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RESEARCH ARTICLE

C-REACTIVE PROTEIN IN PREDICTION OF SUB- CLINICAL INFECTION AS A CAUSE OF PRETERM PRE LABOUR RUPTURE OF MEMBRANES AND PRETERM LABOUR

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ABSTRACT

The aim of the study was to prediction of sub-clinical infection as a cause of preterm- prelabour rupture of membranes (PPROM) and preterm labour. Maternal and cord blood for C-reactive protein (CRP) estimation as screening test and urine, high vaginal swab and placental swabs for culture and sensitivity as a confirmative test for sub-clinical infection. Thirty pregnant of (24-37) weeks gestation with PPROM as study group and 30 pregnant of same gestation age with intact fetal membranes but in labour. All submitted to CRP test, high vaginal swab, placental swab for C/S and cord blood for CRP. CRP positive in study group 18 cases (60%) and control group 8 cases (36.6%) for urine C/S in study group was 11 cases (36.6%) and in control group 2 cases (6.6%) for high the vaginal swab positive in study group 8 cases (27.3%) and in control group 3 cases (10%), CRP test, urine for C/S and high the vag. swab for C/S all were statistically significant. Cord blood CRP and placental swab for C/S were statistically not significant CRP test sensitivity was 78% and specificity was 62.5% So CRP test can used as screening test for infection.

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INTRODUCTION

Preterm prelabour rupture of membranes (PPROM) mean rupture of fetal membranes after 24 weeks gestation and before 37 completed weeks or 259 completed days of gestation. Preterm birth: mean birth occurs before 37 completed weeks or 259 completed days of gestation. It is a leading cause of infant death and several contributing mechanisms to this morbidity have been identified over the past 10 years (Cunningham Macdonald Gant, 2000). It is obvious that several pathways are involved in the pathogenesis of preterm birth, which may explain why it has proved so difficult to predict and prevent, the too early activation of the fetal hypothalamic- pituitary-adrenal axis may result from maternal psychosocial or fetal physiological stress. Such physiological fetal stress may in turn be a consequence of microbial invasion of fetal membranes, amniotic fluid and the fetus itself. The critical mediator of stress-induced preterm birth appear to be corticotrophin-releasing hormone. It stimulates the production of prostaglandins by cells in the amnion, placenta, chorion and utrine deciduas (Staffan Bergstrom, 2003). Local infection of membranes "choriomnionitis" is a cause of preterm labour in 10-20% of cases with intact membranes, this figure is higher if labour fallows preterm prelabour rupture of Membranes.

Pathophysiology: Preterm parturition due to infection is initiated by security products resulting from monocyte activation cytokines including interleukin I, Tumour necrosis factors (TNF) and interleukin-6 are such secretory products implicated in preterm labour. TNF and matrix. metalloproteinase also promote programmed death of amniotic cells, the combined effect of these mechanisms may provoke preterm birth (Lok Wood and Kuczynski, 1999). The rout of access for bacteria with intact membranes is unclear but Escherichia coli can permeate living chorio-amniotic membranes thus intact fetal membranes at the cervix are not necessarily a barrier to ascending bacterial invasion of the amniotic fluid and figure (Cunningham Macdonald Gant, 2000) shows pathway for bacterial initiation of pretenn labour which may not required colonization of the amniotic fluid e.g. the cytokine net work of cell mediated immunity can be activated locally in decidual tissue that line the fore bag fetal membranes (Cunningham Macdonald Gant, 2000). A number of studies have shown a correlation between preterm labour and asymptomatic bacteria and lower genital tract infection-reactive Oxygen species which are generated by the body's response to diverse insults such as infection have also attracted attention, such insult activate collagenolytic enzymes and impair fetal membrane integrity and this impairment is then inhibited by antioxidants like vit. E and vit. C. (Woods *et al.,* 2001).

Other Causes of PPROM

1. Placental abruption.
2. Dynamic uterine dysfunction, uterine a tony or uterine inertia.

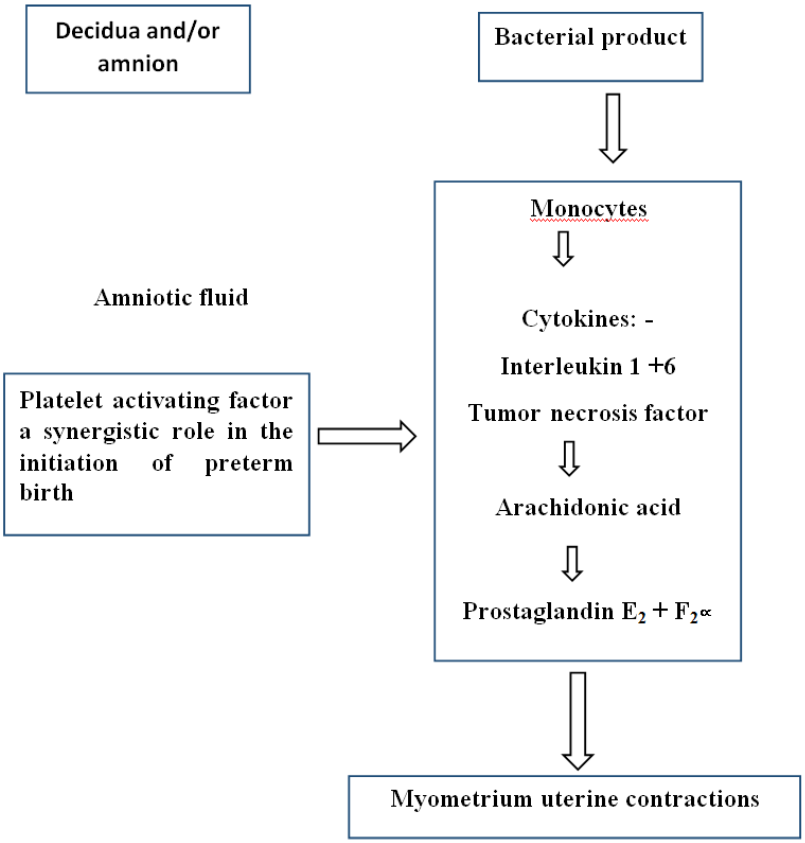

Figure 1. mechanism of action for bacteria to incite preterm labour.

3. Anemia. Recent evidence indicates that signs of inflammation or infection are prevalent in women with anemia. Ther is increased CRP concentration in more than 50% of anemic women means anemia is a sign of maternal morbidity indicating inflammation or infection of unknown origin (Svigo *et al.,* 1999).

Recent literature shows that detection and estimation of surrogate marker such as CRP (C-reactive protein) cytokines and fetal fiberonection help in diagnosing intramniotic infection and in predicting and diagnosing early onset neonatal infections (Lu *et al.,* 2000).

Diagnosis of PPROM

1. History: Women feeling agush of fluid vaginally.
2. A sterile speculum examination to confirm the diagnosis if no liquor is apparent.
3. Reduce fetal movement
4. Ultra-sound should not used as primary means of diagnosis of

PPROM

Laboratory Test for Diagnosis of PPROM:

1. Notarize test for vaginal PH.
2. Fern test: result from drying out of salts containing amniotic fluid.
3. Intra amniotic fluorescein and amnioscopy invasive method, and may enhance the infection.
4. Fetal fibronectin it confirm the rupture membranes and predicted for preterm labour. But it increase perinatal infection (Svigo, 1999).

Complication of PPROM

1. Maternal complication:
   a. Chorioamnionitis.
   b. Endomyometritis.
   c. Abruptio placentae.
   d. Psycho-social sequalae particularly maternal hospitalization,
   e. Induction of labour may lead to prolonged latent stage 16-20 hours which increased the likelihood of operative delivery (Svigo, 1999).

2. Fetal complication:
   a. Fetal pulmonary hypoplasia,
   b. Skeletal deformities "talipes".
   c. Amniotic adhesion and bands of fibrous tissue between the fetus and amnion which may cause auto-amputation,
   d. Cord compression or prolaps, e- Fetal infection and neonatal sepsis.
   e. Fetal intrapartum hypoxia and birth trauma associated with preterm labour involving the very low birth weight infant, whether birth is by the vaginal or abdominal rout with contribute to the perinatal risk (Svigo, 1999).

C-Reactive Protein "CRP": The CRP is a plasma protein molecule consisting of a pentameter of non-glycosylated polypeptide sub-unit that is produced by hepatocytes. This plasma protein normally is found in plasma of healthy persons in trace amounts "< 1 mg/dl" within hours of an acute injury as well as the onset of most types of inflammation or infection, the rate of production of CRP increases markedly with up to 3,000 fold increases in plasma concentration. For this reason,

CRP is considered an "acut phase" protein, the plasma level of CRP rapidly decreases toward the normal range (Narinder, 1997), and CRP increased and decreased more quickly than the red sedimentation rate (ESR), and the value of the CRP in the potentially infected patient exceeds Leukocyte indices. CRP production is stimulated by inter leukin 6 (IL-6), therefore IL-6 is an early and sensitive marker of infection or inflammation, so that the IL-6 should rise before CRP level rise. Median CRP values during pregnany are higher than values for non pregnant individuals. These values are elevated further in labour. In woman not in labour 95% of values were 1.5 mg/dl or less and gestational age didn't affect serum level. In true infection the test for CRP become positive after 12 hours, so estimation of CRP at presentation may not be much value in prediction. So serial determination may be required and have better predictive value than single estimation (Staffan Bergstrom, 2003). Mild CRP elevation "within normal, non acute-phase rang" is emerging as a valuable marker of cardiovascular risk (Jam Coli, 2003).

Method of GRP Test

C-reactive protein test "slide agglutination method". In this test using latex reagent which is a polystyrene latex particles of uniform size coated with the IgG fraction of an anti-human CRP specific serum. Visual observation of Ag-Ab reaction "CRP-IgG anti CRP" if reaction takes place due to presence of CRP in the serum a clear agglutination become evident. A clear agglutination will appear if the serum contains more than 6 mg/L of CRP and if no agglutination mean serum contains less than 6 mg/L of CRP which is normal range.

Reagents

- **a.** Latex reagent: Suspension of polystyrene latex particles coated with IgG anti-CRP in a buffer.
- **b.** Positive control: Diluted human serum containing more than 10 mg/L of CRP ready to use.
- **c.** Negative control: Diluted human serum containing less than 1 mg/L of CRP. All latex reagent positive, control, and negative contain <0.1% Sodium azid.

C-reactive protein assay by using Laser nephelometry measurement of serum CRP concentrations by rate nephelometry using a Beckman Array system protein analyzer, "which is not available here"

A double antibody sandwich enzyme immunoassay for C.R.P. which is high sensitivity CRP test (Saunders, 2003).

Aim of the Study: To evaluation C-reactive protein as a predictor of sub-clinical infection in preterm-prelabour rupture of fetal membranes and in preterm labour with intact fetal membranes.

PATIENT AND METHODS

Present study was carried out in Maternity and Childhood Teaching Hospital in Najaf, from June to October during a year 2003. Selection of Patient: The study consist of 30 cases selected with PPROM beyond 24 weeks of gestation up to 37 incomplete weeks of gestation, "case group". A second group "control group", 30 cases without rupture of fetal membranes but in labour, with same gestational age. Both groups were subjected to various investigation "urine and high vaginal swab for culture and sensitivity and placental swab for culture and sensitivity" as a confirmative tests for sub-clinical infection, patient who are excluded from study were:

1. Evidence of systemic infection.
2. Mai presentation.
3. Twin pregnancy.
4. Polyhydramnios.
5. Connective tissue disease.

Investigation: L Evaluation of CRP by slide agglutination method of mother at admission, as mentioned above.

1. High vaginal swab for culture and sensitivity.
2. Urine for culture and sensitivity.
3. Cord blood for CRP estimation.
4. Placental swab for culture and sensitivity.

Parameter of Infection after delivery

The mother was followed after delivery for evidence of:

1. Maternal fever during 24 hours after delivery.
2. Un healthy lochia "offensive discharge".

Neonatal requiring for neonatal intensive care unit admission. Each new born was admitted after delivery immediately to NICU for observation apgar scor for the first and five minutes of delivery and follow up of the baby during period of admission.

Statistical Analysis: Using Chi-square test "x2". The P value for positive cases <0.05 which mean statistically significant.

RESULTS

In this study 30 patients with PPROM as study cases and 30 patents with preterm labour and intact fetal membranes, as control cases. Both groups, Maternal and cord blood CRP estimation as a screening test for sub-clinical infection as a cause of PPROM and preterm labour. Both mother and neonates were observed post delivery for evidence of infection like maternal fever "unhealthy lochia" and neonate admission in NICU.

Table 1 Demonstrate comparison of maternal CRP in both groups, 18 patients out of 30 "60%" were positive (+ve) CRP in case group and 8 patients "36.6%" in control group and by using $x^2=6.6$, $p<0.05$ that mean statistically significant.

Table 2 and 3 Showed urine and high vaginal swab for c/s, there were 11 cases "36.6%" out of 30 cases were positive results of growth of micro-organism in case group. Vaginal swab showed 8 cases "27.3%" were positive in case group and 3 cases (10%) were positive (+ve) in control group. The micro-organism were isolated as following:

Urine culture

- Six cases isolated M.O were E-coli.
- Two cases the M.O were staphylococcus.
- Three cases klebsella.

Table 1. Comparlson of Maternal GRP values in Both Case and Control Group

Number of cases		percentage	Control	Percentage	Total	Percentage
Positive for CRP	18	60%	8	36.6%	26	48.3%
Negative for CRP	12	40%	22	33.4%	34	51.7%

$X^2 = 6.6$ $p < 0.05$

Table 2. Urine Culture and Sensitivity in Case and Control Groups

	Number in case	Number in control	Total
Organisms grown	11 (36.6%)	2 (6.6%)	13 (21.7%)
No Organisms grown	19(33.7%)	28 (93.4%)	47 (78.5%)

$X^2 = 7.9$ $p < 0.05$

Table 3. Comparison of High Vaginal Swab for Culture and Sensitivity

	Number in case	Number in control	Total
Positive for organism	8 (27.3%)	3 (10%)	11 (16.3%)
Negative for organism	22 (72.7%)	27 (90%)	49 (61.6%)

$X^2 = 5.3$ $p < 0.05$

Table .4 Demonstrate placental SWAB for culture and sensitivity

	Number in group	Number in control	Total
Positive for organism	5 (16.5%)	0	5 (60.3%)
Negative for organism	25 (83.5%)	30 (100%)	55(91.5%)

$X^2 = 2.3$ $p > 0.05$

Tablet 5. Demonstrate CRP in dabies in case and control groups

	Case group	Control group	Total
Positive in CRP	3 (10%)	0	3 (5%)
Negative in CRP	27 (9%)	30 (100%)	57 (95%)

$X^2 = 3.2$ $p > 0.05$

Vaginal swab cultures isolate

- One cases enterobacter.
- Four cases E-coli.
- Two cases staphylococcus aureus.
- One case klebsella.

Three cases monillial infection

Table 4 Demonstrate placental swab for culture and sensitivity, showed only 5 cases (16.5%) were positive, 3 cases the M.O was E-coli, 1 case staph aureus and 1 case enterobacter in case group. And in control group no case positive. X^2 21.1 and $p > 0.05$ mean not significant statistically. This mean no correlation between PPROM and placental infection.

Table 5 Demonstrate cord blood for CRP, were 3 cases "10%" were positive in case group and no case in control group, X^2 3.2 $p > 0.05$, mean no correlation between maternal CRP value and baby's CRP value. There is no correlation between PPROM and placental infection. In this accord the maternal CRP sensitivity was 78% "which resembles the ability of the test to identify those who were have sub-clinical infection". The specificity of CRP is 62.5% "which resembles the ability of the test to identify those who were have no sub-clinical infection".

DISCUSSION

The hypothesis that infection is the cause of PPROM stands proved. Levels of CRP rise when there is a microbial infection or an inflammation without microbes.

This is supported by obtaining statistically significant maternal CRP values in patients with PPROM, which is good predictor of sub-clinical infection specially those patients who were PPROM and not in labour.

- In this study the sensitivity of CRP is 78% and specificity is 62.5% while B.R daial got 79% sensitivity and 80% specificity in predictive effectiveness of CRP as a marker of infection (Desai *et al.,* 1997).
- The difference in the specificity of the test may be due to using another confirmative method such as placental and fetal membranes histopathological study for presence of evidence of inflammation or infection. And maybe we have no culture media or absence of other media for vaginal infection.
- Melee holds that urinary tract infection is the likely focus predisposing to PPROM (Malee, 1992) while in this study the urinary tract infection and lower genital tract infection have correlation with PPROM as demonstrated in table 2 and 3. Cervical swab in this study not performed due to deficiency in our laboratory facilities, placental swab for culture revealed 5 cases out of 30 cases showed +ve growth (16.5%) in study group and no cases in control group. And the micro-organism which were grown in the vaginal swabs are defer from that micro-organisms which grown in the placenta or urinary tract. In the same patient, that mean there were poly microbial infection may cause the condition (Staffan Bergstrom, 2003).
- Rising of maternal CRP was not are liable predictor of prenatal neonatal infectious morbidity as shown in Table 5. Only 3 babies (10%) were positive CRP in case group and no case in control group, but 25 (41.2%) babies of both groups were admitted at neonatal

intensive care unit NICU this due to pre-maturity problems and not due to neonatal infection.

However maternal post-delivery infection, only 2 cases (6.6%) were developed genital tract infection this low percentage it may be due to administration of parantral antibiotics pre and post delivery as a routine role in our labour room management for each case with PPROM. Comparison with study have done in Jawaherialnehru study at 1997 they have no post delivery maternal infection (Desa *et al.,* 1997).

Conclusion

The conclusion of this study is that CRP test can be used a screening test for sub-clinical infection in PPROM. CRP test has sensitively of 78 % and will specificity 62.5%. This test is cheap, easy performed and available and within a short period by agglutination test which take 10 minutes in getting a results. So that, it can be used as a first line for prediction of sub-clinical infection for both maternal and neonatal infection.

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