Original Article

Comparison of CRP and ALK-P serum levels in prediction of preterm delivery

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Abstract

Background: Preterm birth, defined as birth occurring before 37 weeks of gestation, is a common complication of pregnancy and may lead to death or long-term disability in newborns. Accurate diagnosis is, therefore, crucial for identifying those women undergoing preterm labor who are at greatest risk of preterm delivery. This may allow transport to a regional obstetrical center and permit time for corticosteroid therapy. Recent study recommends several markers such as CRP (C-reactive protein) and ALK-P (alkaline phosphatase) to predict preterm delivery.

Materials and Methods: We select a total of 300 pregnant women that had symptoms of premature birth. All of them were under treatment with tocolytic and serum sample were taken to assess the level of CRP-ALKp. Cervix length and the time of response to tocolytic were measured. 110 pregnant of them had preterm labor. 110 patient that had a term labor selected as a control group.

Results: Qualitative evaluation of efficacy CRP level on preterm delivery showed a significant relationship with 27 as a cut of point of CRP ($P < 0.00001$ –OR = 7.5). Investigate of effect of ALK-P level on preterm delivery refers to a significant relationship with 399 as a cut of point of ALKP ($P < 0.00001$ –OR = 5). Inquire of efficacy of CRP level and ALK-P level on preterm delivery demonstrate a significant relationship ($P < 0.0001$ 1OR = 9).

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

Key Words: ALK-P, cervix length, C-reactive protein, Iran, preterm labor

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INTRODUCTION

Preterm birth, defined as birth occurring before 37 weeks of gestation, is a common complication of pregnancy and may lead to death or long-term disability in newborns.[1,2] This happens when uterine contraction cause the dilation of cervix earlier than normal so the fetus can be at risk for health problems. Accurate diagnosis is, therefore, crucial for identifying those women undergoing preterm labor who are at greatest risk of preterm delivery, this may allow transport to a regional obstetrical center and permit time for corticosteroid therapy.[3]

Smoking, inadequate weight gain, occupational factors, genetic factors and infection can cause premature birth. Infections make 25-40% cause

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of preterm delivery.[4] In a pregnant woman with infection, increases cytokines levels in blood which leads to the production of prostaglandin and ultimately cause to induce uterine contractions and dilation of cervix and preterm delivery.[5,6] To find a prediction model for the progression of preterm labor to preterm delivery, many studies focused on the analysis of biochemical markers in blood such as CRP and ALKP.[7,8]

C-reactive protein (CRP) is an ring-shaped protein found in blood plasma, this is an acute-phase protein that synthesized in the liver and increases following interleukin-6 secretion from macrophages. Studies indicate that increase level of CRP is associated with an increased risk of preterm delivery from 1.45 to 2.55 times. CRP is a delicate inflammatory index, In time of need increases and remains at the same level during inflammatory. CRP measurement is naive, noninvasive and safely that can be a helpful test for assessment and classify the risk levels and also predictions the morbidity of both mother and fetus.[9,10]

ALK-P is a hydrolase enzyme accountable for removing phosphate groups from many types of molecules. ALK-P is particularly localized in liver, kidney and bone, the placenta and intestinal mucosa. Normal levels of ALP in adults are approximately 20 to 140 but it is significantly higher in children and pregnant women. different research have noticed that alkaline phosphatase can be used as a probable marker for the diagnosis of preterm delivery.[11,12]

Moawad *et al*. including those who have studied on the relationship between elevation of the risk of preterm birth and ALK-P level in the blood serum. In their studies they found that with elevation of ALK-P level in serum, risk of preterm birth increases.[1,13,14]

Meyer *et al*. found that increased ALK-P serum levels followed by a 6.8 times increased risk of preterm birth at the age of 32 weeks and 5.1 times at the age of 35 weeks.[15]

As regards anticipated and early diagnosis preterm labor is necessary and important to investigate, decided to using these markers and upgrade accurately predict preterm delivery.

MATERIALS AND METHODS

The present study was a hospital – based prospective cohort investigation of women with symptomatic preterm labor between 28 and 37 weeks of pregnancy, conducted on 300 singleton pregnant women, who had been referred to Shahid Beheshti and Alzahra Hospital in Isfahan, Iran, from December, 2013 and January, 2015.

With the diagnosis of newonset preterm labor that was defined as two contractions >40 s within 10 min, with cervix dilation of more than 2 cm, with effacement of 80%.

Inclusion criteria

- Pregnant women age ranged between 18-35 years
- Singleton pregnancy
- Gestational age of 28-37 weeks
- No history of type 1 or 2 diabetes mellitus, hypertension, PPROM, smoker, infection absence of pathologic conditions that could influence the concentration of CRP and ALKP.

Exclusion criteria

- Contraindication of using tocolytic drugs
- Fetus or amniotic fluid anomaly (R/O by sonograghy)
- History of uterine or cervical abnormality
- Emerging conditions during parturition such as preeclampsia, undesirable, abruption and placenta previa.

45 patients exclude from study because of PPROM, vaginal bleeding preeclampsy and incoordination. 5cc serum samples was collected from both groups to analysis for determined the levels of CRP and ALK-P.

C-reactive protein and Alkalan phosphatase was measured quantitatively using the immunoassay method. CRP kits was made by Bionik company (Germany). ALKP kits was made by pars azmoon company (Iran). Then cervical length was measured with transvaginal sonography in all of patient with a radiologist, tocolysis was performed with the use of magnesium sulfate as follows: First with infusion of 4 gr magnesium sulfate 20% within 20 minutes and then 2 gr per hour continued. We follow all patients, 30 of them exclude from study because of vaginal bleeding, premature rupture of memberan during tocolysis.

Case group included 110 pregnant women of them that lead to pretem delivery.

We select 110 of 115 patients who had preterm labor sign but don't lead to preterm delivery (delivere after 37 weeks) as a control group via a easy method. Matched case and control groups was done to prevent biases.

Statistical analysis have been done by SPSS-22. Categorical variables compare between series by Chi-square test and continuous variables compare by using independent sample *t*-test.

RESULTS

The present study included 220 women with symptomatic preterm labor that 110 of them had preterm delivery. The mean gestational age at sampling was 32 ± 2 weeks.

The mean age of patients was 24 in case and 25 years in control group (distribution in Table 1).

Concenteration of CRP level was between 5 to 72 mg/l (median 34) in case group. Concentration of CRP level was between 2 to 36 mg/l (median 8) in control group.

Quantitative evaluation of efficacy CRP level on preterm delivery showed a significant relationship ($P < 0.0001$). Based on this research the odds ratio of preterm delivery for women with high CRP levels was 7.5 rather than women with low CRP.

Efficacy study of CRP levels with cut off point 7.5 on the probability of preterm delivery, showed linear relation ($P < 0.0001$).

CRP level above 27 mg/l (cut off point) the risk of preterm delivery increase significantly (96% were delivered, $P < 0.001$). For CRP levels more than 27 mg/dl, we will be faced with premature delivery.

Concenteration of ALKP level was between 125 to 800 U/l (median 409) in case group.

Concenteration of ALKP level was between 100 to 500 U/l (median 250) in control group.

Investigate of effect of ALK-P level on preterm delivery refers to a significant relationship ($P < 0.0001$).

Odds ratio of preterm delivery for women with high ALK-P levels was 5 rather than women with low ALK-P. Study of ALK-P levels on the probability of preterm delivery showed linear relation. When ALK-P levels toward 399 U/L (cut of point) the risk of preterm delivery prominantly increases (94% were delivered, $P < 0.001$). For ALK-P levels more than 399 U/L, we will be faced with premature delivery surely.

Inquire of efficacy of CRP level and ALK-P level on preterm delivery demonstrate a significant relationship ($P < 0.0001$).

Odds ratio of preterm delivery for women with high ALK-P and CRP level was 9 rather than women with low ALK-P and CRP level.

Efficacy study of CRP and ALK-P levels on the probability of premature birth, showed linear relation [Table 2].

Cervical length and the CRP level on prediction of preterm delivery showed a significant relationship ($P < 0.001$).

Odds ratio of preterm delivery for women with high CRP levels and low cervical length (<22 mm) was 10 rather than women with low CRP levels and high cervical length.

Cervical length and the ALK-P level on prediction of preterm delivery showed a significant relationship ($P < 0.001$).

Odds ratio of preterm delivery for women with high ALK-P levels and low cervical length (<22 mm) was 9.5 rather than women with low ALK-P levels and high cervical length. With reduce the of the cervical length from 22 mm, the risk of preterm delivery Increases ($P < 0.001$).

Review of three factors, CRP and ALK-P level and cervical length on prediction of preterm birth demonstrated a significant relationship ($P < 0.001$).

Odds ratio of preterm birth for women with high CRP level, ALK-P levels and low cervical length was 11.5 rather than women with low CRP, ALK-P levels and high cervical length.

Linear regression models predict relationship a variable time delay preterm birth based on two independent variables of CRP levels and ALK-P in women with preterm labor is estimated as follows:

Hour = (62.96) + (−0.658) Preterm Labor CRP + (−0.008) Preterm Labor AlKP

Patient with CRP level above 18 mg/dl and ALK-P level above 329 U/L we hade poor response to tocolytic as a <48 hours ($P < 0.001$) [Figure 1].

Table 1: Distribution of age in case and control groups

Age	Case group (%)	Control group (%)
18-23	24	26
24-29	46	42
30-35	30	32

Table 2: Cut of point and Odds ratio of CRP and ALK-P

Marker	Cut of point	OR	*P*
CRP	7.5	7.5	<0.0001
ALK –P	265	5	<0.0001
CRP and ALK-P	7.5/265	9	<0.0001

CRP: C-reactive protein, ALK-P: Alkaline phosphatase, OR: Odds ratio

There is no punctual correlation between cervical length and responce to tocolytic ($P < 0.1$) [Figure 2].

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 the world, were prematurity (80%).[1,2]

Various morbidities, largely due to organ system immaturity, are significantly increased in infants born before 37 weeks' gestation compared with those delivered at term.[2]

The annual cost of preterm birth in the United States in 2014 was estimated to be $26.2 billion, or $51,000 per premature infant (Institute of Medicine, 2014).

The economic consequences of preterm birth that reach beyond the newborn period into infancy, adolescence, and adulthood are difficult to estimate. However, they must be enormous when the effects of adult diseases associated with prematurity, such as hypertension and diabetes, are considered.

Many studies have shown that increase levels of CRP and ALKP are assoociated with preterm delivery.

Our results showed that a marked correlation of elevated CRP and ALKP in women with preterm delivery was observed when compared to women without preterm delivery, whereas the best cut-off values of CRP >27 and ALKP >399 were the best values in the prediction of preterm labor.

Sorokin *et al*., in a large, multicenter, prospective trial revealed that elevated maternal serum concentrations of CRP were associated withpreterm birth <32 weeks of gestation, which was in agreement with our results.[16]

Shahshahan and Rasouli, showed that increase levels of CRP in early pregnancy were associated with increased risk of preterm delivery. They also found that CRP with cut off >3.6 increased the risk of preterm delivery.[17]

In our study, we found that CRP cut off >7.5 had increase the risk of preterm delivey.

This diffrence may be because of selected a larger statistical society in our study compared to the previous.

Luca *et al*., showed that increas CRP levels with OR = 8 had statistically significant relationships with preterm birth, which was in agreement with our results.[18]

Huras *et al*., were found that Significantly higher levels of CRP (above 20 mg/l) and ALP (above 300 u/l) in patients from the study group compared to the control group with preterm delivery.[19]

Our study also showed that higher levels of CRP (above 27 mg/l) and ALP (above 399 u/l) had high significant correlation with preterm birth.

Goldenberg *et al*., showed that cervical length <20 mm (odds ratio, 5.8), and high level alkaline phosphatase (odds ratio, 6.8) were as predictor markers for preterm delivery.[13,14]

In our study we showed that increased ALKP and short cervical length <22 mm (OR: 9.5) had significant correlation with preterm delivery.

Although several drugs and other interventions have been used to prevent or inhibit preterm labor, none has been shown to be completely effective.

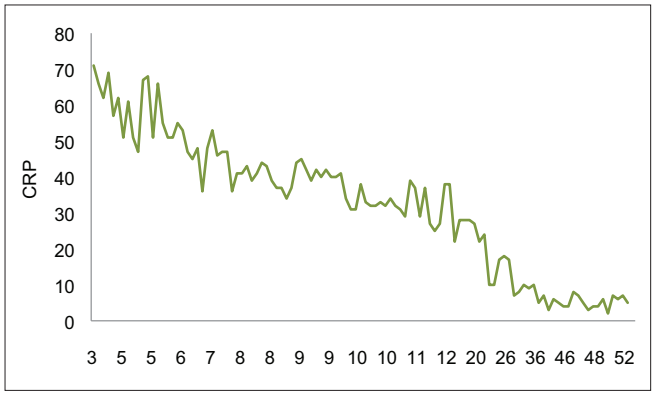

Figure 1: Relation between CRP and response to tocolysis

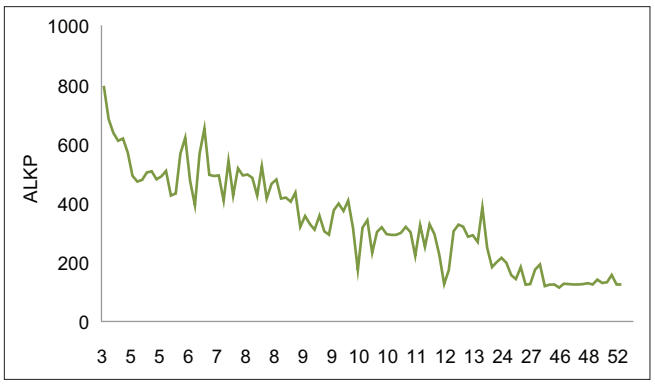

Figure 2: Relation between ALK-P and response to tocolysis

The American College of Obstetricians and Gynecologists (2012a) has concluded that tocolytic agents do not markedly prolong gestation but may delay delivery in some women for up to 48 hours.[20]

This may allow transport to a regional obstetrical center and permit time for corticosteroid therapy.

Smith *et al*., in their study showed that maternal serum concentrations of CRP can be used as appropriate biomarker for predicting the response to tocolytic therapy in pregnant women.[7]

Nowak *et al*. demostrated that the concentrations of serum CRP was significantly higher in the group of failed tocolysis (cut off point 19 mg/L. $P < 0.05$).[21]

In other study Skrablin *et al*., showed that maternal blood CRP could become useful in predicting tocolysis failure (cut off point 8.9 mg/L. $P < 0.001$).[22]

In our study we demonstrated that patient with CRP level above 18 mg/L hade poor response to tocolytic as a <48 hours ($P < 0.001$).

We have not found any previous study about relation between ALKP and response to tocolysis. Diffrence between cut off point in articles maybe due to diffrence in average of maternal age, BMI, socioeconomic stat and genetic.

CONCLUSION

Findings of this study demonstrated that the assessment of maternal concentrations of CRP, ALKP and cervical length can be used as suitable markers for predicting risk of preterm delivery, and also, response to tocolytic therapy in our study was predictable by the evaluation concentrations of CRP and ALKP, however, this observation needs further studies to assess more than these biologic markers as predictor.

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Conflicts of interest
There are no conflicts of interest.

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