How Accurate are the Clinical and Biochemical Markers in Predicting Histological Chorioamnionitis After PPROM?

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Abstract

Objective: To investigate the effects histological chorioamnionitis(HCA) can produce on clinical features and biochemical inflammatory markers in mothers and infants after PPROM which may help with detection of HCA.

Method: This cross-sectional study included 70 mother-infant pairs presenting to GTTH and CPTH Lahore. Gestational age at presentation, duration of ROM, maternal pulse, abdominal tenderness, colour of liquor, maternal and cord blood TLC and CRP, results of HVS, neonatal blood culture and mode of delivery were recorded on a pre-designed proforma.

Results: Mean age of females was 27.5±4.05 years, mean gestational age at ROM was 32 weeks 6 days, median 34 and mode 35 weeks. Mean duration of ROM was 46.4± 51.4 hours. HCA was confirmed in 14/70 patients. Maternal TLC in HCA+ve group was 14784.29±5958.44 / ml3 and in non-HCA group was 12834.29 ± 3772.56 /ml^3. Maternal CRP in HCA and non-HCA group was 23.2±20.58 and 14.82±19.19 mg/L respectively. According to our study the sensitivity and specificity of maternal TLC for detecting HCA was 21.4% and 87.5% respectively. Sensitivity of CRP was 14.2% and specificity 57.1%. Mean cord blood TLC and CRP in HCA +ve was 15182.86±6114.96/ml^3 and 5.958±.27mg/L. In HCA-ve group cbTLC was 13097.04±8437.26 ml^3 and CRP was 5.84±11.88mg/L.

Conclusion: None of the specific clinical features or the biochemical investigations were statistically significant in detecting histological chorioamnionitis in patients presenting with PPROM.

Keywords: Chorioamnionitis, preterm pre-labor rupture of membranes

How to cite: *Sadaqat A, Rathore S, Sultan N, Mushtaq R, Mahmood S. How Accurate are the Clinical and Biochemical Markers in Predicting Histological Chorioamnionitis After PPROM? Esculapio - JSIMS 2022;18(04):248-252*

DOI: https://doi.org/10.51273/esc22.2518424

Introduction

Preterm pre-labor rupture of membranes (PPROM) is the rupture of fetal membranes with resultant loss of amniotic fluid between the gestational age of 24 weeks and 37 weeks before onset of uterine contractions. PPROM complicates up to 3% of pregnancies and is associated with 30–40% of preterm births.[1]

PPROM can result in significant neonatal morbidity and mortality, mainly from prematurity, sepsis, cord prolapse and pulmonary hypoplasia. Furthermore, there are risks associated with chorioamnionitis and placental abruption. Intrauterine infection and inflammation is an important determinant of spontaneous preterm birth following PPROM. The term 'clinical chorioamnionitis' refers to the presence of fever (>37.8°C) and at least two of the following criteria: maternal tachycardia (>100 beats per minute), maternal leukocytosis [white blood cell count (WBC) > 15,000 cells/mm^3], uterine tenderness,

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Submission Date: 15-09-2022
1st Revision Date: 29-09-2022
Acceptance Date: 03-10-2022

fetal tachycardia (>160 beats per minute), and foul-smelling amniotic fluid.[2,3]

Tissue inhibitors of Matrix Metalloproteinases bind to MMPs and inhibit MMP-associated proteolysis, thereby helping to maintain fetal membrane integrity.[4,5] A host of events like subclinical/overt infection, inflammation, mechanical stress and bleeding can disrupt this and initiate a cascade of biochemical changes that culminate in PROM.[6] Chorioamnionitis is definitively diagnosed by histological examination of the placenta. Histological chorioamnionitis (HCA) is often asymptomatic and clinical signs, such as fever, uterine tenderness, maternal or fetal tachycardia and malodorous amniotic fluid, lack both sensitivity and specificity.[7] Amniotic fluid culture has also been used to identify fetal infection but was seen to be negative for microorganism in 50% of cases of HCA.[8] The poor predictive value of clinical signs and amniotic fluid culture for identifying HCA has increased interest in biochemical inflammatory markers. These include Total leukocyte count (TLC) specially and C-reactive protein. The vital decision is whether to induce labor (or perform cesarean delivery) or to manage the pregnancy expectantly. These biochemical markers can help in making that decision. The median latency after PPROM is 7 days and tends to shorten as the gestational age at PPROM advances.[9,10] CRP is an acute phase reactant produced by the liver in response to pro-inflammatory cytokines like interleukin (IL-6). Plasma levels increase 12–24 hours after the onset of inflammation and remains elevated until after the stimulus resolves.[11] We also want to correlate the intrauterine infection and inflammation to neonatal sepsis. Neonatal sepsis is defined as a single isolate cultured from a sterile site with suggestive clinical features and a treatment course of antibiotics.[12]

Materials and Methods

This was a cross-sectional study conducted in Ghurki Trust Teaching Hospital and Central Park Tea-ching Hospital. The sample size was calculated using the following sample size formula[13] which came out to be 79.

$$n_o = Z_{1-\frac{\alpha}{2}}^{2} \frac{p(1-P)}{d^2}$$

Where n_o is the sample size. P is the prevalence rate. Level of significance is 5% and d is the margin of error. Using prevalence rate as 5.4%.[14]

Mothers with fetus having major congenital anomalies and those who refused to give consent were excluded. Gestational age was estimated by LMP. If a woman was unsure of LMP then a dating scan was used to ascertain gestational age.

Diagnosis of PPROM was by direct observation of amniotic fluid leaking from the cervical os or pooling while doing a sterile bivalve cuscos speculum examination. HVS was sent in a sterile tube. Patients' pulse, BP and temperature was recorded 4 hourly and the one recorded in data was closest to decision of delivery. Blood sample from the mother was taken for WBC and CRP.

At delivery cord blood was sent for WBC and CRP. After delivery a section of umbilical cord, membranes and at least one section including the chorionic plate was sent for histopathology in a plastic container containing formalin and saved at 4° C until transported to lab. Histopathological analysis was done by histopathology department (Chughtai institute of Pathology) at Central Park Medical College. It was diagnosed by acute granulocyte infiltration of choriodecidual space. All data was recorded in a predesigned proforma (attached) and analyzed by SPSS 22.0. Continuous data was summarized using non-parametric statistics: medians, and ranges (R). Categorical data was summarized using frequency distributions. Pearson's chi-square tests or Fisher's exact test was used to compare frequency distributions between HCA and non-HCA groups. Sensitivity and specificity, positive predictive value and negative predictive value of metarnal TLC and CRP were calculated.

Results

A total of 79 pregnant women participated in the study, out of which blood samples of two mothers were lost, 3 samples of cord blood were hemolysed and 4 placental specimens were autolysed. We did analysis of 70 patients. Mean age of pregnant participants of the study was 27.5± 4.05 years. Average gestational age at which PPROM occurred was 32 weeks and 6 days (range 25-36 weeks), median 34 weeks and mode 35 weeks. The mean duration of ROM was 46.4± 51.4 hours at the time of delivery either spontaneous or planned due to clinical chorioamnionitis. The median duration of ROM was 28 hours and mode was 48 hours. Mean maternal pulse was 91.9±9.98 per minute (range 82-120/min). Biochemical markers showed mean maternal TLC was 13224.29±4265 cubic ml (range 5000-26000)

and mean maternal CRP was 16.50±19.46 mg/L (range 0.12-62). Mean cord blood TLC and CRP were 13526.47 ±7976.09(range 3800-46900) cubic ml and 5.87± 11.11 (0.01-45.20) mg/L respectively. Labor started spontaneously in 25.7%, induced in 14.3% and 60% opted for cesarean on diagnosis of clinical chorioamnionitis. Out of the spontaneous and induced labors 28.6% had vaginal delivery and 71.4% ended in cesarean delivery. Antenatal steroid was given in 74.3% and in 25.7% it could not be given.

Out of the 70 patients who presented with PPROM

Table 1: *Comparison of parameters in cases with and without HCA.*

Parameters	Chorio-amnionitis	No chorio-amnionitis	p-value
Age(years)	28.9	27.39	0.61
Gest age(weeks)	31	33	0.315
Duration of ROM(hours)	52.43	44.93	0.736
Maternal pulse (per min)	98.5	90.25	0.47
Abdominal tenderness	nil	2	0.612
Discolouration of liquor	2	6	0.93
Maternal TLC (cubic milliiliter)	14784.29± 5958.44	12834.29± 3772.56	0.286
Maternal CRP(mg/L)	23.2±20.58	14.82±19.19	0.312
Spontaneous labor(n)	8	10	0.02
Induced labor(n)	4	6	
Vaginal delivery(n)	8	6	0.61
Cesarean(n)	6	44	
CB TLC	15182.86± 6114.96	13097.04± 8437.26	0.546
CB CRP	5.95±8.27	5.84±11.88	0.312
Neonatal sepsis(n)	4	8	0.37
Birth weight (kg)	1.81	2.09	

20% (14) showed histological chorioamnionitis in the placental specimen submitted after delivery while 80% (56) revealed no evidence of chorioamnionitis.

In cases with histological chorioamnionitis average duration of rupture of membranes was 52.4±32.4 hours, mean maternal pulse was 98.5±13.2 per min, abdominal tenderness was not positive, discolored liquor in 14.2%. No patient was febrile. Maternal TLC in this group was 14784.29±5958.44cubic ml and mean maternal CRP was 23.2±20.58mg/L. Spontaneous labor started in 57.1% and induced in 28.5%(ended up having emergency cesarean) Two women (14.2%) opted for cesarean delivery. Vaginal delivery took place in 57.1% and 42.8% had cesarean delivery. Average level of cord blood TLC was 15182.86±6114.96per cubic milliliter and average cord blood CRP was 5.95±8.27 mg/L. Neonatal sepsis was seen in 28.5%. Mean birth weight was 1.81±0.9 kg. According to our study the sensitivity and specificity of maternal TLC for detecting HCA was 21.4% and 87.5% respectively. Sensitivity of maternal CRP was 14.2% and specificity 57.1%.

Placental specimen with no histological chorioamnionitis revealed following clinical and biochemical parameters. Average duration of rupture of membranes was 44.93 ± 55.63 hours. In this group mean maternal pulse was 90.25±8.48 per min. Abdominal tenderness was positive in just 2 patients out of 56 and yellowish discoloration of amniotic fluid was seen in 6 patients. Maternal TLC and CRP mean values were 12834.29±3772.56 cubic ml and 14.82±19.19 mg/L. respectively. Labor started spontaneously in 17.8% and was induced in 10.7%. It was decided to deliver the baby by cesarean section in 78.5% and vaginal delivery took place in 21.4%. Average cord blood TLC in this group was 13097.04±8437.26 cubic milliliter and mean cord blood CRP 5.84±11.88 mg/L. Neonatal sepsis was seen in 14.2 % cases and mean birth weight was 2.09±0.71 kg.

Discussion

Preterm prelabor rupture of membranes complicates about 0.1 to 0.7% of pregnancies at the verge of viability.[14-16] Upto 14 % of pregnant females stop leaking amniotic fluid and about 25% reaccumulate amniotic fluid who present with PPROM at the verge of viable gestational age. For this reason, there is always a period of latency where obstetricians give this margin of doubt in management, where they weigh and balance the risk of infection with the benefit resealing of membranes can bring. During this wait and see period maternal and fetal surveillance is done to detect chorioamnionitis, give antenatal corticosteroids for fetal lung maturity and antibiotic cover is given for prevention of ascending infection.

In our study the mean age of pregnant females who participated was 27.5± 4.05 years and the mean gestational age at which they presented with PPROM was 32 weeks and 6 days (range 25-36 weeks). Median gestational age at which rupture of membranes occurred and mode in our study was 34 weeks and 35 respectively. Median gestational age at PPROM was 24 weeks in a study conducted by Lorethe E et.al in 2018.[17] The mean duration of ruptured membranes was 46.4±51.4 hours at the time of delivery in our study, median was 28 hours

and mode was 48 hours. It is quoted to be 35.5 ± 20.7 days in a study conducted by Lille University Hospital, France from 2009 to 2018.[18]

Clinical chorioamnionitis was 75% in our study as a result their labor was either induced or cesarean section was done. In 43% of HCA+ve cases clinical suspicion was correct. In HCA –ve cases clinical chorioamnionitis was suspected in 82.2%. In a similar study performed in Obstetrics Department of Rennes University Hospital (level III maternity unit) clinical suspicion of chorioamnionitis was 80% in histology proven chorioamnionitis and 46% in HCA –ve.[19] Quite contrary to what was revealed in our study. Maternal TLC in the group with HCA was 14784.29±5958.44 per cubic milliliter and in non-HCA group was 12834.29±3772.56 per cubic ml. No significant difference was found between them similar to the study conducted by Ivana Musilova in 2017 at Department of Obstetrics and Gynecology, University Hospital in Hradec Kralove, Czech Republic which showed that maternal white blood cell count can not identify the presence of microbial invasion of the amniotic cavity or intra-amniotic inflammation in women with PPROM.[21] Maternal CRP in HCA and non-HCA group was 23.2±20.58 and 14.82±19.19 mg/L respectively. According to our study the sensitivity and specificity of maternal TLC for detecting HCA was 21.4% and 87.5% respectively. Sensitivity of CRP was 14.2% and specificity 57.1%. Abha Suryavanshi conducted a research concluding sensitivity of CRP for diagnosing maternal chorioamnionitis was 48% (95% confidence interval [CI] −35.99–61.12), specificity was 81% (95% CI 71.55%–88.98%) at People's College of Medical Science and Research Centre, Bhopal.[22] PPV of maternal TLC 22.2% and NPV was 87.5%. PPV of maternal CRP was 25% and NPV was 87.5%.

In the HCA+ve group the values of cord blood TLC as well as CRP were similar to the non-histological chorioamnionitis group and not markedly raised. In contrast a study conducted at a tertiary perinatal center in Western Australia by Rebecca A and colleagues showed that both Cord blood TLC and CRP were raised in the HCA group.[20] PPV of cord blood CRP in detecting neonatal sepsis was 22.2% and NPV was 84.6%.

Conclusion

None of the specific clinical features or the the biochemical investigations are statistically significant in detecting histological chorioamnionitis in patients presenting with preterm prelabor rupture of membranes. No association of duration of rupture of membranes or gestational age with HCA. These lab markers only have a high negative predictive value. Newer markers like IL-6, MMP and TNF should be investigated in future researches to find its role in prediction of HCA.

Conflict of Interest *None*

Funding source *None*

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Authors Contribution

AS, RM: Conceptualization of Project
RM, NS: Data Collection
AS: Literature Search
SM, AS: Statistical Analysis
SR, AS: Drafting, Revision
AS: Writing of Manuscript