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Preterm Premature Rupture of Membranes and the Value of Serum Ferritin During Pregnancy /Al-Elwyia Teaching Hospital / Baghdad / 2023

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Abstract

Background: Premature rupture of the membranes (PROM) is the term used to describe membrane rupture that occurs before labor begins. Membrane rupture that occurs before 37 weeks of gestation and before childbirth is referred to as preterm PROM (PPROM). Acute phase reactant ferritin rises in response to inflammation. The purpose of this study was to look at the usefulness of serum ferritin as a PPROM marker. This study aimed to investigate the usefulness of serum ferritin as a marker for PPROM.

Methods: A cross-sectional study was carried out in the department of obstetrics & gynecology of Al-Elwyia Teaching Hospital for 9 months. This study included 180 pregnant women, they were divided into three groups: the PPROM group included 60 women presented with PPROM, the Spontaneous labor group included 60 women presented with spontaneous preterm labor, and the control group included 60 healthy pregnant women. A structured questionnaire was designed, and it

included age, parity, gravidity, gestational age, obstetrical history, and gynecological and past medical histories. Venous blood samples of 5 ml were collected in plain tubes from each patient to measure serum ferritin. ANOVA test with LSD post-hoc test was used to compare the significant difference between the three groups. Analysis of receiver operating characteristic curves was utilized to forecast serum ferritin's diagnostic ability in PPROM. Statistical significance was considered whenever the P value was less than 0.05.

Results: Ferritin levels were significantly different between the three groups. Post hoc multiple comparisons showed that the PPROM group had significantly higher ferritin levels when compared with the spontaneous preterm group and the controls, while there was no significant difference in serum ferritin levels between the spontaneous preterm group and the control group. The optimal cut-off ferritin level for predicting PPROM was 37.41 ng/ml with sensitivity and specificity of 80.8% and 91.6% respectively, and accuracy of 84.4%.

Conclusions: This study concluded that ferritin levels were significantly raised in the PPROM group compared with the other two groups. The use of ferritin as a predictor for PPROM is recommended as it does not require additional instruments when a ferritin kit is available, and the results of the test can be taken rapidly.

Keywords: PPROM, Ferritin, Pregnant Women, Preterm Labor

Introduction

Premature rupture of membranes (PROM) refers to a pregnant who is < 37 weeks' gestation and has been presented with a rupture of membranes before the onset of labor. This event can lead to the leakage of fluid through the birth canal before the initiation of active labor [(1)]. It is divided into two categories based on gestational age: prolonged PROM, which is a case of prelabour rupture of membranes in which more than 18 hours have passed between the rupture and the start of labor, and prelabour rupture of membranes (PROM), which occurs when the fetal membranes rupture early, at least one hour before labor has started. Rupture of membranes during labor before term (PPROM): prelabor membrane rupture that happens before 37 weeks of gestation, as well as mid-trimester PPROM, also known as pre-viable PPROM: prelabor membrane rupture that happens before 24 weeks of gestation [(2)]. Although PROM can have many different etiologies, its genesis is often unclear. The most common causes of postpartum hemorrhage (PPROM) include a history of the condition, short cervical length, vaginal bleeding in the second or third trimester, uterine overdistension, nutritional deficiencies in ascorbic acid and copper, connective tissue disorders, low body mass index, low socioeconomic status, smoking, and illicit drug use [(3)]. When PROM occurs both at term and preterm, it is linked to serious infections in both the mother and the fetus. When it comes to preterm illnesses, chorioamnionitis is the most prevalent type. The prenatal health of infants with PROM is complicated; those born to moms who have the condition may have birth asphyxia, neonatal infection, and ultimately neonatal mortality [(1)].

An estimated 13.4 million babies were born preterm in 2020 [4]. Preterm delivery problems are the leading cause of death for children < 5 years, accounting for over 900,000 deaths in 2019. Preterm birth rates range from 4 to 16 percent of babies born in 2020, depending on the country [5]. Approximately 8% of term pregnancies are complicated with PROM, and 20% of them result in chronic PROM. Less than 1% of pregnancies result in membrane rupture before viability, and PPROM complicates about 30% of all premature births [6, 7]. Prematurity is a financial burden on society as well as an emotional burden on families because it is the primary cause of newborn morbidity and mortality [8]. The gestational age and the presence or absence of problems dictate the course of treatment. Induction of labor is often advised for infants who are at or near term and are not experiencing any difficulties. It is also possible to allow time for labor to start on its own. When there are no difficulties during the first 24 to 34 weeks of pregnancy, corticosteroids and careful monitoring are advised. According to a 2017 Cochrane analysis, delaying before 37 weeks typically produced better results. Individuals who are susceptible to Group B streptococcus may receive antibiotics. In most cases, delivery is advised for individuals experiencing difficulties, regardless of the stage of pregnancy [9].
High serum levels of ferritin have been linked to several acute phase events, including inflammatory disorders. Ferritin is a diagnostic marker. It is hypothesized that by monitoring blood ferritin levels, a sensitive inflammatory marker, one can successfully predict the occurrence of preterm birth in high-risk individuals, given the primary role that inflammation plays in the development and manifestation of preterm delivery. Elevated blood ferritin concentrations and premature labor have been linked by certain researchers [10]. The predictive ability and the cut-off point of serum ferritin as a predictor for preterm delivery have not been substantially identified in Iraqi women. This study aimed to investigate the usefulness of serum ferritin as a marker for PPROM.

Patients And Methods

Study Design and Setting. : This is a descriptive cross-sectional study carried out in the obstetrics & gynecology and laboratories departments at Al-Elwyia Teaching Hospital. The period of the study was from the 1st of April till December 2023. A total of 180 pregnant women were recruited for this study, and they were divided into three groups matched for hemoglobin level and period of gestation. The 1st group included 60 pregnant women who complained from PPROM (PPROM group), the 2nd group included 60 pregnant women who presented with spontaneous preterm labor (Spontaneous preterm group), and the 3rd group included 60 healthy pregnant women (Control group). The participants in this study were pregnant women who visited the Department of Obstetrics and Gynecology, had singleton viable pregnancies, and had gestational ages between 28 and 36 +/- 6 weeks, as determined by obstetrical criteria based on an accurate last menstrual period or early ultrasonography. Patients who refused to participate or had any of the following conditions were excluded from the study: anemia, iron overload state, previous chronic infective disease, multiple pregnancies, polyhydramnios, diabetes, genital tract infections, vaginal douching or sexual intercourse in the previous 24 hours, thyroid disease, liver disease, kidney disease, and tumor.

Data Collection Tools: A structured questionnaire was designed for this study, and it included (the age of participant women, parity & gravidity, abortion history, gestational age, obstetrical & gynecological histories, past medical history, and social history). Supernatants were gathered with care. A serum that has been separated is kept at -60°C or below until the analysis is finished. Sandwich-ELISA is the foundation upon which ELISA kit's function. An antibody specific to Human FE has already been pre-coated on the micro-ELISA plate included with this kit. The micro-ELISA plate wells are filled with standards or samples, and the antibody is then added. Each microplate well is then filled with the Avidin-Horseradish Peroxidase (HRP) conjugate and a biotinylated detection antibody specific for Human FE. The combination is then incubated. Free parts are removed by washing. Pour the substrate solution into every well. The only wells that will be blue in color are those that contain Human FE, biotinylated detection antibody, and Avidin-HRP conjugate. When the stop solution is added, the enzyme-substrate reaction is stopped and the color changes to yellow. Spectrophotometry is used to determine the optical density (OD) at a wavelength of 450 nm ± 2 nm. There is a linear link between the OD value and the Human FE concentration. The concentration of human FE in the samples may be determined by comparing the optical density (OD) of the sample with the standard curve.
Statistical Packages for Social Sciences- version 25 was used for analysis of the collected data. Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). Categorical data is presented by frequencies and percentages. A Shapiro–Wilk test confirmed that the data were normally distributed. Therefore, an independent t-test and Analysis of variances (ANOVA) test with multiple comparisons was used to detect the significant difference among study groups. Analysis of receiver operating characteristic curves was utilized to forecast serum ferritin's diagnostic ability in PPROM. Statistical significance was considered whenever the P value was less than 0.05.

Results

This study included 180 pregnant women with singleton pregnancy. They were divided into three groups: 1st group included 60 pregnant women with PPROM (PPROM group), 2nd group included 60 pregnant women with spontaneous preterm labor (Spontaneous preterm group), and 3rd group included 60 healthy pregnant women (Control group). The mean age was 26.82 ± 5.84 years in the PPROM group, 25.83 ± 6.01 in the spontaneous preterm group, and 25.77 ± 7.23 in the control group. The mean parity was 2.35 ± 1.08 in the PPROM group, 2.28 ± 1.59 in the spontaneous preterm group, and 2.55 ± 1.81 in the control group. The mean hemoglobin level was 12.01 ± 2.66 g/dl in the PPROM group, 12.57 ± 2.63 g/dl in the spontaneous preterm group, and 13.04 ± 1.79 g/dl in the control group. No significant difference was found between the three studied groups regarding age, parity, gestational age, and hemoglobin level. As illustrated in (Table 1).

Table (1): Comparison between the three studied groups according to baseline characteristics

Patients' Characteristics	Study Groups			P - Value
	PPROM Group Mean ± SD	Sp. Preterm Group Mean ± SD	Control Group Mean ± SD	
Age (Years)	26.82 ± 5.84	25.83 ± 6.01	25.77 ± 7.23	0.180
Parity	2.35 ± 1.08	2.28 ± 1.59	3.11 ± 1.35	0.611
Gestational Age (Weeks)	32.05 ± 6.27	33.92 ± 5.34	31.86 ± 7.89	0.540
Hemoglobin (G/Dl)	11.01 ± 2.66	12.57 ± 2.63	12.04 ± 1.79	0.097

This study revealed a statistically significant difference in the mean ferritin levels between the three groups. Post hoc multiple comparisons were run to confirm the differences in the mean serum ferritin between the three groups and showed that ferritin levels were significantly raised in the PPROM group compared with the spontaneous preterm group (42.21 ng/ml vs 28.36 ng/ml, P= 0.001) and the controls (42.21 ng/ml vs 25.11 ng/ml, P= 0.001) while ferritin level was not significantly different between spontaneous preterm group and control group (P= 0.097). As shown in (Table 2).

Table (2): Post hoc multiple comparisons between the three studied groups according to serum ferritin concentrations

Biomarker	Study Groups			P - Value
	PPROM Group Mean ± SD	Sp. Preterm Group Mean ± SD	Control Group Mean ± SD	
Serum Ferritin Ng/Ml	42.21 ± 11.84	28.36 ± 12.27	–	0.001
	42.21 ± 11.84	–	25.11 ± 9.08	0.001
	–	28.36 ± 12.27	25.11 ± 9.08	0.097

According to the Receiver operating characteristic (ROC), the optimal cut-off ferritin level for predicting PPROM was 37.41 ng/ml. Hence, serum ferritin > 37.41 ng/ml is a predictor for PPROM. A large significant area under the curve was (AUC= 89.2%) which indicates a significant association between a higher level of ferritin level and having PPROM. This cut-off level obtained a sensitivity and specificity of 80.8% and 91.6% respectively, with an accuracy of 84.4%. Positive predictive value and negative predictive value were 95.1% and 70.5% respectively. As illustrated in (Figure 1) and (Table 3).

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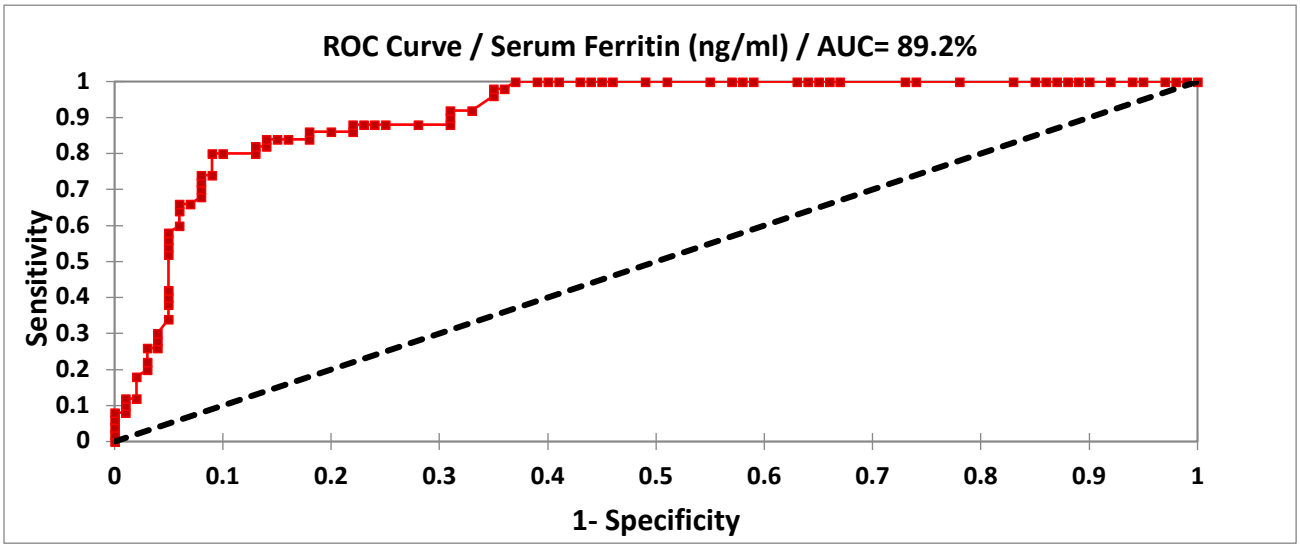

Figure (1): Receiver operating characteristic curve for serum ferritin as a predictor of PPROM

Table (3): Diagnostic accuracy of ferritin level in prediction of PPROM

Serum Ferritin (Ng/Ml)	Cut-Off Value	Sensitivity	Specificity	PPV	NPV	Accuracy
	37.41	80.8%	91.6%	95.1%	70.5%	84.4%

Discussion

The World Health Organization reports that every year, fifteen million babies are born too early and almost one million children die each year due to complications of preterm labor. Early detection of preterm labor is essential to avoid complications. Several biomarkers are now in development and found to measure serum ferritin levels as a sensitive inflammatory marker for prediction in high-risk groups [10]. This study found that the mean ferritin level was significantly different between the three studied groups, and by using Post hoc multiple comparisons we found that the ferritin concentration was significantly higher in the PPROM group compared with the spontaneous preterm and control groups (42.21 ng/ml vs 28.36 ng/ml and 25.11 ng/ml), while it was not significantly different between the spontaneous preterm group and the controls. A similar result was published from a 2015 Indian study, where the P-value of 0.012 indicated a statistically significant difference in the mean ferritin values between the PPROM group and the control group. Additionally, a P-value of 0.180 indicates that there was no statistically significant difference in the mean ferritin values between the spontaneous preterm labor group and the control group in this study [11]. Another agreement was observed in the Saha CK et al study, in which the ferritin level in the study group (PPROM and spontaneous preterm groups) was significantly higher than in the control group [12]. Elevated maternal blood ferritin

concentrations during the second trimester were linked to a higher risk of postpartum hemorrhage (PPROM) but not of spontaneous preterm labor or medically induced preterm birth, according to a Swedish study. It was also noted that women with ferritin values above 64.5 ng/mL had a twofold higher risk of PPROM compared to those with concentrations less than 26.0 ng/mL [13]. In 2018, a study was carried out in Egypt with 236 women, of whom 23 had PPROM, 17 delivered before 37 weeks but without PROM (the study group), and the rest 196 were pregnant and gave birth between 37 and 40 weeks (the control group). The serum ferritin levels of the two groups differed significantly, according to this study [14]. Contrary to our findings, a different study by Khambalia et al. found significant correlations between serum ferritin concentrations in early pregnancy and maternal age, nulliparity, and gestational age in pregnant women who experience spontaneous preterm labor or PPROM [15].

The optimal cut-off ferritin level in the present study was 37.41 ng/ml with an AUC of 89.2% for predicting PPROM. This cut-off level yielded sensitivity and specificity of 80.8% and 91.6% respectively, with an accuracy of 84.4%. 95.1% was the positive predictive value while 70.5% was the negative predictive value. A lower figure was reported from an un-Indian study conducted in 2015, in which the level of ferritin with a maximum sensitivity and logical specificity was 35.5 microgram/L. Sensitivity was 74% and specificity was 66% at this level. Therefore, the best cutoff serum ferritin concentration to estimate the likelihood of PPROM would be 35.5 microgram/L [11]. A different result was reported from a 2018 study that showed a cut-off value of 31 ng/ml for serum ferritin between the two groups, with accuracy of 98.3%, sensitivity of 92.8%, specificity of 99.4%, positive predictive value of 97.5%, and negative predictive value of 98.4% [14].

The observed variations between the studies may be explained by variations in the study design, time of blood collection, study demographics, and lack of or insufficient confounding control. Furthermore, elevated blood ferritin levels in PPROM instances may be caused by an infection linked to the condition, most likely latent chorioamnionitis [16].

Conclusion

This study concluded that, in comparison to the spontaneous preterm group and the control group of women with the same gestational period, the ferritin level was considerably higher in the PPROM group. The optimal cut-off ferritin level for predicting PPROM was 37.41 ng/ml, and this cut-off value was 80.8% sensitive, 91.6% specific, and 84.4% accurate in the prediction of PPROM. Since serum ferritin can be measured quickly and doesn't require additional equipment if a ferritin kit is available, we recommend using it as a marker for PPROM.

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