PREDICTION OF EARLY NEONATAL INFECTION IN PREGNANCIES WITH PRELABOUR RUPTURE OF MEMBRANES

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Abstract

Background: The uncertainty of predicting which pregnancies will have early onset neonatal infection (EONI) with prelabour rupture of membranes (PROM) is a challenge to obstetricians because presence of this condition impacts the decision to do expectant or active management of the case. The most common maternal markers of infection used in our practice are C-reactive protein, white blood cell count, and amniotic fluid glucose concentration.

Objective: The primary objective of the study is to evaluate the accuracy of measuring C-reactive protein and leukocytes in maternal serum and amniotic fluid glucose concentration to predict early onset neonatal infection. The secondary objective of the study is to determine maternal fetal outcome in pregnancies with prelabour rupture of membranes.

Material and methods: This prospective cross-sectional study enrolled 170 pregnant patients who experienced prelabour rupture of chorioamniotic membranes.. The maternal serum and amniotic fluid samples were taken at admission and later used to analyze whether/how the test results were a predictor of early onset neonatal infection.

Results: C-reactive protein concentrations were significantly associated with early onset neonatal infection. Maternal CRP had 92.0% sensitivity and specificity of 62.8 % for predicting early onset neonatal infection. Maternal serum white blood cell count and amniotic fluid glucose concentrations estimation after pre-labour rupture of membranes showed poor predictive value in neonatal early onset infection.

Conclusion: C-reactive protein was more sensitive in predicting Early Onset Neonatal Infection than either white blood cell count or amniotic fluid glucose concentration.

Key words: Early onset neonatal infection, maternal markers, pre-labour rupture of membranes

Academic Discipline And Sub-Disciplines

Medical Science

SUBJECT CLASSIFICATION
Obstetrics and Gynecology

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Background:

Prelabour rupture of membranes (PROM) refers to rupture of the chorioamniotic membranes prior to the onset of labor and prior to the onset of clinically apparent labour contraction. PROM can occur at any gestational age. [1] This condition is classified as "preterm PROM"if the event occurs before 37 weeks of gestation, or "term PROM" if the event occurs after 37 weeks gestation.. [2,3,4,5] A numbers of factors have been associated with PROM including anatomic and pregnancy-related infection. [6] Infection is an important known risk-factor associated with PROM. There is ongoing debate in the medical literature whether intrauterine infection is a cause or a consequence of pre-labor rupture of the fetal membranes.[7] In both cases, subclinical infection may be present before and after PROM and is an etiologic factor in maternal-fetal consequences.

The most frequent maternal consequences associated with intra amniotic infection are endomyometritis, wound infection, pelvic abscess, bacteremia and postpartum haemorrhage.[8,9]

Fetal exposure to infection may lead to numerous adverse outcomes. Early Onset Neonatal Infection-EONI, generally acquired prenatally in pregnancies with PROM, is one of the most serious consequence of maternal infection and is associated with increased neonatal morbidity and mortality.[10]

Early identification of EONI is a desirable clinical goal because late diagnosis with delayed treatment increases neonatal morbidity and mortality. Despite numerous studies focusing on finding efficient markers as predictors of EONI, prediction of EONI remains a critical challenge in pregnancies with PROM[11]. Cost, availability of specimens at the appropriate time, complexity of the assay methods, laboratory turnover time, reliability of the tests, and attitude of attending clinicians are all important factors in determining the suitability of a diagnostic marker for clinical application [12.] The most common maternal markers used in practice are C-reactive protein, white blood cell count and glucose. Recent studies have focused on determining the accuracy of white blood cell count, CRP and glucose concentration separately or in combination for prediction of early onset neonatal infection in pregnancies complicated with PROM, but the results remain controversial.

Objective: The main objective of this research is to investigate the predictive value for EONI of C-reactive protein and leukocyte count in maternal serum and glucose concentration in amniotic fluid in pregnant women with PROM. Secondary objectives of the study aim to determine maternal fetal outcome in pregnancies with pre-labour rupture of membranes.

Ethics: This study was submitted to the Institutional Ethical Review Committee and was found to be in conformity with the laws and regulations of the country in which the research was conducted. Written informed consent was obtained from all subjects. To maintain participant confidentiality numbers instead of names were used on the questionnaire and evaluation forms.

Material and Methods: This prospective cross-sectional study was conducted from June 2013 through March 2015 in Obstetrics and Gynecology Clinic of University Clinical Center of Kosova and investigated the predictive value for EONI of CRP, WBC and glucose concentration in pregnant women with PROM. One hundred and seventy eight pregnant patients between 24-41 weeks of gestational age who were not on either antibiotic or corticoid treatment and who experienced pre-labour rupture of amniotic membranes were assessed for eligibility. Of these 178 patients, 8 pregnant women were excluded due to hypertensive disorders, diabetes mellitus, fetal malformations and giving birth beyond 72 hours after admission.. A total of 170 pregnant women and their newborns (N=170) were then eligible to be included in the study.

Study methods of intervention and data collection included a specific questionnaire and evaluation form used to collect data prospectively at admission and thereafter. Data covering demographic, maternal and neonatal characteristics were recorded and analyzed.

PROM was defined as leakage of amniotic fluid that precedes the onset of uterine contractions and the cervical canal dilatation of less than 2 cm. Confirmation of the diagnosis of rupture of membranes was documented by sterile speculum examination confirming the pooling of amniotic fluid in the posterior vaginal fornix or/and direct visualization of fluid leakage from the cervical canal. Maternal serum and amniotic fluid samples were taken at the admission from all the women.

About two milliliters of blood was collected by venipuncture. .Blood samples were transported to the biochemistry department for total WBC (expressed as cellsx10^9) and CRP (expressed as mg/L) estimation. CRP levels were estimated using a latex agglutination test. The pathological limit for leukocyte count was considered value ≥ 14X10^9 and for CRP value > 6 mg/L. Three milliliters of amniotic fluid were collected vaginally and samples are used to measure the glucose concentration (expressed as mg/dl). Pathological amniotic fluid glucose concentration was considered value ≤ 14 mg/dl.

Outcome definition:

Immediately after the delivery all newborns were observed for complications related to infectious morbidity. The newborns were observed during the first seven days of life respectively during early neonatal period. Neonatal infection was considered probable based on clinical signs and a neonatal CRP ≥ 10 mg/dl and thereafter was confirmed as indicated by radiography, positive blood culture or a positive cerebrospinal fluid culture associated with clinical signs of infection.

Statistical analysis:

Statistical analysis was performed by using statistical package SPSS 17.0 version software. The data are expressed in number and percentage, as well as, in average and standard deviation. The 95% of CI was also calculated. For determining the the accuracy of markers as diagnostic methods, Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value and Likelihood ratio were calculated. Statistical significance was defined as p-value<0.05.

Results:

One hundred and seventy pregnant women with a diagnosis of premature rupture of membranes and their newborns (n=170) were included in this study. The clinical characteristics of the study participants are presented in Table 1. The average age of the pregnant women involved in the research was 27.4 years old (SD ± 5.4 years).The majority of the participants were nulliparous (65,8%). Among all patients, 26.7% (N=8) had previous abortions, 3.35% (N=6) had previous uterus surgery, and 25.2 % (N=43) were smokers. Mean gestational age at birth was 37.4 weeks (SD ± 2.52 weeks) and the mean time interval between PROM and delivery was 24.4 hours (SD ±14.52 hrs). EONI was diagnosed in 25 cases respectively in 14.7 % of newborns. The average weight of newborns was 3064 gram (SD ± 675.2 gram). Twenty seven and a half percent (N=46) of the 170 study participants delivered by cesarean section and the remaining 72.5% (N=124) delivered vaginally.

Table 1. Maternal and Neonatal Characteristics and Mode of Delivery

Women	N=170
Women age, Year (Mean ± SD)	27.4 ± 5.4
Nulliparous, n (%)	112 (65.8)
Previous surgery in uterus, n (%)	6 (3.5)
Previous abortions, n (%)	8 (26.7)
Previous PROM, n (%)	33 (19.4)
Smoking, n (%)	43 (25.2)
Weeks of gestation at delivery, (Mean ± SD)	37.4 ± 2.52
Time from PROM to delivery, (hours Mean ± SD)	24.4 ± 14.52
Neonates	**N=170**
Male gender, n (%)	91 (53.5)
5 minutes Apgar score (Mean ± SD)	8 (1.04)
Newborn weight, gram (Mean ± SD)	3064.2 ± 675.2
Early neonatal infection, n (%)	25 (14.70)
Mode of Delivery	
Spontaneous n (%)	65 (35,88)
Induced n (%)	59 (34.70)
Cesarean Section n (%)	46 (27.05)

Pre-labour Rupture of Membranes is an important cause of maternal and fetal morbidity. Postpartum hemorrhage and retained placenta are most common maternal adverse outcomes observed in our study. EONI was present in 25 cases. In total, 2 neonatal deaths were registered in the group of newborns with confirmed early neonatal sepsis. Neonatal infectious morbidity and other maternal adverse outcomes are presented in Table 2.

Table 2. Maternal / Neonatal Outcome in Pregnancies Complicated with PROM

Maternal morbidity / complications

	Count	Percent	Cumulative
No complications	158	92,94118	92,9412
Chorioamnionitis	2	1,17647	94,1176
PP haemorrhage	3	1,76471	95,8824
Placental abruption	1	0,58824	96,4706
Retained placenta	3	1,76471	98,2353

Pelvic abscess	1	0,58824	98,8235
Endometritis	1	0,58824	99,4118
Wound infection	1	0,58824	100,0000

Early Neonatal Outcome/ Infection

No complications	145	85,29411	85,2941
Clinical infection	3	1,76470	87,0588
SIRS	4	2.35294	89,4117
Pneumonia	8	4,70588	94,1176
Sepsis	10	5,88235	100.0000

In order to verify the hypothesis, which is that serum CRP and WBC and amniotic fluid glucose may serve as a marker for prediction of EONI in pregnancies with PROM, the newborns were divided into two groups. Group I was newborns with no infection (N=145). Group II was,newborns with early onset neonatal infections (N=25). The average value of CRP at mothers who gave birth to newborns of the group with neonatal infections was much higher, a difference of significant statistical importance (P<0.0000). The average value of WBC at mothers of Group II of newborns with neonatal infections was a bit higher but without a significant difference (P>0.05). Value of glucoses in amniotic fluid at mothers of Group II of newborns with neonatal infections was a bit higher but with no significant difference (P>0.05). (Table 3)

Table 3. Mean Value of CRP, WBC and Glucose by Groups

		Group I, No neonatal infection	Group II, With neonatal infection	P value
N Valid		145	25	
CRP mg/ dl	Mean Minimum Maximum ± SD	7,88655 0,500000 69,30000 8,68800	27,48400 2,200000 86,00000 23,58996	0.00000
WBC x10^9	Mean Minimum Maximum ± SD	13,07793 4,100000 33,90000 4,16551	14,55600 9,000000 20,70000 3,50916	0.096068
Glucose mg/dl	Mean Minimum Maximum ± SD	11,27462 0,180000 82,49000 10,38512	11,90560 0,180000 32,60000 10,11329	0.778592

The results in this study report a high sensitivity of CRP for prediction of EONI in pregnancies with PROM, respectively 92.0% (95% CI 75.0 – 97.8) and likehood ratio of 2.44. WBC and glucose do not have significant sensitivity in prediction of EONI in pregnancies with PROM (Table 4).

Table 4. Sensitivity and specificity of CRP, WBC and Glucose on prediction of EONI

	CRP	[95 % CI]	WBC	[95 % CI]	Glucose	[95 % CI]
Sensitivity	0.92	[0.75 to 0.978]	0.6	[0.407 to 0.766]	0.76	[0.566 to 0.885]
Specificity	0.628	[0.547 to 0.702]	0.676	[0.596 to 0.747]	0.269	[0.203 to 0.346]
PPV	0.299	[0.208 to 0.408]	0.242	[0.152 to 0.362]	0.152	[0.1 to 0.225]
NPV	0.978	[0.925 to 0.994]	0.907	[0.838 to 0.949]	0.867	[0.738 to 0.937]
LR+	2.47	[1.942 to 3.143]	1.851	[1.244 to 2.753]	1.04	[0.817 to 1.323]
LR-	0.127	[0.034 to 0.484]	0.592	[0.361 to 0.969]	0.892	[0.423 to 1.884]

Discussion: Leading causes of early neonatal death globally are complications of preterm birth, intra partum related causes and infection. In Kosova, despite the reported decrease, the early neonatal mortality rate remains high compared to other European countries. Infection continues to pose a problem and is implicated in the pathogenesis of pre-labour rupture of membranes. The link between infectious early neonatal morbidity and mortality and pre-labour rupture of membranes is incontestable. It is accepted that women with complicated with pre-labour rupture of membranes have a substantially higher risk of neonatal morbidity and mortality due to infection than women without membrane ruptures.[14]

Prediction of early onset neonatal infection in these cases remains a major challenge and there is no decisive standard protocol on what are the best methods to use. Medical literature reports different invasive and non-invasive methods and markers to predict EONI in pregnancies complicated with PROM. Cost, availability of specimens at the appropriate time, complexity of the assay methods, laboratory turnover time, reliability of the tests, and attitude of attending clinicians are all important factors in determining the suitability of a diagnostic marker for clinical application.[15]

The existing medical research on the accuracy of different maternal markers for prediction of EONI in pregnancies complicated with PROM remains unclear. Different studies have identified different markers as accurate predictors of EONI/PROM and so there is not a consensus of what test is best to use. The paragraphs below summarize existing literature on identifying accurate predictors.

 Several studies reported the accuracy of CRP as a predictive marker including Sung Youn Lee and al (2012). In in their study about relationship between maternal serum CRP and early onset neonatal sepsis, they reported success in finding a good negative predictive value in excluding early-onset neonatal sepsis. Yee et al .reported that that maternal serum CRP level < 8 mg/L had a good negative predictive value in excluding early-onset neonatal sepsis; therefore, this test has potential to be a useful non-invasive adjunct to clinical judgment to identify low-risk patients [16].

Popowski et al.(2011) also concluded that CRP at admission was an accurate marker for predictin EONI.[17] These researchers conducted an investigation in France of maternal markers for detecting EONI and chorioamnionitis in cases of premature rupture of membranes at or after 34 weeks of gestation. In their study of 399 woman with PROM, maternal serum CRP at admission is the most accurate infectious marker for predicting EONI Park et Al (2012) studied the accuracy of measuring CRP and leukocytes in maternal serum to predict the probability of intra-amniotic infection among 171 women with PPROM. In addition to CRP, the study reported that WBC, parity, and gestational age are also highly predictive of IAI in women with PPROMs [18].

Buhimschi et al (2006) also investigated the predictive value for EONI of C reactive protein, white blood cell count, and glucose concentration and showed that maternal serum CRP at admission is the most accurate infectious marker for predicting EONI.
 By ROC curve, the sensitivity and specificity of maternal CRP for early onset neonatal infection in our data was 92 % and 68% respectively. Investigation of maternal WBC and amniotic fluid glucose concentration showed low sensitivity in prediction of EONI.

This study also reported that glucose concentration as a marker used to diagnose infection in other sites such as cerebrospinal fluid was not a good predictor.   Vaginal glucose determination is a readily available, inexpensive, rapid AF marker that can be measured practically in any clinical laboratory. Buhimschi et al (2006) investigated the value of low vaginal pool glucose measurement for prediction of intra amniotic infection. The results showed that vaginal amniotic fluid glucose measurements less than 15 mg/dL have predictive value, but low sensitivity for detection of IAI [20].

Van der Heyden et al (2010), however, did not support the use of CRP. In their study, they researched the accuracy of measuring CRP and leukocytes in maternal serum to predict neonatal infection among 299 women with PROM. The results showed that in women with PROM, CRP and leukocytes should not be measured routinely. [19]

Conclusion:

Prelabour Rupture of Membranes remains an important cause of maternal and fetal morbidity and increased rate of cesarean section delivery. Postpartum haemorrhage, retained placenta and chorioamnionitis are the most common maternal complicatio. Neonatal infection related to PROM is an important factor of neonatal morbidity especially in pre term born infants.

 CRP, WBC count and Glucose concentration are the most common markers of infection used in practice. This study found that in cases with pre-labour rupture of membranes, maternal CRP is a more accurate predictor of EONI in pregnancies with PROM than WBC and glucose concentration. These study results contribute to the ongoing research question of determining the accuracy of infection markers and the results add to the growing number of studies that report CRP as an accurate predictor of EONI.

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