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Original Research Article

Correlation of levels of serum C reactive protein in second trimester with fetomaternal outcome

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ABSTRACT

Background: The aim of the study was to evaluate the association between levels of second trimester C Reactive protein (CRP) with adverse pregnancy outcomes.
Methods: Present study was a prospective analytical study carried out among 359 pregnant women between 14-18 weeks. All were primigravida, who attended antenatal OPD at RGGWCH between January 2019 to June 2020. All subjects fulfilled inclusion and exclusion criteria. Informed written consent was obtained in each case. A detailed history, clinical and ultrasound examination was done to confirm the gestational age. Then blood was collected and sent for serum CRP estimation. Patients were followed upto discharge of the mother and baby and fetomaternal outcome studied. Once the sample size was attained, the correlation between CRP levels and fetomaternal outcome was studied.
Results: Increased levels of serum CRP in early second trimester in primigravida were significantly associated with adverse pregnancy outcomes like preterm delivery (p value 0.001), PROM (premature rupture of membranes) (p value 0.01) and low APGAR (p value 0.01).
Conclusions: Early detection of higher levels of serum CRP in pregnancy can be used as predictor of inflammation and may help in early intervention, follow up and timely referral of the patients to minimize adverse maternal and fetal complications.

Keywords: C- reactive protein, Preterm labour, PROM, Low APGAR

INTRODUCTION

C-reactive protein is an annular (ring shaped) protein found in blood plasma. The name is credited to an acute phase reactant produced by hepatocytes that reacted with somatic 'C' carbohydrate antigen of pneumococcus in patients with inflammation that was first identified in the year 1930.[1,2] 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).[3] 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. Increased inflammatory changes during pregnancy may be explained by different stimuli occurring at different phases of pregnancy such as implantation and monocyte/macrophage production stimulated by interleukin-6 (IL-6), the necrotic process associated with placental ageing and the progressive increment in estrogen level.[4] The normal level of CRP in second trimester is 0.04-2 mg/dl

Pregnancy, childbirth and their consequences are still the leading cause of disease, disability and death amongst women of reproductive age in developing countries.[5] Human pregnancies associated with profound

inflammatory changes during early phase, resulted 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.

Elevated C reactive protein levels are associated with increased risk of common disease such as cardiovascular disease and type 2 diabetes. Serum CRP and TNF-α concentrations were significantly increased in the last trimester of gestation in preeclamptic women compared to normotensive pregnant women and the control group and may plays a role in pathogenesis of preeclampsia.

It was found that bacterial products such as endotoxin stimulate decidual monocytes to produce cytokines which in turn stimulates arachidonic acid and then prostaglandin E2 (PGE2) and F2alpha act in a paracrine fashion to stimulate myometrium to contract and cause preterm labour and then preterm delivery.[6] Maternal infections may contribute to 40–50 percent of all preterm births.[7] 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 concentrations of proinflammatory cytokines such as interleukin-6 and interleukin-8 in serum have been reported in women with symptoms of preterm labor and have been prospectively associated with preterm birth.[8] Measurement of circulating inflammatory markers may thus provide an alternative method of detecting women at high risk of preterm delivery.

In GDM patients, there was a significant correlation between CRP and BMI before pregnancy. The studies using animal models have also shown an association between maternal infection during pregnancy and abnormal behaviors in offspring and suggested that maternal immune activation might be one pathway by which maternal infection can lead to elevated risk of autism in the offspring.[9-11] Fever, an acute inflammatory response to various environmental factors including infections, has been suggested to increase the risk of autism and developmental delays.[12,13] Maternal obesity during pregnancy is associated with an increased risk of obesity and an adverse cardio-metabolic risk profile in childhood and adulthood.[14] The mechanisms underlying these associations remain unclear but might involve obesity-mediated inflammatory mechanisms, which may adversely influence fetal development.[15] In non-pregnant women, obesity is associated with low-grade systemic inflammation and oxidative stress.[16,17] Similar associations are present among pregnant women.[18] Pregnancy itself also involves a state of mild maternal systemic inflammation and placenta produce a range of immunomodulatory hormones and cytokines.[19] Maternal obesity-mediated inflammation and placental-mediated inflammation may interact with each other, creating an abnormal environment for fetal development.[11,20-22] In line with this hypothesis, animal studies have shown that maternal inflammation and oxidative stress during pregnancy, due to a high-fat maternal diet or maternal obesity, are associated with increased adiposity levels and adverse cardio-metabolic outcomes in offspring.[23,24]

METHODS

Present study was a prospective analytical study carried out among 359 pregnant women between 14-18 weeks. All were primigravida, who attended antenatal OPD at Rajiv Gandhi Government Women and Children Hospital, Puducherry between January 2019 to June 2020. All subjects fulfilled inclusion and exclusion criteria. Informed written consent was obtained in each case. A detailed history, clinical and ultrasound examination was done to confirm the gestational age. Then blood was collected and sent for serum CRP estimation. Patients were followed up to discharge of the mother and baby and fetomaternal outcome studied. Once the sample size was attained, the correlation between CRP levels and fetomaternal outcome studied.

Inclusion criteria

Singleton pregnancy, primigravida and BMI between 18-24 kg/ m2.

Exclusion criteria

BMI >24 kg/m2, history of hypertension, diabetes, heart diseases, acute and chronic infection history and any other acute/ chronic medical morbidities, addiction like tobacco chewing, smoking, ART conceived pregnancies and multigravida.

Outcome studied

In mother

Premature rupture of membranes, hypertensive disorders of pregnancy, gestational diabetes mellitus, preterm labour, oligohydramnios.

In fetus and neonate

Intrauterine growth retardation, preterm babies, low birth weight babies, low APGAR and NICU admission.

Statistical analysis

Data was collected and entered into MS excel, coding, recoding, refining and clearing of data was done. Data analysis was analysed by using Statistical package for social sciences (SPSS) software version 24.0. Results are explained in terms of descriptive and inferential statistics. Descriptive statistics was explained by frequencies, mean, standard deviation and range for numeric variables and by proportions and percentages for categorical variables. Chi square / Fisher Exact test has been used to find the

significance of study parameters on categorical scale between two or more groups. Fisher Exact test used when cell samples are very small. Results were presented using appropriate graphs and charts wherever applicable. P<0.05 is suggestive of significance.

RESULTS

Total number of study participants are 359. Correlation of levels of serum C reactive protein in second trimester with fetomaternal outcome was observed. Out of 359 study participants, 329 delivered in our hospital, 21 delivered in other hospitals and 9 lost to follow up, were excluded. (9= excluded).

Table 1: Distribution of study participants based on CRP levels (n=350).

CRP (mg/dl)	No of participants	Percentage
<0.6	296	84.57
>0.6	54	15.43
Total	350	100

In our study, out of 350 study participants, 54(15.43%) had CRP >0.6mg/dl and 296(84.57%) had CRP <0.6mg/dl.

Table 2: Distribution of study participants based on age (n =350).

Age(years)	Total	percentage
<20	33	9.43%
20-30	301	86%
> 30	16	4.57%
Total	350	100%

In our study, majority of participants in between age group of 20-30 years.

Table 3: Comparison of study participants based on CRP levels and incidence of GHTN and GDM (n= 350).

CRP mg/dl	GHTN		GDM	
	Yes	**No**	**Yes**	**No**
<0.6	18 (6.1%)	278 (93.9%)	25 (8.45%)	271 (91.55%)
>0.6	7 (12.96%)	47 (87.04%)	6 (11.11%)	48 (88.89%)
P value	0.07		0.52	

In our study, 25 (7.14%) participants had GHTN, among them 7 had CRP >0.6 mg/dl and 31 (8.86%) participants had GDM, among them 6 had CRP >0.6mg/dl. There is no statistically significant correlation in levels of CRP in incidence of GDM and GHTN.

Out of 350 study participants 12 had spontaneous abortions and 2 had partial mole at gestational age ≤20 weeks. So, these 14 participants were excluded in further evaluation of APH, oligohydramnios, IUGR, preterm delivery, PROM and in neonatal outcome.

Table 4: Comparison of study participants based on CRP levels and incidence of oligohydramnios and IUGR (n=336).

CRP (mg/dl)	Oligohydramnios		IUGR	
	Yes	**No**	**Yes**	**No**
<0.6	40 (14.13%)	243 (85.87%)	21 (7.42%)	262 (92.58%)
>0.6	9 (16.98%)	44 (83.02%)	3 (5.66%)	50 (94.34%)
P value	0.58		0.64	

Table 5: Comparison of study participants based on CRP levels and incidence of preterm delivery and PROM (n=336).

CRP mg/dl	Preterm delivery		PROM	
	Yes	**No**	**Yes**	**No**
<0.6	5 (1.77%)	278 (98.23%)	41 (14.49%)	242 (85.51%)
>0.6	6 (11.32%)	47 (88.68%)	15 (28.3%)	38 (71.7%)
P value	0.001		0.01	

Table 6: Comparison of study participants based on CRP levels and neonates birth weight (n=336).

Birth weight category	CRP		Total
	<0.6	**>0.6**	
<2.5 kgs	34	10	44
	12.02%	18.87%	13.09%
2.5-4 kgs	249	42	291
	87.63%	81.13%	86.61%
>4 kgs	1	0	1
	0.35%	0.0%	0.30%
Total	284	52	336
	100%	100%	100%
P value	0.41		

In our study, 44 neonates have low birth weight among them 10 participants had CRP >0.6 mg/dl.

In our study, 49 (14.58%) participants had oligohydramnios, among them 9 had CRP >0.6 mg/dl and 24 (7.14%) participants had IUGR, among them 3 had CRP >0.6 mg/dl. There is no statistically significant correlation with CRP levels and incidence of oligohydramnios and IUGR.

Table 7: Comparison of study participants based on CRP levels and new born APGAR (n=336).

APGAR	CRP(mg/dl)		Total
	<0.6	>0.6	
<7	7	5	12
	2.47%	9.43%	3.57%
≥7	276	48	324
	97.53%	90.57%	96.43%
Total	283	53	336
	100%	100%	100%
P value	0.01		

In our study, 12 had APGAR <7, among them 5 had CRP >0.6 mg/dl. There is statistically significant correlation in levels of CRP and new born APGAR and 5 (1.49%) participants had still birth, among them 2 had CRP >0.6 mg/dl

Table 8: Comparison of study participants based on CRP levels and NICU admissions (n=336).

NICU admission	CRP(mg/dl)		Total
	<0.6	>0.6	
No	236	36	272
	84.29%	70.59%	82.18%
Yes	44	15	59
	15.71%	29.41%	17.82%
Total	280	51	331
	100%	100%	100%
P value	0.12		

In our study, 11 (3.27%) participants had preterm delivery, among them 6 had CRP >0.6 mg/dl and 56 (16.67%) participants had PROM, among them 15 patients had CRP >0.6 mg/dl. There is statistically significant correlation in levels of CRP and incidence of preterm delivery and PROM.

In our study, out of 336 newborns 5 had still birth were excluded from NICU admissions. 59 (17.82%) neonates had NICU admissions, among them 15 participants had CRP levels >0.6 mg/dl. There is no statistically significant correlation between CRP levels and NICU admissions. Majority of neonatal admissions were due to respiratory distress 43 (72.8%) among them 12 (20.33%) had CRP >0.6 mg/dl.

The results of the study are as follows

Out of 359 study participants, 329 delivered in our hospital, 21 delivered in other hospitals and 9 lost to follow up, were excluded. In our study, out of 350 study participants, 54 (15.43%) had CRP >0.6 mg/dl and 296 (84.57%) had CRP <0.6 mg/dl. In our study, majority of the participants, 276 (78.86%) were delivered between 37-40 weeks of gestation. 14 (4%) participants had ≤20 weeks and 50 (14.29%) and 10 (2.85%) participants were delivered between 21 weeks-36 weeks+6 d and >40 weeks respectively.

In our study, 25 (7.14%) participants had GHTN, among them 7 had CRP >0.6mg/dl and 31 (8.86%) participants had GDM, among them 6 had CRP >0.6mg/dl and 4(1.19%) participants had APH (3 abruptio placenta, 1 placenta previa) and among them 1 had CRP >0.6 mg/dl. There is no statistically significant correlation in levels of CRP in incidence of GDM, GHTN and APH.

In our study, 49 (14.58%) participants had oligohydramnios, among them 9 had CRP >0.6 mg/dl and 24 (7.14%) participants had IUGR, among them 3 had CRP >0.6 mg/dl. There is no statistically significant correlation with CRP levels and incidence of oligohydramnios and IUGR.

In our study, 11 (3.27%) participants had preterm delivery, among them 6 had CRP >0.6 mg/dl and 56 (16.67%) participants had PROM, among them 15 patients had CRP >0.6 mg/dl. There is statistically significant correlation in levels of CRP and incidence of preterm delivery and PROM.

In our study, 12 had APGAR <7, among them 5 had CRP >0.6 mg/dl. There is statistically significant correlation in levels of CRP and new born APGAR and 5 (1.49%) participants had still birth, among them 2 had CRP >0.6 mg/dl.

In our study, out of 336 newborns 5 had still birth were excluded from NICU admissions. 59 (17.82%) neonates had NICU admissions, among them 15 participants had CRP levels >0.6 mg/dl. There is no statistically significant correlation between CRP levels and NICU admissions. Majority of neonatal admissions were due to respiratory distress 43 (72.8%) among them 12 (20.33%) had CRP >0.6 mg/dl.

DISCUSSION

The present was undertaken in district hospital (Rajiv Gandhi Government Women and Children Hospital) in Pondicherry from January 2019 to June 2020. Study population includes 359 women.

The primary aim was correlation of levels of C-reactive protein in second trimester with fetomaternal outcome. Pregnancy associated complications are known to be often responsible for maternal and fetal morbidity and mortality. Early detection followed by preventive therapy may decrease the complications and related fetomaternal risks. It could be possible only if the pregnant women prone to develop disorders are identified quite early.

Age

In present study, majority of study participants were between age group of 20-30 years (86%)and P value is 0.57 which is statistically insignificant. In Bayar et al study on CRP as indication of preterm labour, study participants between 18-30 are 53%.[24] In Teran et al study on CRP in normal and preeclamptic women, mean age group is 21±3 years.[25] In Nikbakht et al study on early maternal CRP to predict FGR and preterm delivery age group between 19-35 year with mean age of 26.5±4.4 years.[26]

Gestational age

In present study, majority of study participants were delivered between 37-40 weeks (77.4%). In study of Dhamayanthi et al study on measurement of serum CRP in second trimester as a predictor of preterm delivery, most of the participants were delivered at >37 weeks (79%).[27] In study of Ernst et al CRP level in early pregnancy with fetal growth patterns and neonatal risk, most participants were delivered at mean gestational age of 36.6-42.3 wks.[28] In Nikbakht et al study on early maternal CRP to predict FGR and preterm delivery, gestational age at delivery was between 31.2-41 weeks with mean gestational age of 37.2±1.7 week.[26]

Gestational hypertension

In present study, 25 (7.14%) participants had GHTN, among them 7 had CRP >0.6 mg/dl with 28% and p value 0.07, statistically insignificant. In study of Kumari et al Out of 300, 93 (31%) participants had GHTN, among them 77 patients had CRP >0.5 mg/dl and p value 0.001.[29] In study of Dhok et al out of 139 participants 3 (2.15%) had GHTN among them all 3 had CRP >0.3 mg/dl and p<0.01.[30] In study of Teran et al25 out of 207 participant 24(13%) had GHTN among them CRP get increasing after 20 weeks and CRP measurement <20 weeks not a predictor of preeclampsia. P value is 0.06. In study of Rout et al out of 350 subjects, 160 had GHTN and cases had mean CRP 10.01+6.98mg/L and p<0.001.[31]

Gestational diabetes mellitus

In present study, 31 (8.86%) participants had GDM, among them 6 had CRP >0.6 mg/dl and p value 0.52 statistically insignificant. In study of Mahdieh et al out of 89 participants, 30 (33.7%) had GDM with mean CRP (7.5 mg/L) and P value 0.1.[32] In study of Qiu et al out of 851 participants 38 (4.46%) had GDM and elevated CRP was positively associated with GDM risk and p value 0.007.[33] In study of Leipold et al showed that GDM was not related to increased CRP at 24-28 weeks but related to CRP at 37-38 weeks.[34]

Premature rupture of membranes

In present study, 56 (16.67%) participants had PROM, among them 15 had CRP >0.6 mg/dl and p value 0.01 and statistically significant. In study of Kumari et al out of 300; 57 participants had PROM (19%) among them 49 had CRP >0.5 mg/dl and p value 0.003.[29] In study Dhok et al, out of 139 participants 4 had PROM but all 4 had CRP<0.3 mg/dl and p>0.05.[30]

Preterm delivery

In present study, 11 (3.27%) participants had preterm delivery, among them 6 had CRP >0.6 mg/dl and p value 0.001, statistically significant. In study of Kumari et al, out of 300, 82(27.3%) participants had Preterm delivery, among them 72 patients had CRP >0.5 mg/dl and p value 0.001.[29] In study of Dhok et al, out of 139 participants 12 (8.6%) had preterm delivery, among them 9 had CRP>0.3 mg/dl and p<0.01.[30] In study of Dhamayanthi et al most of the participants were delivered >37 weeks (79%) but most of the participants with preterm delivery (<37 weeks) (21%) had CRP <1.5 mg/dl with p<0.001.[27] In study of Hvilsom et al found that high CRP level at the beginning of pregnancy associated with nearly two fold increased risk of preterm delivery.[35] In Roshan Nikbakht et al study on early maternal CRP to predict FGR and preterm delivery, out of 120 participants, 12 (10%) had preterm delivery with p<0.001.[36]

IUGR

In present study, 24 (7.14%) participants had IUGR among them 3 had CRP >0.6 mg/dl and p value 0.64 and statistically not significant. In study of Kumari et al, out of 300, 90 (23%) participants had IUGR, among them 70 had CRP >0.5 mg/dl and p value 0.003.[29] In study of Dhok et al, out of 139 participants 8 (5.7%) had IUGR, among them 2 had CRP >0.3 mg/dl and p>0.05.[30] In study of Ernst et al28 showed that women with CRP >2.5 mg/L associated with fetal growth restriction, increased risk of preterm birth and SGA at birth. Tjoa et al reported that higher levels CRP during first trimester in pregnancy who later developed preeclampsia or delivered a growth restricted baby.[36]

NICU admission and APGAR

In present study, out of 336, 5 had still birth among them 2 had CRP >0.6 mg/dl and 59 (17.8%) had NICU admissions, among them 15 had CRP >0.6 mg/dl and p value 0.12 statistically not significant. In present study, 1 preterm delivery had APGAR 6/10, admitted in NICU due to extreme preterm/ very low birth weight / respiratory distress and died on 5th postnatal day. In study of Kumari

et al,29out of 300, 156 (52%) neonates had NICU admission, among them 74 patients had CRP >0.5 mg/dl and p value 0.001 and 5 still birth among them 2 had CRP >0.5 mg/dl and p value 0.6. In study of Dhok et al out of 139, 22 (15.8%) new borns had NICU admission in this 9 has CRP >0.3 mg/dl and p<0.05 and 1 still birth has CRP >0.3 mg/dl and p<0.05.[30]

Low birth weight

In present study, out of 336, 291 (86.6%) neonates had birth weight between 2.5-4 kg, 44 (13.09%) had low birth weight (<2.5 kg), among them 10 had CRP >0.6 mg/dl and 1 (0.3%) had weight >4 kg. In study of Kumari et al out of 300, 137 (45.66%) neonates had LBW among them 81 had CRP >0.5 mg/dl and p value 0.001.[29] In study of Dhok et al,30 Out of 139, 29 (20.86%) neonates had LBW among them 8 had CRP >0.3 mg/dl and p>0.05. In study of Roshan et al study on early maternal CRP to predict FGR and preterm delivery.[26] Out of 120, 6 had small for gestational age and p value 0.15 but birth weight <2 kg had 13 neonates with p<0.001. In study of Gaillard et al, high maternal CRP level was associated with higher mid childhood fat mass index (FMI) and trunk FMI with p value 0.06.[37]

Limitations

Long term outcome of neonate could not be studied as neonate were followed until discharge only. Inability to conclude whether elevation of CRP levels occurred after conception or whether the elevated levels existed at their baseline as the subjects entered the study only in 14-18weeks of gestation. Impossible to determine whether systemic inflammation was induced by specific pregnancy related factors or by factors that predated pregnancy.

CONCLUSION

Increased levels of serum CRP in early second trimester in primigravida were significantly associated with adverse pregnancy outcomes like preterm delivery, PROM and low APGAR. Early detection of higher level of serum CRP in pregnancy can be used as predictor of inflammation related adverse pregnancy outcomes and help in early intervention, timely referral and tertiary care of the patients to minimize maternal and fetal complications.

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