Original Article

The use of maternal C-reactive protein in the predicting of preterm labor and tocolytic therapy in preterm labor women

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Abstract

Background: Levels of a number of some biomarkers have been associated with spontaneous preterm birth. This study was aimed to evaluate the relation between C-reactive protein (CRP) with preterm labor and response to tocolytic therapy.

Materials and Methods: Seventy five pregnant women with symptoms of preterm labor (cases) in compare with 75 term women (controls) were enrolled. Baseline data and CRP was recorded. So, cases were under treatment tocolysis with the use of magnesium sulfate, and then they were followed till delivery time to assess the response to the treatment.

Results: Sixteen patients with symptoms of preterm labor did not response to the treatment and delivered prematurely and 59 women response to tocolytic treatment and delivered at term. The curve constructed cut-off value for >3.6 (AUC, 0.683; SE, 0.041; $P < 0.0001$) for CRP, indicating a significant relationship with preterm labor. Also, there was significant relationship between CRP level with response to the treatment in cut-off >1.8 (AUC, 0.738; SE, 0.076; $P = 0.001$) for CRP.

Conclusions: Maternal concentrations of CRP can be used as appropriate biomarker for predicting preterm labor and response to tocolytic therapy in pregnant women.

Key words: CRP: C-reactive protein, cytokines, magnesium sulfate, preterm birth, preterm labor, tocolytic

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INTRODUCTION

Frequency of preterm birth which is also known as child birth at less than 259 days of gestation or 37 completed weeks since the first day of the women's last menstrual period is from 5% to 13% in high income countries and the incidence is increasing[1,2] compared to term-birth infants in infants born prematurely, higher morbidity and mortality rates was reported.[3] Preterm birth is the one of Leading cause of child deaths and perinatal morbidity and mortality worldwide, in almost all high-income and middle-income countries. The rate of annual neonatal deaths is reported 3.1 million in the world, of which preterm birth complications are estimated to be answerable for 35% of them.[4] Also, after pneumonia, preterm birth is the second most common cause of death in children less than 5 years.[5] Across the world, preterm birth is an important perinatal health problem, and has high economic and social cost in terms of neonatal intensive care, for the families and health-care systems.[6-8]

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Spontaneous preterm birth is known as the cause of around half the preterm births, for which there are no known effective preventive measures.[1] Early detection of preterm labor is hard because primary symptoms are often mild and later symptoms often occur too late to intervene.[9] Obstetrical history or symptoms and epidemiological risk factors, usually used methods to predict preterm delivery, are neither sensitive nor specific.[10,11]

C-reactive protein (CRP) is a sensitive inflammatory marker whose serum level increases and then remains constant during the infectious and inflammatory processes; on the other hand, CRP measurement is quick, noninvasive, and risk-free that can be a useful diagnostic test for evaluating and categorizing the risk levels and also anticipating the morbidity of both mother and fetus.[12,13] Also, some studies show that in women with intrauterine infections CRP levels of amniotic fluid is higher comparing to the control group.[14,15] Based on findings in several studies, CPR concentration are risk factor for preterm birth <32 weeks.[7,9,16]

Even though tocolytics have not been shown to improve neonatal outcomes, they are an important intervention in obstetrics to delay preterm delivery.[17,18] The aim of tocolysis is to delay preterm delivery long enough for antenatal corticosteroids to be administered or for the mother to be transported to a tertiary care centre, thereby reducing neonatal morbidity and mortality.[19,20] The use of tocolytic agents in contemporary obstetric practice should be customized and based on the available evidence base for efficacy and fetomaternal safety, gestational age, the maternal condition, and potential side-effects of the drug.[21] Magnesium sulfate is one of tocolytic agents which the administration of this to women at risk of preterm birth helps to protect the baby's brain, reduce rates of cerebral palsy, and improve long-term neonatal health outcomes and despite maternal side effects, magnesium sulfate is commonly used for tocolysis.[22]

The incidence of preterm labor could be prevented by effective diagnosis and preventive factors, because of the importance of neonatal mortality and the fact that no effective treatment is currently available.[19,20] Therefore, this study was designed to hypothesized: Evaluation and compare of maternal serum concentrations of CRP, in the prediction of women at risk of preterm labor, and prediction of response to tocolytic treatment in these women.

MATERIALS AND METHODS

This study was conducted on 150 singleton pregnant women, who had been referred to 'ShahidBeheshti' hospital in Isfahan, Iran, from May, 2012 and Oct, 2012. Case group included 75 pregnant women with the diagnosis of new-onset preterm labor that was defined as four contractions in 20 min, as eight contractions in 60 min or cervix dilation of more than 1 cm, with effacement of 80%. The control group included 75 healthy pregnant women in the term labor, with uncomplicated gestation. All cases did not have any clinical signs of infection or of any other maternal or fetal complications. This study was approved by Institutional Review Board at the Isfahan University of Medical Sciences, and the written informed consent was obtained from all participants after the purpose of participating and study guidelines were explained.

Pregnant women age ranged between 18-35 years with singleton pregnancy and gestational age of 24-34 complete weeks were eligible if they had less than five parturition, no history of type 1 or 2 diabetes mellitus, hypertension, cardiovascular disease, and infectious diseases.

Criteria for study inclusion in the review were age range between 18-35 years old, singleton pregnancy, gestational age of 24-34 complete weeks (was proved by LMP and sonography in the first trimester of pregnancy), less than five parturition, no history of type 1 or 2 diabetes mellitus, hypertension, cardiovascular disease, and infectious diseases. Also, women with contraindication by using tocolytic drugs, fetus or amniotic fluid anomaly, uterine or cervical abnormality, emerging some undesirable conditions during parturition such as preeclampsia, and abruption were excluded from the study.

Baseline data were collected to assess comparability of the study groups, also, serum that was collected at 24 and 34 weeks was analyzed for determined the levels of CRP. C-reactive protein was measured quantitatively using the immunoassay method. Thereafter case group tocolysis in women was performed with the use of magnesium sulfate as follows: First with infusion of 4 gr magnesium sulfate 20% and then 2 gr per hour continued, after that, they were followed till delivery time to assess the response to the treatment.

All statistical analysis was done by SPSS-20 (SPSS IBM, New York, U.S.A). Data were reported using number (%) for categorical variables and means ± SD for continuous variables. Categorical variables were compare between groups using Chi-square test and continuous variables were compare using independent sample *t*-test. For CRP, a receiver operating characteristic (ROC) curve analysis was

used to establish the cut-off values that optimized the prediction of preterm labor or response to tocolytic therapy. Sensitivity, specificity, positive predictive value (PPV), negative predictive values (NPV), and Likelihood ratio (LR) were then calculated. Additionally, areas under curves (AUC) were evaluated for all study tests. *P* values less than 0.05 were considered to indicate statistical significance.

RESULTS

All women from the control group delivered at term and 59 women from the case group after successful tocolytic treatment delivered at term but 16 of them despite tocolytic therapy delivered prematurely.

The mean age for the samples was 27.8 ± 4.5 years. The comparison of sample characteristics and the concentration of CRP, between study group and control group are shown in Table 1. As shown, there were no significant differences between case and control groups for age, gestational age, history of miscarriage, and gravidity. To determine the critical values that could predict preterm labor, ROC curves were generated for CRP. The curve constructed for CRP was >3.6 (AUC, 0.683; SE, 0.041; *P* <0.0001), indicating a significant relationship with preterm labor [Figure 1]. Cut-off values, likelihood ratio and other predictive values for CRP to predict preterm labor are shown in Table 2.

Women in the case group were assessed in two groups in regards to results of tocolytic therapy; women with successful treatment (*n*=59) and women with unsuccessful tocolytic treatment (*n* = 16). Table 3 shows the differences between these women for age, gestational age, history of miscarriage, gravidity, and CRP levels, there were no significant differences for age, gestational age, history of miscarriage, and gravidity. However, in women with unsuccessful tocolytic treatment levels of CRP was significantly higher than women with successful treatment.

The results of ROC describing the values of the CRP in predicting response to tocolytic therapy in women with symptoms of preterm labor is shown in Figure 2. There was significant relationship between CRP level with response to the treatment in cut-off >1.8 for CRP (AUC, 0.738; SE, 0.076; *P* = 0.001). Also, the sensitivity, specificity, PPV, NPV, and LR for CRP levels to predict response to tocolytic therapy in preterm women are shown in Table 4.

DISCUSSION

Preterm birth is a major obstetric and neonatal challenge, and every preterm birth imposes a considerable burden on limited health care resources and is a main cause of mortality and morbidity for newborns. The most important causes of newborn death, in Iran, were prematurity (63.3%), constituting nearly two-thirds of neonatal mortalities. Changes in perinatal management have been associated with a significant increase and better outcome of these infants, over the last two decades. One of the most important challenges in modern maternity care is the prevention of preterm birth.[2,23]

Table 1: Comparison of characteristics, and the concentration of IL-6 and IL-8 between study groups

	Group (*n*=75)		*P* value
	Case	Control	
Age	28.1±4.6	27.1±4.9	0.12*
Gestational age	30.3±2.4	29.7±2.7	0.15*
History of miscarriage	26 (34.7)	17 (22.7)	0.17†
Gravidity			
1 Pregnancy	26 (34.7)	30 (40)	0.67†
2 Pregnancy	31 (41.3)	31 (41.3)	
3 or more pregnancies	18 (24)	14 (18.7)	
C-reactive protein	5.28±8.2	2.14±5.3	0.007*

Data are mean±SD and number (%). *P* values calculated by *Independent sample *t* test and †Chi square test

Table 3: Comparison of characteristics and the concentration of IL-6 and IL-8 between cases regard to response to tocolytic therapy

	Women with preterm labor under treatment		*P* value
	Successful (*n*=59)	Unsuccessful (*n*=16)	
Age	26.4±4.8	27.5±4.3	0.41*
Gestational age	30.1±2.2	30.7±3.5	0.4*
History of miscarriage	14 (23.7)	3 (18.7)	0.9†
Gravida			
1 Pregnancy	25 (42.4)	5 (31.3)	0.12†
2 Pregnancy	21 (35.6)	10 (62.5)	
3 or more pregnancies	13 (22)	1 (6.3)	
C-Reactive protein	3.81±6.4	10.74±12.4	0.045*

Data are mean±SD and number (%). *P* values calculated by *Independent sample *t* test and †Chi square test

Table 2: The prognostic value of evaluation of maternal serum IL-6 and IL-8 for prediction of preterm labor

	95% CI (%)					
	Sensitivity	Specificity	+PV	-PV	+LR	-LR
C-reactive protein (>3.6)	41.3 (30.1-53.3)	89.3 (80.1-95.3)	79.5 (63.5-90.7)	60.4 (50.6-69.5)	3.9 (2.9-5.1)	0.66 (0.3-1.3)

PV: Predictive value, LR: Likelihood ratios

Table 4: The prognostic value of evaluation of maternal serum IL-6 and IL-8 in preterm women for prediction of response to tocolytic therapy

	95% CI (%)					
	Sensitivity	Specificity	+PV	–PV	+LR	–LR
C-reactive protein (>1.8)	87.5 (61.6-98.1)	57.6 (44.1-70.4)	35.9 (21.2-52.8)	94.4 (81.3-99.2)	2.6 (1.6-2.8)	0.2 (0.06-0.8)

PV: Predictive value; LR: Likelihood ratios

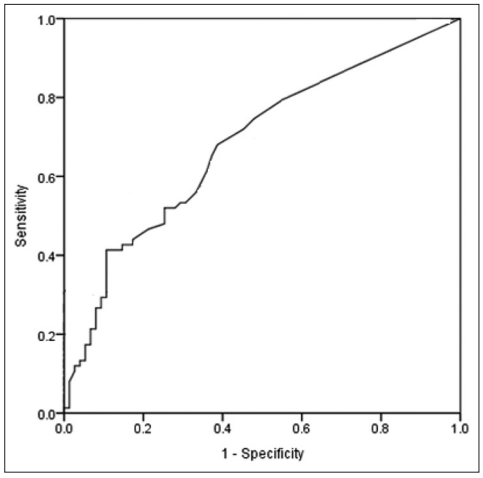

Figure 1: Receiver operating characteristic curves for maternal C-reactive protein (area under the curve, 0.683; SE, 0.041; P < 0.0001) levels for predicting preterm labor in pregnant women

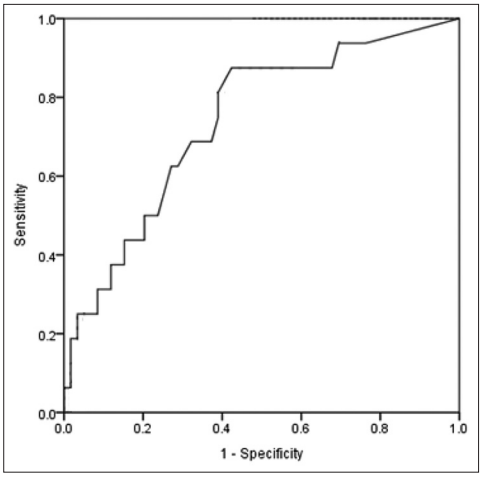

Figure 2: Receiver operating characteristic curves for maternal C-reactive protein (area under the curve, 0.738; SE, 0.076; P = 0.001) levels for predicting response to treatment in women with symptoms of preterm labor

A maternal serum concentration of CRP as prediction factors for preterm labor in pregnant women was the first hypothesis which were assess. Our results showed that a marked correlation of elevated CRP in women with preterm labor was observed when compared to healthy pregnant women, whereas the best cut-off values of CRP >3.6 with a sensitivity and specificity of 41.3, 89.3, respectively, were the best values in the prediction of preterm labor.

Sorokin and colleagues in a large, multicenter, prospective trial revealed that elevated maternal serum concentrations of CRP were associated with preterm birth < 32 weeks of gestation,[16] which was in agreement with our results. Both LR+ and LR- are of clinical interest in at risk populations. CRP, as a marker of preterm labor in symptomatic women[24] with LR + 6.3, and SENS 38% and in asymptomatic women[25] with LR+1.8, and SENS 26%, were noted. Also, CRP (week 34) with LR + 6.8 and LR- 0.7,[24] CRP (week 35) with LR+2.8 and LR- 0.6,[26] and CRP (week 37) with LR + 4.5 and LR- 0.3,[27] were reported in preterm labor prediction. Our results on evaluation of CRP in gestational age of 24 to 34 week showed that CRP with LR + 3.9, LR-0.66, SENS 41%, as a marker of preterm labor was in agreement with these studies.

The second hypothesis that was assessed in this study was CRP level in pregnant women with signs of preterm on predict response to tocolytic therapy. We observed that the elevated CRP level in preterm women with successful tocolytic therapy was markedly higher than preterm women with unsuccessful tocolytic therapy. We found that cut-off value of IL CRP >1.8 with a sensitivity of 87% respectively was the best values in the prognosis of successful tocolytic therapy in preterm women. Using ELISA techniques CRP can be measured in serum that gives the opportunity to detect these cytokines easily in routine practice. Evaluating their impact on preterm treatment results can be useful. Our results showed that to predict response to tocolytic therapy in preterm women before 34 weeks serum concentration of CRP is a good marker. Whereas CRP with LR+2.6, LR- 0.2, and SENS 87.5% can be used as biomarkers for the response to tocolytic therapy.

The main limitation of our study may be its small sample size in prediction of response to tocolytic therapy, whereas, 16 patients did not response to treatment in compare to 59 patients who response to treatment. We believed that these biomarkers must be assessed in further studies with large sample size.

CONCLUSION

In conclusion, findings of this study demonstrated that the assessment of maternal concentrations of CRP can be used as suitable biomarker for predicting preterm

labor, and also despite of the limitation in the number of patients, response to tocolytic therapy in our study was predictable by the evaluation concentrations of CRP of these women, however, this observation needs further studies to assess more than these biologic markers as predictor.

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