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Research Article

Maternal Serum Ferritin, C-Reactive Protein, and Procalcitonin Levels for Predicting Subclinical Intra-Amniotic Infection in Preterm Premature Rupture of Membrane

Balsam N. Ibrahim*[1], Maad M. Shallal[2]
[1] *Department of Obstetrics and Gynecology, Baghdad Teaching Hospital, Baghdad, Iraq.*
[2] *Department of Obstetrics and Gynecology, College of Medicine, University of Baghdad, Baghdad, Iraq.*

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Abstract

Background: The preterm premature rupture of the membrane is linked to various perinatal problems, including chorioamnionitis.

Objectives: To evaluate the use of serum ferritin, C-reactive protein, and procalcitonin as early indicators for predictions of subclinical intra-amniotic fluid infection.

Methods: A case-control study was conducted at Baghdad Teaching Hospital from January to October 2021. A convenient sample of 90 singleton pregnant women with a live fetus between 24 - 36 weeks of gestation were divided into three groups: Group 1 (controls) included 30 women with intact membranes and no signs of labour seen in the outpatient obstetrics clinic in Baghdad Teaching Hospital; Group 2 included 30 women with preterm premature rupture of membrane (PPROM) but without chorioamnionitis; and Group 3 included 30 women with PPROM and chorioamnionitis. The second and third groups were collected from the labour room in Baghdad Teaching Hospital.

Results: There was no significant difference in the levels of C-reactive protein between the study groups. Serum ferritin and Procalcitonin levels were normal in all of the participants, with a significant difference in the level of Procalcitonin between group 2 (PPROM with chorioamnionitis) and group 3 (PPROM without chorioamnionitis).

Conclusion: Procalcitonin might be used to detect the presence of chorioamnionitis. Serum ferritin and C-reactive protein had no role in the detection of chorioamnionitis among patients with preterm premature membrane rupture.

Keywords: C-reactive protein; Chorioamnionitis; Procalcitonin; Preterm premature rupture of membrane; Serum ferritin.

Introduction:

The World Health Organization defined Preterm birth as any birth occurring before 37 completed weeks of gestation or within 259 days after a woman's last menstrual cycle. Preterm delivery is the main cause of mortality in children under the age of five, accounting for around 35% of newborn infant deaths and 16% of all deaths (1).

Preterm birth is a global issue with 15 million children delivered prematurely each year (2). However, discrepancies in gestational age, preterm definitions, and data collection and reporting methods complicate estimations. The incidence rates are higher in developing countries than in developed countries (3, 4). About 30-35% of preterm births are caused by maternal or fetal factors in which labour is induced or the infant is delivered via cesarean section, 40-45% are due to spontaneous preterm births with intact membranes, while preterm premature rupture of the membrane (PPROM), regardless of vaginal or cesarean delivery, accounts for 25-30% of preterm births (5). PPROM is the rupture of the amniotic membranes (amnion and chorion) before the 37th week of gestation, and it complicates about 1% of deliveries (6, 7).

Chorioamnionitis is an acute inflammation of the placental membranes and chorion produced by infection of polymicrobial bacteria that ascend following membrane rupture. Clinical chorioamnionitis refers to the presence of certain clinical indicators, whereas subclinical chorioamnionitis refers to the absence of specific clinical signs (8). Early and definitive diagnosis of subclinical chorioamnionitis is critical for preventing maternal and newborn death and morbidity, especially in situations of PPROM. Some biochemical biomarkers with high diagnostic accuracy and the ability to detect subclinical chorioamnionitis early in

* *Corresponding Author: Balsam.nahedh@gmail.com*

pregnancy would be extremely valuable in clinical practice (9).

Serum ferritin can be considered as an indicator for infections in PPROM. The elevated ferritin levels could indicate an acute phase response to a subclinical genital tract infection or inflammation and a latent infectious process that is associated with preterm delivery and causes tissue damage (10).

C-reactive protein (CRP) is an acute-phase protein. During an infection, the liver produces CRP in response to interleukin-6 synthesis. Although maternal serum CRP levels increase somewhat with gestational age, this measure is nevertheless utilized as a predictor of intrauterine infection, particularly in PPROM instances, despite reports suggesting its benefits are inconsistent (11).

Procalcitonin (PCT) is a peptide precursor of calcitonin, but the biological function and induction are different from that of calcitonin. It consists of 116 amino acids(12). The production of PCT is elicited by endotoxin or mediators released in bacterial infections, and this production correlates with the severity and extent of the infection (13). As the PPROM is associated with an inflammatory process, PCT can be used as a good indicative marker of infection for preterm labour (1).

The study aims to evaluate the use of serum ferritin, CRP, and PCT as an early indicator for predictions for subclinical intra-amniotic infection.

Patients and Methods:

An analytic case-control study was conducted at Baghdad Teaching Hospital during the period from the 1st of January to the 1st of October 2021.

The study was approved by the Scientific Council of Gynecology and Obstetrics of the Iraqi Board of Medical Specializations. Women were asked to participate voluntarily after an adequate explanation about the study's aim and methods. All participants were assured of anonymity and confidentiality of information.

Sampling method and inclusion criteria:

A convenient sampling method was used to select 90 singleton pregnant women with a live fetus between 24 to 36 weeks of gestation who were sub-divided into three groups, 30 members each:

Group 1 (control group): Included 30 women at preterm gestation without labour, and with intact membranes, the sample was collected from the outpatient clinic of obstetrics in Baghdad Teaching Hospital.

Group 2: Included 30 patients with PPROM but without chorioamnionitis.

Group 3: Included 30 patients with PPROM and chorioamnionitis.

The second and third groups were collected from the labour room in Baghdad Teaching Hospital.

Exclusion criteria:

- Women who had medical or obstetrical diseases including diabetes mellitus, hypertension, chronic kidney disease, chronic liver disease, cancer, heart disease, infectious disease, and antepartum haemorrhage.
- Evidence of intrauterine growth restriction (IUGR) or congenital abnormalities of the fetus
- Consumption of non-steroidal anti-inflammatory drugs (NSAIDs), or immunosuppressant drugs such as steroids.

Data collection:

A structured questionnaire form was used for data collection. The gestational age was calculated by the date of the last menstrual period, early ultrasound, or both. To confirm the diagnosis of PPROM, a warm speculum was inserted in the vagina under aseptic conditions to detect the pooling of clear fluid in the posterior fornix of the vagina or leakage of fluid from the cervical os with the woman in dorsal position. Five milliliters of venous blood samples were taken from each participant by the researcher and sent to the Teaching Laboratories in the Directorate of the Medical City where they were centrifuged for 10 minutes at 3500 rpm. After that, the serum was separated and stored at −20 to −80°C and sent to a private laboratory to detect the levels of serum ferritin, CRP and Procalcitonin.

Statistical analysis:

The data was entered and analyzed by the Statistical Package for Social Sciences (SPSS) version 22. Descriptive statistics were presented as frequencies and percentages and were applied to explain the characteristics of participants. The mean values of the study parameters in the study group were compared using the t-test and the associations between the variables were tested using the Chi-Square test. A P-value of less than 0.05 was considered statistically significant.

Results:

Table 1 shows that there was no significant association between CRP tests and the presence of PPROM with chorioamnionitis. The sensitivity was 60%, specificity 64%, positive predictive value (PPV) 70%, and negative predictive value (NPV) 53%. Similarly, there was no significant association between CRP tests and the presence of PPROM without chorioamnionitis. Sensitivity was 48%, specificity 48%, PPV 43%, and NPV 35%.

Table 1: Distribution of C-reactive protein test in the controls and the PPROM with, and without chorioamnionitis groups

Groups	CRP		Total (100.0%)	P-value
	Positive- N (%)	Negative- N (%)		
PPROM with chorioamnionitis	21 (70.0)	9 (30.0)	30	0.066
Controls	14 (46.7)	16 (53.3)	30	
Total	35 (58.3)	25 (41.7)	60	
PPROM without chorioamnionitis	13 (43.3)	17 (56.7)	30	0.795
Control	14 (46.7)	16 (53.3)	30	
Total	27 (45.0)	33 (55.0)	60	

The serum ferritin levels were normal in the three study groups with no significant difference in their mean values between control group and PPROM with chorioamnionitis groups and without chorioamnionitis groups respectively, Table 2.

Table 2: Mean± SD serum ferritin level in the three study groups

Groups	N	Serum ferritin (ng/mL)		P-value
		Mean	±SD	
Control	30	48.64	57.952	0.620
PPROM with chorioamnionitis	30	55.60	49.819	
Control	30	48.64	57.952	0.683
PPROM without chorioamnionitis	30	42.97	48.643	

Table 3 shows that all groups had a normal mean level of procalcitonin. When the ANOVA test was applied, a significant difference was detected between the mean values of PCT in the three study groups.

Table 3: Mean ±SD serum Procalcitonin level in the three study groups

Groups	N	Procalcitonin (ng/ml)		P-value
		Mean	±SD	
Controls	30	0.21	0.039	0.011
PPROM with chorioamnionitis	30	0.23	0.028	
PPROM without chorioamnionitis	30	0.20	0.029	

Significant association according to ANOVA and Post Hoc test

As a significant difference in the level of PCT between the study groups was found, the Receiver Operating Characteristic (ROC) Curve analysis for medical diagnostic test evaluation was done to estimate a cut-off point between normal and abnormal values with better sensitivity and specificity (Figure 1).

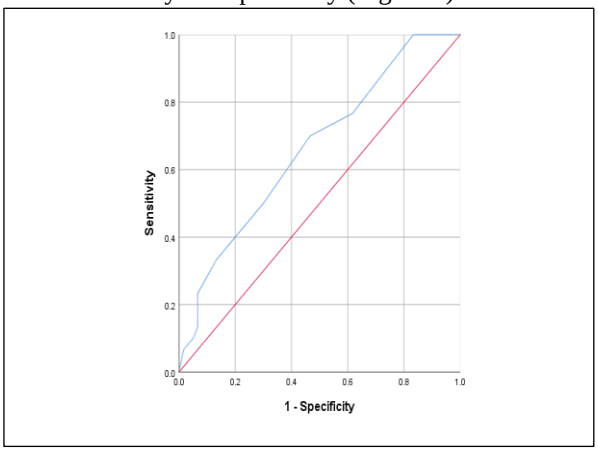

Figure 1: Roc curve analysis for diagnostic evaluation of procalcitonin

According to the ROC test, the better cut-off point was 0.21 ng/ml with 70% sensitivity and 60% specificity, with a significant association between the test results and the presence or absence of chorioamnionitis, (P <0.05), Table 4.

Table 4: Distribution of procalcitonin according to the cut-off point of 0.20 ng/ml

Procalcitonin	Groups N (%)		Total N (%)	P-value
	PPROM* With chorioamnionitis	PPROM* without chorioamnionitis		
Positive	21 (70.0)	12 (40.0)	33 (55.0)	**0.018**
Negative	9 (30.0)	18 (60.0)	27 (45.0)	
Total (100.0%)	30	30	60	

Sensitivity=70%. Specificity=60%. ***Preterm premature rupture of membrane***

Discussion:

The mother and the fetus are at risk of problems if chorioamnionitis is not detected early (14). This study is one of the studies that tried to evaluate the diagnostic value of positive maternal CRP, serum ferritin, and procalcitonin in association with maternal clinical chorioamnionitis.

The initial finding of the current study was the absence of a significant link between CRP test results and the existence of chorioamnionitis in the study groups. An earlier study by Wiwanitkit in Thailand revealed that the overall diagnostic activity showed the values of sensitivity, specificity, PPV, and NPV of 72.8%,

76.4%, 23.6%, and 27.2%, respectively (15). Balciuniene et al found the values of the same indicator to be 84%, 77%, 74%, and 86% respectively (16). A systematic review by Martinez et al concluded that of the eight studies reviewed, three studies concluded that CRP was a useful diagnostic tool for chorioamnionitis while the other five studies concluded the opposite (17). The discrepancy in the results of CRP and its diagnostic effectiveness in the diagnosis of chorioamnionitis might be related to the participant's condition and may affect the level of CRP, the accuracy of the investigation, and the methodology of these studies.

In the current study, there was no significant difference between the study groups regarding the mean of serum ferritin. In contrast, Valappil et al found that serum ferritin was significantly higher in PPROM cases when compared to the control group of women with the same gestational period (10). Khattab *et al.* concluded that serum ferritin levels may serve as a marker of infection among women with premature rupture of membranes (18). The difference in these results could be due to the prevalence of iron deficiency in different populations.

In the current study, all the participants had normal PCT levels, but the mean was significantly higher in patients who had PPROM with chorioamnionitis than those without chorioamnionitis. The same finding was reported by Şen C *et al.* who found that the mean procalcitonin values among PPROM with chorioamnionitis patients were significantly higher than those among PPROM without chorioamnionitis (19), while other studies concluded that serum PCT is a poor predictor for clinical or pathological chorioamnionitis (20). With a cut-off value of 0.05ng/mL, the sensitivity of PCT was 54%, and the specificity was 79%, with positive and negative predictive values of 60% and 75%, respectively (21). Bakar et al concluded that low or average PCT does not rule out bacterial infections, particularly in localized infections like chorioamnionitis, because PCT's sensitivity and specificity in the diagnosis of chorioamnionitis are low (22). The discrepancy in the results of inflammatory markers between different studies might be related to the prevalence of other asymptomatic infections that may impact the results.

Limitations:

1. Small sample size.
2. Short data collection time.
3. Long distance between sample collection place and private laboratory.
4. Relatively high investigation cost.

Conclusion:

Procalcitonin might be used to detect the presence of chorioamnionitis. Serum ferritin and CRP had no role in the detection of chorioamnionitis among patients with preterm premature rupture of the membrane.

Authors' declaration

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for re-publication attached to the manuscript. Authors sign on ethical consideration's Approval-Ethical Clearance: The project was approved by the local ethical committee in the Scientific Council of Gynecology and Obstetrics of the Iraqi Board of Medical Specializations according to the code number (55) on (8th of November 2020)

Conflict of Insert : None.

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Authors' contributions

Study conception & design: (Maad M. Shallal). Literature search: (Balsam N. Ibrahim). Data acquisition: (Balsam N. Ibrahim). Data analysis & interpretation: (Balsam N. Ibrahim). Manuscript preparation: (Balsam N. Ibrahim). Manuscript editing & review: (Maad M. Shallal).

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مستويات الفيريتين في مصل الأم والبروتين سي التفاعلي والبروكالسيتونين للتنبؤ بالعدوى داخل السلى تحت الإكلينيكي في تمزق الغشاء المبكر قبل الأوان

بلسم ناهض إبراهيم، مستشفى بغداد التعليمي، بغداد، العراق.
معد مهدي شلال، فرع النسائية والتوليد، كلية الطب ، جامعة بغداد، بغداد، العراق.

الخلاصة
الخلفية: يرتبط تمزق غشاء الحمل قبل الأوان بالعديد من المضاعفات في الفترة المحيطة بالولادة بما في ذلك إلتهاب المشيمة والسلى.
الهدف: لتقييم إستخدام الفيريتين في مصل الدم وبروتين سي التفاعلي والبروكالسيتونين كمؤشرات للتنبؤات بعدوى السائل الأمنيوسي.
الطريقة المنهجية: تم إجراء دراسة تحليلية للحالات والشواهد في مستشفى بغداد التعليمي خلال الفترة من 1 كانون الثاني إلى 1 تشرين الأول 2021. تم تسجيل عينة ملائمة من 90 إمرأة حامل بجنين واحد حي في عمر حمل من 24 إلى 36 أسبوعًا.
النتائج: لم تجد الدراسة فرقا ذا دلالة إحصائية في نتائج بروتين سي التفاعلي بين مجموعات الدراسة. كان لدى جميع المرضى مستوى طبيعي من البروكالسيتونين والفيريتين في مصل الدم.
الإستنتاج: يمكن استخدام البروكالسيتونين للكشف عن وجود التهاب المشيمة والسلى. لم يكن للفيريتين في مصل الدم وبروتين سي التفاعلي دور في الكشف عن التهاب المشيمة والسلى بين المرضى الذين يعانون من تمزق الغشاء المبكر قبل الأوان.
الكلمات المفتاحية: الفيريتين في مصل الدم، البروكالسيتونين، بروتين سي التفاعلي، التهاب المشيمة والسلى.