International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Halder A et al. Int J Reprod Contracept Obstet Gynecol. 2013 Mar;2(1):47-51
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: 10.5455/2320-1770.ijrcog20130208

Research Article

Predictive significance of C reactive protein in spontaneous preterm delivery: a prospective cohort study

Ajay Halder*, Rachana Agarwal, Saroj Sharma, Sudesh Agarwal

Department of Obstetrics & Gynecology, Sardar Patel Medical College, Bikaner 334003, Rajasthan, India

Received: 15 December 2012
Accepted: 6 January 2013

***Correspondence:**
Dr. Ajay Halder
E-mail: drajayhalder@yahoo.com

ABSTRACT

Background: To evaluate the predictive significance of C- reactive protein in spontaneous preterm delivery.
Methods: A group of 280 pregnant women between 12-22 weeks of gestational age attending antenatal clinic were included in a prospective cohort and followed through the pregnancy, delivery and early puerperium till discharge. Finally details of 250 women were available for analysis. CRP estimation in early pregnancy is done. Patients followed up to delivery. Gestational age determined by LMP or ultrasound estimation. Status of the newborn at birth, and at discharge, and its gestational age is noted. Data were analyzed by descriptive statistics like chi-square test, *p*-value and odds ratio. Main outcome measures gestational age at delivery and neonatal condition at discharge.
Results: Out of 250 patients, 78 (31.2%) were CRP positive and 172 (68.8%) were CRP negative. CRP positivity showed positive association with preterm labour with odds ratio 2.384 (95% CI: 1.153-4.928 & *p* value 0.01). Neonatal morbidity & mortality was also higher in newborns of CRP positive mothers.
Conclusions: CRP positivity in early pregnancy is associated with nearly a two fold increased risk of preterm delivery. Neonatal complications like preterm, low birth weight, septicaemia, birth asphyxia and others are more common in CRP positive mothers.

Keywords: C-reactive protein, preterm delivery, neonatal outcome

INTRODUCTION

Preterm labour and its subsequent complications makes it the most common, costly and catastrophic complication of pregnancy.[1] Preterm labour is one of the main causes of perinatal mortality and morbidity.[2] Intrauterine infection contributes to 40-50% of all preterm births.[3,4] Systemic maternal infections and genital tract infections are known to predispose to preterm delivery. C Reactive Protein (CRP) is a protein synthesized in hepatocytes in response to infection and tissue injury. High levels of CRP in early pregnancy reflect infection or inflammation in body which may lead to preterm labour. In present study we investigated whether elevated CRP concentration in early pregnancy could predict preterm delivery.

C-reactive protein (CRP) was first described in 1930 by Tillet and Francis[5] who observed that sera from patients during acute febrile illness had the ability to precipitate the C-substance (later designated C-polysaccharide, CPS) of pneumococcal cell walls. The serum factor responsible for this reaction was defined as a "C-precipitin", and later designated "C-reactive". This protein was found to appear in the blood during a variety of reactions of tissue destruction or inflammation and has served as a useful clinical index of this process.[6]

CRP is synthesized by hepatocytes and is normally present as a trace constituent of the plasma. Normal serum levels of CRP are not precisely defined. However, most studies in adults reveal a large cluster of values under 1 µg/mL with a range of 0.068 to 8.2 µg/mL, with a median of 0.58 µg/mL and a mean of 1.3 µg/mL. The serum concentration may reach peak levels of as much as

300 μg/mL within 24-48 hours.[7] A CRP specific human complementary probe has been isolated. It is also known that CRP gene is located on chromosome one.[8]

The exact function of CRP in vivo is not known. It is probably an early broad spectrum recognition mechanism to pathogenic microorganisms. The main role of CRP is to recognize in the plasma the potentially toxic autogenous materials released from damaged tissues, to bind to them, and thereby to detoxify them and/or facilitate their clearance.[7]

CRP binds selectively to T-lymphocytes, inhibit their ability to form spontaneous rosettes with sheep erythrocytes and inhibit their response to allogenic cells in mixed lymphocyte culture reactions. By contrast, CRP does not bind to B lymphocytes, nor does it alter the B - cell functions. CRP also causes inhibition of mixed lymphocyte reactivity and generation of cytotoxic lymphocytes.[9]

CRP inhibits the aggregation of human platelets stimulated by either modified human immunoglobulin or thrombin. So this property of CRP may play an important role in the control of platelet responsiveness during reaction of inflammation, defence and repair.[10] CRP is a potent activator of the classical complement pathway starting with C1q.[11] CRP, like antibodies can thus bind to ligands, opsonise materials for phagocytosis, and initiate cell damage and inflammatory reactions.[7]

METHODS

Three hundred and six pregnant women between 12-22 weeks of gestational age with any parity attending antenatal clinic were assessed for eligibility. Out of these, 26 women with known medical disorders were excluded. Out of remaining 280 women, 28 patients who were lost to follow up & two patients who had second trimester pregnancy loss were excluded from study (Figure 1).

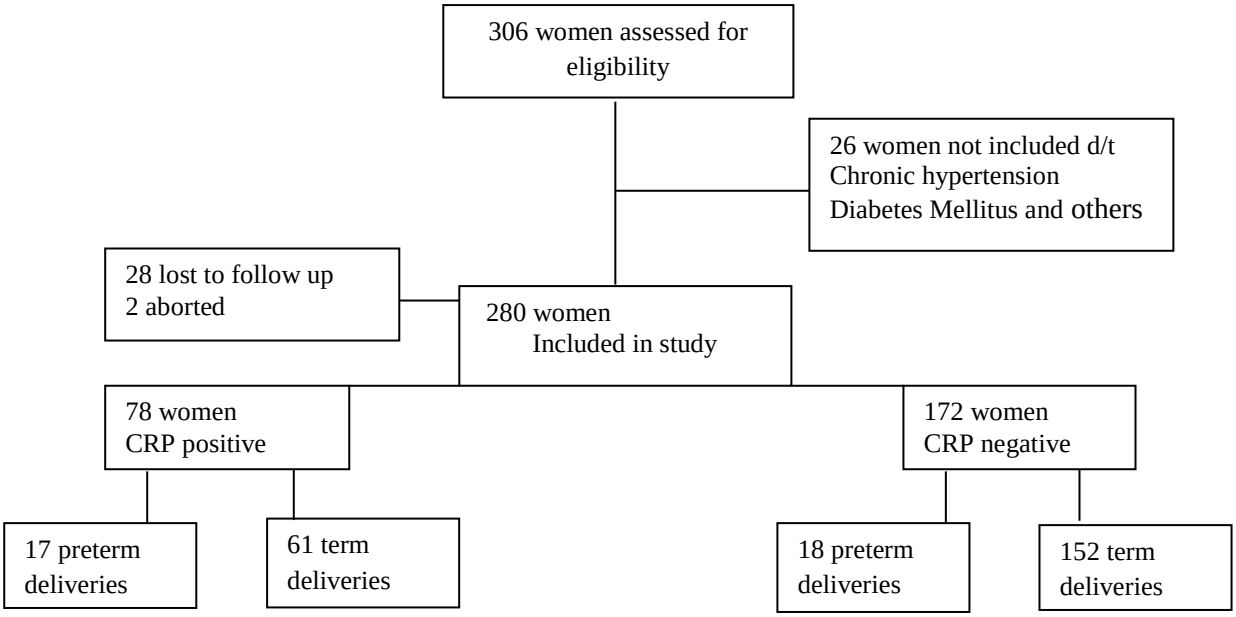

Figure 1: Distribution of cases according to CRP and preterm delivery.

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 by a validated high sensitivity immune turbid metric assay by using reagent latex particle coated with goat IgG. A value of 6mg/l was taken as cut off. Women with CRP value equal or more than this level were called CRP positive and valve less than that were called CRP negative. Women were followed up to delivery. Gestational age was determined by a reliable Last Menstrual Cycle (LMP) or first trimester ultrasound. Gestational age at delivery was noted. Neonatal outcome was noted. Data was analyzed by descriptive statistics like chi-square test, *p*-value and odds ratio.

RESULTS

Out of 250 women who were available for final analysis 78 (31.2%) were CRP positive and 172 (68.8%) were CRP negative. Total of 35(14%) women had preterm delivery (<37weeks of gestation age). No relation was found between high CRP level (>6mg/l) in early pregnancy with parity or socioeconomic status of patients. However high CRP levels were seen in older mothers and increasing BMI. High CRP level was shown

to be associated with increased incidence of preterm labour with odds ratio 2.384, 95% CI: 1.153-4.928 & *p*-value 0.01 (Table 1). Women in whom other known risk factors of preterm labour like smoking, tobacco chewing, previous history of abortion/preterm delivery, previous gentio urinary infection etc was present, these women were more likely to have high CRP levels(53.08% vs. 20.71%) in early pregnancy and these patients had increased risk of preterm labour and delivery (25.92% vs. 8.2%) (Table 2).

Women who were CRP positive in early pregnancy had more risk of developing adverse complications of pregnancy like fetal growth restriction, oligohydramnios, and preterm premature rupture of membranes. But these observations were not statistically significant.

Neonates born to CRP positive mother had complication rate (preterm, low birth weight, septicemia & other) more than CRP negative group (61.5% Vs 44.18 %). These data were statistically significant (X^2-6.46, *p*-0.013). In CRP positive group very preterm (<34 weeks) and extreme preterm newborn were more likely (11.53% Vs 5.80%) (Table 3).

Table 1: Relation between maternal CRP in early pregnancy and preterm labour.

Gestational Age at Delivery	Total Patients	CRP Positive Group		CRP Negative Group	
		No	%	No	%
Preterm < 37weeks)	35	17	21.79	18	10.46
Term > 37wek	215	61	78.20	154	89.55
Total	250	78		172	
X^2 5.72, *p*=0.01; Odds Ratio: 2.384 CI @ 95%: 1.143-4.928					

Table 2: Relation between patient showing risk factor of preterm labour with maternal CRP in early pregnancy and preterm labour.

Risk Factors	CRP Positive			CRP Negative		
	No	Preterm	%	No	Preterm	%
Patients with Risk Factors	43	16	37.20	38	5	13.15
No Known risk factor	35	1	2.85	134	13	9.70
Total	78	17		172	18	

Table 3: Relation between maternal CRP and neonatal complications.

Neonatal Complication	Total	CRP Positive group		CRP Negative group	
		No	%	No	%
Preterm < 34	19	11	14.10	8	4.65
LBW < 2.5kg	105	41	52.5	64	37.2
Septicemia & other	25	12	15.38	13	7.55
Total 1+2+3 complication	149	64	82.0	85	49.4
Uncomplicated	96	11	14.10	85	49.4
Death in Utero	5	3	3.84	2	1.16
Total	250	78		172	
X^2-26.14, *p*-0.001					

DISCUSSION

Maternal concentrations of CRP have been studied as an aid to diagnosing sub clinical infection in pregnant women who experience preterm labour and premature rupture of membranes.[19,20] It has been suggested that women in preterm labour with normal CRP levels do not require amniocentesis for the purpose of ruling out intra uterine infection.[21] Recently, elevated levels of CRP measured during gestation have been linked to adverse pregnancy outcomes such as preeclampsia and intrauterine growth restriction.[22,23] Hvilsom et al[24] reported a significant association of elevated serum CRP levels with a nearly twofold increased risk of delivery before 37 weeks' gestation. Ghezzi et al[25] found no relation between circulating CRP levels and preterm delivery. In this study, we found that a serum CRP level of more than 6mg/L has a significant association with preterm labour with an odd ratio 2.384, 95% CI: 1:153-4.928. This result supports the Massachusetts study done in 1999-2002. They found that women with CRP level >8 mg/l had greater than 2 fold higher odds for preterm delivery.

We also found positive association between BMI of patients and CRP positivity in early pregnancy (52.9% vs. 47.05%). Patients with other risk factors for preterm labour were more likely to be CRP positive in early pregnancy. These patients went into preterm labour more often (p=0.013) Women who were CRP positive in early pregnancy were more likely to develop adverse pregnancy outcome like IUGR (50% vs. 14.21%) in our study. Maternal CRP has been studied[26] extensively as an adjunct in the diagnosis of sub clinical infection among pregnant women with preterm labour or PROM. Studies have shown that median CRP value in normal pregnancy appear to be higher than standardized value for non pregnant individuals and CRP value is further elevated in labour. Although a chorioamniotic infection or inflammation may be associated with preterm labour and delivery, it remains unclear whether elevated CRP level is a response to infection or to labour.

CONCLUSIONS

We conclude that raised CRP level (>6mg/dl) in early pregnancy in the absence of any medical /surgical or obstetric complication can predict high likelihood of preterm labour. Oligohydramnios, IUGR, PROM also has a positive correlation with CRP. It can also be shown that neonatal outcome is less likely to be good in cases of raised CRP level as LBW, preterm delivery, septicaemia and birth asphyxia is more likely to occur. The limitation of the study lies in the fact that CRP is raised in response to both pathological as well as physiological conditions. Hence widespread applicability of CRP as a predictor of poor pregnancy and neonatal outcome needs further supportive evidence.

Funding: This work was supported by the institutional fluid research grants
Competing interests: There are no competing interests to declare
Ethical approval: The study was approved by the Institutional Review Board and Ethics Committee

REFERENCES

1. Yeast JD, Lu G. Biochemical markers for the prediction of preterm labor. Obstet Gynecol Clin North Am 2005;32:369-81.
2. Hilier SL, Nugent RP, Esenbach DA, et al. Association between bacterial vaginosis and preterm delivery of a low birth weight infant. N Eng J Med 1995:333:1737-42.
3. Goepfert AR, Goldenberg RL. Prediction of prematurity. Curr Opin Obstet Gynecol 1996;8:417-27.
4. Lockwood CJ, Kuczynski E. Markers of risk for preterm delivery. J Perinat Med 1999;27:5-20.
5. Tillet S, Francis T Jr. Serological reactions in pneumonia with a non protein somatic fraction of pneumococcus. J Exp Med 1930;52:561-71.
6. Mortensen RF, Osmand AP, Gewurz H. Effect of c reactive protein in the lymphoid system. I. binding to thymus dependent lymphocytes and alteration of their functions. J Exp Med 1975;141:824-39.
7. Pepys MB. C-reactive protein fifty years on. Lancet 1981;1:653-7.
8. Whitehead AS, Bruns GAP, Markham AF, et al. Isolation of human C-reactive protein complementary DNA and localization of the gene to chromosome-1. Science 1983;221:69-71.
9. Mortensen RF, Osmand AP, Lint TF, Gewurz H. Interaction of C-reactive protein with lymphocytes and monocytes: complement-dependent adherence and phagocytosis. J Immunol 1976;117:774-81.
10. Fied BA, Gewurz H. Effect of C reactive protein on Platelet Function. I. Inhibition of platelet aggregation and release reactions. J Immunol 1976;116:1289-94.
11. Kaplan MH, Volanakis JE. Interaction of C-reactive protein complexes with the complement system. I. Consumption of human complement associated with the reaction of C- reactive protein with pneumococcal C-polysaccharide and with the choline phosphatides, lecithin and sphingomyelin. J Immunol 1974;112:2135-47.
12. Arias F. Practical guide to High risk pregnancy and delivery. Fernando Arias (edit) 3rd edn. New Delhi: Harcourt India Pvt Ltd; 2001:216-39.
13. Papiernik E. Prediction of the preterm baby. Clin Obstet Gynecol 1984;11:315-36.
14. Gonik B, Creasy RK. Preterm labor: Its diagnosis and management. Am J Obstet Gynecol 1986;154:3-8.
15. Hein M, Helimig RB, Schonheyder HC, et al. An in vitro study of antibacterial properties of the cervical mucus plug in pregnancy. Am J Obstet Gynaecol 2001;185:586-92.

16. Challis JR, Sloboda DM, Alfaidy N, et al. Prostaglandins and mechanisms of preterm birth. Reproduction 2002;124:1-17.
17. Loudon JA, Groom KM, Bennett PR. Prostaglandin inhibitors in preterm labour. Best Pract Res Clin Obstet Gynecol 2003;17:731-44.
18. Goldenberg RL, Hauth JC, Andrews WW. Intrauterine infection and preterm delivery. N Engl J Med 2000;342:1500-7.
19. Doods WG, Iams JD. Maternal C-reactive protein and preterm labour. J Reprod Med 1987;32:527-30.
20. Mazor M, Kassis A, Horowitz S, et al. Relationship between C-reactive protein level and Intra amniotic infection in women with preterm labour. J Reprod Med 1993;38:799-803.
21. Bek KM, Nielsen FR, Qvist I, et al. C-reactive protein (CRP) and pregnancy. An early indicator of chorioamnionitis: A review. Eur J Obstet Gynecol Reprod Biol 1990;35:29-33.
22. Wolf M, Kettyle EM, Sandler L, et al. Obesity and preeclampsia: the potential role of inflammation. Obstet Gynecol 2001;98:757-62.
23. Gluck L, Wood HF, Fousek MD. Septicemia of the newborn. Pediatr Clin North Am 1966;13:1131-48.
24. Hvilsom GB, Thorsen P, Jeune B, et al. C-reactive protein: a serological marker for preterm delivery? Acta Obstet Gynecol Scand 2002;81:424-9.
25. Ghezzi F, Franchi M, Raio L, et al. Elevated amniotic fluid C-reactive protein at the time of genetic amniocentesis is a marker for preterm delivery. J Obstet Gynecol 2002;186:268-73.
26. Watts DH, Krohn MA, Wener MH, et al. C-reactive protein in normal pregnancy. Obstet Gynecol 1991;77:176-80.

DOI: 10.5455/2320-1770.ijrcog20130208
Cite this article as: Halder A, Agarwal R, Sharma S, Agarwal S. Predictive significance of C reactive protein in spontaneous preterm delivery: a prospective cohort study. Int J Reprod Contracept Obstet Gynecol 2013;2:47-51.