Original Research Article

Indian Journal of Obstetrics and Gynecology
Volume 8 Number 4, October–December 2020
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.8420.5

Maternal Serum C – Reactive Protein: A Biomarker for Prediction of Preterm Delivery and Neonatal Outcome at Early Pregnancy

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How to cite this article:
Suhail Iqbal, Heena Kaurani, Asifa Ashraf. Maternal Serum C – Reactive Protein: A Biomarker for Prediction of Preterm Delivery and Neonatal Outcome at Early Pregnancy. Indian J Obstet Gynecol. 2020;8(4):227–231.

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Abstract

Background: Preterm labour defined as less than 37 weeks of gestation is responsible for most of the neonatal morbidity and mortality worldwide. This study was conducted to estimate the relation between C reactive protein (CRP) with preterm labour.

Method: This prospective observational cohort study was conducted from February 2018 to January 2019 at Obstetrics and Gynecology department of Srimati Heera Kunwar Ba hospital, Jhalawar Medical College, Jhalawar, Rajasthan with 150 outpatient singleton pregnant women of <20 weeks of gestation enrolled at the prenatal visit. Baseline data and serum CRP values were taken in all participants. Conventional statistical methods were used for analysis.

Result: We discovered measurably critical contrasts in the CRP levels estimated in early pregnancy between the women delivering preterm and those delivering at term. The baseline cut off value for maternal CRP was 5.5 mg/l with sensitivity of 100%, and specificity of 95.7%, positive and negative predictive value for serum CRP to predict preterm labour were 95.8 % and 99.2% respectfully.

Conclusion: Maternal serum concentration of CRP can be utilized as fitting biomarker for foreseeing preterm delivery.

Keywords: Preterm; Labour; CRP; Biomarker; Prospective observational cohort study.

Introduction

"Preterm birth is defined as childbirth before 37 completed weeks or less than 259 days of gestation since the first day of women's last menstrual period. It is a common complication of pregnancy and may lead to death or long-term disability in newborn".[1] Preterm pregnancy accounts for about 10% of total pregnancies. Almost 70% of neonatal deaths are due to preterm delivery.[2] After pneumonia, preterm delivery is the second most common cause of death in children in less than 5 years.

All the women coming with the symptoms of preterm labour do not go for preterm birth, more than 70% of these women continue for the full term. So it is necessary to find out who will progress to preterm birth. This can reduce the unnecessary treatment and hospital stay. Early detection of preterm labour is hard because primary symptoms are often mild and later symptoms often occur too late to intervene.[3]

Subclinical infection and chronic inflammation may be the main factors of preterm birth during pregnancy.[4,5] In addition, 25–40% of these deliveries are caused by infection. Identification of early markers of preterm birth may help to successfully intervene.[6]

CRP is a pentameric protein found in blood plasma. It is an acute phase reactant that is synthesized in the liver in response to factors released by macrophages (Interleukin–6). It is a sensitive inflammatory biomarker whose serum level increases and then remain constant during the infectious and inflammatory process. Various studies demonstrate that increased level of CRP

is associated with an increased risk of preterm delivery from 1.45 to 2.55 times.[1] CRP level of amniotic fluid was found higher in women with intrauterine infection compared to control groups in some studies.

CRP measurement is a quick, noninvasive and safe method for assessment of the risk level and prediction of the morbidity of both mother and fetus.

The main aim of this study was to evaluate and compare the maternal serum concentration of CRP in prediction of women at risk of preterm labour.

Materials and Methods

Study Design

The prospective cohort study was conducted on 150 pregnant women who delivered at Obstetrics and Gynecology Department of Shrimati Heera Kunwar Ba Hospital, Jhalawar Medical College, Jhalawar, Rajasthan from February 2018 to January 2019. Pregnant women with positive urine pregnancy test before 20 weeks of gestation attending their first antenatal visit were included in the study. Demographic, medical and obstetrics history was obtained by verbal interview. Maternal characteristic i.e. age, height, pre pregnancy body weight and exact date of last menstrual period was obtained. Maternal body mass index (BMI) was calculated by the pre pregnancy body weight (kg) divided by the square of height (m^2). Blood and urine samples were collected on first antenatal visit. The study group was followed up till delivery.

Before starting the study, written informed consent was taken from the participants.

Inclusion criteria

The inclusion criteria were women aged 20– 35 years old, BMI ranging 18.5– 25 kg/m^2, regular menstrual cycle, recalling exact date of last menstrual period, single fetus and gestational age less than 20 weeks (6.5–20 weeks) in the first visit.

Exclusion criteria

The exclusion criteria were history of preterm labour, multiple pregnancy, bed obstetrics history, failure to recall exact date of last menstrual period, BMI more than 25, history of smoking, alcohol consumption, drug addiction, uterine or cervical anomaly, liver disease, kidney disease, cardiovascular disease, hypertension, Diabetes (Type 1 or 2), autoimmune disease, HIV, urinary tract infection, inflammation disease, cancer,patient on hormone therapy, history of still birth, induced labour, macrosomia or anomalous baby, any other maternal or fetal complication.

In this study, gestational age was confirmed by LMP and sonography of first trimester by using crown lump length.

About 5 ml. venous blood after overnight fasting was drawn from the participants and CRP level were tested. Serum CRP concentrations were measured quantitatively by high sensitivity enzyme-linked immunosorbent assay (ELISA).

Ethical Approval

This study was approved by ethical committee of Jhalawar Medical College, Jhalawar and the written informed consent was obtained from all participants after the purpose of participating and study guidelines were explained.

Statistical Analysis

Data was entered in a Microsoft Excel spreadsheet. Continuous variables were summarized as mean and standard deviation. All statistical analysis was done using SPSS 18.0 for windows. The mean of serum CRP levels was compared between subgroups of variables including maternal age, BMI, gravidity, birth weight, time of delivery. The means of serum CRP levels between variables were compared using either independent students's- t test for two groups or one-way ANOVA for more than two groups. ROC curve analysis was used to determine the best cut-off point of serum CRP levels for preterm delivery. The odd ratios and accuracy were calculated to examine the risk of preterm delivery. P-value < 0.05 was considered statistically significant.

Result

As shown in Table 1, the ranges of participants' age, GA at study assignment, and GA at delivery were 20–35 years, 6.5–20 weeks, and 32.1–40.6 weeks, respectively. The mean of serum CRP levels of patients was 3.1+/–2.5 mg/dl. Of the 150 pregnant women, the rates of cases with term labour and preterm labor were 84% and 16%. The mean of CRP

levels in preterm deliveries was much higher than the term deliveries (p < 0.001) (Table 4). We did not find significant differences in the CRP levels between maternal age subgroups (p =0.64), maternal BMI subgroups (p = 0.18), and gravidity subgroups (p = 0.0585) (Table 2). Maternal serum CRP levels exhibited a sensitivity of 95.8%, the specificity of 99.2%, the area under the curve of 0.960at a cut−off value = 5.5mg/l as a preterm delivery predictive marker (p < 0.001) (Table 5). The CRP level ≥ 5.5 mg/l was significantly associated with a dramatically higher rate of preterm delivery (95% CI, p < 0.0001). There was a significant difference in the occurrence of neonatal asphyxia (p =0.00), neonatal sepsis (p = 0.00) and neonatal death (0.00) with respective mean of 6.7917+/–3.9905,7.3333+/–1.0066 and 12.5000+/–0.000 (Table 3).

Table 1: Maternal characteristic of study population.

Characteristics	Mean +/– SD	Range
Age (yrs)	24.76+/–4.09	20–35
BMI (kg/m^2)	21.61+/–1.821	18.5–25
Gravida (median)	1	1–6
Gestational age (weeks)	14.48+/–8.830	6.5–20
Level of CRP (mg/l)	3.119+/–2.5543	0.5–15.4
Gestational age at time of delivery (wk.)	38.016+/–8.830	32.1–40.6

Table 2: Relation of Serum CRP with maternal and neonatal characteristic.

Variables		N	Mean+/-SD	P value
Maternal age (Years)	20–25	102	3.0378+/–2.38	
	26–30	34	2.600+/–1.84	0.64
	31–35	14	3.35+/–3.5	
BMI (kg/m^2)	18–20.9	57	2.7786+/–1.9114	0.18
	21–25	93	3.3547+/–2.889	
Gravidity	1	97	2.7636+/–1.8863	
	2	20	3.8174+/–3.8057	0.0585
	3 or >3	33	3.8036+/–3.1505	
Preterm delivery	Yes	23	7.6348+/–2.9170	<0.001
	No	127	2.3016+/–1.3543	
Birth weight (kg)	<2	12	8.13+/–2.42	
	2–2.49	33	4.32+/–3.16	<0.0001
	2.5–3	93	2.18+/–1.15	
	>3	12	2.12+/–1.42	

Table 3: Association of CRP with Neonatal outcome.

Variables	N	CRP (Mean+/– SD)	P value
Neonatal asphyxia	12	6.7917+/–3.9905	
Neonatal sepsis	3	7.3333+/–1.0066	0.0000
Neonatal death	1	12.5000+/– 0.000	

Table 4: ROC curve for maternal serum CRP to predict preterm delivery.

Variable	Area under curve	Pvalue	CI 95%	
			Lower limit	Upper limit
Preterm delivery	0.960	0.001	0.885	1.000
Neonatal outcome	0.878	0.001`	0.772	0.983

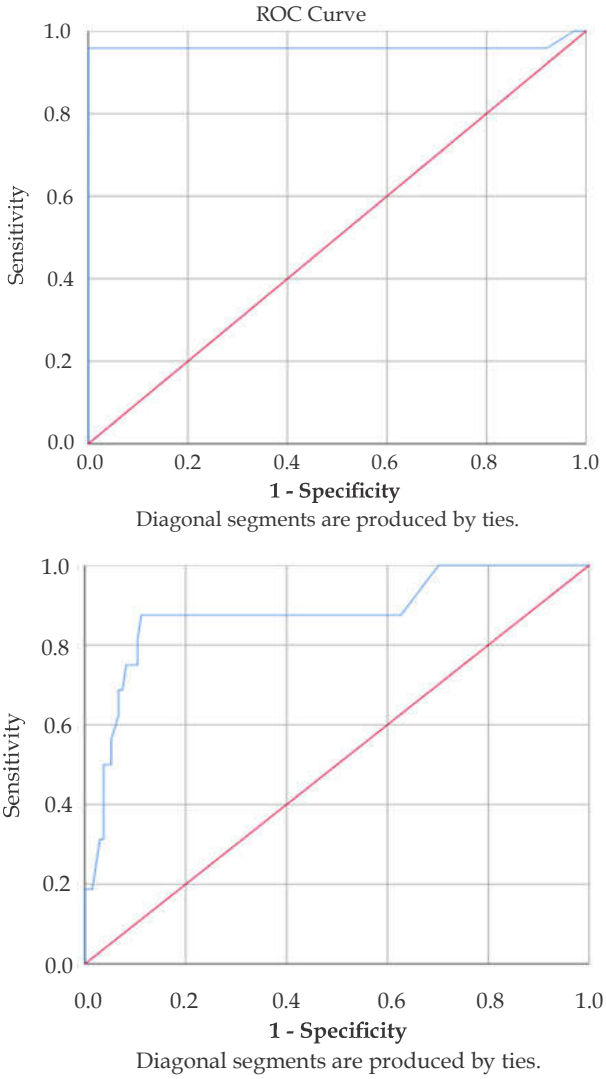

Table 5: Accuracy parameters.

Variable	Sensitivity	Specificity	PPV	NPV
Preterm delivery	95.8%	99.2%	95.8%	99.2%
Neonatal outcome	50.0%	96.8%	75%	91%

Discussion

CRP is an acute phase reactant protein in the innate immune response synthesized primarily in liver cells in response to proinflammatory cytokines. It is a non-specific biomarker of inflammation that is usually used as a marker for diagnosis of many

inflammatory, infective and malignant conditions. Elevated concentration of CRP in maternal peripheral circulation is related to the existence of intrauterine infection.

The preterm labour is a common obstetric complication that will most likely not lead to preterm delivery. Clinical and biological assessment are used to search for a maternal cause, assess the likelihood of an underlying infection and to estimate outcome of pregnancy and the newborn.[7] The CRP is one of the biomarkers requested during a preterm labour.

Many studies have shown that increasing levels of CRP are linked to preterm birth.[8] Our study also showed that maternal CRP levels at early gestation is useful predictor of preterm labour. This finding is similar to other studies that measured serum CRP levels before 20 weeks of gestation.[9,10,11] In a study done by Ferguson et al they observed for the first time an increase in CRP levels early in pregnancy up to approximately 20 weeks gestation, followed by a decline in later pregnancy in women who went on to deliver at term. Shahshahan et al.[3] also found increased level of CRP at 24–34 weeks of gestation in preterm delivered group as compared to term deliveries. In a study done by Shengzhu et al[6] they found that highly expressed CRP and PTB were remarkably association in the first trimester, but no relationship was found in the second trimester and the third trimester. Oliveria et al[12] also found association of CRP with preterm delivery. In our study, the case selection was carefully done. We wound up with only idiopathic, singleton and spontaneous deliveries; as all other preterm deliveries were excluded (i.e. twin pregnancies, medically induced deliveries and still births. It very well might be a shortcoming of this investigation that the CRP estimations were not taken at precisely the same time in all the pregnancies. Another issue is that CRP levels change quite fast, as the half-life is 8–9 h, and the increase in an infectious state also happens quite rapidly, i.e. we do not know whether the CRP level will keep on expanding, diminish or stay consistent during the rest of the pregnancy. Furthermore, the variation in the normal range in women, both pregnant and nonpregnant, is considerable, and we do not know anything about the CRP levels in these women before its measurement or before their pregnancy.

In our study the best cut off value of maternal CRP level up to mid pregnancy for predicting preterm deliverywas 5.5 mg/dl.The cut off value is different in various studies.The potential explanations rely onnumerous elements such as the inclusion and exclusion criteria of the study populations and mainly a time period of measurement. The increase in maternal serum CRP in preterm deliveries reflects an activated inflammatory pattern as a result of upregulated secretion of cytokines. Our finding that maternal serum CRP levels at a gestational age of 6.5–20 weeks are associated with preterm delivery suggests that inflammatory process exists from early pregnancy. Previous studies from literature have shown that 20–40% of preterm deliveries may be caused by infection. However, in this study we could not rule out the presence of subclinical chorioamnionitis.

Conclusion

All in all, findings of this study exhibited that the assessment of maternal concentrations of CRP can be used as reasonable biomarker for predicting preterm labour.Nonetheless, the number of cases to draw a firm conclusion from this study is insufficient. Besides, the range to measure CRP has been too wide which might reduce the significance of the study and produce biasness. Another limitation or constraint that needs to be mentioned is that CRP itself is a very nonspecific marker which in spite of using strict exclusion criteria can be positive or high for other reasons that can produce some biasness. Our research only found that elevated serum CRP increase the risk of preterm birthand is not a diagnosis in itself. There are many pathways leading to preterm birth and the prevention of each requires different types of scientific inquiry and clinical strategies, which together encompass a wide array of measurement systems and clinical interventions across many health-care disciplines. We need to direct further studiesto affirm whether applicable biomarker can be utilized as pointer of preterm labour.

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