Estimation of Serum Ferritin Level in Preterm Labour

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ABSTRACT

Background: Preterm birth is the leading cause of newborn deaths and also the leading cause of death in children under 5 years of age. There is wide spread suspicion that subclinical infection is a common accompaniment and cause of preterm labour. Ferritin is an acute phase reactant and it increases during inflammation.

Aim: The objective of this study is to measure serum ferritin level in cases of established preterm labour (PTL) as a possible marker of infection.

Study Setting: This study conducted at Ain Shams University Maternity Hospital from March 2015 to November 2015.

Study design: A case-control study.

Patients and Methods: The study involved 2 groups.

Study population: 60 cases divided into two groups:

- **Group (I):** included 30 patients with established (PTL) between 30 to 34 weeks gestational age (GA).
- **Group (II): (Control group)** 30 patients with uncomplicated pregnancies between 30 to 34 weeks GA. Serum ferritin was analyzed in the 2 groups.

Results: The results pointed out that there was statistically significant difference between two groups as regarding serum ferritin level as p value was <0.0001 . The median serum ferritin level in preterm labour group and control group was 150 (100 – 150) ng/ml and 20 (15 – 25) ng/ml respectively. The best cut off value of serum ferritin as predictor of preterm labour was >55 ng/ml with a sensitivity of 96.7% and specificity of 96.7 %.

Conclusion: Serum ferittin can be used as a marker of preterm labour.

Keywords: Infection, Preterm labour, Serum Ferritin

INTRODUCTION

Preterm labour is defined as regular uterine contractions before 37 completed weeks of gestation with intact membranes with 4cm or more of cervical dilatation observable during a 2hour period[1].

The World Health Organization (WHO) factsheet revealed that 15 million babies are born too early every year and almost 1 million children die each year due to complications of preterm birth[2] .

Preterm birth, i.e., birth before 37 weeks of gestation period, an important obstetric problem, is the major cause of neonatal mortality and morbidity across the globe. Nearly 70% of the neonatal deaths are due to preterm delivery (PTD)[3].

Preterm pregnancy accounts for about 10% of the total pregnancies. There has been an increase in the number of preterm deliveries in the last 25 years[4].

The causes of preterm labour (PTL) include multiple pregnancies, infections, and chronic conditions such as diabetes and high blood pressure. The reports also suggest that PTL may be due to one or more of the pathophysiologic processes such as amnio-chorionicdecidual or systemic inflammation, activation of the maternal or fetal hypothalamic-pituitary-adrenal axis, decidual hemorrhage, or pathologic distension of the uterus. But a clear understanding of the molecular mechanism has not developed yet[5]. Many maternal and biochemical data as well as other demographic and behavioral factors have been used and tried for the prediction of PTD but none of them have succeeded[6]. Thus, there is an urgent necessity to develop such a marker which can render information regarding PTD.

In response to the call for early detection of PTD, several diagnostic biomarkers are currently in development. According to the main role of inflammation on appearance and progression of preterm delivery, it is hypothesized that measuring serum ferritin level as a sensitive inflammatory marker can effectively predict this event in the high risk group. Some investigators have reported a relationship between elevated serum ferritin concentrations and preterm labour[7].

SUBJECTS AND METHODS

This study is a case-control study conducted at Ain Shams University Maternity Hospital from March 2015 to November 2015.

Before the start of this study, permission was obtained from Ethical Committee in the faculty of medicine, Ain Shams University, Also signed informed written consent from patients included in the study was obtained.

SUBJECTS

60 cases divided into two groups:

- **Group (I):** included 30 patients with established (PTL) between 30 to 34 weeks gestational age (GA).
- **Group (II): (Control group)** 30 patients with uncomplicated pregnancies between 30 to 34 weeks GA. The **inclusion criteria were** singleton pregnancy, gestational age between 30 to 34 weeks , average BMI(19-24 kg per m^2) and ultrasound (U/S) in late first trimester (crown rump length between 9-11 weeks gestation), for accurate calculation of gestational age. Every patient was subjected to detailed history with exclusion of patients with anemia (hemoglobin <10.5 g/dl), pre-existing chronic infective disease, multiple pregnancy, polyhydramnios, diabetes mellitus, preeclampsia, eclampsia, liver disease, renal disease, alcoholics, smokers, cerclage in cases oincompetent cervix, previous history of abortion or PTL due to incompetent cervix and intra uterine fetal death (IUFD), also all patients were subjected to clinical examination, investigations including hemoglobin (Hb), hematocrit value and C reactive protein (CRP) and pelvic ultrasound.

METHOD

Ten milliliters of blood was collected by venipuncture and was allowed to clot in iron-free tubes at room temperature. Serum was separated within 2 h and stored at −20°C until final estimation for serology. Serum ferritin was assayed by Immunospec Ferritin Quantitative Test Kit . This is a solid phase enzyme- linked immunosorbent assay (ELISA) kit.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

Statistical analyses

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA). Normality of numerical data distribution was examined with the Shapiro-Wilk. Normally distributed numerical variables were presented as mean ± SD and inter-group differences were compared using the unpaired Student *t* test. Non-normally distributed numerical variables were presented as median and interquartile range and between-group differences were compared using the Mann-Whitney U test. Categorical variables were presented as number (%) and inter-group differences were compared using Fisher's exact test. Ordinal data were compared using the chi-squared test for trend.

Receiver-operating characteristic (ROC) curve analysis was used to examine the value of CRP or serum ferritin for discrimination between patients with preterm labour and normal controls. The DeLong method was used to compare the area under different ROC curves. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

Patients' characteristics in both studied groups are shown in table 1 while table 2 shows the results of laboratory work-up in these two groups. Figure 1 represents the serum ferritin level in the two studied groups. Also, Figure 2 illustrates the receiver-operating characteristic (ROC) curve for discrimination between patients with preterm labour and normal controls using serum ferritin. Furthermore, table 3 presents the receiver-operating characteristic (ROC) curve analysis for the value of serum ferritin for discrimination between patients with preterm labour and normal controls.

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Table (1): Characteristics of patients in both studied groups

Variable	Preterm labour group (n=30)	Control group (n=30)	t	f	P-value
Age (years)	26.7 ± 5.0	26.6 ± 5.2	.101	8	0.920¶
Gestational age (weeks	32.7 ±1.4	32.0 ± 1.2	.196	8	0.083¶

Data are mean ± SD or number (%).   ¶Unpaired *t* test.

Table (2): Results of laboratory work-up in both studied groups

Variable	Preterm labour group (n=30)	Control group (n=30)	t/U	df/z	P-value
Hemoglobin level (g/dl)	11.0 ± 0.4	11.2 ± 0.9	1.041	58	0.302¶
Hematocrit (%)	33.6 ± 2.4	34.2 ± 2.2	1.029	58	0.308¶
Serum ferritin (ng/ml)	150 (100 – 150)	20 (15 – 25)	9.5	5.577	<0.0001§

Data are mean ± SD, median (interquartile range), or number (%). *t*, t statistic; U, U statistic; *df*, degree of freedom; *z*; z-statistic. ¶Unpaired *t* test. §Mann-Whitney test.
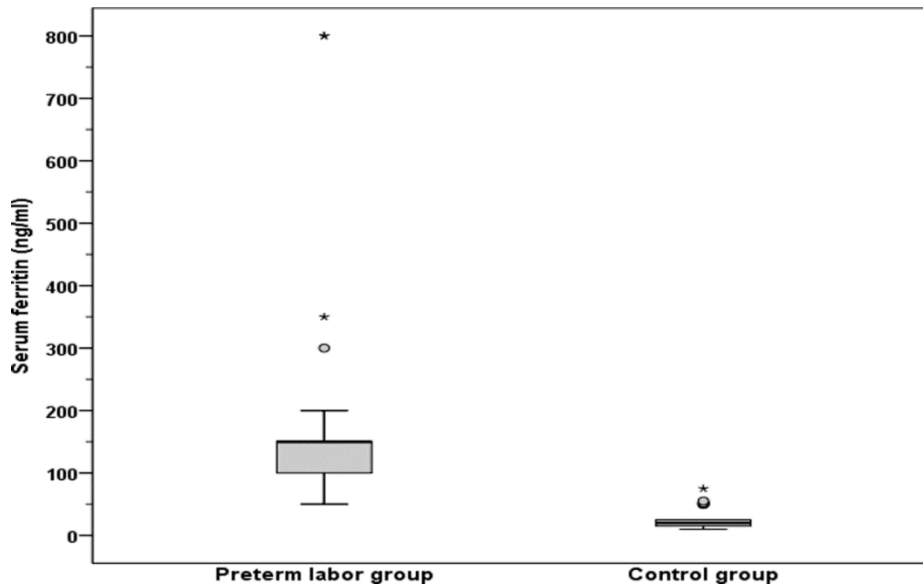

Figure (1): Box plot showing the serum ferritin level in the two studied groups. Box represents the range from the first to third quartile (interquartile range). Line inside the box represents the median (second quartile). Whiskers represent the range between the minimum and maximum values excluding outliers (rounded markers) and extreme observations (asterisks).

Table (3): Receiver-operating characteristic (ROC) curve analysis for the value of serum ferritin for discrimination between patients with preterm labour and normal controls.

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Sample size	60
Positive group (preterm labour)	30 (50%)
Negative group (controls)	30 (50%)
Disease prevalence	50%
Area under the ROC curve (AUC)	0.989
Standard error	0.008
95% confidence interval	0.973 to 1.000
z statistic	57.627
P-value ($AUC_0=0.5$)	<0.0001
Youden (J) index	0.933
Cut-off criterion	>55 ng/ml
Sensitivity, %	96.7
95% CI for sensitivity	82.8 - 99.9
Specificity, %	96.7
95% CI for specificity	82.8 - 99.9
Positive likelihood ratio (LR+)	29.0
95% CI for LR+	4.2 - 199.4
Negative likelihood ratio (LR-)	0.0
95% CI for LR-	0.005 - 0.2
Positive predictive value (PPV), %	96.7
95% CI for PPV	82.8 - 99.9
Negative predictive value (NPV), %	96.7
95% CI for NPV	82.8 - 99.9
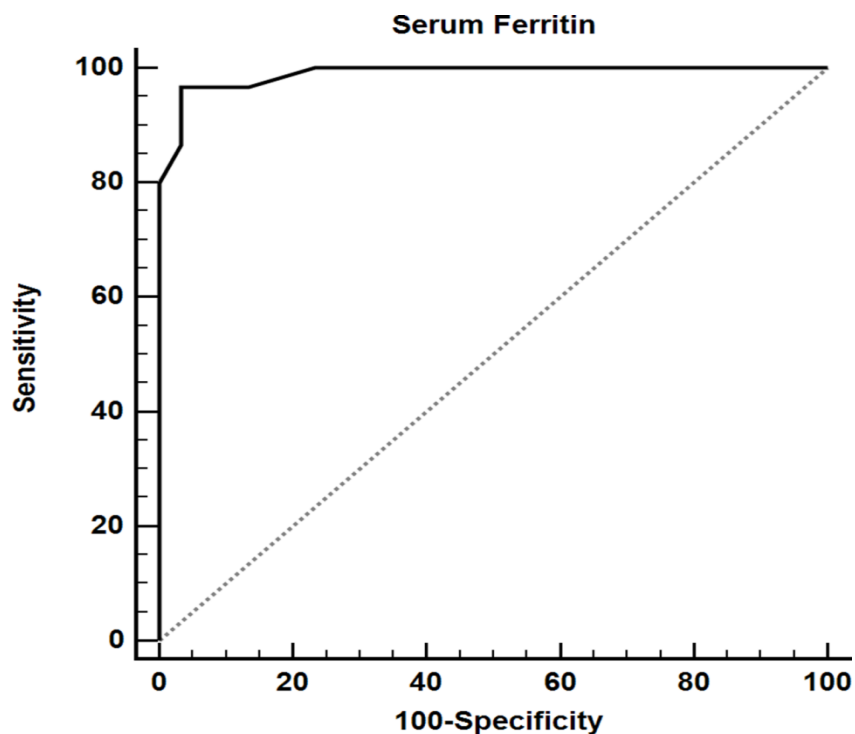
Figure (2): Receiver-operating characteristic (ROC) curve for discrimination between patients with preterm labour and normal controls using serum ferritin.

DISCUSSION

Preterm labour is the single most important complication of pregnancy in the absence of congenital abnormality, as it is recognized as a worldwide problem responsible for more than 80% of neonatal deaths and more than 50% of long term morbidity in the surviving infants[8].

Pregnancy tends to predispose to vaginocervical infection due to altered vaginal pH. The chorion-decidual interface is infiltrated by macrophages following bacterial colonization and ferritin is produced as an acute phase reactants[9].

In this study there was no significant difference between the two groups as regards age and gestational age.

There was no significant difference between the two groups as regards hemoglobin level and hematocrit value. There was statistically significant difference between two groups as regarding serum ferritin level.

Receiver operator characteristics (ROC) curves were constructed for serum ferritin as predictor of preterm labour. Serum ferritin was a highly significant predictor of preterm delivery.

This agrees with a study which was done by **Nandini *et al*.**[1] on 100 pregnant women divided into two groups, group 1(preterm delivery, case group) and group 2 (term delivery, control group). Findings of their study showed serum ferritin levels were significantly higher in preterm labour and its values ranged from 4.4 µg/dl to 841.2 µg/dl and 9.8 µg/dl to 67 µg/dl in preterm and control patients respectively .

Another case control study was done by **Movahedi *et al*.**[10] on 222 singleton pregnancies, 69 (31.1%) had preterm delivery and 153 (68.9%) had term delivery.). Women who delivered before 37 weeks had a higher mean serum ferritin concentration than those who delivered after 37 weeks of gestation (26.7 ± 5.5 ng/ml *vs.* 19.8 ± 3.6 ng/ml, $P < 0.001$). Receiver operator characteristic (ROC) curve was constructed to the serum ferritin values to determine the level that would predict preterm delivery with reasonable sensitivity and specificity. Serum ferritin level of 22.5 ng/ml yielded the best combination with sensitivity of 78.3%, specificity of 83.0%, positive predictive value of 67.5%, and negative predictive value of 89.4% for prediction of preterm delivery.

This disagrees with a descriptive cross sectional study (Comparative study) of **Valappil *et al*.**[11] Their Objectives were to compare the ferritin levels in 50 patients of PPROM, 50 patients of spontaneous preterm labour and 50 pregnant women matching with haemoglobin and same gestational age. And also, to estimate serum iron, TIBC and transferring saturation percent in the above 3 groups. They reported that there was significant statistical difference in the mean ferritin values between the control group and PPROM group as indicated by the p-value of 0.012. However, there was no significant statistical difference in the mean ferritin values between the control group and spontaneous preterm labour group as indicated by a p-value of 0.180.

However, **Gopal *et al*.**[12] in their retrospective study had shown a negative relation between serum ferritin levels and preterm labour.

Our study has both strengths and limitations. One of the strengths of this study was that more confounding variables were matched compared to other studies. other strengths include accurate assessment of gestational age, exclusion of or restriction to other causes of preterm labour rather than infection and iron overload has been excluded in our study by considering various hematological parameters. Thus the high serum ferritin level in the study group is most likely a part of acute phase reaction to a subclinical infection and not due to iron overload. However our study has some limitations, including, the relatively small number of subjects available for group analyses resulted in imprecise measures of associations as reflected by the very wide 95% confidence intervals, a single measurement of ferritin is not likely to provide a time integrated measurement of maternal inflammation status during the index pregnancy .

CONCLUSION

Our results assessed the relation between preterm labour and serum ferritin level. Possibly because that reflects an acute phase reaction to subclinical infection that is closely associated with preterm delivery.

Elevated serum ferritin concentrations are highly significant associated with spontaneous

preterm delivery and serum ferritin values more than 55 ng/mL was the optimal cut-off point.

RECOMMENDATIONS

The present study recommends the use of serum ferritin as a marker of preterm labour.

The current study had helped to evolve a cut off value of 55ng/ml of serum ferritin for diagnosis of preterm labour.

Although there is not enough evidence from well-controlled experimental studies to advocate routine use such prediction scales in improving maternal or neonatal outcomes.

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