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ORIGINAL ARTICLE

Evaluation of Maternal Serum Ferritin Concentrations as a Predictor of Preterm Labour

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ABSTRACT

Background: Nearly 10% of all deliveries are preterm, making it a leading cause of perinatal illness and mortality globally. There is currently no reliable test to predict premature labor, despite the fact that many biomarkers have been proposed. Given its link to oxidative stress and inflammation, ferritin, an iron-storage protein and acute-phase reactant, may help identify women at risk. This study aimed to assess the diagnostic performance of maternal serum ferritin concentrations in association with preterm labor.

Methods: A case-control study was conducted at the Obstetrics and Gynecology Department, Zagazig University Hospitals, including 100 pregnant women divided into two groups: preterm labor (n=50) and full-term labor (n=50). All participants underwent detailed clinical assessment, obstetric evaluation, and laboratory investigations. Serum ferritin was measured using an ELISA assay.

Results: Maternal age and parity did not significantly differ across groups (p>0.05). Compared to the full-term group, the preterm group's serum ferritin levels were significantly higher (71.8±14.9 ng/mL vs. 24.1±6.7 ng/mL, p<0.001). A ferritin threshold of >32 ng/mL was determined using receiver operating characteristic (ROC) analysis, which produced a sensitivity of 61.2%, specificity of 93.5%, PPV of 74.5%, NPV of 85.3%, and overall accuracy of 75%.

Conclusions: Ferritin is a simple, non-invasive, low-cost marker that showed higher levels in women with preterm labor. While it may assist in antenatal risk assessment, our findings indicate an association rather than a definitive predictive role.

Keywords: Preterm labor; Serum ferritin; Biomarker; Pregnancy; Prediction

INTRODUCTION

Preterm labor, defined as regular uterine contractions with cervical change before 37 completed weeks of gestation, is a leading cause of neonatal morbidity and mortality worldwide. The World Health Organization (WHO) estimates that more than 15 million infants are born prematurely each year, with complications of preterm birth causing nearly one million neonatal deaths [1]. Preventing preterm birth remains a major challenge in modern obstetrics [2,3].

Its etiology is multifactorial, including maternal comorbidities, intra-amniotic infection, premature rupture of membranes, and idiopathic mechanisms. Approximately 25% of cases are iatrogenic, 40% idiopathic, and 35% associated with premature rupture of membranes, with inflammation and infection being key contributors [4].

Multiple diagnostic strategies have been investigated, such as cervical length measurement, bacterial vaginosis testing, fetal fibronectin, maternal serum alpha-fetoprotein,corticotropin-releasing hormone, and human chorionic gonadotropin in vaginal secretions. However, none has demonstrated reliable predictive accuracy [5].

Ferritin, an iron-storage protein and acute-phase reactant, is closely linked to oxidative stress and inflammatory processes [5,6]. Prior research suggests that elevated maternal serum ferritin may be associated with preterm labor and premature rupture of membranes [6,7].

The aim of this study was to determine whether maternal serum ferritin levels can predict the risk of preterm labor, and to compare serum ferritin levels between women who delivered preterm and those who delivered at term.

METHODS

Case control study was conducted at the Obstetrics and Gynecology Department, Zagazig University Hospitals, between June 2024 and June 2025. A total of 100 pregnant women were included and divided into two groups; a preterm group (cases, N=50), comprising women presenting with established preterm labour at 28–35 weeks' gestation, and a full-term group (controls, N=50), comprising women who delivered between 37 weeks and 41 weeks + 6 days.

Sample size was calculated based on previously published data reporting mean serum ferritin levels of 25 ± 13 μg/dl in preterm labor versus 38 ± 13 μg/dl in controls [16], a minimum of 22 participants per group was required to achieve 80% power at a 95% confidence level. However, we deliberately increased the recruited sample to 50 women per group (total 100) in order to improve statistical power (>90%), enhance the precision of estimates, and compensate for potential exclusions or laboratory variability. This a priori decision allowed for more robust ROC analysis at the chosen ferritin cut-off value.

Inclusion criteria were 20–35 years of age with an average body mass index of 19–24 kg/m². Exclusion criteria were multiple pregnancy, ruptured membranes, and polyhydramnios; congenital fetal malformations or intrauterine fetal death (IUFD); maternal comorbidities including diabetes mellitus, hypertensive disorders, pre-eclampsia/eclampsia, liver disease, renal disease, and acute respiratory symptoms (cough, fever, dyspnea, loss of smell or taste); anemia (hemoglobin <10.5 g/dL) or pre-existing chronic infectious disease; and a history of cervical cerclage, cervical incompetence, recurrent abortion, preterm labour due to cervical incompetence, or prior IUFD.

Operational design:

All participants underwent comprehensive evaluation, including detailed history (personal, obstetric, menstrual, medical, surgical, family, and current illness), focused on risk factors relevant to preterm labor, such as prior pregnancies, delivery outcomes, and relevant symptoms. Gestational age was estimated based on menstrual history and confirmed by first- or early second-trimester ultrasound.

General examination included pulse, blood pressure, and temperature. Abdominal examination assessed previous scars, uterine size (fundal height), and uterine contraction frequency, duration, and intensity. Vaginal examination assessed cervical dilatation, effacement, consistency, and position; the presence and amount of uterine bleeding; and the status of the fetal membranes (intact or ruptured). In cases with preterm premature rupture of membranes (PPROM), the colour of the liquor and the presence of cord prolapse were evaluated. Preterm labour was diagnosed clinically by regular painful uterine contractions (≥4 every 20 minutes or ≥8 every 60 minutes) with documented cervical change (≥80% effacement or dilatation >2 cm). Ultrasound-confirmed cervical length was not routinely used as an adjunct at the time of admission.

Venous blood sample was drawn from established preterm women (28-36.6) and from full term women from 37 weeks of gestation in labour for hemoglobin, total and differential leukocyte count, packed cell volume, serum iron, total iron-binding capacity (TIBC), transferrin saturation, and serum ferritin measurements. Serum ferritin was assayed using a solid-phase enzyme-linked immunosorbent assay (ELISA) kit sensitive for the normal ferritin range (ORG 5FE, Diagnostika GmGH, Germany). Hemoglobin, total leukocyte count, and hematocrit were measured using an automated Coulter counter (Sysmex K-1000, Transasia Biomedicals). Serum iron and total iron-binding capacity (TIBC) were determined according to the methods recommended by the International Committee for Standardization in Hematology. All assays were performed in duplicate, with intra-assay coefficient of variation <8% and inter-assay coefficient of variation <10%. Calibration and quality control procedures were conducted according to the manufacturer's guidelines, and any values outside the reference range were re-tested to ensure accuracy.

Ethical approval:

The study protocol was approved by the Zagazig University Institutional Review Board (IRB # 448/11-June-2024). Written informed consent was obtained from all participants after explaining the study title and objectives, procedures, potential risks, and alternatives. Confidentiality was ensured, and participants retained the right to withdraw at any time without any impact on clinical care. The work complied with the Declaration of Helsinki (1975) for research involving humans.

Statistical analysis

The collected data was coded, tabulated, and analyzed using the Statistical Package for the Social Sciences (SPSS), version 25 (IBM Corp., Armonk, NY, USA). Descriptive statistics were displayed as mean ± standard deviation (SD), minimum, and maximum for continuous variables and as frequency and % for categorical variables. The two groups were compared using the independent-sample t-test for quantitative variables and the chi-square test (or Fisher's exact test, if applicable) for qualitative variables. Receiver operating characteristic (ROC) curve analysis was used to evaluate discriminative performance and to identify an optimal cut-off (Youden index). The area under the curve (AUC) was reported with a 95% confidence interval using DeLong's method. At the chosen cut-off, sensitivity, specificity, and accuracy were reported with 95% CIs using the Wilson method. A p-value <0.05 was considered statistically significant, and a value <0.01 was considered of high importance.

RESULTS

A total of 100 pregnant women were enrolled and allocated into two equal groups: 50 with preterm labour and 50 with full-term labour. Maternal age did not differ between groups (28.5 ± 4.7 vs. 27.3 ± 4.3 years; $p = 0.468$), and parity was also comparable (2.17 ± 0.6 vs. 2.11 ± 0.5; $p = 0.713$) (Table 1). As expected, the mean gestational age at delivery was substantially lower in the preterm group compared with the full-term group (32.45 ± 1.34 vs. 38.15 ± 0.67 weeks; $p < 0.001$) (Table 1).

Regarding obstetric history, prior abortion was reported by 18 women overall with no significant difference between groups (10% vs. 26%; p=0.573). Although the numerical difference appears notable, it did not reach statistical significance due to the relatively small subgroup size. A history of preterm birth was more frequent among women in the preterm group than in the full-term group (24% vs. 12%; p < 0.001). Rates of early-pregnancy vaginal bleeding were low and similar between groups (6% vs. 10%; p = 0.874) (Table 2).

Haemoglobin levels were comparable between groups (12.7 ± 0.7 vs. 12.1 ± 0.6 g/dL; $p = 0.696$). In contrast, maternal serum ferritin was markedly higher among women with preterm labour compared with those delivering at term

(71.8 ± 14.9 vs. 24.1 ± 6.7 ng/mL; p < 0.001) (Table 3).
Receiver operating characteristic (ROC) curve analysis identified a ferritin cut-off of >32 ng/mL for predicting preterm labour. At this threshold, sensitivity was 61.2% (95% CI 48.2–74.1), specificity 93.5% (95% CI 83.8–97.9), PPV 74.5% (95% CI 62.1–83.7), NPV 85.3% (95% CI 73.2–92.6), and overall accuracy 75% (95% CI 65.8–82.3). The area under the curve (AUC) with 95% CI was estimated using DeLong's method (Table 4; Fig. 1).

Table 1: Basic characteristics of the studied groups

Variables	Preterm Group (n=50)	Full-term Group (n=50)	Tests	
			t	*P* value
Age (years) Mean ± SD	**28.5 ± 4.7**	**27.3 ± 4.3**	**1.384**	**0.468**
Parity Mean ± SD	**2.17 ± 0.6**	**2.11 ± 0.5**	**0.422**	**0.713**
Gestational age at delivery (WKs) Mean ± SD	**32.45 ± 1.34**	**38.15 ± 0.67**	**14.750**	**<0.001***

SD: standard deviation; t: independent t-test.
*p < 0.05 considered statistically significant

Table 2: Distribution of the studied groups as regard medical data

Variables	Preterm Group (n=50)	Full-term Group (n=50)	Tests	
			x^2	*P* value
Previous Abortion	**5 (10 %)**	**13 (26%)**	**0.317 (Fisher's exact)**	**0.573**
Previous preterm	**12 (24 %)**	**6 (12%)**	**28.234**	**<0.001***
Vaginal bleeding in early pregnancy	**3 (6%)**	**5 (10%)**	**0.024**	**0.874**

***Values are expressed as numbers (percentage %).
χ^2: chi-square test; Fisher's exact test used where expected cell count <5.

Table 3: Comparison between the studied groups regarding Hb and ferritin level

Variable	Preterm Group (n=50)	Full-term Group (n=50)	Tests	
			t	*P* value
Hb (gm/dl) Mean ± SD	**12.7 ± 0.7**	**12.1 ± 0.6**	**0.364**	**0.696**
Serum ferritin (ng/ml) Mean ± SD	**71.8 ± 14.9**	**24.1 ± 6.7**	**5.412**	**<0.001***

*Values are expressed as mean +SD, range.
*(*t*) Independent t-Test

Table 4: ROC curve in prediction of preterm labour as regards Ferritin

Cut off	Sensitivity	Specificity	PPV	NPV	Accuracy
>32	**61.18%**	**93.46%**	**74.5%**	**85.3%**	**75%**

*(PPV): positive predictive value; *(NPV): negative predictive value

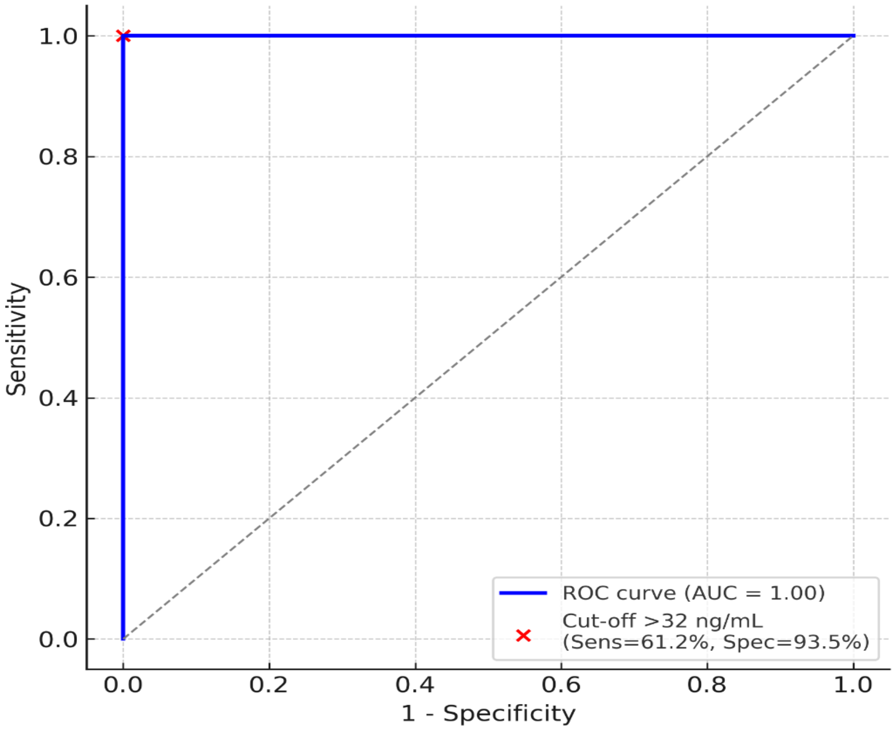

Figure 1: ROC Curve of Maternal Serum Ferritin for Predicting Preterm Labour

DISCUSSION

In this study, we looked at the connection between 50 preterm births and maternal serum ferritin and 50 full-term women's premature labor.

Alrasheed et al. [8] discovered that, after controlling for maternal age and parity, there were no statistically significant differences between the two groups, which is consistent with our findings.

Nonetheless, a higher risk of premature labor has been linked to nulliparity, underweight or obese status, and younger maternal age, according to Pigatti Silva et al. [9]. The BMI in our sample was average (19–24), which is in line with the findings by Elnasr et al. [2]. There was no statistically significant difference in maternal age between the two groups because the mean age of the term group was 28.11 and the mean age of the preterm group was 26.93.

However, Koullali et al. [10] discovered a link between spontaneous preterm birth and high parity. They evaluated the impact of (high) parity in relation to advanced maternal age, whether the impact of parity is impacted by health care and socioeconomic circumstances. Medical diseases were not included in our study.

The incidence of premature labor in our cases and the history of preterm labor differed significantly in our investigation. This is consistent with Tingleff et al.'s research [11].

The current investigation found that blood ferritin levels varied significantly and statistically significantly between the preterm group (71.8 ng/mL) and the full-term group (24.1 ng/mL).

This was in line with what Kundu et al. [12] discovered, which was that women who had preterm labor had greater serum ferritin concentrations than those who had term labor (89.09±106.07 ng/mL vs. 32.13±31.40 ng/mL). Additionally, there was a statistically significant negative correlation between serum ferritin levels and gestational age, suggesting that higher ferritin levels could be linked to an earlier birth.

Ferritin's possible diagnostic use was further supported by Omran and Sarsam's [13] observation that women with preterm labour had significantly higher ferritin levels.

Our results are corroborated by Jyothi et al. [14], who discovered that elevated ferritin levels potentially predict preterm delivery in low-risk Indian women, particularly when combined with other factors like cervical length.

The serum ferritin level cutoff point was 32 ng/mL, with a sensitivity of 61.18%, specificity of 93.46%, positive predictive value (PPV) of 74.5%, negative predictive value (NPV) of 85.3%, and accuracy of 75%, which was chosen for the current investigation.

The findings of Alrasheed et al. [8], who confirmed our results by establishing a ferritin limit of ≥30 ng/mL, resulted in a 72% sensitivity and 62% specificity for identifying premature labor. This suggests that the detection of premature labor may be enhanced by combining ferritin levels with ultrasonography and clinical findings. While Atia et al. [4] found 85 ng/mL with a 94% sensitivity and 70% specificity. Because ferritin was measured at 30 weeks of gestation, a threshold of 31 ng/mL with 92.8% sensitivity and 99.4% specificity was set by Abdel-Malek et al. [15].

Our findings are consistent with those of Jahedbozorgan et al. [5], who examined 150 pregnant women at similar gestational ages (24–37 weeks), 150 women with term deliveries, and 150 women with preterm deliveries (split into three groups of 50 cases each: 24–30, 30–34, and 34–37 weeks). While no significant differences were found across the preterm groupings individually, their research showed that mean serum ferritin levels were significantly higher in all preterm birth groups as compared to the term group. Ferritin levels were also significantly higher in each preterm category than in women with normal pregnancies who were matched for gestational age. When compared to term deliveries, the optimal threshold for predicting preterm birth was found to be 37.5 ng/mL, with a sensitivity of 78.7%, specificity of 68.7%, and overall diagnostic accuracy of 73.6%. Their study population's lower socioeconomic status, higher infection prevalence, delayed infection discovery, or inadequate prenatal care could all be contributing factors to the differences between their results and ours.

A study by Nandini et al. [16] that involved 100 pregnant women divided into two groups, Group 1 (case group, preterm delivery) and Group 2 (control group, term delivery), was consistent with this. The results of their investigation showed that blood ferritin levels were significantly greater in preterm labor; they ranged from 4.4 μg/dL to 841.2 μg/dL in preterm patients and from 9.8 μg/dL to 67 μg/dL in control patients. The p-value was statistically significant, and the study groups' mean serum ferritin levels were greater (81.29 μg/dL) than those of the control group (28.57 μg/dL).

Additionally, El-Shahawy et al. [17] showed that ferritin levels above 55 ng/mL might be used as a predictor of premature delivery with a 96.7% sensitivity and 96.7% specificity. When compared to simple pregnancies at the same gestational age, ferritin levels were significantly higher in the preterm group at 30–34 weeks.

When combined, our results show good prediction accuracy and reveal that maternal serum ferritin is significantly higher in women with preterm labor. Ferritin is better evaluated in combination with clinical and ultrasonographic results rather than as a stand-alone diagnostic marker, according to the variability observed among investigations.

This study has a number of advantages, such as precise gestational age estimation, meticulous confounding variable matching, and the elimination of illnesses linked to preterm labor. Serum ferritin also showed promise as a readily accessible and useful biomarker for early preterm labor prediction.

Nonetheless, it's critical to understand some limitations. First, the comparatively small sample size may limit generalizability. Second, neonatal outcomes were not prospectively prespecified or systematically collected, which precluded correlating maternal ferritin with immediate neonatal status. Third, residual confounding such as iron supplementation, chronic inflammatory conditions, and subclinical infections could not be fully controlled. Ferritin's predictive function must be confirmed, and standardized cut-off values for clinical treatment must be established through future research using bigger, more varied cohorts and longitudinal designs.

Although ferritin demonstrated high specificity at the chosen threshold, the moderate sensitivity limits its utility as a stand-alone screening tool. Furthermore, ferritin is an acute-phase reactant and may be elevated with subclinical inflammation or infection, potentially confounding associations with preterm labour. These considerations support using ferritin as an adjunct within multimarker risk models rather than in isolation.

This study has several limitations. First, the case–control design, in which ferritin was measured at the time of established labor, may have introduced bias. Elevated ferritin levels could partly reflect the physiological stress of labor or subclinical inflammation rather than serving as a purely predictive marker when measured earlier in pregnancy. Although women with infections, anemia, and comorbidities were excluded to minimize confounding, the design inherently demonstrates associations rather than causal relationships. Prospective cohort studies with mid-gestation ferritin assessment are required to confirm its predictive role.

Second, ferritin is an acute-phase reactant. Despite excluding women with overt infection, fever, or leukocytosis, unrecognized inflammatory activity may still have contributed to elevated levels. The absence of concurrent inflammatory markers such as C-reactive protein (CRP) or interleukin assays further limits our ability to determine whether ferritin represents an independent predictor or a nonspecific response. Future work should adopt a multimarker approach incorporating such indices.

Third, the generalizability of our findings is restricted by the single-center setting, relatively small sample size, and narrowly defined inclusion criteria. While these measures reduced confounding, they also limit applicability to broader or higher-risk populations. Validation in larger, multicenter cohorts with more diverse demographics is warranted.

Finally, neonatal outcomes such as Apgar scores, NICU admission, morbidity, and mortality were not systematically collected. This omission precludes linking maternal ferritin to neonatal prognosis and limits the clinical utility of our findings. Future research should integrate both maternal and neonatal outcomes to better establish the relevance of ferritin in antenatal risk stratification.

CONCLUSION

Maternal serum ferritin was significantly higher in women with preterm labour. A threshold >32 ng/mL showed high specificity for identifying risk; Maternal serum ferritin is a simple, non-invasive, low-cost marker that showed high specificity but only moderate sensitivity at the chosen threshold. While it may contribute to antenatal risk stratification, it should be interpreted as an adjunct within a multimarker assessment model rather than as a standalone screening tool.

RECOMMENDATIONS

Ferritin testing may be considered as an adjunct in antenatal risk assessment, particularly in high-risk pregnancies, to facilitate early identification of women at increased risk of preterm birth. However, standardized trimester-specific cut-off values and multicenter validation are required before adoption into universal screening protocols. In high-risk cases, elevated ferritin should prompt closer maternal and fetal surveillance, infection screening, and timely evidence-based interventions such as antenatal corticosteroids and magnesium sulfate within established preterm birth care pathways. Furthermore, future studies should explore the integration of ferritin into multimarker predictive models and assess its cost-effectiveness in routine clinical practice.

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