

# Diagnostic performance and discriminative value of the serum ferritin level for predicting preterm labor

Mino Movahedi<sup>1</sup>, Mahmoud Saiedi<sup>2</sup>, Mojgan Gharipour<sup>3</sup>, Omid Aghadavoudi<sup>4</sup>

<sup>1</sup>Assistant Professor, Department of Gynecology and Obstetrician, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

<sup>2</sup>Assistant Professor, Department of Cardiac Surgery, School of Medicine, Isfahan Cardiovascular Research Center, Isfahan, Iran.

<sup>3</sup>Researcher, Isfahan Cardiovascular Research Center, Isfahan Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

<sup>4</sup>Associate Professor, Department of Critical Care, Isfahan University of Medical Sciences, Isfahan, Iran

**Background:** The measuring serum ferritin level as a sensitive inflammatory biomarker might effectively predict preterm delivery, but the power and the best cut-off point of this biomarker for predicting preterm labor in Iranian population has not been substantially identified. Our purpose was to determine what concentrations of serum ferritin could identify patients at risk for preterm delivery in Iranian population for the first time. **Materials and Methods:** This case control study involved 222 singleton pregnancies that were referred to referral university hospitals clinics in Isfahan. Women with spontaneous preterm delivery before 24–26 weeks (preterm delivery group,  $n = 69$ ) and those who delivered at term (term delivery group,  $n = 153$ ) were compared with respect to serum ferritin concentration. Venous blood samples were analyzed for the serum ferritin level using the ferritin quantitative test system-sensitive for the normal ferritin range. **Results:** Women who delivered before 37 weeks had a higher mean serum ferritin concentration than those who delivered after 37 weeks of gestation ( $26.7 \pm 5.5$  ng/mL versus  $19.8 \pm 3.6$  ng/mL,  $P < 0.001$ ). A 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. **Conclusion:** The serum ferritin level provides an appropriate discrimination in predicting preterm delivery with an optimal cut-off value of 22.5 ng/mL in Iranian population.

**Key words:** Cut off, ferritin, predict, preterm labor, serum

## INTRODUCTION

Recent experimental and clinical evidences have revealed an association between intrauterine inflammatory processes and preterm delivery. In fact, women with preterm delivery at less than 37 weeks have higher concentrations of inflammatory indicators in serum and amniotic fluid than those women who delivered at term.<sup>[1]</sup> In this context, a number of chemical and laboratory biomarkers have been studied for predicting preterm labor.<sup>[2-4]</sup> Ferritin as an intracellular iron storage protein has been identified as a diagnostic marker that its high serum levels is associated with a variety of acute phase reactions, including inflammatory conditions.<sup>[5,6]</sup> According to the main role of inflammation on appearance and progression of preterm delivery, it is hypothesized that the 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 labor.<sup>[7-9]</sup> However, based on our knowledge, the predictive power and the best cut-off point of this biomarker for predicting preterm

delivery has not been substantially identified in Iranian population. Our purpose in this study was to determine if concentrations of serum ferritin could identify patients at risk for spontaneous preterm delivery.

## MATERIALS AND METHODS

This case-control study was conducted between April 2008 and April 2009, involved 222 singleton pregnancies that were referred to referral university hospitals Alzahra and Beheshti clinics in Isfahan. Research ethics approval was obtained from the Isfahan University of Medical Sciences before the initiation of the study and written informed consent was obtained from all patients. Women with spontaneous preterm delivery before 24–26 weeks and those who delivered at term were compared with respect to serum ferritin concentration. Subjects with conditions known to alter serum ferritin levels such as Iron deficiency anemia (hemoglobin  $< 10.5$  g/dL), iron overload states, chronic infective or inflammatory disorders, known malignancy or liver disease at the time of enrollment, uti, urt infection, vaginitis,

**Address for correspondence:** Mahmoud Saiedi, Assistant Professor, Department of Cardiac Surgery, School of Medicine, Isfahan Cardiovascular Research Center, Isfahan, Iran. E-mail: saiedi@med.mui.ac.ir

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common, IUGR, PA, placenta abnormality, any vaginal bleeding during pregnancy, MDS disorder, common cold, and those who consumed iron tablets, for anemic treatment any congenital malformations or chromosomal abnormality were excluded from the study. Women with obstetric problems such as multiple pregnancy, polyhydramnios, cervical incompetence or known uterine malformation, placenta praevia, diabetes mellitus and preeclampsia were also excluded. Smokers and subjects with uncertain gestation were not recruited in the study. Gestational age was based on the last menstrual period and confirmed by ultrasound examination, prior to 20 weeks of gestation. Venous blood samples were drawn at 24 to 26 weeks of gestation and analyzed for the serum ferritin level. Serum ferritin was assayed using the ferritin quantitative test system-sensitive for the normal ferritin range. All the pregnancies were followed until delivery. Women with spontaneous preterm delivery before 37 weeks (preterm delivery group,  $n = 69$ ) and those who delivered at term (term delivery group,  $n = 153$ ) were compared with respect to age and serum ferritin concentration. Continuous data were shown as mean and standard deviation (SD) and categorical variables were presented as percentages. Patients' characteristics were compared across the term and preterm groups by means of the t test for continuous variables and the chi-square test or the Fisher's exact test for categorical variables. The Pearson  $r$  was calculated to measure the association of the serum ferritin level and maternal age.

Descriptive statistics including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of serum ferritin in determining the presence or exclusion of the preterm labor were calculated. Receiver operator characteristic (ROC) curves were constructed to investigate the diagnostic power of the variable. The cut-off score was estimated for the prediction of preterm labor by the ROC curve analysis (the empirical point that maximizes sensitivity and specificity of the ferritin level for predicting of the preterm labor).

$P$  values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13 (SPSS Inc., Chicago, IL, USA) and the STATA statistical package (version 10.0; College Station, TX, USA).

## RESULTS

Of 222 pregnancies entered prospectively in the study, 69 (31.1%) had preterm delivery and 153 (68.9%) had term delivery. Table 1 shows subjects characteristics in both preterm and term groups. There were no significant

differences between mean of age in both groups. There was no significant difference between the preterm and term groups with respect to maternal age ( $26.3 \pm 3.2$  versus  $23.4 \pm 3.6$ ,  $P = 0.080$ ). Women who delivered before 37 weeks had a higher mean serum ferritin concentration than those who delivered after 37 weeks of gestation ( $26.7 \pm 5.5$  ng/mL vs.  $19.8 \pm 3.6$  ng/mL,  $P < 0.001$ ). Table 1 shows significant differences between mean of the ferritin level in term and preterm groups ( $P = 0.001$ ). Figure 1 shows a positive correlation between serum ferritin levels and maternal age in the total cohort (Pearson's  $r = 0.23$ ,  $P = 0.001$ ). It means that the serum ferritin levels have been shown to increase with the advancing maternal age.

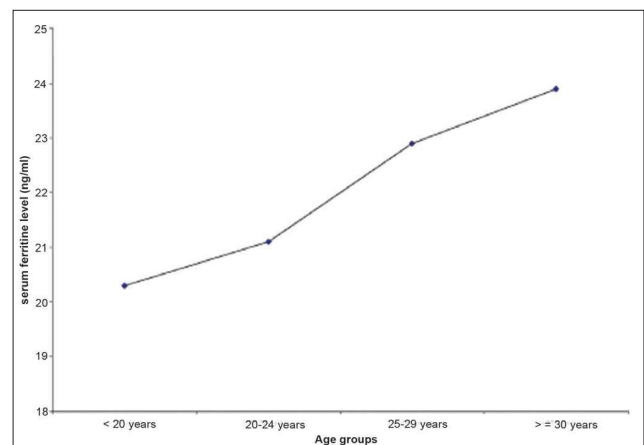
Receiver operator characteristic (ROC) curve was constructed to the serum ferritin values to determine the level that would predict preterm delivery with reasonable sensitivity and specificity. Serum ferritin level of 22.5 ng/mL yielded the best combination with sensitivity of 78.3%, specificity of 83.0%, positive predictive value of 67.5%, and negative predictive value of 89.4% for prediction of preterm delivery.

## DISCUSSION

In this study, we showed that elevated serum ferritin concentrations are significantly associated with

**Table 1: Characteristics of participants based on preterm and term labor**

	Preterm Labor	Term labor	P value
N(%)	69 (31)	153 (68.9)	<0.000
Mean age	$26.3 \pm 3.2$	$23.4 \pm 3.6$	0.08
Serum ferritin levels (ng/ml)			
<15	1.4	9.2	<0.000
15-19	10.1	49.7	<0.000
20-24	21.7	29.4	<0.000
25-29	40.6	11.1	<0.000
$\geq 30$	26.1	0.7	<0.000



**Figure 1: Relationship between serum ferritin levels and advancing maternal age**

spontaneous preterm delivery among Iranian population. Parallel to our study, some previous researches obtained similar findings. Ulmer and his colleagues<sup>[10]</sup> observed a correlation between an altered serum ferritin concentration and preterm labor or premature rupture of the membranes. They also observed an association between the incidence of the preterm labor and low serum ferritin concentrations in the second trimester. Besides, later studies could show that elevated serum ferritin concentrations during the second trimester were predictive of preterm delivery.<sup>[11]</sup> A cross-sectional study by Saha *et al.*<sup>[3]</sup> has also found significantly high levels of serum ferritin in patients who had preterm delivery. It seems that elevated mid-pregnancy serum ferritin levels can be predictive of spontaneous preterm delivery, especially those occurring at early gestational ages. Some mechanisms have been suggested for these evidences. First, the presence of increased levels of ferritin might reflect an acute phase reaction to subclinical genital tract infection or inflammation.<sup>[12]</sup> In addition, it may be also explained by the covert process of infection associated with preterm delivery that causes tissue damage resulting in increased serum ferritin levels that act as an acute phase reactant.<sup>[13,14]</sup> Regarding the best cut-off point for the serum ferritin level to predict and discriminate preterm delivery, ROC curve revealed that the serum ferritin values of more than 22.5 ng/mL was the optimal cut-point, yielded the best combination with sensitivity of 78.3% and specificity of 83.0%. In this study, we emphasized on the role of serum ferritin for predicting preterm labor and showed that this association can be potentially affected by maternal age. Another study showed that a serum ferritin level higher than 41.5 ng/mL at 28 weeks increased the risk of having a preterm delivery ninefold.<sup>[5]</sup> In fact, our obtained cut point was notably lower that were reported in previous similar studies and thus might be accompanied by higher accuracy for discriminating preterm and term labor. However, it seems that a serial estimation of serum level rather than a single value may give a clue to the possibility of preterm delivery that should be considered in further studies.

## CONCLUSION

Our results showed elevated serum ferritin concentrations are significantly associated with spontaneous preterm delivery among Iranian population and serum ferritin values of more than 22.5 ng/mL was the optimal cut-point.

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