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RESEARCH ARTICLE

PLASMA C - REACTIVE PROTEIN IN EARLY PREGNANCY AS A PREDICTIVE TOOL FOR PRETERM DELIVERY

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ABSTRACT

Background: To study the role of plasma C - reactive protein in early pregnancy as a predictive tool for preterm delivery.
Methods: A total of 125 patients between 12-22 weeks of gestation attending OPD were included in the prospective study and followed up to delivery. Finally 100 patients were available for the final study design. C - reactive protein was measured and maternal and fetal outcome of the deliveries was estimated.
Results: Out of 100 women available for the final analysis, 32 (32%) were CRP positive and 68 (68%) were CRP negative. A total of 15 (15%) women had preterm deliveries (<37 weeks) out of which 25 % were CRP positive. High CRP levels were associated with increased incidence of preterm labour with odds ratio of 2.908.Neonatal morbidity was higher in newborns of CRP positive mothers.
Conclusion: There is a positive association of elevated maternal CRP levels in early pregnancy and risk of preterm labour and hence it can predict high likelihood of preterm labour.

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INTRODUCTION

Preterm labour is defined as the onset of labour prior to the completion of 37 weeks of gestation is a pregnancy beyond 20 weeks of gestation. Preterm is considered to be established if regular uterine contractions can be documented at least 4 in 20 minutes, or 8 in 60 minutes with progressive change in cervical score in the form of effacement of 80% or more and cervical dilatation >1 cm. (American college of Obstetricians and Gynaecologists, 1995) Preterm labour and its subsequent complications make it the most common, costly and catastrophic complication of pregnancy. (Yeast and Lu, 2005) Preterm labour is one of the main causes of perinatal mortality and morbidity. Intrauterine infections contribute to 40-50% of all the preterm births. (Goepfert and Goldenberg, 1996) Systemic maternal infections lead to increased inflammatory cytokine levels, which in turn stimulate prostaglandin production. This process can lead to the induction of uterine contractions and cervical ripening culminating in preterm parturition. High concentration of proinflammatory cytokines suck as interlukin-6 and interlukin-8 in serum have been reported in women with symptoms of preterm labour and have been prospectively associated with preterm birth. (Goldenberg *et al.,* 2000) While preterm labour is associated with elevated levels of interlukin-6 in amniotic fluid and fetal plasma sampled by cordocentesis, the associated of maternal plasma interlukin-6 with preterm labour is less consistent. (Gomez *et al.,* 1997; Romero *et al.,* 1998)

CRP is a sensitive marker of systemic inflammation and is primarily synthesized in hepatocytes in response to infection and tissue injury. (Pepys and Balts, 1983) Production of C-reactive protein stimulated by the release of proinflammatory cytokines including interlukin-1, interlukin-6 and Tumour necrosis factor-alpha. C - reactive protein plays many roles in the inflammatory process. It binds to the surface of pathogens and opsonises them for uptake of phagocytes. C - reactive protein can also activate the classic complement cascade by binding to C1q. (Janeway *et al.,* 2001) Apart from infections, inflammation and trauma, factors associated with increased levels of C-Reactive protein include obesity, cigarette smoking, hormone use, metabolic syndrome and cardiovascular disease. (Pearson *et al.,* 2003) Maternal concentrations of CRP have been studied as an aid to diagnosing subclinical infection in pregnant women who experience preterm labour and premature rupture of membranes. (Dodds and Iams, 1987) Also, elevated levels of C- Reactive protein measured during pregnancy have

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been linked to adverse pregnancy outcomes such as preeclampsia and intrauterine growth restriction.

Objective of the study

1) To study the association of serum C - reactive protein levels with subsequent preterm labour.
2) To establish serum C - reactive protein levels as a predictive tool for preterm labour, as to reduce the morbidity and mortality resulting in preterm delivery.

MATERIALS AND METHODS

This study was carried out in Department of Obstetrics and Gynaecology, Government Medical College, SRINAGAR from January 2014 to January 2015.A total of 125 patients were taken with gestational age between 12-22 weeks of gestation were taken and followed till delivery. Maternal C - reactive protein levels were taken in early pregnancy and were correlated with the time of delivery (term/preterm).

Inclusion criteria

1) Patients attending prenatal visit at OPD with gestational age less than 22 completed weeks.
2) Patients with a singleton pregnancy.

Exclusion criteria

1) Multiple pregnancy
2) Patients with uterine anomalies such as cervical incompetence, malformations of uterus.
3) Patients with known medical and surgical illnesses.
4) Gestational age >22 weeks at initial prenatal visit.

AT initial prenatal visit serum sample for CRP estimation was collected after providing detailed explanation of study to patients and taking informed consent. Laboratory estimation was done to measure CRP levels at our hospital biochemistry lab. A value of 6mg/l was taken as cut off for CRP positive or negative. Women were followed up to delivery.

Table 1. Relation of maternal CRP and Gestational age at delivery

Gestational age at delivery	Total patients	CRP Positive group		CRP Negative group	
		No	%	No	%
preterm (<37 weeks)	15	8	25	7	10.2
term >37 weeks	85	24	75	61	89.8
total	100	32		68	
p=0.01,odds ratio;2.908					

Table 2. Relation between maternal CRP and risk factors of preterm labour

Risk factors	CRP Positive			CRP Negative		
	No	preterm	%	No	preterm	%
patients with risk factors	17	6	35.2	15	2	13.3
no known risk factors	15	1	6.66	53	5	9.4
total	32	7		68	7	

Table 3. Relation between neonatal complications and maternal CRP

Neonatal complications	Total	CRP Positive No	%	CRP Negative No	%
Preterm<34	7	4	12.5	3	4.41
LBW <2.5KG	51	19	59.3	32	47
Septicemia	10	5	15.6	5	7.35
Total(1,2,3)	68	28	87.4	40	58.7
Uncomplicated	30	3	9.37	27	39.7
Death in utero	2	1	3.12	1	1.47
Total	100	32		68	
p=0.001					

Gestational age was determined by a reliable Last Menstrual Cycle (LMP) or first trimester ultrasound. Gestational age at delivery was also noted. Data was analyzed by descriptive statistics, p value and odds ratio.

RESULTS

Out of 125 women who were taken up for the study, 25 women lost to follow up and a total of 100 women were available for the final analysis. 32 (32%) were CRP positive and 68 (68%) were CRP negative. A total of 15 (15%) women had preterm deliveries(<37 weeks) out of which 25 % were CRP positive, An association between high CRP levels and high risk factors was sought. No relation was found between high CRP levels in early pregnancy with parity and socioeconomic status. High CRP levels were observed in women with increasing BMI. High CRP levels were associated with increased incidence of preterm labour with odds ratio of 2.908. Out of 32 CRP positive patients 17 patients had risk factors of preterm labour like smoking, tobacco chewing, previous history of abortion/preterm delivery; previous genitourinary infections etc and 13 had no risk factors. Out of 17 CRP positive patients with risk factors, 6 (35.2%) patients had preterm labour and out of 15 patients with no risk factors 1 patient (6.66%) had preterm labour. (Table 2) Women who were CRP positive in early pregnancy had more risks of developing complications of pregnancy like preterm premature rupture of membranes, oligohydramnios and fetal growth restriction. Neonates born to CRP positive mother had more complications than CRP negative group that included preterm babies (12.5%), Low birth babies (59.3%), and Septicemia (15.6%). 9.37% babies had no complications in CRP positive group. (Table 3)

DISCUSSION

Preterm birth is a leading cause of perinatal morbidity and mortality worldwide associated with deaths of infants. Elevated CRP levels have been linked with adverse pregnancy outcomes like preeclampsia and intrauterine growth restriction. Many studies have proved association between maternal elevated CRP levels and increased risk of preterm delivery like studies conducted by Hvisom *et al.* (Hvilsom *et al.,* 2002) and Ghezzi *et al.* (Ghezzi *et al.,* 2002), Halder *et al.* (Halder *et al.,* 2013) Massachusetts study also showed association between elevated CRP levels and preterm birth. In our study we found positive association of elevated maternal CRP levels and preterm labour. We also found positive association between BMI of patients and CRP positivity in early pregnancy. Women with high CRP levels in early pregnancy had more risk of developing neonatal complications like IUGR. These findings suggest that inflammation, as represented by elevated CRP levels, could lead to the physiologic changes that result in preterm delivery. The widespread clinical use of amniotic fluid and umbilical cord blood is limited because of invasive nature of amniocentesis. Measurement of circulating inflammatory markers may thus provide an alternative method of detecting women with high risk of preterm delivery.

Conclusion

We conclude a positive association of elevated maternal CRP levels in early pregnancy and risk of preterm labour and hence it can predict high likelihood of preterm labour. The association was apparent primarily for spontaneous preterm delivery. These results are consistent with the hypothesis that chronic low-grade inflammation may raise CRP levels and cause preterm delivery. Also maternal elevated CRP levels can lead to neonatal complications like Low birth weight, intrauterine growth restriction and even death.

Limitations of study

In this study, we were unable to evaluate whether CRP levels were elevated before as well as after conception. We also do not know whether the association of CRP with preterm delivery reflects causality; that is, if reducing CRP levels would result in less preterm delivery.

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