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Chorioamnionitis and Diagnostic Value of C-reactive Protein, Erythrocyte Sedimentation Rate and White Blood Cell Count in its Diagnosis Among Pregnant Women with Premature Rupture of Membranes

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Abstract: Several laboratory parameters have been used in these studies to diagnose chorioamnionitis leading to controversies to some extent. The aim of this study was to assess the diagnostic value of C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and White Blood Cell (WBC) count in chorioamnionitis among pregnant women with Premature Rupture Of Membranes (PROM). In a cross-sectional diagnostic test research, 71 patients presented with PROM before the 37th week of gestation were enrolled. A blood sample was taken from all the patients. Hematologic automatic blood cell counter was used to count the blood cells and their differentiation. ESR and CRP were also measured using the same blood sample at the laboratory. Sensitivity, specificity, correct classification rate and likelihood ratios were calculated. Receiver operating curves were plotted and area under curve was estimated along with its 95% confidence interval. A total of 71 patients were studied. None of the patients had a positive drug history or a history of hypertension before the 20th week of gestation or during her previous pregnancy. Contrary to ESR, WBC count and CRP results didn't provide minimum acceptable diagnostic accuracy measures for diagnosis of chorioamnionitis. The sensitivity and specificity of a positive ESR test at a cutoff value of 52 were 66.7 and 60%, respectively. The area under curve was calculated to be 0.62. The findings of the present study were not supportive of using CRP, WBC as a reliable diagnostic test to identify chorioamnionitis in women with PROM. The results of CRP and WBC were not acceptable but ESR diagnostic value was minimally acceptable.

Key words: Erythrocyte sedimentation rate, leukocyte count, inflammatory factors, diagnostic value, sensitivity, specificity

INTRODUCTION

Premature Rupture Of Membranes (PROM) is still a significant problem in obstetrics and gynecology needing proper management and investigation (Garland *et al*., 2002; Wiwanitkit, 2005). Preterm PROM occurs in three percent of pregnancies and is the main cause of at least one third of premature births (Rudigoz, 2008).

Up to 50% of the cases of premature rupture of membranes could be attributed to an infectious cause (Ratanakorn *et al*., 2005). Chorioamnionitis can be considered as an unwanted aftermath of PROM and is capable of causing considerable perinatal morbidity and mortality. It is not much recent that a strong association between existence of the histopathologic chorioamnionitis and preterm delivery is reported suggesting that occult antepartum infection of the genital tract is an important cause of preterm delivery (Guzick and Winn, 1985). Recent systematic reviews have shown that chorioamnionitis is a risk factor of cerebral palsy (Wu and Colford Jr., 2000). Acute chorioamnionitis has also been recognized as a major threat to both mother and fetus. A major challenge will be to distinguish reliable diagnostic methods for timely identification and treatment of the problem. Some studies have addressed this issue. Several laboratory parameters have been used in these studies to diagnose chorioamnionitis, among which we can mention Erythrocyte Sedimentation Rate (ESR), CRP and White Blood Cell (WBC) counts (Gojnic *et al*., 2005; Van der Ham *et al*., 2008; Wiwanitkit, 2005; Woldesenbet *et al*., 2008; Yoon *et al*., 1996). These tests are of low cost and easily accessible. However, the results of the studies have been controversial not resulting in a definite conclusion.

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The aim of this study was to assess the diagnostic value of CRP, ESR and WBC count in chorioamnionitis among pregnant women with Premature Rupture of Membranes (PROM).

MATERIALS AND METHODS

Study design and participants: In a cross-sectional diagnostic test research, 71 patients presented with PROM before the 37th week of gestation were enrolled. Patients with a history of any known inflammatory disease such as rheumatoid arthritis and lupus, history of hepatic cirrhosis, history of long-term use of immunosuppressive drugs and those suffering from acute febrile disease due to other etiologies at presentation were excluded from the study. Consecutive sampling method was used in this study and all the eligible patients during the year 2009 were studied.

The main studied variables included patient demographics, pregnancy history, the reason for referral and the onset and type of presenting symptoms.

Ethical issues: The study protocol was approved by the committee of ethics in Urmia University of medical sciences. Informed consent was obtained from all the participants of the study. The patients were not charged for the laboratory assessments. The security of the information was guaranteed by the main researcher.

Laboratory measurements: A blood sample was taken from all the patients and was sent to the laboratory as soon as possible. Hematologic automatic blood cell counter was used to count the blood cells and their differentiation. ESR and CRP were also measured using the same blood sample at the laboratory. Quantitative method was used for CRP measurement and its blood level was obtained. After delivery, a macroscopic examination of the placenta was performed and its characteristics were recorded. It was sent intact to the pathology laboratory to be evaluated for chorioamnionitis by a pathologist.

Statistical analysis: SPSS statistical software package was used for statistical data analysis applying independent t-test, chi-square and non-parametric Mann-Whitney U tests as appropriate. Sensitivity, specificity, correct classification rate and likelihood ratios were calculated. Receiver operating curves were plotted and area under curve was estimated along with its 95% confidence interval.

RESULTS

A total of 71 patients were studied. None of the patients had a positive drug history or a history of hypertension before the 20th week of gestation or during her previous pregnancy. Only one of the cases had a past medical history of diabetes with disease duration of 4 years. Heart and lung auscultation was normal in all patients. Most of the samples included individuals within their first pregnancy (51.4%), experiencing their first delivery (61.4%), with no history of abortion (84.3%) and trying vaginal delivery (62.9%). Demographic and obstetric characteristics of the samples are presented in Table 1. Placental pathology was normal in 91.5% of the samples and chorioamnionitis was present in 8.5%.

Male was the dominant sex (53.1%) among newborns. 27 newborns (33.3%) had some problems at birth. Most of the newborns were in good condition at discharge (86.4%). Among the 11 died neonates, 2 were born during a twin pregnancy and 3 were born during a triplet pregnancy.

The results did not show a significant relationship between chorioamnionitis in the recent pregnancy and history of previous abortion.

The results did not show any significant relationship between chorioamnionitis in the recent pregnancy and type of delivery. Contrary to ESR, WBC count and CRP results didn't provide acceptable diagnostic accuracy measures for diagnosis of chorioamnionitis. The area under curve was 0.42 and 0.46, respectively for CRP and WBC. the area under curve was under 0.5 for both cases and the receiver operating curve was plotted and presented As only for the ESR for which the area under curve was calculated to be above 0.6 (Fig. 1).

Table 1: Demographic and obstetrical characteristics of the study samples

	Frequency	
Demographic and obstetric characteristics	No.	%
No. of pregnancies		
One	36	51.4
Two	16	22.9
Three	10	14.3
Four and more	8	11.4
History of abortion		
Zero	59	84.3
One	8	11.4
Two	2	2.9
Three	1	1.4
Delivery type		
Natural vaginal delivery	44	62.9
Caesarean section	26	37.1
Dead child		
Yes	2	2.9
No	68	97.1
Chorioamnionitis		
Yes	6	8.5
No	65	91.5
Sex of the neonate		
Boy	43	53.1
Girl	38	46.9

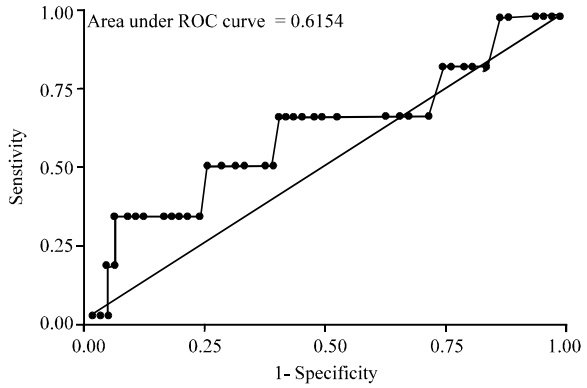

Fig. 1: The receiver operating curve (ROC) for ESR in diagnosis of chorioamnionitis

Table 2: Sensitivity, specificity, correct classification rates and likelihood ratios for possible cutoff values of ESR in diagnosing chorioamnionitis

Cutpoint	Sensitivity (%)	Specificity (%)	Correctly classified (%)	LR+	LR-
≥2	100.00	0.00	8.45	1.0000	-
≥4	100.00	1.54	9.86	1.0156	0.0000
≥22	100.00	3.08	11.27	1.0317	0.0000
≥23	100.00	4.62	12.68	1.0484	0.0000
≥27	100.00	10.77	18.31	1.1207	0.0000
≥28	100.00	12.31	19.72	1.1404	0.0000
≥29	83.33	15.38	21.13	0.9848	1.0833
≥30	83.33	18.46	23.94	1.0220	0.9028
≥32	83.33	20.00	25.35	1.0417	0.8333
≥33	83.33	23.08	28.17	1.0833	0.7222
≥34	83.33	24.62	29.58	1.1054	0.6771
≥35	66.67	27.69	30.99	0.9220	1.2037
≥36	66.67	32.31	35.21	0.9848	1.0317
≥37	66.67	33.85	36.62	1.0078	0.9848
≥38	66.67	36.92	39.44	1.0569	0.9028
≥40	66.67	47.69	49.30	1.2745	0.6989
≥41	66.67	50.77	52.11	1. 3542	0.6566
≥46	66.67	52.31	53.52	1.3978	0.6373
≥47	66.67	55.38	56.34	1.4943	0.6019
≥49	66.67	56.92	57.75	1.5476	0.5856
≥51	66.67	58.46	59.15	1.6049	0.5702
≥52	66.67	60.00	60.56	1.6667	0.5556
≥53	50.00	61.54	60.56	1.3000	0.8125
≥55	50.00	63.08	61.97	1.3542	0.7927
≥57	50.00	67.69	66.20	1.5476	0.7386
≥58	50.00	69.23	67.61	1.6250	0.7222
≥59	50.00	72.31	70.42	1.8056	0.6915
≥60	50.00	75.38	73.24	2.0312	0.6633
≥61	33.33	76.92	73.24	1.4444	0.8667
≥64	33.33	80.00	76.06	1.6667	0.8333
≥65	33.33	81.54	77.46	1.8056	0.8176
≥67	33.33	83.08	78.87	1.9697	0.8025
≥68	33.33	84.62	80.28	2.1667	0.7879
≥71	33.33	89.23	84.51	3.0952	0.7471
≥77	33.33	90.77	85.92	3.6111	0.7345
≥81	33.33	92.31	87.32	4.3333	0.7222
≥82	33.33	95.38	90.14	7.2222	0.6989

The sensitivity and specificity of a positive ESR test at a cutoff value of 52 were 66.7 and 60%, respectively. Sensitivity, specificity, correct classification rates and likelihood ratios (LR) for other possible cutoff values are given in Table 2. As can be sought in this table the sensitivity and specificity measures may be considered for a tradeoff through cutoff value ranges of 47-52. The highest sensitivity value while keeping specificity above 50% was 66.7% that belonged to the ESR cutoff ≥41. The highest specificity value while keeping sensitivity above 50% was 60% that belonged to the ESR cutoff ≥51.

There was no significant relationship between chorioamnionitis in the recent pregnancy and the mother's vital signs. Mother's vital sign statistics are compared between chorioamnionitis and others in Table 3. As can be found in Table 3, only very tiny differences were observed between the two groups in most cases. For example both systolic and diastolic blood pressures were trivially higher in normal group, but the observed difference was not found to be statistically significant. Although none of the differences between the groups was found to be statistically significant, the lowest probability of rejecting the null hypothesis was 23% belonging to the difference in heart rate.

DISCUSSION

The understanding on chorioamnionitis is controversial as it refers to a heterogeneous group of risk factors, clinical pathways and presentations. The general and remarkable ambiguity in the definition and interpretation of the histological findings of the disease, makes it difficult to understand how to prevent chorioamnionitis (Van der Ham *et al*., 2008). It is postulated that the inflammatory response of the host is the first effective factor that influences the events leading to preterm labor and PPROM. Inflammation and inflammatory factors have been a focus of interest in many studies in the region (Asemi *et al*., 2011; Sheikhi *et al*., 2007; Saeedi *et al*., 2007; Mostafa-Gharebaghi *et al*., 2010). Some studies have established the participatory role of inflammatory processes as a response to infection (Goldenberg *et al*., 2008; Holzman *et al*., 2007; Hemalatha *et al*., 2008).

During the last three decades, CRP has been used by obstetrics and gynecology specialists in order to identify

Table 3: Comparison of placental pathology in the examined samples regarding the mother's vital signs

Pathology	Chorioamnionitis (mean)	Normal (mean)	Median	Range	p-value
Systolic blood pressure	110.00±0.00	113.23±12.63	110	100-160	0.76
Diastolic blood pressure	70.00±9.71	72.00±0.00	70	60-110	0.84
Heart rate	81.00±1.09	81.62±1.47	82	76-86	0.23
Respiratory rate	16.00±0.00	16.49±1.26	16	16-21	0.30
Body temperature	37.00±0.00	37.03±0.24	37	37-39	0.76

many inflammatory conditions such as chorioamnionitis (Wiwanitkit, 2005). In this study, CRP proved to have a low diagnostic value in identifying chorioamnionitis. This is consistent with most of the previous studies (Trochez-Martinez *et al*., 2007; Van der Ham *et al*., 2008; Wiwanitkit, 2005; Yoon *et al*., 1996). This is while very few studies have identified CRP test as a reliable diagnostic test for chorioamnionitis (Chavarria *et al*., 1989; Nowak *et al*., 1998).

In a systematic review by Van der Ham *et al*. (2008) articles that had enrolled 610 pregnant women diagnosed with chorioamnionitis were considered. In three of these articles it was concluded that CRP can be useful for the diagnosis of chorioamnionitis while 5 articles did not achieve this result (Van der Ham *et al*., 2008). Considering the controversial findings of the studies, it seems that CRP is not beneficial in as an indicator of clinical or histological chorioamnionitis. The differences in clinical definitions, research projects, gestational age at the time of marker measurement, research methodology and reference values, as well as differences in the relationship between the clinical, histological and microbiological findings in study populations must be considered. On the other hand, it is questioned if histological chorioamnionitis can be considered as a criterion of infection, because the researchers have identified this kind of chorioamnionitis in 20-30% of normal deliveries (18, 19). Histological chorioamnionitis was intended in the present study as well. Some researchers have recommended CRP to be measured along with other parameters, not as a pathogenomic test, to prove infection, as it is obvious that CRP is a non-specific acute phase reactant.

In our study WBC was also found to have a low diagnostic value. Although, the area under curve for ESR was found to be acceptable as a fair diagnostic value, the sensitivity and specificity were not large enough for recommending it in diagnosing chorioamnionitis during the PROM.

Through, multivariate analysis, Yoon *et al*. (1996) found that amniotic fluid WBC performs better than C-reactive protein and maternal blood WBC in the diagnosis of positive amniotic fluid culture, histologic and clinical chorioamnionitis and neonatal morbidity in women with preterm PROM. A study comparing CRP , WBC and ESR on serial measurements found that the efficacy of WBC (abnormal tests: > 12500>15000>12500 mm^{-3} and increasing in two consecutive days) and ESR (abnormal tests: >60 mm >60 mm h^{-1} and increasing in two consecutive days) serial evaluations was significantly lower than CRP and in cases of chorioamnionitis CRP increased above the upper limit of normal 3 days earlier than WBC or ESR (Nowak *et al*., 1998).

CONCLUSION

The findings of the present study were not supportive of using CRP and WBC as a reliable diagnostic test to identify chorioamnionitis in women with PROM. The results of CRP and WBC were not acceptable but ESR diagnostic value was minimally acceptable. Future research is recommended to focus on ESR investigation rather than CRP or WBC.

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