Research Article

The predictve value of Early Second Trimester C-Reactive Protein for detection of preterm labour and neonatal outcome

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Abstract
To evaluate the predictive significance of C- reactive protein in preterm delivery**. Methods:** A group of 600 pregnant women between 14-24 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 500 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 500 patients, 156 (31.2%) were CRP positive and 344 (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
PTD, defined by the World Health Organization (WHO) as birth occurring before 37 weeks of gestation, is considered a major global health problem and is strongly associated with neonatal mortality as well as short- and long-term morbidity[1]-[3]. Spontaneous PTD is a common, complex condition with a prevalence of approximately 7%[4]. Modern obstetrics are still not able to predict, prevent or treat PTD[5]

Pregnancy, childbirth and their consequences are still the leading cause of disease, disability and death amongst women of reproductive age in developing countries. Human pregnancies are associated with profound inflammatory changes during early phase(6), resulting in adverse pregnancy outcomes like premature rupture of membrane, hypertensive disorders of pregnancy gestational diabetes mellitus, preterm labour, intrauterine growth retardation, low birth weight baby etc. Attempts are being made continuously for having screening tests with high sensitivity and positive predictive value so that timely preventive prophylactic therapies can be tried to avoid such pregnancy complications.

Measurement of circulatory inflammatory markers may provide an alternative method of detecting women at high risk of delivery(7). C-reactive protein (CRP) is an acute phase reactant produced by the liver in response to the pro-inflammatory cytokines interleukin (IL-6) and tumor necrosis factor (TNF)(8). Since it has a relatively short half-life, the serum CRP level is dependent almost entirely on the rate of hepatic synthesis therefore; it is a sensitive index of systemic inflammation..(9) and reflects ongoing inflammation and/or tissue damage much more accurately compared to other laboratory parameters of the acute-phase response(10).

Recently, improved high sensitive and standardized quantitative assay in serum has allowed a re-evaluation of its potential as a diagnostic test. It can be use as an early marker of low grade inflammation and further help in detecting pathophysiological process early in pregnancy, so as to predict adverse pregnancy outcome and try preventive therapies well in time. Since there is paucity of data on maternal CRP level for predicting adverse pregnancy outcome

Methods

THIS was a prospective cohort study done in obstetrics and gynecology department Zagazig university hospitals from May 2014 to May 2015 six hundred and six pregnant women between 14-24 weeks of gestational age with any parity attending antenatal clinic were assessed for eligibility. Out of these, 100 women with known medical disorders were excluded. Out of remaining 500 women, 100 patients who were lost to follow up & six patients who had second trimester pregnancy loss were excluded from study.

General physical and obstetrical examination was done for every patient. Vaginal speculum examination, abdominal ultrasonography for measurement of AFI, transvaginal ultra-sonography for measurement of cervical length, high vaginal swab for evidence of bacterial vaginosis, CRP test, general urine examinations and culture and sensitivity were performed. The gestational age was calculated from the date of the LMP and confirmed by early second trimester ultrasonographic examination before 20 wks gestation. 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 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 500 women who were available for final analysis 156(31.2%) were CRP positive and 344(68.8%) were CRP negative. Total of 70(14%) women had preterm delivery (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 606 women assessed for eligibility 500 women Included in study 344 women CRP negative 34 preterm deliveries1 22 term deliveries 36 preterm deliveries 304 term deliveries 156 women CRP positive72 women not included d/t Chronic hypertension Diabetes Mellitus and others 28 lost to follow up 6aborted 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 pre-mature 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 (X2 - 6.46, p-0.013). In CRP positive group very preterm (< 37weeks)

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)	70	34	21.79	36	10.46
Term > 37wek	430	122	78.20	308	89.55
Total	500	156		344	
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	86	32	37.20	76	10	13.15
No Known risk factor	70	2	2.85	268	26	9.7
Total	156	34		344	36	

Table 3: Relation between maternal CRP and neonatal complications.

Neonatal Complication	Total	CRP Positive group		CRP Negative group	
		NO	%	NO	%
Preterm < 34	38	22	14.10	16	4.65
LBW < 2.5kg	210	82	52.5	168	37.2
Septicemia & other	50	24	15.38	26	7.55
Total 1+2+3 complication	298	128	82.0	170	49.4
Uncomplicated	192	22	14.10	170	49.4
Death in Utero	10	6	3.84	4	1.16
Total	500	156		344	
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.[11,12] 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.[13] Recently, elevated levels of CRP measured during gestation have been linked to adverse pregnancy outcomes such as preeclampsia and intrauterine growth restriction.[14,15] 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%).

Reron A et al.,[16] concluded that CRP is a useful marker of preterm delivery overtaking the result of vaginal culture. The results obtained in this study are comparable with these findings. Karimen L et al.,[17] in their study demonstrated that when Chlamydia trachomatis immunoglobulin G levels and CRP levels were present simultaneously the risk of preterm was four fold. In contrast Ghezzi F et al.,[18] observed that there was no statistically significant correlation between early second trimester elevated CRP and preterm delivery.

There was no increase in CRP level in the subjects with Premature Rupture of Membrane (PROM). This supports the finding of Vitool L et al.,[19] that showed elevated CRP concentration in early pregnancy was significantly associated with increased risk of preterm but not with PROM.

Regarding cervical canal length as a risk factor for preterm delivery specially when it is associated with high CRP, there are studies showing that the elevated concentrations of inflammatory markers were found to be strongly associated with the presence of short cervix less than 2.5 cm. It is possible that elevated cytokines levels initiate breakdown of connective tissue in the cervix or conversely, that a short cervix may provide easier access for ascending infection to the uterus, resulting in increase in cytokine levels as the study done in Denmark by Vogel, et al., (2006)[20] that cervical length, serum TNF- α and cervico-vaginal IL-6 are a clinically useful prediction of recurrent preterm birth in early second trimester. Another study in Philadelphia of Berghella, Iams, et al., (2004)[21] observed that in women with cervical length of < 2.5 cm at 22–24 weeks of gestation with frequent premature uterine contractions, there was a two fold increase in the risk of preterm births.

Maternal complications significantly increase the risk of maternal mortality and morbidity. Indeed numbers of tests have been proposed for predicting development of the maternal inflammation which adverse the pregnancy outcome but have limitation as screening tools in clinical setting. Any investigation aimed at prevention of the development of adverse pregnancy outcome would have to be instituted as early as possible as treatment options are limited. The implementation of preventive measures would be more effective than treatment initiated after establishment of the disorder. Numerous efforts at prevention, early diagnosis and treatment are being made. Among the predictive tests proposed by many workers, some are simple, while others are invasive. Some of them have been studied extensively, others are still under clinical investigations, and moreover, most of these tests have limitations because of their complexity, high incidence of false positive results. The ideal predictive test should be simple and easy to perform early in pregnancy and be reproducible non-invasive with high predictive value. Many workers have tried one or another screening test especially biochemical markers like CRP in second trimester to predict pregnancy outcome like preterm[22,23], premature rupture of membranes[24], Pregnancy induced hypertension[25]…etc. Since there is paucity of data on maternal CRP level for predicting adverse pregnancy outcome, it needs to evaluate the association, if any, between CRP in early second trimester and pregnancy outcome

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. 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 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. Future studies should evaluate whether changes in CRP levels over the course of pregnancy are predictive of gestational duration and confirm whether a dose-response relation between CRP and preterm delivery is restricted to women whose CRP levels are above a certain threshold

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