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ORIGINAL ARTICLE

Association between C-Reactive Protein and Premature Rupture of Membrane

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ABSTRACT

Background and Objectives: Early diagnosis of clinical chorioamnionitis (ChAm) in patients with premature rupture of membrane (PROM) is essential for its prompt treatment with antibiotics. Amniocentesis may be used to detect subclinical infections in cases of PROM. But the procedure is an invasive one. The present study was undertaken to study the role of plasma C-reactive protein (CRP) in the prediction of clinical chorioamnionitis in case of PROM.

Materials & Methods: The cross-sectional study was carried out in the of Departments of Obstetrics & Gynaecology, Khulna Medical College Hospital, Khulna over a period 1 year from July 2014 to June 2015. A total of 90 clinically diagnosed cases of PROM (rupture of the membrane with release of the amniotic fluid more than 1 hour prior to the onset of labor) were consecutively included in the study based on predefined enrolment criteria. Clinical ChAm is defined by findings such as leukocytosis [WBC count, >15,000/μL, fetal tachycardia, maternal fever (temperature, >100.4°F), fundal or uterine tenderness, or foul-smelling amniotic fluid]. A CRP value of > 10 mg/L was considered as raised or positive CRP. The risk of developing clinical ChAm in patients with raised CRP was then estimated by computing the Odds ratio.

Result: The mean age of the women with PROM was 23.9 years. The patients presented with fundal or uterine tenderness (10%), raised maternal temperature (8.9%), foetal tachycardia (10%), maternal tachycardia (13.3%), foul smelling amniotic fluid (6.7%). Over half (52.2%) of the patients were preterm PROM and the rest were term PROM. Positive CRP was found in 16.7% cases. Raised WBC count and raised ESR were found in 11.1 and 33.3% cases respectively. Over two-thirds (70%) who developed clinical chorioamnionitis had raised CRP as opposed to 10% of those who did not develop the condition. The risk of having raised CRP in patients who developed clinical chorioamnionitis was > 20-fold (4.5 - 97.7) higher than those who did not develop the condition ($p < 0.001$). The sensitivity and specificity of CRP in diagnosing and ruling out chorioamnionitis respectively in cases of PROM were 70% and 90% respectively. The positive and negative predictive values of the test are 46.7% and 96% respectively.

Conclusion: The study concluded that a substantial proportion of the PROM cases with clinical chorioamnionitis is manifested with raised CRP compared to PROM cases without chorioamnionitis. However, CRP is moderately sensitive to diagnose chorioamnionitis and highly specific to rule out the condition in cases with PROM.

Key words: C- reactive protein; Premature Rupture of Membrane; Chorioamnionitis.

INTRODUCTION

Premature Rupture of Membrane is still a significant problem in obstetrics and gynecology needing proper management and investigation.[1,2] It refers to membrane ruptured before the onset of uterine contractions. Preterm PROM (PROM presented before 37 completed weeks) is strongly associated with both histological chorioamnionitis and prematurity[3] and complicates 2-4% of all

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singleton and 7-20% of all twin pregnancies and is associated with over 60% of preterm births.[4-6]

Up to 50% of the cases of PROMs could be attributed to an infectious cause.[7] Clinical ChAm, which is diagnosed before delivery using only clinical findings, complicates 0.5 - 10% of pregnancies is considered a risk factor for increasing rates of perinatal death, neonatal respiratory distress syndrome, and neonatal infection.[8] Traditionally, clinical ChAm diagnosis is dependent on findings such as leukocytosis (white blood cell [WBC] count, >15,000/μL), fetal tachycardia, maternal fever (temperature, >100.4°F), fundal or uterine tenderness, or foul-smelling amniotic.[9] A major challenge is to determine reliable diagnostic methods for timely identification and treatment of the problem. Several laboratory tests erythrocyte sedimentation rate (ESR), and WBC counts have been used to diagnose chorioamnionitis,[2,10-12] but the results of these tests are not promising to reach a definite conclusion. However, CRP, a marker of inflammation is claimed to be superior in early diagnosis of chorioamnionitis and genital infection leading to PROM. CRP is synthesized by hepatocytes and is normally present as a trace constituent of the plasma and is raised at least 48 hrs before the onset of sign and symptoms of chorioarnnionitis.[13] High levels of CRP in early pregnancy reflect infection or inflammation in body which may lead to preterm labour.

Preterm PROM is a predisposing factor for serious maternal infections such as intra-amniotic infection, endometritis or septicemia. The fetus remains at a greater risk of Preterm PROM-related morbidity and mortality than the mother. Fetal infections may appear as early neonatal infections such as pneumonia, meningitis and sepsis.[14] Neurodevelopmental delay and cerebral palsy are potential long-term sequelae. Preterm neonates who develop early infection commonly have subtle and non-specific clinical symptoms. Balancing the benefits of prolonging pregnancy to allow for maturation of the fetus against the risks of infection in cases of Preterm PROM presents a major challenge to obstetricians. Early detection of infection would allow PTB to be expedited. Early infection is not reliably predicted by commonly used laboratory variables such as erythrocyte sedimentation rate, white blood cell count, neutrophil count or vaginal bacterial culture. Clinical signs such as fever and fetomaternal tachycardia usually appear late.[15]

CRP has been widely used in obstetric practice, despite conflicting reports of its benefit, particularly in the early diagnosis of chorioamnionitis in the absence of clinical signs of infection. The present cross-sectional study is, therefore intended to find whether there is any association between abnormal rise of plasma CRP and chorioamnionitis in PROM cases.

MATERIALS AND METHODS

This cross-sectional study was conducted over a period of 1 year from July 2014 to June 2015 in the Department of Obstetrics & Gynaecology, Khulna Medical College Hospital, Khulna. All women attended with confirmed PROM after 28 weeks of gestational age and onwards were study population. However, pregnant women with rheumatoid arthritis, SLE, PIH/preeclampsia/eclampsia, enteric fever or other medical disorders or women with known intrauterine fetal death or congenital fetal anomaly were excluded from the study. A total of 90 such patients were enrolled in the study. Clinical ChAm is defined by findings such as leukocytosis [WBC count, >15,000/μL, fetal tachycardia, maternal fever (temperature, >100.4°F), fundal or uterine tenderness, or foul-smelling amniotic fluid]. A CRP value of > 10 mg/L was considered as raised or positive CRP. The risk of developing clinical ChAm in patients with raised CRP was then estimated by computing the Odds ratio. Data

were processed and analysed using software SPSS (Statistical Package for Social Sciences) version 16.0. The statistics used to analyses the data were Chi-square (χ^2), Odds ratio and accuracy test.

RESULTS

More than 55% of the patients were between 20-30 years, 35.6% < 20 years and 8.8% 30 years old or more. The mean age of the patients was 23.9 years (range: 17-40 years). Over half (52.2%) of the cases were preterm PROM and the rest were term PROM. Approximately 58% of women were nullipara, 21% primipara and another 21% multipara. One-third (33.3%) of the patients had past history of abortion. One-third (33.3%) of the women received antenatal check-up regularly and 46.7% received it irregularly and another 20% did not receive any antenatal check-up. Only 2.2% had multiple pregnancies. In terms of past obstetric history, about one-quarter (24.0%) had history of abortion, 3.0% preterm delivery, 7.0% still-birth (Table I).

TABLE I. Pregnant women by their age & obstetric profile (n = 90)

Maternal age & obstetric profile	Frequency	Percentage
Maternal age* (years)		
< 20	32	35.6
20 - 30	50	55.6
30 - 40	4	4.4
≥40	4	4.4
Current and past obstetric profile		
Parity		
Nullipara	52	57.8
Primipara	19	21.1
Multipara	19	21.1
Past history of abortion	30	33.3
Antenatal check-up		
Received regularly	30	33.3
Received irregularly	42	46.7
Not received	18	20.0
Multiple pregnancy	2	2.2
Past obstetric history Nothing contributor	59	66.0
Abortion	22	24.0
Still birth	6	7.0
Preterm delivery	3	3.0

Mean age = 23.9 ± 5.5 yrs; range = (17 - 40) yrs.

In terms of clinical presentation 10% patients presented with fundal or uterine tenderness, 8.9% raised maternal temperature, 10% foetal tachycardia, 13.3% maternal tachycardia, 6.7% foul smelling amniotic fluid. Positive CRP was found in 16.7% cases, Raised WBC count and raised ESR were found in 11.1 and 33.3% cases respectively (Table II). Out of 90 cases, 10(11.1%) developed clinical chorioamnionitis (Fig. 1).

TABLE II. Distribution of patients by their clinical presentation & investigations (n = 90)

Clinical presentation & investigations	Frequency	Percentage
Clinical presentation		
Fundal or uterine tenderness	9	10.0
Raised maternal temperature (>100.4°F)	8	8.9
Foetal tachycardia	9	10.0
Maternal tachycardia	12	13.3
Foul smelling amniotic fluid	6	6.7
Investigations		
CRP (mg/L)		
Positive (> 10 mg/L)	15	16.7
Negative (≤ 10 mg/L)	75	83.3
WBC count		
Raised (>15,000/ml)	10	11.1
Not raised (≤15000/ml)	80	88.9
ESR		
Raised (> 50 mm)	30	33.3
Not raised (≤ 50 mm)	60	66.7

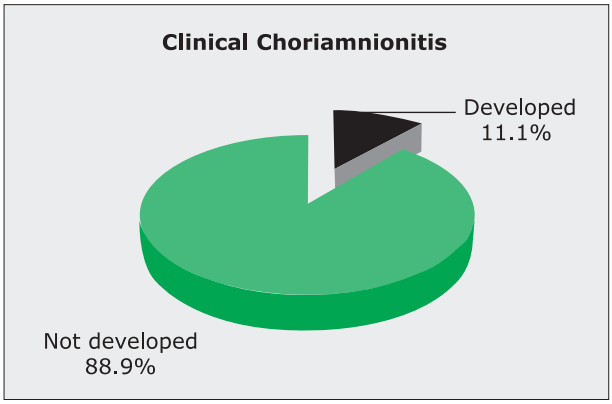

FIGURE 1 : *Distribution of patients by their outcome (n= 90)*

Seventy percent of the patients who developed clinical chorioamnionitis had raised CRP (> 10 mg/L) as opposed to 10% of those who did not develop the same. The risk of having raised CRP in patients who developed clinical chorioamnionitis was > 20-fold (4.5 - 97.7) higher than those who did not develop the condition ($p < 0.001$). The sensitivity of the test in differentiating clinical choriamnionitis from those who did not develop the condition was 70% and the specificity of the test in correctly detecting those who do no not have the condition was 90%. The positive and negative predictive values of the test were 46.7% and 96% respectively, while the percentage of false positives and false negatives were 53.3% and 4% respectively (Table III).

TABLE III. Association between clinical chorioamnionitis and level of CRP

CRP*	Clinical chorioamnionitis developed		Odds Ratio (95% CI of OR)	p-value
	Developed (n = 10)	Not developed (n = 80)		
Positive	7(70.0)	8(10.0)	21(4.5-97.7)	< 0.001
Negative	3(30.0)	72(90.0)		

Figures in the parentheses indicate corresponding %;
**Chi-squared Test (χ^2) was done to analyze the data.*

DISCUSSION

Premature rupture of membrane especially if preterm is associated with significant maternal risk particularly of infection in the form of chorioamnionitis. Although the incidence of subclinical or histopathological ChAm is high, serious maternal systemic infection is uncommon, especially with prompt and appropriate treatment when suspected or diagnosed. The intrapartum risk to the mother is obstetric interventions that may be required as a consequence of the PROM. Induction of labor often with an unfavorable cervix predisposes to a prolonged labor and higher risk of operative deliveries. Postnatal maternal risks include endometritis and pelvic infection as indicated by lower abdominal pain, fever and foul smelling vaginal discharge.[16]

So management of PROM presents a dillema to the obstetrician. While active management leads to increased obstetric intervention (caesarean section, operative vaginal deliveries) and prematurity in cases of Preterm PROM. On the other hand prolonging pregnancy involves the risk of infection in mother is choriamnionitis which may result in adverse neonatal outcomes. Various studies have indicated that an elevated maternal serum CRP can be used as an early marker of chorioamnionitis in PROM. It is raised at least 48 hrs. before the onset of sign and symptoms of chorioarnnionitis.[13]

In the present study over two-thirds (70%) of the patients with clinical chorioamnionitis had raised CRP as opposed to 10% of those who did not have the clinical ChAm. The risk of having raised CRP in patients who developed clinical chorioamnionitis was > 20-fold (4.5-97.7) greater than those who did not develop the condition ($p < 0.001$). Salzer and associates[17] showed that 40% of the infants whose mothers had presented with prolonged rupture of amniotic membranes (PROM) and/or amnionitis were CRP positive (i.e. ≥ 6 mg/L) within the first 6 hrs. Clinically, all infants with positive CRP developed symptoms suggesting bacterial infection and both the absolute immature neutrophil counts as well as the ratio immature/total neutrophils were significantly higher in them on day 2 of life than in infants with negative CRP. Blood cultures were only positive in infants with positive CRP. Thus, CRP can be regarded as an early marker for neonatal bacterial infection due to PROM and/or amnionitis. Kodanky and Telang[18] in a study demonstrated that there total 5 cases of chorioamnionitis in PROM group, but not a single case of chorioamninitis was there in control

group. Puerperal pyrexia was present in 16 cases as compared to 3 cases in control. A number of studies have demonstrated clinical chorioarnnionitis may be associated with the subsequent development of adverse neonatal outcomes such as neonatal death. Periventricular leukomalacia, intraventricular hemorrhage, cerebral palsy and bronchpulmonary dysplasia are other complications related to PROM. Some of them had occult chorioamnionitis.[19]

The present study revealed that the sensitivity of CRP in diagnosing chorioamnionitis in cases of PROM is moderate but its specificity is appreciably high indicating that the test is more useful in differentiating the PROM cases that do not develop the chorioamnionitis than who does develop the condition. The positive and negative predictive values of the test (46.7% and 96% respectively) also suggest that the test yields a high percentage of false positive (53.3%) cases and an extremely low percentage of false negative cases (4%). Various studies have been conducted showing elevated CRP as a marker of subsequent development of choriamnionitis in case of PROM. Kurki et al[20] in their study reported that 22.4% patients with preterm rupture of the membranes (PROM) developed chorioamnionitis. There was no difference in the highest antepartum CRP between patients with or without chorioamnionitis suggesting that elevated antepartum CRP may be misleading in the diagnosis of chorioamnionitis. However, use of serial CRP measurements increases the test performance. The high negative predictive value suggests that CRP is useful in predicting the absence of chorioamnionitis. In a study done by Mathur et al[13] sensitivity and specificity of CRP in prediction of ChAm was 100% and 97.6% respectively which was very high. Romem et al[22] indicates that CRP is a valid and early marker for predicting clinical chorioamnionitis. Nowak et al[21] found that elevated CRP level in predicting ChAm has sensitivity, specificity, positive predictive value and negative predictive value of 91.5%, 57%, 86% and 70.5% respectively. Chaaban et al[23] concluded that CRP can be considered as an early biological marker which is sensitive and cheap in the clinical supervision of cases with early rupture of membranes. Awara et al[24] studied the predictive value of CRP in maternal serum and cord blood on 10 pregnant women at various gestational ages with intact membranes till labor began and 25 pregnant women also at various gestational ages who had PROM. They found the sensitivity and specificity of CRP in predicting choroamnionitis was 100% and 93.3% respectively. They concluded that CRP can reduce unnecessary premature delivery of many PROM cases which occur due to fear of developing infections in both the mother and fetus. Saini et al[25] in a case control study (25 cases of preterm PROM and 25 controls of preterm with intact membranes between 28-36 weeks of pregnancy), the sensitivity and specificity was found to be 80% each as an early predictor of subclinical chorioarnnionitis reaching to a conclusion that CRP estimation is a reliable marker for detection of early chorioarnnionitis.

Despite recent advances in perinatal care, Preterm PROM continues to lead to important obstetric complications beginning a high-risk period for both mother and fetus.[26,27] Although the assessment of various inflammatory mediators in the amniotic fluid is highly accurate in the diagnosis of amnionitis, it requires a invasive amniocentesis. Moreover, the procedure may be difficult to perform in patients with PROM, because the amniotic fluid volume is often reduced.[28] Therefore, CRP could be considered as a non-invasive, reliable method of detecting chorioamnionitis in patients with PROM.

CONCLUSION

A substantial proportion of the PROM cases with clinical chorioamnionitis is manifested with raised

CRP compared to PROM cases without chorioamnionitis. However, CRP is moderately sensitive to diagnose chorioamnionitis and highly specific to rule out the condition in cases of PROM.

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