Predictive value of C-reactive protein levels during pregnancy in adverse pregnancy outcomes: One year study at Swaroop Rani Nehru Hospital & Kamla Nehru Hospital (Motilal Nehru Medical College Allahabad)

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Abstract

Objective: To evaluate the association, if any, between serum CRP levels in first and early second trimester of pregnancy and adverse pregnancy outcomes.

Materials and Methods: The present study was carried out in 300 antenatal cases attending the department of Obstetrics and Gynaecology at Swaroop Rani Nehru Hospital & Kamla Nehru Hospital (Motilal Nehru Medical College Allahabad), over a period of one year.

Inclusion Criteria: Pregnant women < 20 weeks.

Exclusion Criteria: Multiple gestation, previous H/O PTL or mid trimester abortions, endocrine disorder, medical illnesses, HIV infection and substance abuse. Serum C-Reactive protein levels were tested and the participants were divided into 2 groups. Group1 included all pregnant ladies with CRP level > 5mg/L (Study Group) and Group2 with CRP level < 5mg/L (Control Group). These patients were followed till delivery and pregnancy outcomes like preterm labour, PPROM, fetal growth restriction, preeclampsia, mode of delivery, low birth weight, still births and neonatal intensive care unit admissions were noted. The statistical significance of differences of variables were made out by calculating the p-value.

Result: Raised level of serum CRP had positive correlation with adverse pregnancy outcomes and effect of elevated CRP level was maximum on PPROM (p value-0.002), preeclampsia (p value-0.004) and low birth weight (p value-0.002). Elevated CRP had no significant impact on still birth (0.06).

Conclusion: Early detection of higher level of serum CRP in pregnancy can be used as predictor of inflammation and may help in early intervention and follow up of the patients to minimize adverse maternal and fetal complications.

Keywords: C-reactive protein, Preterm labour, Fetal growth restriction, Preeclampsia, Low birth weight, Still births.

Introduction

C-reactive protein (CRP) is an annular (ring-shaped), pentameric protein found in blood plasma. The name is credited to an acute phase reactant produced by the hepatocytes that reacted with the somatic ‘C’ carbohydrate antigen of Pneumococcus¹ in patients with inflammation that was first identified in the year 1930.² Its level rises in response to a wide range of acute and chronic inflammatory conditions such as bacterial, viral, or fungal infections; rheumatic and other inflammatory diseases; malignancy; and tissue injury and necrosis due to secretion of inflammatory cytokines such as interleukin-1 and interleukin-6 by macrophages, T cells and fat cells (adipocytes). Its physiological role is to bind tlyosophatidylcholone expressed on the surface of dead or dying cells and some types of bacteria in order to activate the complement system via the C1q complex,³ promoting phagocytosis by macrophages, which clears necrotic and apoptotic cells and bacteria. Thus it plays a role in innate immunity as an early defense system against infections.

CRP rises within two hours of the onset of inflammation, up to a 350-400 mg/L and peaks at 48 hours.⁴ Its half-life of 18 hours is constant, and therefore its level is determined by the rate of production and hence the severity of the precipitating cause. CRP is thus a screen for inflammation. Higher levels of CRP are found in mild inflammation and viral infections (10–40 mg/L), active inflammation, severe bacterial infections and burns (>200 mg/L).⁵

CRP as a measure of diagnosing asymptomatic subclinical infection during pregnancy will definitely help us to predict various infection related morbidities and complication during pregnancy.

Materials and Methods

Place of Study: Department of Obstetrics and Gynaecology at Swaroop Rani Nehru hospital, Allahabad and Kamla Nehru Memorial hospital, Allahabad.

Duration of Study: One year; 2016-2017.

Type of Study: Interventional

Sample Size: 300

Sample Collection Method: Incidental sampling.

Inclusion Criteria: All antenatal cases attending OPD were included in the study except the cases as specified in exclusion criteria.

Exclusion Criteria:
1. ANC with >20 weeks of gestation.
2. Patients with multiple gestation.
3. Patient with increased BMI (>25kg/sq.m).
4. Patient with medical disorders like cardiovascular
   diseases, chronic hypertension, chronic kidney
diseases, chronic lung diseases etc.
5. Endocrine disorders such as Diabetes Mellitus and
   Thyroid Disorders.
6. Immunocompromised and HBsAg Reactive
   patients.
7. Patient diagnosed as preeclampsia.
8. Patient with previous history of preterm delivery
   and cervical incompetence.
9. Patient with addiction to alcohol and smoking.

**Intervention:** All participants underwent blood sample
examination for C-reactive protein level which was
done by Latex turbidimetry method. After these
participants were assigned into 2 study groups and
group 2 served as control group.

**Group I:** Pregnant ladies with CRP level > 5mg/L
(Study Group).

**Group 2:** Pregnant ladies with CRP level < 5mg/L
(Control Group).

**Statistical Analysis**

The statistical significances were measured by
calculating P value (P Value<0.05). These patients were
followed with defined schedule of visits that is monthly
up to 28 weeks, fortnightly up to 36 weeks and weekly
thereafter along with general examinations and
systemic examinations, routine investigations and
ultrasonography till delivery. Gestational age at time of
delivery and pregnancy outcomes such as intrauterine
growth restriction, premature rupture of membrane,
preterm labor, mode of delivery, low birth weight, still
births, neonatal deaths, neonatal intensive care unit
admissions were noted. Parameters of the two groups
were compared and data analyzed by P-value.

**Result**

Out of 300 patients 98 patients had serum CRP
level > 5 mg/L and 202 patients had serum CRP level <
5 mg/L (Table 1) which means 32.6% of sample size
was attributed to Group I (study group) and rest of them
that is 67.4 were assigned to Group II (control group).
Among 98 patients of Group I maximum number of
patients(59.1%) had S.CRP level between 10-14.9
mg/L and 20.4% had their S.CRP levels between 5 - 9.9
mg/L and ≥15 mg/L. Average mean level of S.CRP
came to be 12.5 + 3.22 mg/L. The mean age of patients
of Group I was 22.2 ± 3.8 years and in Group II it was
22.9 ± 4.7yrs with P-value = 0.60. In both, Group I and
Group II, maximum number of patients (89.7%) and
(60.3%) respectively were primigravida (Table 2).

When variables of Group I were compared, increased
CRP level was significantly common in primigravida (p
value- 0.02). Same was the situation with Group II but
when variables of both the groups were compared to
each other there was no significant difference. Highest
mean CRP (14.2 ± 3.3mg/L) level belonged to
primigravida in group I which was statistically
significant with p value of 0.02 when compared to other
gravidas whereas in group 2, highest level of mean CRP
(2.3 ± 1.1 mg/L) was found in G3 and lowest level(1.41
+ 0.5mg/L) in gravid 2 with no significant statistical
difference among variables of group 2. Highest level of
mean CRP in study group was 14.8 ± 2.3 mg/L, found
to be present in lower socioeconomic class which was
statistically significant with p value of 0.01. Similarly,
in control group significantly high level of mean value
of CRP was 2.3 ± 1.1 mg/L, found in lower
socioeconomic class with p value of 0.04. Amongst
Group I maternal complications (Table 3), incidence of
Preeclampsia was 78.5% that of preterm delivery was
73.4% while that of Premature Rupture of Membrane
was 50% and incidence of IUUGR was 71.4%. In Group
II incidence of respective complications were 7.9%,
3.9%, 4.9% and 9.9%. When compared among both the
groups, the incidences of all adverse maternal outcomes
were significantly high in group I (higher mean CRP
level) and statistically significant p value of 0.01,
suggesting positive correlation of adverse maternal
outcome with raised CRP levels.

In Group I out of 98 patients 28.4% delivered
vaginally and 71.4% delivered by Caesarean Section.
When variables of Group I compared statistically, rate
of delivery by caesarean section was significantly high
with the p value of 0.01. In Group II 67.3% patients
delivered vaginally and 32.3% by Caesarean Section
with statistically significant high number of vaginal
mode of delivery with p value of 0.03. On comparing
variables of both the groups, the difference of mode of
delivery was significant with the p-value of
0.01(<0.05). Babies born to mothers with raised CRP
had following birth weight distribution (Table 4),
20.4% babies had weight <1.5kg followed by 62.2%
babies with weight lying between 1.6-2.4 kg and 17.3%
babies were of ≥2.5kg with the mean weight of
2+0.3kg. In group II 3.9% babies had weight <1.5kg
followed by 23.7% babies with weight lying between
1.6-2.4 kg and 72.2% babies were of ≥2.5kg with the
mean weight of 2.6+0.3kg respectively. On calculating
statistical difference among the mean weights of both
the groups, difference was significant with the P-value
of 0.04(<0.05).

**Table 1**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Control group (CRP &lt;5mg/L)</th>
<th>Study group (&gt;5mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients (%)</td>
<td>67.4</td>
<td>32.6</td>
</tr>
<tr>
<td>Mean CRP + SD (mg/L)</td>
<td>1.5 + 0.78</td>
<td>12.5 + 3.4</td>
</tr>
</tbody>
</table>
Table 2: Difference between mean CRP in relation to gravidity

<table>
<thead>
<tr>
<th>Gravida</th>
<th>Control Group (n=202)</th>
<th>Study Group (n=98)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRP level &lt; 5 mg/L</td>
<td>CRP level &gt; 5 mg/L</td>
</tr>
<tr>
<td></td>
<td>Number of patients</td>
<td>% of patients</td>
</tr>
<tr>
<td>G1</td>
<td>122</td>
<td>60.3</td>
</tr>
<tr>
<td>G2</td>
<td>50</td>
<td>24.7</td>
</tr>
<tr>
<td>G3</td>
<td>20</td>
<td>9.9</td>
</tr>
<tr>
<td>&gt;G4</td>
<td>10</td>
<td>4.9</td>
</tr>
<tr>
<td>p-value</td>
<td>0.04(&lt;0.05)</td>
<td>0.02(&lt;0.05)</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Maternal complications</th>
<th>Group I (Study Group)</th>
<th>Group II (Control Group)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=98)</td>
<td>CRP level &gt; 5 mg/L</td>
<td>(n=202)</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>PE</td>
<td>77</td>
<td>78.5</td>
<td>16</td>
</tr>
<tr>
<td>PROM</td>
<td>49</td>
<td>50.0</td>
<td>8</td>
</tr>
<tr>
<td>PTL</td>
<td>72</td>
<td>73.4</td>
<td>10</td>
</tr>
<tr>
<td>IUGR</td>
<td>70</td>
<td>71.4</td>
<td>20</td>
</tr>
</tbody>
</table>

| Mode of Delivery | Vaginal | 28 | 28.5 | 136 | 67.3 | 0.01(<0.05) |
|                 | Caesarean Section | 70 | 71.4 | 66  | 32.3 | 0.01(<0.05) |
| p-value | 0.01 | 0.03 |

| Fetal outcomes | LBW | 81 | 82.6 | 56  | 27.7 | 0.001(<0.05) |
|               | Still birth | 2 | 2 | 3 | 1.4 | 0.6 (>0.05) |
|               | NICU Admission | 74 | 36.6 | 82 | 83.6 | 0.01(<0.05) |
| p-value | 0.01 | 0.03 |

Table 4

<table>
<thead>
<tr>
<th>Birth Weight(Kg)</th>
<th>Control Group (n=202)</th>
<th>Control Group (n=202)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CRP level &lt; 5 mg/L</td>
<td>CRP level &lt; 5 mg/L</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>&lt;1.5</td>
<td>20</td>
<td>3.9</td>
</tr>
<tr>
<td>1.6-2.4</td>
<td>61</td>
<td>23.7</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>17</td>
<td>72.2</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2.6±0.3</td>
<td>2±0.3</td>
</tr>
<tr>
<td>P-value</td>
<td>0.04(&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>APGAR Score at 1 mint</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>0-3</td>
<td>9</td>
<td>4.4</td>
</tr>
<tr>
<td>4-6</td>
<td>28</td>
<td>13.9</td>
</tr>
<tr>
<td>7-10</td>
<td>163</td>
<td>81.2</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>7±1.2</td>
<td>5.86±1.7</td>
</tr>
<tr>
<td>P value</td>
<td>0.04 (&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>APGAR Score at 5 mints</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>0-3</td>
<td>4</td>
<td>1.9</td>
</tr>
<tr>
<td>4-6</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>7-10</td>
<td>181</td>
<td>92</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>8.1±1.23</td>
<td>7.34±1.36</td>
</tr>
<tr>
<td>P value</td>
<td>0.06(&gt;0.05)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

In cases of normal pregnancy, physiological inflammatory changes occurring as a result of foreign conceptus and its implantation are tolerated well by the women as a result of increase in T- helper cells that counteract the adverse effects of inflammatory cytokines released from the conceptus and pregnancy gets established uneventfully. Pathologically infection
anywhere in the body may cause release of endotoxins and activation of cell mediate immunity and release of several cytokines and interleukins-6 which may also act locally on the decidua’s and fetal membranes leading to arachidonic acid stimulation and synthesis of prostaglandin E2 (PGE2) and F2α acting in a paracrine fashion. This results in various adverse pregnancy outcomes like pregnancy induced hypertension, intra uterine growth retardation, preterm labour, premature rupture of membrane, low birth weight, Still birth etc. In similar fashion as infection; metabolic disease, cardiovascular disease and cancers also induce array of increased pro-inflammatory cytokines and production of acute phase reactants adversely affecting pregnancy. Maximum risk of adverse pregnancy outcome is documented when there is local urogenital infection either symptomatic or asymptomatic. They release bacterial products and endotoxins leading to cell mediated immunity activation within the decidua tissue and fetal membranes. A cascade of events occur locally producing local prostaglandin (PGE2 and F2α) that stimulate myometrium contractions and cause preterm labour and then preterm delivery.6

Measuring serum CRP as a marker of non-evident or subclinical infection and inflammation anywhere in the body and/or exaggerated inflammatory response to pregnancy in absence of infection to predict adverse pregnancy outcomes seems promising.

The utility of the measuring CRP in the blood and prediction of pregnancy complications may enable us to identify those pregnant women who are prone to have complications, and hence they can be managed in a keener and more appropriate way with multidisciplinary approach for happy pregnancy outcome with safe mother and baby. The cost effectively of this simpler test further enhances its utility as a predictor of many adverse pregnancy outcomes.

Conclusion

Early detection of higher level of serum CRP in pregnancy can be used as predictor of inflammation related adverse pregnancy outcomes and may help in early intervention, timely referral and tertiary care of the patients to minimize devastating maternal and fetal complications.

Reference


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