Research Article

Role of Maternal Plasma Procalcitonin Level in The Diagnosis of Subclinical Chorioamnionitis in Pregnancy Complicated by Preterm Prelabor Rupture of Membrane

Fadia Jassim Mohammed, *M.B.Ch.B, C.A.B.O.G;* **Aseel mahmood Kadim,** *M.B.Ch.B.*
Gynecology And Obstetrics AL Yarmook Teaching Hospital – AL Mustasiriyah Medical College

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Address for Correspondence:
Dr. Fadia Jassim Mohammed M.B.Ch.B, C.A.B.O.G, Gynecology And Obstetrics AL Yarmook Teaching Hospital – AL Mustasiriyah Medical College
E-mail: fmjafalizzi@yahoo.co.uk

Abstract

Background: At any time during pregnancy, intrauterine infection is an important risk factor for neonatal sepsis and is a frequent cause of mortality and morbidity in newborn infants

Objectives: to evaluate maternal plasma procalcitonin levels in the pregnant women complicated with preterm prelabor rupture of membrane and prelabor rupture of membrane at term and compare it with healthy pregnant women at preterm and term and determine the role of procalcitonin in the diagnosis of subclinical chorioamnionitis in PPROM **cases**

Study design: A prospective case-control study

Patients and Methods: One hundred women 18_40 years old with singleton pregnancies were seen in Al-Yarmuk teaching hospital between September 2015 to August 2016. Women were divided into 4 groups according to weeks of gestation and membrane status (intact or ruptures). Group 1 included 30 women with gestational age between 28-36 weeks and membrane rupture without uterine contraction. Group 2 included 25 women with rupture membrane at term (37-41weeks) without uterine contraction. Group 3 included 20 healthy women at preterm (28 - 36 weeks) with intact membrane. Group 4 included 25 healthy women at term (37-41weeks) not in labor with intact membrane; the last two groups represented the control groups. In all groups, we measured maternal plasma procalcitonin level, white blood cells(WBC), C reactive protein (CRP), send placenta for histopathology and check birth weight of the baby and sign of neonatal infection.

Results: the mean PCT level in the women of group one (the PPROM group) was higher (0.171 ±0.078) ng/ml than PROM and control groups with a p-value of <0,001. In addition, it was more significant in the detection of histological chorioamnionitis in PPROM patients than neonatal infection, as the cut off value was 0.08, with high sensitivity 96%, specificity 82%, positive predictive value (PPV) 84.2% and negative predictive value (NPV) 95.3%.

Conclusions: Maternal plasma PCT level was significantly higher in PPROM than in term PROM and controls groups. PCT was more significant in predicting histological chorioamnionitis than neonatal sepsis. PCT was superior to CRP and WBC count in detecting subclinical intraamniotic infection by its ability to detect histological chorioamnionitis and neonatal sepsis.

Key words: *Procalcitonin, PPROM, PROM and chorioamnionitis*

INTRODUCTION

Preterm Prelabor Rupture of Membranes (PPROM) is the loss of amniotic fluid from the uterine cavity of a pregnancy prior to 37 weeks in the absence of labor.[1] It complicates around 2 % to 4 % of singleton deliveries,[2,3] and is responsible for more than 30% of births before 37 weeks.[4,5] The rupture of membrane in normal labor is almost a physiological process while in

PPROM usually there is an underlying pathology.[1] The common cause of PPROM is infection. Subclinical intrauterine infection of the choriodecidual space and amniotic fluid is the most widely studied aetiological factor underlying spontaneous preterm births.[5]

The accurate diagnosis of either PROM or PPROM is very important since many interventions will relay on it. If undertaken unnecessarily, these interventions will undoubtedly increase maternal and fetal morbidity.[1] The major complication of preterm PROM is Chorioamnionitis which may be acute or subclinical in type. Subclinical chorioamnionitis is an infection of the products of conception without clinical signs or symptoms of disease. Subclinical chorioamnionitis occurs frequently in women in preterm labor with rupture of membrane or incompetent cervix. Uterine contraction may be the only sign of subclinical chorioamnionitis present with advanced cervical dilatation or with uterine contractions resistant to conventional treatment with tocolytics agents.[6]

The diagnosis is made by suggestive history, general, abdominal and speculum examination with specific tests.

Serial WBC & CRP is the most common laboratory tests used in the clinical practice to evaluate systemic inflammatory response to an infectious agent.CRP is an early marker commonly used as a diagnostic, predictor, and monitoring marker in patients with acute sepsis,[7] although this has not been shown to improve management.[5]

The only laboratory studies that help support the diagnosis of chorioamnionitis involve sampling of the amniotic fluid. Although culture is the gold standard for confirming the diagnosis, it is not particularly useful in the acute setting,[2] and it is invasive.

Procalcitonin (PCT) is a hormone that is produced by the parafollicular C cells of the thyroid and involved in calcium homeostasis. It is also produced by the neuroendocrine cells of the lung and intestine and is released as an acute-phase response to inflammatory stimuli, mainly those of bacterial origin.[8,9] PCT is a more reliable marker than others involved in the diagnosis of bacterial sepsis, allowing better differentiation among sepsis-related mortalities.[10] PCT is also a useful early diagnostic marker for detection of bacteremia in febrile neutropenia and has better diagnostic value than CRP,[11] in addition it helps in distinguishing bacterial from viral infections, including meningitis,[12] to monitor therapeutic response to antibacterial therapy and reduce antibiotic exposure[13,14] and to aid in the diagnosis of systemic secondary infection after surgery and in severe trauma, burns, and multiorgan failure.[15]

PATIENTS AND METHODS

This prospective case control study was carried out at Al_ Yarmouk Obstetrics and Gynaecology department during the period between September 2015 _August 2016 in Baghdad city after approval by the supervising committee of Arabic Board Obstetrics and Gynecology and informed consent was taken from all of the women. One hundred pregnant women 18-40 years with singleton pregnancies were included. Some of those women seen as an outpatient and others as an inpatient. Woman with Multiple pregnancies, Clinical signs of infection (fever, tachycardia and uterine tenderness), active labor, maternal complications such as (pre-eclampsia, diabetes, antepartum hemorrhage…) and fetal complications like IUGR, congenital anomaly were excluded.

The women were divided into 4 groups depending on weeks of gestation (confirmed by the LMP and an early ultrasound) & Membrane status; whether ruptured or intact. Additional information regarding age, parity, body mass index (BMI) were recorded

Group 1 included 30 women with gestational age between 28-36 weeks and membrane ruptured without uterine contraction, Group 2 involved 25 women with membrane rupture at term (between 37-41 weeks gestation) without uterine contraction, Group 3 involved 20 women with preterm gestation (between 28-36 weeks) and intact membrane and Group 4 involved 25 women at term between 37-41 weeks gestation not in labor with intact membrane. The last two groups considered as control groups of women and were taken randomly routine ambulatory visits, where venous blood samples were collected and sent for PCT, CRP and WBC count. Women in group 1 with PPROM were admitted and venous blood samples collected at time of admission and within 6 hours before administration of any drug and sent for PCT, CRP and WBC count evaluation. All members of this group were admitted for bed rest with fetal heart monitoring and uterine activity assessment performed twice daily and chart observation of vital signs and received prophylactic oral antibiotics (Erythromycin capsule 250 mg every 6 h) and steroids to enhance lung maturity. After delivery, the placentae were sent for histopathology . Women in group 2, again maternal venous blood samples were collected at time of admission and sent for PCT, CRP and WBC count evaluation then, induction of labor was started if spontaneous labor did not begin within 12 hours. After delivery, the placenta sent for histopathology.

After delivery the neonate was checked by pediatrician by calculating the Apgar score, birth weight and send to the neonatal care unit to be checked for any sign of infection, by checking the general condition of the baby and taking blood samples for WBC count, CRP, PCV% and blood culture. Antibiotic was given to the neonates for 3 days. Subclinical infection (without signs of infection: fever, tachycardia and uterine tenderness) was categorized with WBC count of ≥ 15000 c/mm³ and CRP of being positive. Histological chorioamnitis, which is diagnosed by microscopical analysis of placenta and the neonatal congenital infection, which was assessed by neonatologist depending upon clinical signs and laboratory tests, which were WBC counts and CRP.

Each patient assigned a serial identification number. The data were analyzed using Statistical Package for Social Sciences (SPSS) version 20. Analysis of variances (ANOVA test) was used to assess the significance of differences between the continuous variables, with LSD post-hoc test. Receiver operator curve (ROC) was done for prediction of validity values for Procalcitonin and White blood cell in differentiating of chorioamnionitis and neonatal infection and P-Value less than 0.05 was used as alpha level of significance.

RESULTS

In our study, we observed the level of PCT in four groups (PPROM, PROM, healthy preterm and term groups) and its role in diagnosis of subclinical chorioamnionitis .

There was significant difference in birth weight and gestational age between the groups as group 1 and 3 includes preterm pregnancy with PROM and healthy preterm pregnancy respectively and group 2 and 4 include term pregnancy. There was no significant difference detected regarding other factors like age, maternal body mass index (BMI), parity and mode of delivery as shown in table 1 .

In table 2 and 3 the level of maternal plasma PCT was significantly higher in group 1 (0.171 ±0.078) ng/ml than in group 2 (0.09 ± 0.052) ng/ml and other healthy control groups 3&4 (0.03 ± 0.015 and 0.038 ± 0.021) ng/ml. Also higher in group 2 than group 3 and 4 regardless of weeks of gestation.

WBC count was significantly higher in group 1 (13691 ± 2569) c/mm³ in comparison with group3 (9504 ±1795) c/mm³ of the same gestational age and group 4 (6959 ±1797) c/mm³. However, there was no significant difference between group 1 and group 2 (12013 ± 2603) c/mm³.

Although the number of patients with positive CRP results was higher in group 1 than the other 3 groups, there was no significant difference between these groups, as the p-value 0.328. There was no significant difference regarding neonatal infection between the four groups as the p-value 0.096.

Table 1: Comparison among study groups, according to clinical characteristics of the patients, N=100.

Parameters	Group 1 N=30 Mean ± SD	Group 2 N=25 Mean ± SD	Group 3 N=20 Mean ± SD	Group 4 N=25 Mean ± SD	p-value [a]
Age (years)	27.2 ± 4.1	28.1 ± 4.6	28.8 ± 4.7	27.4 ± 4.2	0.574
Birth-weight (g)	1697± 615	3148 ± 327	2975 ± 264	3376 ± 271	<0.001 *
Maternal BMI (kg/m2)	29.3 ± 3.8	29.0 ± 3.6	29.6 ± 4.0	28.4 ± 2.9	0.623
Gestational age (weeks)	31.7 ± 2.8	38.2 ± 1.1	32.1 ± 2.4	38.0 ± 0.9	<0.001 *
Variables	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**p-value [b]**
Primi-gravida	9 (30)	13 (52)	8 (40)	15 (60)	0.115
Caesarean section	14 (46.7)	12 (48)	11 (55)	13 (52)	0.937

*Significant at 0.05 level, [a] ANOVA test, [b] chi-square test

Table 2: Comparison among study groups, according to laboratory indices, N=100.

Parameters	Group1 N=30 Mean ± SD	Group2 N=25 Mean ± SD	Group3 N=20 Mean ± SD	Group4 N=25 Mean ± SD	p-value [a]
WBC c/mm³	13691 ± 2569	12013 ±2603	9504 ± 1795	6959 ± 1797	<0.001*
Procalcitonin (ng/ml)	0.171 ± 0.078	0.09 ± 0.052	0.03 ± 0.015	0.038 ± 0.021	<0.001*
	No. (%)	No. (%)	No. (%)	No. (%)	p-value [b]
Positive C-RP	6 (20%)	4 (16%)	2 (10%)	1 (4%)	0.328
Neonatal infection	7 (23.3%)	5 (20%)	1 (5%)	1 (4%)	0.096

*Significant at 0.05 level, [a] ANOVA test, [b] chi-square test

Table 3: Mean difference among patients groups (group 1 and 2) and control groups (group 3 and 4) (LSD post-hoc test). N=100.

Dependent Variable	(I) Groups	(J) Groups	Mean Difference (I-J)	p-value
Procalcitonin (ng/ml)	Group 1	Group 2	0.08096	<0.001 *
		Group 3	0.14064	<0.001 *
		Group 4	0.13264	<0.001 *
	Group 2	Group 3	0.05968	<0.001 *
		Group 4	0.05168	<0.001 *
WBC	Group 1	Group 2	678.64	0.284
		Group 3	3187.28	<0.001 *
		Group 4	5732.64	<0.001 *
	Group 2	Group 3	2508.64	<0.001 *
		Group 4	5054	<0.001 *

* The mean difference is significant at the 0.05 level.

In table 4, we did comparison between PCT, WBC and CRP regarding their role in diagnosis of neonatal sepsis and histological chorioamnionitis in-group 1.

Table 4. Prognostic value of maternal PCT, CRP and WBC in the prediction of neonatal infection and histological chorioamnionitis

	Validity values	Procalcitonin (ng/ml)	WBC c/mm3	C-RP
histological chorioamnionitis	Cut off value	0.08	15000	
	Sensitivity (%)	96.0%	88.0%	90.5%
	Specificity (%)	82.0%	76.0%	40.0%
	PPV (%)	84.2%	78.6%	55.4%
	NPV (%)	95.3%	86.4%	88.0%
neonatal infection	Cut off value	0.05	15000	
	Sensitivity (%)	85.7%	64.3%	89.3%
	Specificity (%)	48.8%	73.3%	48.0%
	PPV (%)	62.6%	75.6%	58.0%
	NPV (%)	77.4%	77.2%	85.7%

PCT was more significant in detection of histological chorioamnionitis than in neonatal sepsis, as the cut off value was 0.08, with high sensitivity 96%, specificity 82%, positive predictive value (PPV) 84.2% and negative predictive value (NPV) 95.3%. While in neonatal infection, the cut off value of 0.05 with sensitivity 85.7%, specificity 48.8%, PPV 62.6% and NPV 77.4 % showed that PCT was not so significant in detection of neonatal infection.

PCT was more significant than WBC and CRP in detection of histological chorioamnionitis.

WBC count was significant in detection of histological chorioamnionitis more than neonatal infection, with a cut off value of 15000, sensitivity 88%, specificity 76%, PPV 78.6%, NPV 86.4%; while in neonatal infection the sensitivity 64.3%, specificity 73.3%, PPV 75.6%, NPV 77.2%.

CRP was significant in detection of both histological chorioamnionitis (sensitivity 90.5%, specificity 40%, PPV55.4 and NPV 88%) and neonatal infection ((sensitivity 89.3%, specificity 48%, PPV58 and NPV 85.7%). CRP was more significant than PCT in detection of neonatal infection.

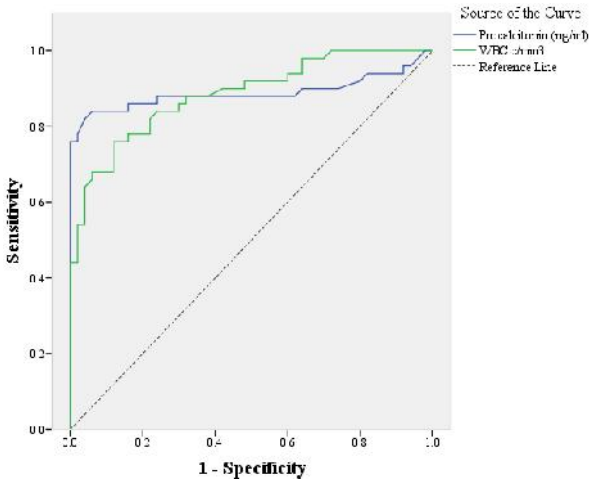

Figure 1: Receiver–operator curve analysis of Procalcitonin and white blood cell (WBC) count for the prediction of histological chorioamnionitis.

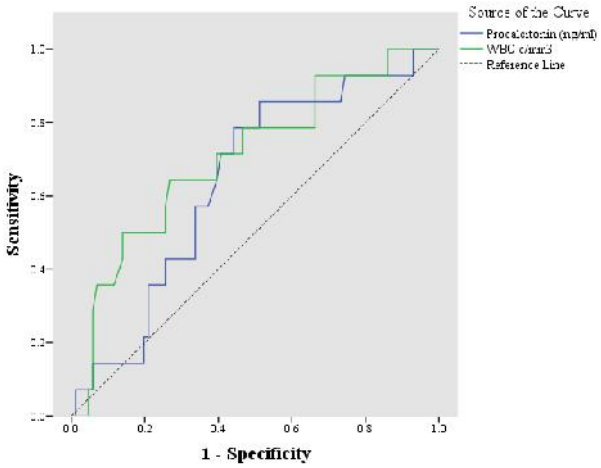

Figure 2: Receiver–operator curve analysis of Procalcitonin and white blood cell (WBC) count for the prediction of neonatal infection.

DISCUSSION

PPROM management remains a challenge for obstetricians. The current management is generally observation with bed rest antibiotic prophylaxis and steroid therapy until labor started or signs of infection developed.[16,17] Early recognition of intraamniotic infection is very important in women with rupture membrane wither term or preterm.[18] This early recognition is very important because clinically intrauterine infection may not appear until the fetus is affected neurologically and fetal inflammatory response syndrome (FIRS) developed.[19]

Numerous studies have demonstrated that measuring various mediators in amniotic fluid by amniocentesis, although highly accurate, is an invasive technique may be difficult to perform when there is sever oligohydramnious,[18] carry risk of complications mainly intrauterine infection and cannot be repeated frequently.[20] Therefore, alternative indirect non-invasive methods are proposed using various maternal serum markers such as proinflammatory cytokines, CRP, WBC, neutrophil counts, granulocyte elastase, ferritin or glycodelin.[18]

PCT is very important marker in the evaluation of infection (mainly bacterial), and direct correlation is seen between PCT level and final outcome.[21]

In our study we found that maternal plasma PCT was significantly higher in group 1 (PPROM) than in group 2 (PROM) and control group 3 & 4 (preterm and term healthy control groups respectively) and higher in group 2 than in group 3 & 4, but the difference was not significant. Our result agree with two studies done by Trobe et al., in 2004 & 2007,[18] and agree with T. Oludag et al and S.G. Ahmetasevic et al. in 2014, all showed significantly higher maternal plasma PCT level in pPROM than PROM at term and control groups.[22,23]

Our result disagree with the study of Thornburg LL, et al. on 2015 found that PCT was not detected in PPROM patients at admission or in uncomplicated control group.[24]

No significant differences in the PCT levels was observed in our study among group 3 (0.03 ng/ml) and group 4 (0.038 ng/ml) control group. This was in agreement with Morgenthaler et al. study on 2002.[25]

Second aim of our study was detection of subclinical intrauterine infection; WBC and CRP were measured in group 1 patients and compared the result with the mean PCT level, we find that PCT is more significant in the detection of histological chorioamnionitis; with a cut off value of 0.08 and sensitivity 96 %, specificity 82 %, PPV 84.2 %, and NPV 95.3 %; than in neonatal infection with a cut off value of 0.05 and sensitivity 85.7 %, specificity 48.8 %, PPV 62.6 %, and NPV 77.4%. It is also more significant than WBC and CRP in detection of histological chorioamnionitis. This agree with results of Kopyra P. et al. study in 2010 on 46 patients with PROM and comparison between PCT, IL-6, and CRP to assess the usefulness of these markers in detection of intraamniotic and newborn infection. They concluded that PCT was superior than others in prediction of infection.[26] Also agree with T.Oludag. et al study on 2014 Who found that PCT was more significant in prediction of histological chorioamnionitis than neonatal infection and it was more significant in prediction of histological chorioamnionitis than CRP and WBC count.[22]

Another study agree with us done by S. G. Ahmetasevic et al. on 2014 who did a study on 120 pregnant women, 60 patients with PROM and 60 healthy control pregnant women, they measure PCT and CRP, did comparison between them. Their result was both markers were predictive for chorioamnionitis and neonatal infection with almost similar significance.[23]

Finally Cetin O. et al. agree with us by his study on 2016 on 57 pregnant patients complicated with PPROM aimed to comparing the early diagnostic accuracy of maternal blood WBC, CRP and PCT in predicting early onset neonatal sepsis among early PPROM pregnancies. They found maternal blood PCT levels were superior to maternal blood CRP and WBC count in predicting early onset neonatal sepsis.[27]

Our results disagree with the result of Trobe. et al who did a study in 2007 on 142 patients (PPROM, PROM, control preterm and term groups), and found that the value of maternal plasma PCT determinations in the diagnosis of subclinical intraamniotic infection, as well as for prediction of newborn infection or histological chorioamnionitis was unsatisfactory. As the cutoff value for PCT against newborn infection or histological chorioamnionitis showed highest sensitivity and specificity corresponded to a concentration of 1.9 ng/ml, but the predictive values were generally poor, as well as the predictive values of WBC count and CRP level.[18]

Regarding WBC count in our study, WBC was more significant in detection of histological chorioamnionitis than in neonatal infection, with a cut off value of 15000 and sensitivity 88 %, specificity 76 %, PPV 78.6 %, NPV 86.4 %, in relation to a cut off value of 15700 and sensitivity 64.3 %, specificity 73.3 %, PPV 75.6 %, and NPV 77.2 %. During pregnancy,

WBC normally increase and we can't rely on.[28] Our results disagree with the result of Trobe.et al on 2007 who found that WBC was poor in prediction of both newborn infection and histological chorioamnionitis.[18] Also disagree with T. Oludag et al who found that WBC was more of value in the evaluation of neonatal sepsis than histological chorioamnionitis.[22]

Finally, our study found that CRP is significant in diagnosis of both histological chorioamnionitis with sensitivity 90.5 %, specificity 40 %, PPV 55.4 %, and NPV 88 %; and in neonatal infection with sensitivity 89.3 %, specificity 48 %, PPV 58 %, and NPV 85.7 %. CRP is more significant than PCT in diagnosis of neonatal infection. Therefore, CRP appears to be better than PCT for anticipating neonatal infection because a PCT reference value during first 72 hours of life is not established yet. This agrees with T.Oludag. et al on 2014 who found that CRP was significant in detection of both histological chorioamnionitis and neonatal infection, and it was better than PCT in prediction of neonatal infection.[23] Also agree with S. G.Ahmetasevic et al on 2014 who found that CRP had similar significance of PCT in detection of neonatal infection and histological chorioamnionitis.[23] The result disagree with Trobe et al, 2007,[18] Kopyra P.et al 2010,[26] and Cetin O.et al, 2016.[27] They found that CRP was not so useful in the detection of both type of infection.

This disagreement between our study and other studies may be due to difference in the number of samples in each study, type of the kits and methods of measurement, gestational age, and socioeconomic state.

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