Preterm Premature Rupture of Membranes and the Value of Serum Ferritin during Pregnancy

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ABSTRACT:

BACKGROUND:

Preterm premature rupture of membranes occurring from 24-37 weeks gestation. Ferritin is an acute phase reactant as it increases during inflammation that inflammation can predispose to preterm premature rupture of membranes during pregnancy.

OBJECTIVE:

To investigate the value of serum ferritin as a marker for preterm premature rupture of membrane.

PATIENTS AND METHODS:

The study includes 150 pregnant women attending the department of Obstetrics and Gynecology with a gestational age ranging from 28^{+0} – 36^{+6} weeks. 50 of them presented with Preterm premature rupture of membrane (group A), 50 women were presented with spontaneous preterm labor (group B), and the other 50 were without any complaint (group C). Venous blood samples of five ml were collected on admission for measurement of serum ferritin level by enzyme-linked immunosorbent assay.

RESULTS:

No statistically significant differences between study groups regarding age, parity, gestational age and hemoglobin level ($P \geq 0.05$). The mean of serum ferritin was significantly higher among pregnant women presented with Preterm premature rupture of the membranes than those presented with spontaneous preterm labor and healthy women (45.07 versus 26.22 and 22.83 ng/ml respectively) (P= 0.001). By receiver operating characteristic curve analysis, the cut point of serum ferritin value was 38.6 ng/ml.

CONCLUSION:

Measurement of serum ferritin level is a simple rapid and accurate test. It can be applied as a marker for preterm premature rupture of membrane.

KEYWORDS: pregnancy, PPROM, serum ferritin, preterm labor.

INTRODUCTION:

Preterm labor (PTL) is defined as delivery of a baby before 37 completed weeks of gestation. The limit of viability is defined as 24 weeks of gestation. The incidence of preterm birth varies significantly across the globe. In most developed nations the rate of preterm birth is below 10%, while in Malawi, Congo, Gabon, Pakistan, Indonesia, and Botswana the rates exceeding 15%. Approximately 45-50% of PTLs are idiopathic or spontaneous, 30% are related to preterm rupture of membranes, and another 15-20% is attributed to medically indicated or elective preterm deliveries [(1)].

Preterm premature rupture of membranes (PPROM) occurring from 24-37 weeks' gestation is far more difficult to manage than premature rupture of membranes (PROM) at term. It occurs in 3% of pregnancies and is the cause of approximately one-third of preterm deliveries. It can lead to significant perinatal morbidity and mortality [(2)].

Ferritin is a universal intracellular protein that stores iron and releases it in a regular fashion. In humans, it acts as a buffer against iron deficiency and iron overload [(3)]. Plasma ferritin is also an indirect marker of the total amount of iron stored in the body; hence serum ferritin is used as a diagnostic test for iron deficiency anemia.

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Iron storage concentrations decrease with advancing gestation, hence the values of ferritin also decrease up to 32% in the first trimester, 39% in the second and even 53% during the third trimester[4].The lowest values of ferritin are recorded between 30 and 32 gestational weeks, after which the concentrations stay on constant levels. The decrease of ferritin levels is in correlation with the decrease of iron reserves in the maternal organs resulting from increased uptake (by the mother, placenta and fetus) as well as from hem dilution. The missing decrease of ferritin levels points to decreased extraction of iron from the blood of the pregnant woman by the fetoplacental unit, which can be in correlation with the development of intrauterine growth restriction (IUGR) which is one of the leading causes of PPROM [5]. Ferritin is an acute-phase reactant and it increases during inflammation which is also the common cause of PPROM during pregnancy [6].

AIM OF STUDY:

To investigate the value of serum ferritin as a marker for preterm premature rupture of membrane.

PATIENTS AND METHODS:

This is a comparative study that was conducted in the Department of Obstetrics and Gynecology of Al-Yarmook Teaching Hospital in cooperation with the laboratories department of the hospital from 1st of March through November 2018.The study protocol was approved by Scientific Council of Obstetrics and Gynecology Specialization / Iraqi Board for Medical Specialization.

The study included 150 pregnant women attending the department of Obstetrics and Gynecology who had Singleton viable pregnancy with a gestational age ranging from 28 – 36^{+6} weeks depending on accurate last menstrual period and / or by early ultrasonography. They were informed about the nature of the study and verbal consent was obtained from them. The women included in the study were divided into three groups.

- **Group A:** Includes 50 Pregnant women presented with PPROM.
- **Group B:** Includes 50 Pregnant women presented with spontaneous preterm labor with intact membrane.
- **Group C:** Includes 50 Pregnant women without any complaint.

All groups were matched for hemoglobin level and period of gestation.

Exclusion Criteria

- Anemia: Hb< 11 g/dl
- Multiple pregnancies.
- Vaginal bleeding.
- Fetal compromise or with known fetal malformation.
- Chorioamnionitis
- History of vaginal douching or sexual intercourse in the previous 24 hours.
- Preexisting medical disease including thyroid, liver, renal, or hypertensive disease.
- Abnormal placentation or history of cervical pathology.

Detailed history was obtained. General and systemic examinations were done. Sterile vaginal speculum examination for assessment of cervical state (dilatation and effacement), pooling of amniotic fluid in the vagina, and nitrazine paper test was done to confirm the diagnosis of preterm premature rupture of membrane in group A.

Maternal blood sample collected at the time of admission from women in the three groups and sent for blood group, full blood count, and random blood sugar. Ultrasound also had been done.

Serum ferritin estimation was done by collection of additional 5 ml of venous blood in plain tube from each patient. The sample allowed clotting for 10 – 20 minutes at room temperature then centrifuged at (2000 – 3000 RPM) for 20 minutes collect the supernatants carefully. Serum separated and stored at – 60 ▯ C or below till analysis performed by Test Principle which is ELISA kit uses the Sandwich-ELISA principle. Detection range of the kit that used was 20 - 250 ng/mL.

Statistical Analysis

The data analyzed using Statistical Package for Social Sciences (SPSS) version 25. The data presented as mean, standard deviation and ranges. Categorical data presented by frequencies and percentages. Independent t-test and Analysis of variances (ANOVA) (two tailed) was used to compare the continuous variables

among study groups accordingly with LSD post-hoc test for significant values. Receiver operating characteristic (ROC) curve analysis was used for prediction of serum ferritin level as diagnostic of PPROM. A level of P – value less than 0.05 was considered significant.

RESULTS:

The total number of pregnant women in this study was 150. Group A included 50 pregnant women presented with PPROM, group B included 50 pregnant women with spontaneous preterm labor, and group C included 50 pregnant women without any complaint.

The distribution of pregnant women between study groups by general characteristics is shown in table (1). The age was ranging from 21 to 39 years with a mean of 28.2 and standard deviation of ± 9.44 years. It was noticed that 49.3% of pregnant women were aged between 27 – 32 years, 61.3% were multiparous, 41.3% were presented with GA between 32 – 34^{+6} weeks. Duration of rupture of membrane was ranging from 4 – 48 hrs. with a mean of 12.4 hrs. and SD of ± 4.21 hrs.

Table 1: Distribution of study groups by general characteristics.

s. Variable	Group A (%) No=50	Group B (%) No=50	Group c (%) No=50	Total (%) No=150
Age (Years)				
21 – 26	18 (36.0)	22 (44.0)	14 (28.0)	54 (36.0)
27 – 32	23 (46.0)	21 (42.0)	30 (60.0)	74 (49.3)
33 – 39	9 (18.0)	7 (14.0)	6 (12.0)	22 (14.7)
Parity				
Prim gravida	22 (44.0)	17 (34.0)	19 (38.0)	58 (38.7)
Multigravida	28 (56.0)	33 (66.0)	31 (62.0)	92 (61.3)
Gestational Age (Weeks) at admission				
28 – 31 +6	17 (34.0)	8 (16.0)	15 (30.0)	40 (26.7)
32 – 34 +6	19 (38.0)	25 (50.0)	18 (36.0)	62 (41.3)
35 - 36 +6	14 (28.0)	17 (34.0)	17 (34.0)	48 (32.0)

Table (2) shows the comparison between study groups by general characteristics. No statistically significant differences (P ≥ 0.05) between the three groups regarding age, parity, GA and hemoglobin level.

Table 2: Comparison between study groups by general characteristics and Hb level.

Variable	Group A Mean±SD	Group B Mean ± SD	Group C Mean ± SD	P-Value
Age (Years)	24.3 ± 8.41	22.8 ± 9.5	24.8 ± 6.22	**0.445**
Parity	3.2 ± 1.25	3.7 ± 1.41	3.5 ± 0.89	**0.116**
GA (Weeks)	33.7 ± 6.6	34.7 ± 9.3	35.6 ± 5.1	**0.422**
Hemoglobin (Hb)	11.2 ± 1.43	11.5 ± 2.88	11.8 ± 1.33	**0.331**

Table (3) shows the comparison of serum ferritin level among the study groups. It was obvious that mean of serum ferritin was significantly (P= 0.001) higher among pregnant women presented with PPROM (Group A) than the other study groups (B and C) (45.07 ng/ml versus 26.22 ng/ml and 22.83 ng/ml) respectively.

Table 3: Comparison of serum ferritin level between study groups

Study Group	Serum Ferritin (ng/ml) Mean±SD	P-Value
Group A	45.07 ± 12.33	**0.001**
Group B	26.22 ± 12.72	
Group C	22.83 ± 5.97	

Post hoc tests (LSD) were run to confirm the differences among the three groups and showed that serum ferritin was significantly higher in group A than that in group B (45.07 versus 26.22 ng/ml, P= 0.001) and higher than that in group C (45.07 versus 22.83 ng/ml, P= 0.001). No significant difference detected in serum ferritin between group B and group C (26.22 versus 22.83 ng/ml, P= 0.076) as shown in table (4).

Table 4: Serum ferritin level in study groups by post hOC test (LSD)

	Group A Mean±SD	Group B Mean ± SD	Group C Mean ± SD	P-Value
Serum ferritin (ng/ml)	45.07 ± 12.33	26.22 ± 12.72	-	**0.001**
	45.07 ± 12.33	-	22.83 ± 5.97	**0.001**
	-	26.22 ± 12.72	22.83 ± 5.97	**0.076**

As shown in table (5), the cut point of serum ferritin value was 38.6 ng/ml, so serum ferritin > 38.6 ng/ml can be considered as a diagnostic marker of PPROM. Serum ferritin was 80% sensitive, 88.9% specific, and 87.3% accurate as a marker for diagnosis of PPROM.

Table 5: Diagnostic accuracy of serum ferritin in PPROM group

Serum Ferritin (ng/ml)	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
	38.6	80%	88.9%	81.6%	90.1%	87.3%

Table (6) shows the comparison in means of serum ferritin among pregnant women presented with PPROM by certain characteristics. It shows that there were no statistically significant differences (P ≥ 0.05) in means of serum ferritin by GA, duration of rupture membrane and parity.

Table 6: Comparison in means of serum ferritin among pregnant women presented with PPROM by certain characteristics

Variable	Serum Ferritin in group A (ng/ml) Mean±SD	P - Value
Gestational Age (Weeks)		
28 – 31+6	47.21 ± 15.13	**0.633**
32 – 34 +6	43.33 ± 11.05	
35 - 36 +6	44.72 ± 9.23	
Parity		
Primigravida	47.2 ± 13.2	**0.335**
Multigravida	43.7 ± 11.7	
Duration of rupture membrane at time of admission		
≤24 hrs	44.1±11.6	**0.437**
< 24 hrs	46.28±9.65	

DISCUSSION:

Preterm premature rupture of membranes (PPROM) is the cause of approximately one third of preterm deliveries. It can lead to significant perinatal mortality and morbidity and maternal complication like chorioamnionitis and placental abruption. So appropriate evaluation and management are important for improving maternal and neonatal outcome[7].

In the current study, (49.3 %) of pregnant women in study groups were 27 – 32 years; (61.3 %) were multiparous ; (38.7 %) were primigravida ; (41.3 %) were presented with GA between 32 – 34 + 6 weeks, which shows no statistically significant differences among study groups regarding age, parity, and gestational age (P 0.05) and this agrees with Mahdi and their colleagues [8], Mubarak et al. [9] and Gahwagi et al. [10] studies.

The current study, shows that the mean of serum ferritin was significantly higher among pregnant women in Group A than the groups B and C (45.07 ng/ml versus 26.22 ng/ml and 22.83 ng/ml) receptively with (P= 0.001). No significant difference detected in serum ferritin between group B and group C (26.22 ng/ml versus 22.83 ng/ml, P= 0.076). These results were in consistent with two studies;

First study done by Valappil et al. that compared ferritin levels in 50 patients of PPROM, 50 patients of spontaneous preterm labor and 50 healthy pregnant women [11], in which there was a significant statistical increase in serum ferritin in the PPROM group than other two groups (p-value < 0.05) which agree with this study.

The other study done by Saha CK et al. in which they measured serum ferritin level for 50 women with PTL, 49 women with PPROM and 50 women without complaint [12], they found that mean serum ferritin concentration in both PTL and PPROM groups was significantly higher than in the control group (P=0.001).

Abdel-Malak et al. study in which they studied two groups: control group (196 healthy pregnant women) and case group (23 women with PPROM and 17 women with spontaneous preterm labor) [13]. They observed that the mean level of serum ferritin in case group was significantly higher than in control group (76.3 ng/ml, 20.2 ng/ml) respectively which agreed with the current study.

Our study shows no statistically significant differences of serum ferritin level in relation to gravidity and parity in PPROM group. This is also in agreement to study done by Abdel-Malak et al.[13] in which they didn't notice significant difference between the groups participated in their study with gravidity and parity.

The current study reveales that the cutoff point of serum ferritin value is 38.6 ng/ml with 80% sensitivity, 88.9% specificity, and 87.3% accuracy. These results agree to study done by Valappil et al. in which the serum ferritin level was 35.5 ng/ml with 74% sensitivity and 66% specificity. The study considered that serum ferritin can be ideal to predict the probability of PPROM [11]. Again Abel-Malak et al. study revealed that the cut off value of serum ferritin was 31 ng/ml with 92.8% sensitivity, 99.4%, specificity, 97.5% positive predictive value, 98.4% negative predictive value and 98.3% accuracy [13] and it agrees with our study.

Regarding the duration of rupture membranes in group A and the mean serum ferritin level in patient presented with PPROM less than 24 hours and those more than 24 hours , this study reveals no statistically significant differences ($P \geq 0.05$) in means of serum ferritin by duration of rupture membrane.

There was no study found regarding the correlation between serum ferritin level and duration of rupture membranes in PPROM cases.

CONCLUSION:

Measurement of serum ferritin is a simple rapid and accurate test. It can be applied as a marker for preterm premature rapture of membrane.

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