Comparison of serum ferritin levels in pregnant women with preterm and term deliveries

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Abstract

Introduction: Despite high rates of mortality and morbidity due to preterm delivery, none of the diagnostic and biochemical tests could help to accurately identify the cases at risk of preterm delivery.
Objectives: Since ferritin is an acute phase reactant, this study aimed to evaluate serum ferritin levels in women with preterm and term delivery.
Methods: This study was conducted on 150 women with preterm delivery (50 cases in each of the groups 24-30, 30-34, and 34-37 weeks of pregnancy), 150 women with term delivery, and 150 pregnant women who were between 24-37 weeks of pregnancy (same as preterm delivery groups).
Results: The mean ferritin level in all preterm groups was significantly higher than that in the term group, but there was no difference among the preterm groups. In addition, ferritin level in each preterm group was significantly higher than those in the normal pregnancy group at the same gestational age. In preterm deliveries, ferritin levels were significantly higher in cases with prelabor rupture of membranes (PROM) or with a prolonged leakage (longer than 12 hours). In addition, in patients with PROM or prolonged leakage, ferritin levels were significantly higher in preterm deliveries than in term deliveries. A ferritin level of 37.5 ng/mL recognized as the best cut-off for preterm delivery, as compared with term delivery, and its sensitivity, specificity, and diagnostic accuracy was 78.7%, 68.7%, and 73.6%, respectively.
Conclusion: The findings of the present study showed that serum ferritin level can be used to find patients at risk of preterm delivery.

Introduction

Preterm delivery is a delivery occurring prior to 37 weeks of gestation. Every year, about 15 million babies are born prematurely, more than one in 10 of all babies born around the world, and its complications are the leading cause of mortality of children less than 5 years, causing about one million deaths annually (1,2). The pathophysiology of preterm delivery is not yet fully understood, however, it has several risk factors such as a history of preterm delivery, a history of abortion, vaginal bleeding, moderate to severe anemia at 12 weeks of gestation, inadequate weight gain during pregnancy, and uterine and cervical problems (3). There is evidence indicating that prelabor rupture of membranes (PROM) is the most important cause of preterm delivery, which may be caused by subclinical infection and chronic inflammation of the uterus (3). Under such conditions, microorganisms produce prostaglandins directly or through phospholipase A2 production, resulting in uterine contraction and cervical relaxation (4).

Various tests and biochemical markers,

Key point

In a study on 150 women with preterm delivery, 150 women with term delivery and 150 pregnant women who were between 24-37 weeks of pregnancy, we found that ferritin level of 37.5 ng/mL with a sensitivity of 78.7% and specificity of 68.7% could indicate preterm delivery.

such as cervical length measurement through transvaginal ultrasound, bacterial vaginosis tests, fetal fibronectin, hCG in cervical and vaginal secretions (5,6), maternal corticotropin releasing hormone (CRH) (7), and maternal serum alpha fetoprotein in 11-13 weeks (8), have been suggested to predict preterm delivery; however none of them are able to accurately identify cases at risk for preterm delivery and its related complications (9, 10).

Acute phase response is defined as the systemic response to inflammation and tissue damage that occurs within hours to days (11). Many acute-phase reactants such as C-reactive protein (CRP), interleukins,

albumin, pre-albumin, iron, calcium, and zinc have been identified so far (11). Ferritin is also a primary intracellular storage protein that holds iron in an insoluble and non-toxic state, while it has been reported to increase in a number of acute-phase reactions such as inflammation (12). Maternal subclinical infection may increase ferritin level as an acute phase reactant and cause spontaneous rupture of the membranes (13). Some studies have reported that ferritin level could be used as a predictor of preterm delivery (14-16); however, the results of studies in this area are controversial.

Objectives
The present study was conducted to compare serum ferritin levels between women with preterm delivery and women with term delivery and also pregnant women in 24-37 weeks of gestation.

Patients and Methods
Study design
In this cross-sectional study, 300 pregnant women with labor pain, who referred to Mahdieh hospital in Tehran, were selected and enrolled into four groups with a gestational age of 24-30 weeks, 30-34 weeks, 34-37 weeks, and over 37 weeks. In addition, 150 pregnant women, who were in similar gestational weeks and referred to the gynecology clinic for routine checkups, were selected as the control group. Accordingly, a total of 150 pregnant women with preterm delivery (50 cases in each of the groups 24-30, 30-34, and 34-37 weeks of pregnancy), 150 pregnant women with term delivery, and 150 pregnant women in the control group at 24-37 weeks of gestation (50 cases in each of the groups 24-30, 30-34, and 34-37 weeks of pregnancy) participated in the study. Inclusion criteria were single pregnancy and gestational age of above 24 weeks. Exclusion criteria were anemia (hemoglobin level of less than 9.7 g/dL in the second trimester and less than 9.5 g/dL in the third trimester), elevated serum iron levels (above 178 µg/dL in the second trimester, and above 193 µg/dL in the third trimester), chronic infectious diseases, multiple pregnancies, fetal anomalies, fetal intrauterine death, severe polyhydramnios, diabetes mellitus, alcohol consumption, smoking and drug abuse, ferritin level enhancers including rheumatoid arthritis, hemochromatosis, hyperthyroidism, adult-onset Still's disease, leukemia, Hodgkin's lymphoma, and multiple blood transfusions.

After obtaining written consent from the participants, a form was applied to collect maternal information including age, body mass index (BMI), gravidity, parity and gestational age. In addition, the research team registered maternal risk factors including PROM, history of vaginal bleeding in early pregnancy, overweight and obesity, inadequate maternal weight gain during pregnancy, age less than 18 or over 40 years, congenital abnormalities of fetus, a time interval of less than 18 months between pregnancies, history of preterm delivery, anemia (hemoglobin less than 10 g/dL), history of preterm delivery in first-degree relatives, intrauterine growth restriction, polyhydramnios, uterine abnormalities, and prolonged leakage (longer than 12 hours). Blood samples were then collected from the participants under sterile conditions and stored in iron-free tubes at room temperature. Serums of the samples were separated within two hours and stored at minus 20°C. Serum ferritin level measured via particle enhanced immunoturbidimetric method with a fully automatic analyzer. In addition, hemoglobin level was measured using a fully automatic spectrophotometer.

Ethical issues
The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Shahid Beheshti University of Medical Sciences approved this study. The institutional ethical committee at Shahid Beheshti University of Medical Sciences approved all study protocols (IR.SBMU.MSP.REC.1396.900). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from M.D thesis of Maryam Naserieh at this university (Thesis#884).

Statistical analysis
Qualitative variables (frequency and percentage) and quantitative variables (means and standard deviation) were used in this study. Chi-square, independent sample t test, and one-way ANOVA and Bonferroni post hoc tests were used for data analysis. Moreover, using the receiver operating characteristics curve (ROC curve) and area under the curve (AUC), the cut-off points of ferritin level for preterm delivery were determined and its efficiency (sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy) calculated. SPSS 25 software was used for data entry and analysis and $P < 0.05$ was set as the level of significance.

Results
Table 1 compares pregnancy status and risk factors for preterm delivery between the study groups. The frequency of nulliparity in preterm delivery was significantly higher than that in the term delivery and control groups ($P < 0.001$). Moreover, the frequency of some risk factors such as PROM, vaginal bleeding in early pregnancy, overweight and obesity, history of preterm birth in the patient herself and her first-degree relatives, and prolonged leakage was significantly higher in preterm deliveries than in term and control groups ($P < 0.05$).

The mean (SD) age of all patients was 28 ± 6 years, ranging from 16 to 45 years and the mean (SD) serum ferritin level of them was 49 ± 31 ng/mL, ranging from 10 to 201 ng/mL. Table 2 compares the age, BMI, hemoglobin and ferritin levels between the study groups. These results showed that age and hemoglobin levels were not significantly different between the preterm groups and term group, and between

Table 1. Comparison of pregnancy status and risk factors of preterm delivery between study groups

	All (n=450)	Preterm labor (n=150)	Term labor (n=150)	Control group (24-37 weeks) (n=150)	P value*
Pregnancy status					
Nulliparous	181 (40%)	80 (54%)	57 (38%)	44 (29%)	<0.001
Primiparous	171 (38%)	53 (35%)	55 (37%)	63 (42%)	
Multiparous	98 (22%)	17 (11%)	38 (25%)	43 (29%)	
PROM	150 (33%)	88 (59%)	62 (41%)	0 (0%)	<0.001
Early pregnancy vaginal bleeding	43 (10%)	22 (15%)	10 (6%)	11 (7%)	0.033
Overweight and obesity	169 (38%)	59 (39%)	72 (48%)	38 (25%)	<0.001
Inadequate weight gain during pregnancy	3 (1%)	3 (2%)	0 (0%)	0 (0%)	0.050
Age <18 years or >40 years	17 (4%)	9 (6%)	3 (2%)	5 (3%)	0.181
Congenital fetal malformations	4 (1%)	3 (2%)	1 (1%)	0 (0%)	0.171
Less than 18 months between pregnancies	15 (3%)	8 (5%)	7 (5%)	0 (0%)	0.020
History of preterm labor	15 (3%)	13 (9%)	1 (1%)	1 (1%)	<0.001
Anemia (Hb <10 g/dL)	6 (1%)	3 (2%)	3 (2%)	0 (0%)	0.219
History of preterm labor in first-degree relatives	12 (3%)	9 (6%)	3 (2%)	0 (0%)	0.005
IUGR	13 (3%)	7 (5%)	6 (4%)	0 (0%)	0.033
Polyhydramnios	6 (1%)	4 (3%)	2 (2%)	0 (0%)	0.132
Uterine malformations	4 (1%)	4 (3%)	0 (0%)	0 (0%)	0.018
Prolonged leakage (longer than 12 hours)	23 (5%)	19 (13%)	4 (3%)	0 (0%)	<0.001

PROM: Prelabor rupture of membranes.
* Chi-square test.

Table 2. Comparison of age, BMI, hemoglobin and ferritin level between study groups

	Preterm (24-30 wk)	Preterm (30-34 wk)	Preterm (34-37 wk)	Term (>37 wk)	P value[a]	Pregnancy 24-30 wk	Pregnancy 30-34 wk	Pregnancy 34-37 wk	P value[b]	P value[c]	P value[d]
Age, year	29 ± 7	28 ± 5	27 ± 6	29 ± 6	0.259	30 ± 6	27 ± 5	28 ± 6	0.750	0.768	0.356
BMI, kg/m²	25.7 ± 3.9	25.2 ± 3.0	25.9 ± 3.9	25.6 ± 3.7	0.781	24.6 ± 2.2	24.0 ± 2.5	23.6 ± 2.7	0.084	0.041	0.001
Hemoglobin, g/dL	11.9 ± 0.9	11.9 ± 1.1	12.1 ± 1.1	11.7 ± 0.9	0.087	11.8 ± 0.8	11.7 ± 0.7	11.7 ± 0.8	0.615	0.311	0.072
Ferritin, ng/mL	58.4 ± 29.0	59.9 ± 27.6	71.7 ± 41.1	35.1 ± 20.2	<0.001[e]	37.4 ± 32.5	33.4 ± 22.4	33.6 ± 24.8	0.001	<0.001	<0.001

[a] Comparison among preterm groups and term, One way ANOVA
[b] Comparison between the preterm group at 24-30 weeks and pregnancy at 24-30 weeks, independent sample *t* test.
[c] Comparison between the preterm group at 30-34 weeks and pregnancy at 30-34 weeks, independent sample *t* test.
[d] Comparison between the preterm group at 34-37 weeks and pregnancy at 34-37 weeks, independent sample *t* test.
[e] The mean ferritin level in all preterm groups was significantly higher than in the term group, but there was no difference among the preterm groups, Bonferroni post hoc test.

each preterm group and the normal pregnancy group at the similar gestational age (*P* < 0.05). Moreover, BMI was significantly different between some groups. On the other hand, mean ferritin level in all preterm groups was significantly higher than in the term group, however, there was no difference among the preterm group. Furthermore, ferritin levels in each preterm group were significantly higher than those in the normal pregnancy group at the same gestational age (*P* < 0.05). However, ferritin levels were not significantly different between term delivery in comparison with pregnancies at weeks 24-30, 30-34, and 34-37 (*P* = 0.642, *P* = 0.603, and *P* = 0.663, respectively) (Figure 1).

Furthermore, in preterm deliveries, ferritin levels were significantly higher (*P* < 0.05) in patients with PROM or a prolonged leakage; however, in term deliveries, there was no significant difference in ferritin level between patients with and without PROM or a prolonged leakage. In addition, ferritin levels were significantly higher in

preterm deliveries than term deliveries in patients with PROM or a prolonged leakage (*P* < 0.001; Table 3).

Table 4 and Figures 2-4 present the cut-off of ferritin level for preterm delivery under different conditions. Considering all cases of preterm delivery, a ferritin level
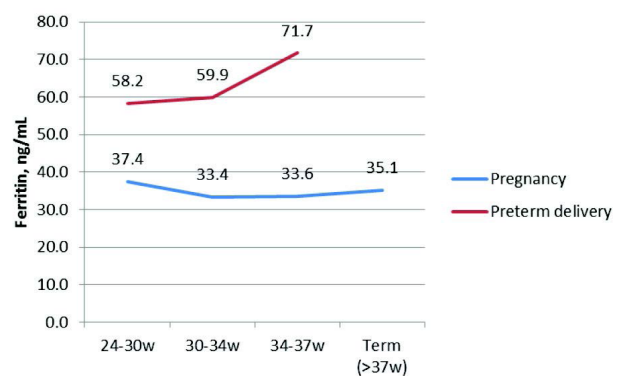

Figure 1. The mean of ferritin level.

Table 3. Comparison of ferritin level in preterm and term deliveries in terms of membrane status

			Ferritin level (ng/mL)	P value*
Preterm labor (n =150)	PROM	No (n = 62)	53.6 ± 27.0	0.002
		Yes (n = 88)	70.1 ± 35.9	
	Prolonged leakage (longer than 12 hours)	No (n = 131)	57.4 ± 27.4	<0.001
		Yes (n = 19)	103.7 ± 42.8	
Term labor (n = 150)	PROM	No (n = 88)	34.6 ± 20.3	0.676
		Yes (n = 62)	36.0 ± 20.2	
	Prolonged leakage (longer than 12 hours)	No (n = 146)	34.9 ± 20.4	0.336
		Yes (n = 4)	44.8 ± 10.4	
PROM (n = 150)		Preterm (n = 88)	70.1 ± 35.9	<0.001
		Term (n = 62)	36.0 ± 20.2	
Prolonged leakage (longer than 12 hours) (n = 23)		Preterm (n = 19)	103.7 ± 42.8	<0.001
		Term (n = 4)	44.8 ± 10.4	

PROM: Prelabor rupture of membranes, IUGR: Intrauterine growth restriction.
* Independent sample *t* test.

Table 4. Diagnostic efficacy of ferritin cut-off levels for preterm delivery in different conditions

Comparison groups	Ferritin cut-off level(ng/mL)	True Positive	False Positive	True Negative	False Negative	Specificity	Specificity	PPV	NPV	Accuracy
Preterm (n = 150) vs. term deliveries (n = 150)	37.5	39.3%	15.7%	34.3%	10.7%	78.7%	68.7%	71.5%	76.3%	73.6%
Preterm deliveries (n = 150) vs. pregnancies at 24-37 weeks (n = 150)	38.5	38%	12.3%	37.7%	12%	76%	75.3%	75.5%	75.8%	75.7%
Preterm deliveries at 24-30 weeks (n = 50) vs. other preterm and term deliveries (n = 250)	37.5	13%	42%	41.3%	3.7%	78%	49.6%	6.2%	91.9%	54.3%
Preterm deliveries at 24-30 weeks (n = 50) vs. pregnancies at 24-30 weeks (n = 50)	36.5	40%	17%	33%	10%	80%	66%	70.2%	76.7%	73%
Preterm deliveries at 30-34 weeks (n = 50) vs. other preterm and term deliveries (n = 250)	57.5	9.7%	23.7%	59.6%	7%	58%	71.6%	29%	89.5%	69.4%
Preterm deliveries at 30-34 weeks (n = 50) vs. pregnancies at 30-34 weeks (n = 50)	38.5	36%	11%	39%	17%	72%	78%	76.6%	73.6%	75%
Preterm deliveries at 34-37 weeks (n = 50) vs .other preterm and term deliveries (n = 250)	39.5	13.7%	37.3%	46%	3%	82%	55.2%	26.8%	93.9%	59.7%
Preterm deliveries at 34-37 weeks (n = 50) vs. pregnancies at 34-37 weeks (n = 50)	34.5	43%	13%	37%	7%	86%	74%	76.8%	84.1%	80%
PROM: Preterm (n = 88) vs. term deliveries (n = 62)	44.5	44.7%	8.7%	32.6%	14%	76.1%	79%	83.8%	70%	77.4%
Prolonged leakage (longer than 12 hours): Preterm (n = 19) vs. term deliveries (n = 4)	51	82.6%	4.4%	13%	0%	100%	75%	95%	100%	95.6%

NPV: Negative predictive value, PPV: Positive predictive value, PROM: Prelabor rupture of membranes

of 37.5 ng/mL identified as the best cut-off for preterm delivery, as compared with term delivery, with a sensitivity, specificity, and diagnostic accuracy of 78.7%, 68.7%, and 73.6%, respectively. Moreover, the best cut-off of ferritin level for preterm delivery, as compared with pregnancy at 24-37 weeks, was 38.5 ng/mL. In addition, the best cut-off of ferritin level for preterm delivery in patients with PROM and a prolonged leakage was 44.5 ng/mL and 51 ng/mL, respectively.

Discussion
The results of this study showed that mean serum ferritin level was significantly higher in all preterm groups than in term group, as well as in each preterm group than in each normal pregnancy group at the same gestational age. Furthermore, serum ferritin level was significantly higher in case of PROM or a prolonged leakage (longer than 12 hours) in preterm deliveries but not in term deliveries. In addition, in case of PROM or a prolonged leakage, ferritin levels were significantly higher in preterm deliveries than in term deliveries. A ferritin level of 37.5 ng/mL was the best cut-off for preterm delivery in comparison with term delivery and a ferritin level of 38.5 ng/mL was the best cut-off for pregnancies at 24-37 weeks.
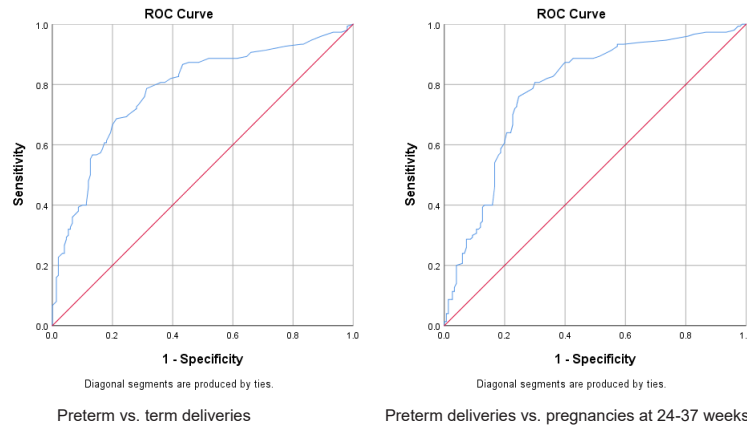
Preterm vs. term deliveries

Preterm deliveries vs. pregnancies at 24-37 weeks

Figure 2. ROC curve of preterm versus term deliveries and pregnancies at 24-37 weeks.

It is now well proved that ferritin is an acute phase reactant (17). There are some evidence indicating a relationship between upper and lower genital tract infections and preterm delivery. Bacterial infection at the site of placenta and endometrium stimulates the activity of mononuclear leukocytes and produces inflammatory factors such as cytokines and interleukins. Ferritin, which is an iron storage protein, can be released from these leukocytes and act as a host defense against microbial invasion; through

collecting and storing iron. Therefore, it can protect iron as a nutrient against microbial agents (18). Apparently, the mentioned process is one of the mechanisms leading to an increase in ferritin level induced by infection and inflammation. Since preterm delivery in many cases may occur due to subclinical infections, therefore, an increase in ferritin level in preterm delivery can be justified.

Valappil et al reported that serum ferritin level could be an indicator of PROM, but not a good indicator of
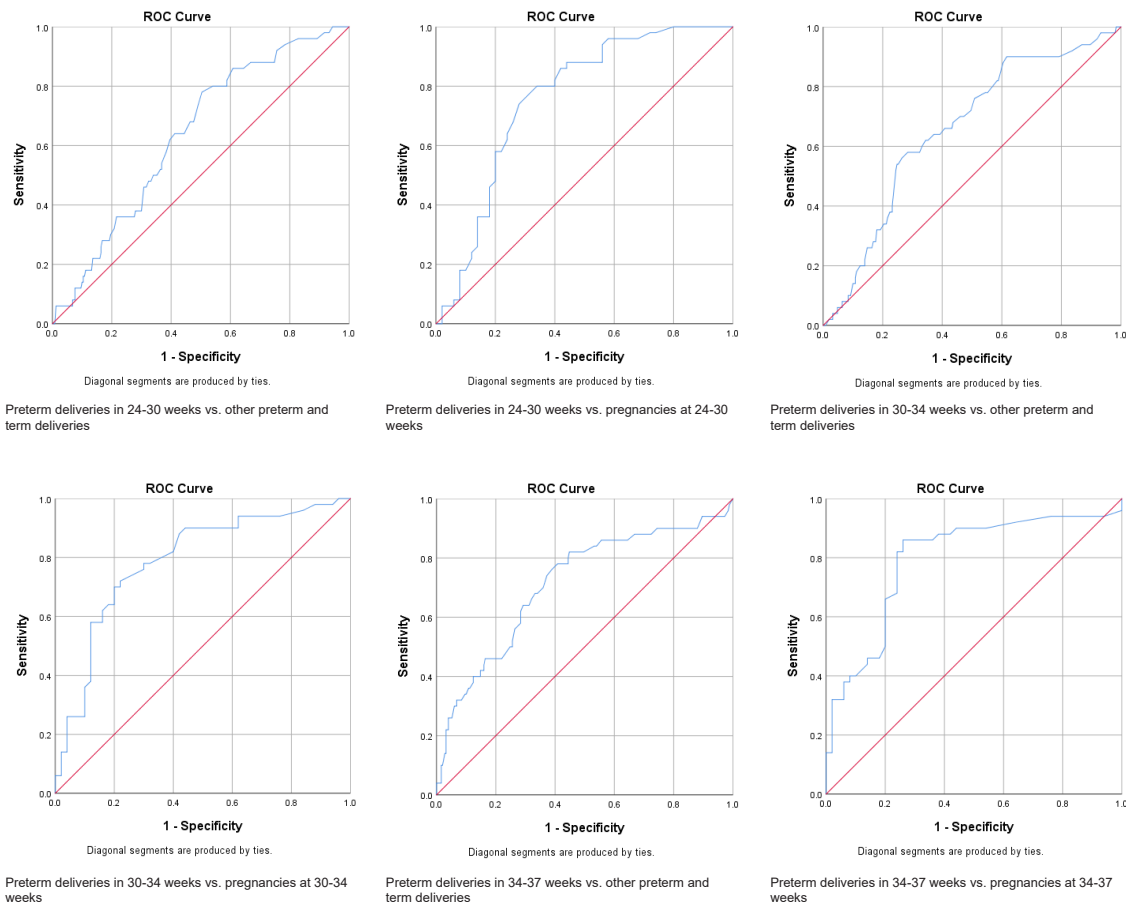

Preterm deliveries in 24-30 weeks vs. other preterm and term deliveries

Preterm deliveries in 24-30 weeks vs. pregnancies at 24-30 weeks

Preterm deliveries in 30-34 weeks vs. other preterm and term deliveries

Preterm deliveries in 30-34 weeks vs. pregnancies at 30-34 weeks

Preterm deliveries in 34-37 weeks vs. other preterm and term deliveries

Preterm deliveries in 34-37 weeks vs. pregnancies at 34-37 weeks

Figure 3. ROC curve of preterm deliveries by week versus other deliveries and pregnancies in the same gestational age.
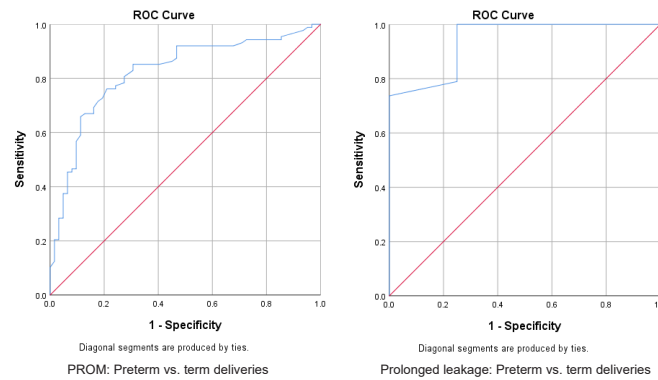
Figure 3. ROC curve of preterm deliveries by week versus other deliveries and pregnancies in the same gestational age.

spontaneous preterm delivery. They proposed a cut-off point of 35.5 ng/mL for predicting cases at risk of PROM (19). Similarly, our study showed that in patients with PROM, ferritin level was higher in the preterm group than in the term group while our cut-off point is close to their finding (19).

Nandini et al highlighted that the mean ferritin level in women with preterm and normal vaginal delivery was 81.296 ng/mL and 28.576 ng/mL, respectively, which was significantly higher in women with preterm delivery (20). In our study, ferritin levels in the preterm group were lower and in the term group was higher than their study. However, similar to their study, ferritin level was significantly higher in preterm than in term delivery.

Weintraub et al concluded that a ferritin level above 30 ng/mL in the second trimester could be a predictor of preterm delivery; however, due to the lack of relationship between ferritin level and gestational age at birth, they recommended to conduct further studies to ensure the use of ferritin level as an indicator for predicting preterm delivery (16). Nonetheless, our study showed that ferritin level at the time of delivery was significantly higher in all preterm groups than in the term group.

In addition to the above studies, which determine a cut-off point for ferritin level for predicting preterm labor, several studies have addressed the predictive role of ferritin in preterm delivery (14,15,21-23). Singh et al reported that ferritin was a better predicting biomarker for preterm delivery than other indicators (22). Besides, Khambalia et al revealed that high maternal ferritin level in the early time of pregnancy (12 weeks of gestation) was associated with an increased risk of preterm delivery (23). El-Shahawy et al also showed that ferritin level was significantly higher in the preterm group at 30-34 weeks than in uncomplicated pregnancies at the same age of gestation, and ferritin level above 55 ng/mL with a sensitivity of 96.7% and specificity of 96.7% could be used as a predictor of preterm delivery (15). Finally, Abdel-Malek et al showed that serum ferritin level at week 30 of gestation was significantly higher in the preterm group (76.3±29.4 ng/mL) than in the control group (20.2±5.0 ng/mL). In addition, a serum ferritin level

of 31 ng/mL with a sensitivity of 92.8% and specificity of 99.4%, and a positive predictive value of 97.5%, and negative predictive value of 98.4%, and accuracy of 98.3% were able to detect preterm delivery (14). In our study, the results of comparing ferritin level in preterm group and control group at the same age of gestation also showed an increase in ferritin level in women with preterm delivery. With increasing gestational age, there was a growth in the trend of ferritin level in preterm deliveries; however, ferritin levels did not differ significantly between different preterm groups. As noted above, in various studies, different levels of ferritin were reported as a risk factor for preterm delivery. The differences between studies may be attributed to differences in sample size as well as differences in the frequency of risk factors for preterm delivery.

Overall, consistent with previous studies, our study showed that serum ferritin level in preterm deliveries at different gestational age was higher than those in term delivery and higher than those in normal pregnancies at the same gestational age. Given that in our study, women in preterm and term groups had labor pain and the results showed higher ferritin level in preterm delivery than in term delivery, we suggest that ferritin level measurement, even at the onset of delivery pain, could help to predict the risk for preterm delivery. Therefore, considering the results of other studies, it can be stated that ferritin level can be used to detect patients at risk for preterm delivery. However, it is suggested to conduct further multicenter prospective studies to evaluate the predictive value of serum ferritin levels in different high-risk groups and compare it with other biochemical parameters of preterm delivery such as fetal fibronectin.

Conclusion
The findings of the present study showed that the mean serum ferritin level in all preterm groups was significantly higher than that in both term group and normal pregnancies at the same gestation age. In addition, a ferritin level of 37.5 ng/mL, with a sensitivity of 78.7% and specificity of 68.7% could indicate preterm delivery.

Therefore, it seems that serum ferritin level can be used to find patients at risk of preterm delivery.

Limitations of the study
Our design was a cross-sectional study, therefore we suggest conducting further multicenter prospective studies to evaluate the predictive value of serum ferritin levels in different high-risk groups and compare it with other biochemical parameters of preterm delivery such as fetal fibronectin.

Authors' contribution
All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. MN, TJB and MY designed the protocol of study. MN developed the protocol and performed it. Critical revision of the manuscript for important intellectual content was performed by MN, TJB and MY. Analysis of data performed by MN. All authors read and approved the final paper.

Conflicts of interest
The authors declare that they do not have any conflict of interest.

Ethical considerations
Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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