ORIGINAL STUDY

C-Reactive Protein in the Premature Rupture of the Membranes

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Abstract:

Premature rupture of the membranes (PROM) defined as a rupture of membranes before onset of labor, which is one of the most complications of pregnancy that leads to significant maternal and neonatal morbidity and mortality. These complications depend on the gestational age to which it occurred. The aim of this study is to determine diagnostic value of CRP during pregnancy complicated by PROM. Retrospective study performed at Hamad Women's Hospital in Qatar. Data collected from files in the Medical Records over a two period from 27/11/2000 to 27/11/2002. One hundred and fifty cases were chosen and divided into: Group (1a) 50 patients with PROM before 37 wks. Group (1b) 50 patients with PROM after 37 wks. Group (2) 50 patients as control. Statistical analysis showed high incidence of Oligohydroamnios and polyhydramnios in the group 1 compared with control. Measurement of maternal blood CRP early before 37 week, indicated significant relation between the prevalence of premature rupture of the membranes, associated oligohydramnios with the incidence of positive results of CRP. We recommend that further investigations needed to document our data and to prove the beneficial effect of the test especially before 37 week of gestations.

Introduction:

Premature rupture of the membranes (PROM) defined as rupture of membranes before onset of labor[1], which is one of the most common complications of pregnancy. It occurs in approximately 10% of all pregnancies, and it implicated in more than one third of preterm deliveries. Approximately 80% of all cases of PROM occur in term of gestations more than or equal 37 weeks; the other 20% occur in preterm gestations less than 37 weeks. Therefore, the clinical significance of PROM depends on the gestational age at which it occurs[2].

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The etiology of PROM is multifactorial[3]. It is clear that changes in maternal enzymes, maturational and mechanical forces, and Chorionic-amniotic membrane phospholipids content, and collagen disruption, amniotic cell cytokines induced by fetal signals and bacterial phospholipases and collagenases all play major and interrelated roles[4]. Risk factors of PROM are variety of factors contribute with each other and lead to its occurrence, including pervious history of patient, cervical and vaginal infection, intrauterine infection[5], abnormal membrane physiology, nutritional deficiencies as mineral and vitamin deficiencies, multiple pregnancy and cervical incompetence[1].

In diagnosing premature rupture of the fetal membranes (PROM), the history and physical examination alone often are inadequate to confirm the status of the membranes. Fluid may not be present in the, vagina for evaluation. Furthermore, fluid at times may be contaminated with urine, cervical mucus, bath water vaginal discharge, blood, or meconium. Because of these difficulties, multiple cytologic, biochemical, colorimet-ric; and sonographic methods have been developed for the detection of ruptured membranes. Despite significant advances in technology, no single test had been found to be completely accurate, and diagnosis still requires an integration of historic factors, physical examination, and laboratory testing[6].

C-reactive protein (CRP) is an abnormal serum glycoprotein produced by the liver during acute inflammation. Its production regulates by Interleukins 1b and 6 and tumour necrosis factor. Also, it had been a measure of acute phase reactions to inflammation for the last 15 years. Recently improved high sensitive and standardized quantitative assays in serum and cerebrospinal fluid (CSF) had allowed a re-evaluation of its potential as a diagnostic laboratory test. Because it disappears rapidly when inflammation subsides, its detection signifies the presence of a current inflammatory process. Further, by serial measurements important information can be obtained on the resolution or continuation of the inflammatory process[7].

Therefore, the aim of this study to determine diagnostic value of C-reactive protein (CRP) during pregnancy complicated by premature rupture of the membranes (PROM) according the age, body mass index, gestational age, clinical symptoms as vaginal

bleeding, leaking, and cervix dilatation, present or absent of infection, ultrasound investigations, clinical diagnosis, medical problems , onset and duration of PROM.

Materials and Methods:

This analysis included 150 women who participated in a retrospective study at HMC Women's Hospital in Doha over a two-year period from 27/11/2000 to 22/11/2002. One hundred and fifty cases were chosen and divided into: Group (1a) 50 patients with PROM before 37 wks. Group (1b) 50 patients with PROM after 37 wks. Group (2) 50 patients as control. Data were collected from medical records for variety variables, including maternal age, body metabolic rate, and blood pressure, disease during pregnancy, pervious obstetric history, and family history. Also, ultrasound investigation maternal blood test for white blood cells count , haemoglobulin, platelet count, C-reactive protein and semi-quantitative of C-reactive protein QCRP, result of cultures by high and low vaginal swab and urine culture, management, medical problem, clinical diagnosis, induction of labor, onset and duration for PROM. Additionally, perinatal outcome information as sex, weight, week of delivery, malformation, apgar score, live, stillbirth and admission of Neonatal Intensive Care Unit (NICU).

Data were analyzed with SPSS statistical software at Medical statistic Department in Hamad Medical Corporation, Analysis included descriptive statistics, relative risk, Chi-square Tests, 95% confidence intervals and odd ratio.

Results:

One hundred and fifty patients enrolled in the study and according to the line with the aim of this study, the results presented as follows: firstly, baseline information for all patients. Secondly, cases defined, as PROM with CRP was preformed.

Baseline information represented as descriptive data information; showed in ***Table 1***,that there were no significant differences according to age, nationality, BMI and parity.

Table 1: Maternal Demographic Characteristics

Descriptive Variables		Group 1 PROM	Group 2 Control
Age		28.7±7.35	27.68±6.69
Nationality:	Qatari	61.91%	60 %
	Non Qatari	38.09%	40 %
BMI		32.54±1.14	31.57±0.68
Gravida:	Multiparas	78.57%	95%
	Nulliparas	21.43%	5%

Data presented as mean ± standard error or percentage

In studying the relationship of maternal past medical history in PROM, it was found that diabetic women and pregnant women who had UTI had higher incidence of PROM comparing with Group 2 as shown in ***Table 2***.

Table 2: Maternal Medical History

Descriptive Variables	Group 1 PROM	Group 2 Control
Diabetes	19.05%	0.00%
Hypertension	7.14%	9.90%
Anemia	9.52%	12 .00%
UTI	7.14%	0.00%
Asthma	4.76%	2.50%
Other	2.39%	0.00%

Many risk factors contributed with each other to lead to premature rupture of the membranes. These factors were listed in next ***Table 3***.

Table 3: Risk Factors of PROM

Risk factors		Percent
Cause of Administration:	Leaking	90.50%
	Vaginal bleeding	24.00%
	Cervical incompetency	7.14%
	Infection	50.00%
Past Obstetric History:	Previous PROM	42.90%
	Previous C.S.	28.60%
	Previous abortion	35.70%

We found in table 3 that most of cases presented by leaking of amniotic fluid (90.5%) and (50%) of cases were accompanied by infection, and to less extend with vaginal bleeding (24%) and cervical competence (7.14%). According to the past Obstetric history the patients who had pervious PROM (42.90%) had higher incidence of recurrent PROM.

In studying the exact cause of PROM, only 25% of cases were accurately diagnosed. The most common cause was acute histological chorioamnionitis (21%) and the remaining cause was cellulites (4%). The rest of cases (75%) were unknown.

Maternal blood samples for CRP collected from pregnant women with PROM during administration at Hamad Women Hospital (HWH) showed that there were a high percentage of cases (74.2%) with positive result of CRP from group (1a), compared to those in group (1b) more than or equal 37 week of gestation (25.8 %) ($P < 0.05$) ***(Table 4)***.

Table 4: Maternal Blood CRP and onset of PROM

Maternal Blood CRP	Onset of PROM		Total	Chi Square Test Fishers' Exact Test 2 sided
	Group1a[x]	Group1b[#]		
Positive result	74.20%	25.80%	100%	0.011*
Negative result	27.30%	72.70%	100%	

[x] Group 1a means onset of PROM less than 37 wk of gestation

[#] Group 1b means onset of PROM more than or equal 37 wk gestation

*Significantly relationship between results of maternal blood CRP and onset of PROM

Semi quantitative measurement of C-reactive protein in Group1 showed in ***Figure 1***. We found that C-reactive protein level in 50 % patients was 12 mg/l, 20% was 48 mg/l or 24 mg/l and remaining with 10% was 6 mg/l.

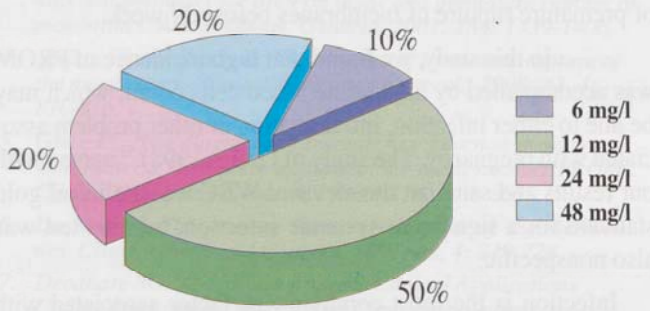

Figure 1: Semi quantitative measurement of positive result of maternal blood CRP (mg/l).

Ultrasound investigation during pregnancy is important to confirm or establish the gestational age, to exclude the structural abnormalities and multiple gestations, and to localize the placenta. The next ***Table 5*** showed high incidence of oligohydramnios and polyhydramnios in Group1 comparing with control Group 2.

Table 5: Ultrasound investigation

	Group 1 PROM	Group 2 Control
Week of Ultrasound	**31.45 ± 0.937**	**32.55 ± 0.758**
Amniotic fluid:		
Normal	45.24%	70%
Oligohydroamnios	38.09%	20%
Polyhydramnios	16.67%	10%
EFW	**2112.1 ± 153.4**	**2203.3 ± 132.1**
Placenta:		
Single	90.48%	100%
Multiple	4.76%	0%
Abnormalities	0%	0%

Data presented as mean ± standard error or percentage

Table 6: Maternal blood White blood cells and onset of PROM

Onset of PROM	WBCs		Total
	< 10	> = 10	
< 37 week	15.40%	84.60%	100%
> 37 week	37.50%	62.50%	100%

According to ***Table 6***, it was found that high percentage of incidence of PROM was accompanied by high WBCs count, about 84.6% of patient with less than 37 week and (62.5%) after or at 37 week .

Infection was the most common risk factor associated with PROM. The data indicated that fifty percent of patients had positive results of infection and the other fifty had no infection. Out of the infected patients, it was found that Group B Beta-Haemolytic streptococcus (BGS) was the most common micro-organism isolated from lower genital tract by low and high vaginal swab 61%, followed by Candida albican (29%) Bacteria vaginosis 5% and Trichomanis vaginalis 5%.

Relationship between maternal blood CRP and infection showed in ***Table 7***, that there was no significant relation between results of CRP and results of infection.

Table 7: Maternal Blood CRP and Infection

Result of CRP	Result of Infection		Total	Chi Square Test Fishers' Exact Test 2 sided
	Positive	Negative		
Positive result	51.60%	48.40%	100%	1
Negative result	45.50%	54.50%	100%	

Studying the management of PROM, it was found that PROM was managed mainly by using antibiotics (90.48%), dexamethazone (78.57%), induction of labor (96%) and cervical circulage (7.14%).

Latent period of PROM was about eight days in average. The relationship between the onset of PROM and the latent period of PROM before delivery, showed that there was significant relationship(P = 0.007). As all cases of PROM after 37wks delivered before 8 days and(64%) of cases with PROM before 37 wks delivered before 8 days ***(Table 8)***.

Table 8: Onset of PROM and latent period before delivery

Onset of PROM	Latent period before delivery		Total	Chi Square Test Fishers' Exact Test 2 sided
	< 8 days	>=8 days		
Group 1a	64%	36%	100%	0.007*
Group 1b	100%		100%	

* *significantly relationship between onset of PROM and latent period before delivery*

There was no significant relationship between maternal blood CRP and latent period before delivery as shown in table 9

Table 9: Maternal Blood CRP and Latent period before delivery

Result of CRP	Latent period before delivery		Total
	< 8 days	>=8 days	
Positive result	76.70%	23.30%	100%
Negative result	75%	25%	100%

Table 10 showed the different characteristics of neonatal outcomes in Group 1 and Group 2. We found that group1 had low weight infants, high incidence of C.S., and high percentage of boy infants comparing with Group 2.

Table 10: Neonatal Outcome

		Group 1 PROM	Group 2 Control
Week of presenting		**31.45 ± 0.937**	**32.55 ± 0.758**
Week of delivery		**34.29 ± 0.965**	**37.55 ± 0.897**
Sex:	Boy	52.4%	45.2%
	Girl	47.6%	54.8%
Weight		**2407.244 ± 171.4**	**3008 ± 132**
Mode of Delivery:			
	Normal	64.3%	95.2%
	C.S.	35.7%	4.8%

Data presented as mean ± standard error or percentage

Discussion:

In this study, we found that younger age, multiparas pregnant women had high body mass index. This could be related to wrong eating habits and less exercise during the pregnancy. Comparing with other study that measured BMI before pregnancy and found there was no relation between low BMI (<19.8 kg/m2) and premature rupture of the membranes[8]. Deodhare, 2002[7] showed that obese women 6 times more likely to have elevated CRP levels than their counterparts of normal weight.

The most common causes of administration to HMC Women Hospital was uncontrolled leaking that was accompanied with vaginal bleeding and cervical incompetence. Harger, et al. 1990[9], stated that, when vaginal bleeding was present in more than one trimester, it was considered as a significant risk factor for PROM (odds ratio, 7.4; 95% confidence interval, 2.2, 25.6 versus control patients). Allan, 1991[1] agreed with our result about cervical incompetence as risk factor for PROM but the relationship between cervical incompetency and spontaneous PROM was not well documented.

In our study, we found that most of cases were multiparas women with past pervious premature rupture of the membranes and recurrent abortion. This agreed with study Allan 1991[1], who found that the recurrence rate was 21% for PROM, which was much higher than the usual rate 14 -17% for the general obstetric population.

By qualitative measurement of maternal blood CRP, we found that high percentage of cases with positive CRP before 37 week were associated with cases of premature rupture of membranes before 37 week. Ultrasound investigation of amniotic fluid volume, showed high incidence of Oligohydroamnios and polyhydramnios in the Group 1 (PROM) compared with the control. Oligohydramnios was frequently associated with premature rupture of membranes and is a risk factor for the subsequent development of clinical chorioamnionitis and neonatal sepsis[10]. Positive results of CRP had significantly associated with high incidence of oligohydramnios especially with cases of premature rupture of membranes before 37 week.

In this study, we found that high incidence of PROM was accompanied by high white blood cells count, which may be due to either infection, inflammation or other problem associated with pregnancy. The study of Greig (1998)[5] agreed with our results and said that the elevated WBC was a clinical gold standard for a significant systemic infection, but this test was also nonspecific.

Infection is the most common risk factor associated with premature rupture of the membranes. Most of cases had infection but there is no significant relationship between onset of premature rupture of the membranes and infection. Using different cultures by low and high vaginal swab, and urine cultures; we found that, there was high prevalence of Group B Beta hemolytic streptococcus and Candida albican. This agreed with Romero, et al, 1991[11]. However, direct evidence (i.e. isolation of the same microorganism from both the amniotic fluid and the vagina of the same patient) was not currently available). The most commonly associated organisms found were those causing bacterial vaginosis, trichomonas vaginalis, mycoplasma, chlamydia trachomitis, neisseria gonnorhea and Group B streptococci.

In studying the relation between positive results of CRP and positive result of infection, we found no significant relationship. Therefore, CRP was not specific prediction for infection. The study of Yoon, et al.1996[12] and Greig 1998[5], agreed with our results, they said that in cases of intrauterine infection, cytokines produced within the uterine cavity first mount a local inflammatory response and must reach the maternal circulation and then the liver to stimulate the synthesis of C-reactive protein by hepatocytes or bone marrow targets to induce leukocytosis

Management of premature rupture of the membranes mainly by corticosteroids and antibiotics. Corticosteroids administration to promote fetal pulmonary maturation before delivery of

preterm infant is one of the most effective intrapartum obstetric interventions in reducing perinatal morbidity[13]. Mercer et al.1997[14] agreed with our result and said that broad-spectrum antibiotic therapy increases the duration of latency after PPROM and reduces the risk of perinatal morbidity, including respiratory distress and necrotizing enterocolitis.

We concluded that the Incidence of PROM was high in multiparas younger women, with high body mass index. Positive maternal blood CRP early before 37 weeks, indicate a high prevalence of premature rupture of the membranes which were highly associated with oligohydramnios. However, CRP is not specific indicator for infection

Further investigations are required to document our data and to prove the beneficial effect of the test especially before 37 week of gestations. Care must be taken to rule out any factors as infection, inflammation, and others that may interfere with the results of the test.

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