.

Keywords: C reactive protein, Preterm premature rupture of membranes, premature rupture of membranes, white blood cell count

Introduction
Spontaneous membrane rupture that occurs before the onset of labor is termed as premature rupture of membranes (PROM). Prelabor rupture of membranes before the 37th week of gestation, termed preterm premature rupture of membranes (PPROM), is a common obstetric complication which occurs in approximately 3-4.5% of all pregnancies [1]. PPROM is associated with 30% of neonatal morbidities and mortalities in preterm delivery and remains a challenge for the obstetrician [2, 3].
Acute inflammation of the membranes (amnion and chorion), chorioamnionitis, indicates high risk of adverse neonatal outcomes [4-8]. Chorioamnionitis is typically the result of microbial invasion in patients with PPROM and PROM, but can also be caused by genital mycoplasmas, such as Ureaplasma and Mycoplasma hominis or systemic infection inspite of intact membranes [9]. Clinical chorioamnionitis is diagnosed in patients presenting with two or more of the following criteria: high temperature, maternal tachycardia, fetal tachycardia, uterine tenderness, foul smelling amniotic fluid, maternal leukocytosis with bands, and positive C reactive protein (CRP) [10]. Maternal serum C-reactive protein (CRP) has been studied as an adjunct in the diagnosis of subclinical infection among pregnant women with preterm labor or preterm rupture of membranes. CRP is an acute-phase protein produced in the hepatocytes of the liver, and is normally present as a trace constituent in the serum. A significant rise in the concentration is seen following injury and inflammation [11]. Once released, CRP is bound to altered or necrotic membrane structures, and its biological effects include enhancement of phagocytosis, stimulation of leucocyte motility and opsonic effects, suggesting a specific role in tissue regeneration and repair [12]. Possible humoral mediators are the macrophages of the endothelial system, the endogene pyrogens and the prostaglandins [13]. Maximal concentrations are seen 24-48 h after the inducing stimulus. The half-time is 8-9. CRP is not transferred across the placenta [14]. Various non-invasive markers have been studied to diagnose chorioamnionitis in the

preclinical stage. The laboratory indicators most often used to predict intra-amniotic infection are total leucocyte count (TLC), differential leucocyte count (DLC), urine culture, vaginal culture. The present study was conducted with the aim to compare maternal CRP and WBC count in predicting intra-amniotic infection in pregnancies complicated with rupture of membranes.

Material & Methods

This study was conducted in department of obstetrics & gynaecology at Chhatrapati Shivaji Subharti Hospital, Meerut for a period of two years (November' 2014-2016). After obtaining informed consent, 100 women were included as subjects in this prospective study, out of which 50 had ruptured membranes and 50 were gestational age matched controls with intact membranes.

History taking, general, systemic and obstetrical examination of subjects was done. Diagnosis of rupture of membranes was made by gush of fluid seen coming through the cervical os on coughing on sterile per speculum examination. On admission, investigation like CBC & C-reactive protein levels estimation were done in both study and control group. Markers of intrauterine infection were maternal WBC count more than 15,000 cells/cu.mm with positive C-reactive protein levels. CRP determination was done using latex agglutination method with the help of CRP reagent kit. CRP values were considered abnormal (positive), when the values exceeded 6 mg/l. In subjects with leaking per vaginum on speculum examination, vaginally obtained amniotic fluid was sent for aerobic and anaerobic culture to confirm presence of intraamniotic infection.

Inclusion Criteria

1. Pregnant women with gestational age > 28 weeks and with ruptured membranes.
2. Singleton pregnancy.

Exclusion criteria

1. Pregnant women with congenital anomalies, antepartum haemorrhage, pre-eclampsia.
2. Pregnant women with medical disorders like diabetes, hypertension, cardiac disease and renal disease.
3. Intrauterine death
4. Clinical features of chorioamnionitis including maternal tachycardia (>100 beats/min), fetal tachycardia (>160 beats/min), uterine tenderness and foul smelling amniotic fluid.
5. Pregnant women with multiple pregnancy.

Result

Socio-demographic characteristics: A total of 100 antenatal women were enrolled in the study. The distribution of cases into preterm premature rupture of membranes (pPROM) and premature rupture of membranes (PROM) was 31 and 19 respectively. Fifty gestational age matched controls were equally distributed between pPROM and PROM. Out of 31, 17 cases of pPROM were in age group of 16-25 and 14 cases were in 26-35 years. In PROM, 8 cases belonged to 16-25 years and 11 cases between 26-35 years. Regarding gravid status, 9 cases in pPROM and 10 cases in PROM were primigravida and 22 out of 31 and 9 out of 19 were multigravida in pPROM and PROM cases respectively. Rupture of membranes was more commonly found in women belonging to low socio-economic status in both pPROM and PROM group. The mean gestational age of rupture of membranes in pPROM and PROM subjects was 33±1 weeks and 38±1 weeks respectively. (Table 1)

Table 1: Showing distribution according to age, parity and socio-economic status.

Characteristic	pPROM (31)	Gestational age - matched controls (25)	PROM (19)	Control (25)	n=100
Age in years					
15-25	17	15	8	12	52
26-35	14	10	11	13	48
Gravidity					
Primigravida	9	13	10	8	40
Multigravida	22	12	9	17	60
Socio-ecomonic status					
Low	8	25	12	16	61
Middle	21	0	5	9	35
High	2	0	2	0	4

Table 2 shows the results of two markers of intra-amniotic infection. In pPROM, 26 cases were positive for maternal CRP while 14 out of 19 were positive in PROM group. Maternal CRP was also found positive in 8 gestational age matched controls. Regarding WBC count more than 15,000 cells/cu.mm. taken as cut off for intra-amniotic infection, 11 pPROM cases out of 31 indicated presence of infection. Among PROM group, 13 cases had maternal WBC count > 15,000 cells/cu.mm. Only 13 in control group had WBC count > 15,000 cells/cu.mm. 26 out of 50 showed growth on aerobic culture of amniotic fluid of which 18 belonged to pPROM group and 8 were from PROM group. Seven subjects had streptococcus species and 3 had acinetobacter baumanii on aerobic culture of amniotic fluid.

Table 2: Showing Markers of intra-amniotic infection

Marker	pPROM (31)	Gestational age - matched controls (25)	PROM (19)	Control (25)	n=100
Maternal CRP					
Positive	26	3	14	5	49
Negative	5	22	5	20	51
WBC count					
>15,000 / cu.mm	11	8	13	5	37
≤15,000 / cu.mm	20	17	6	20	63
Amniotic fluid culture					
Growth present	18	6	8	5	37
Growth absent	13	19	11	20	63

In 31 cases of pPROM, 17 CRP positive patients had growth present in amniotic fluid culture while all 3 cases in control group who were CRP positive had positive cultures. For WBC count > 15,000 cells/cu.mm, 7 cases had positive amniotic fluid culture report in pPROM group while 4 were positive in control group. (Table 3)

Table 3: Amniotic fluid culture results in pPROM and controls

	pPROM(31)		Controls(25)	
	Culture(+ve)	Culture(-ve)	Culture(+ve)	Culture(-ve)
CRP Positive	17	9	3	0
CRP Negative	1	4	3	19
WBC Count / cu.mm.				
>15,000 cells	7	4	4	4
≤15,000 cells	11	9	2	15

Amniotic fluid cultures were positive in 6 CRP positive cases of PROM and 2 CRP negative cases of PROM. Two CRP positive cases also had growth in culture from control group. Amniotic fluid culture results were positive in 5 PROM patients in whom WBC count > 15,000 cells/cu.mm. whereas 3 culture positive patients had WBC count < 15,000 cells/cu.mm. (Table 4)

Table 4: Amniotic fluid culture results in PROM and controls

	PROM (19)		Controls (25)	
	Culture(+ve)	Culture(-ve)	Culture(+ve)	Culture(-ve)
CRP Positive	6	8	2	3
CRP Negative	2	3	3	17
WBC Count / cu.mm.				
>15,000 cells	5	8	1	4
≤15,000 cells	3	3	4	16

The sensitivity and specificity of maternal CRP was 83.33% and 80.76% respectively. The sensitivity and specificity of WBC count in predicting intra-amniotic infection was 64.86% and 58.73% respectively. (Table 5)

Table 5: Comparision of maternal CRP and WBC count in present study

Marker	Sensitivity	Specificity	PPV*	NPV*
Maternal CRP	83.33%	80.76%	80%	84%
WBC Count	64.86%	58.73%	48%	74%
*PPV - Positive predictive value				
*NPV - Negative predictive value				

Discussion

Chorioamnionitis or intra-amniotic infection is an acute inflammation of the membranes and chorion of the placenta, typically due to ascending polymicrobial bacterial infection in the setting of membrane rupture. Expectant management for preterm premature rupture of membranes is now an accepted modality of treatment. Nevertheless, the main clinical concern is still the danger to the mother of acquiring chorioamnionitis. Early detection of infection is of utmost importance during the conservative management of premature rupture of membranes (PROM).

In the present study, the sensitivity of maternal CRP in predicting intra-amniotic infection in premature rupture of membranes was 83.33%, specificity 80.76%, positive predictive value was 80% and negative predictive value was 84%. The sensitivity of WBC count in predicting intra-amniotic infection was 64.86%, specificity 58.73%, positive predictive value 48% and negative predictive value was 74% with amniotic fluid culture as the reference standard. The study is comparable to study done by Saini S *et al*., in which sensitivity and specificity of CRP determination was found to be 80% each as an early predictor of subclinical chorioamnionitis [15]. TLC had a low sensitivity of 20% and specificity of 60% in detecting subclinical chorioamnionitis. Study done by Ibarra V *et al*. showed CRP as an early detector of amniotic infection with a sensitivity of 94.12% and a specificity of 100%, positive predictive value of 100% and a negative predictive value of 98.86% [16]. Our study also co-relates with study done by Aggarwal A *et al*., wherein they concluded that CRP was the earliest and most reliable diagnostic marker of clinical as well as histological chorioamnionitis in patients with preterm premature rupture of membranes.[17] Ismail MA *et al*. in their study concluded that C-reactive protein level is a very sensitive predictor of infectious morbidity in premature rupture of membranes, its specificity is not high.[18] In study done by Kurki T *et al*. concluded that use of serial CRP measurements increases the test performance and the high negative predictive value suggested that CRP was useful in predicting the absence of chorioamnionitis [19].

Conclusion

It is concluded from the present study that CRP is a reliable diagnostic marker than WBC count for predicting intra-amniotic infection in pregnancies complicated with rupture of membranes. If CRP is found positive (>6 mg/l) on admission, pregnancy should be terminated as soon as possible to salvage the baby as well as the mother.

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