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Serum ferritin level as a marker of preterm labor

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Abstract
Introduction: Preterm birth defined as birth between 24 0/7 weeks of gestation and 36 6/7 weeks of gestation. The diagnosis of preterm labor generally is based on clinical criteria of regular uterine contractions accompanied by a change in cervical dilation, effacement, or both, or initial presentation with regular contractions and cervical dilation of at least 2 cm. Less than 10% of women with the clinical diagnosis of preterm labor actually give birth within 7 days of presentation.
Aim of the study: To evaluate the value of serum ferritin level as predictors in preterm labor
Patients and Method: A prospective cross-sectional study, conducted at the department of Obstetrics and Gynecology at Elwiya maternity teaching hospital, from the first of Feb 2019 to the end of July 2019. The sample collected from the pregnant lady who visited the outpatient clinic.
Results: The current study included 216 respondents, half of them (100) for case group (preterm) and other half for normal healthy group and 16 ladies were lost from follow up. With total mean age (29±5) years (range=18-40) years, S. ferritin was highly significantly decreased in full term than that in preterm (P<0.001). Validity of the test to diagnose preterm show that sensitivity was (91.0%), specificity (95.0%), NPV (94.8%), PPV (68.0%) and the accuracy of the test was (93.0%).
Conclusion: Elevated serum ferritin level during the third trimester may be of use in prediction of preterm labor.

Keywords: Serum ferritin, preterm labor, third trimester

Introduction

Preterm birth defined as birth between 24 0/7 weeks of gestation and 36 6/7 weeks of gestation. The diagnosis of preterm labor generally is based on clinical criteria of regular uterine contractions accompanied by a change in cervical dilation, effacement, or both, or initial presentation with regular contractions and cervical dilation of at least 2 cm. Less than 10% of women with the clinical diagnosis of preterm labor actually give birth within 7 days of presentation. It is important to recognize that preterm labor with intact membranes is not the only cause of preterm birth; numerous preterm births are preceded by either rupture of membranes or other medical problems necessitating delivery [1].

Prevalence: As a primary cause of neonatal mortality, preterm birth (childbirth <37 weeks) presents a major public health problem, since 15 million annual births or 11% of all births worldwide are preterm [2]. Approximately 90% of preterm births occur in developing countries, with 11 million (85%) in Africa and Asia, and 0.9 million in Latin America and the Caribbean. Prematurity is the leading cause of neonatal deaths and short- or long-term morbidities, implicating adverse consequences for not only individuals, but also their families, health agencies, facilities, and societies. The highest preterm birth rates occur in low-income settings, where the majority of preterm deliveries caused by spontaneous labor. Maternal complications such as infectious diseases and hypertension are the most common direct causes of preterm delivery [2, 3]. The prevalence of preterm delivery in Iran was reported to range between 5.6% and 13.4% [4]. Preterm delivery is the cardinal cause of fetal mortality and morbidities such as cerebral palsy, severe brain injury, retinopathy, necrotizing enterocolitis, and respiratory disorders. Compared to normal children, the risk of motor sensory disorders, learning disabilities, and behavioral complications is higher in premature children. A multitude of factors can contribute to this condition including low levels of maternal hemoglobin, gestational weight gain, biological and genetic factors [5]. Risk Factors for Preterm Delivery There have been attempts to design a stratification tool to determine the risk of preterm delivery based on risk factors. For instance, the rate of preterm delivery differs greatly between black and white women

With 2015 preliminary data showing a rate of 13.4% in blacks and 8.9% in non-Hispanic whites.2 Although many risk scoring systems have been developed, their ability to identify at-risk women and subsequently prevent a preterm delivery has not been evaluated.8 In the absence of such evidence, risk recognition and subsequent management of contributing factors are the best strategy to prevent preterm delivery [6].

Serum ferritin

Ferritin is a highly symmetrical and stable iron-containing protein that was discovered, crystallized and named in 1937, 80 years ago. It was defined as the major iron storage protein since it possesses a large cavity that can accumulate great amounts of iron. One of the ferritin major properties is its capacity to attract iron ions and to induce their mineralization by using its ferroxidase activity together with the chemical properties specific of the cavity environment. The mineral core can contain up to 4000 Fe atoms in a mineral form and is protected and maintained in solution by the protein coat. Ferritin is almost ubiquitous and a number of functions have been attributed to it. [7, 8] Its location is manly cytoplasmic; however, it has been found also in nucleus, in animal mitochondria, in plant plastids, in insect ER, and it is also secreted in the circulating plasma. Although extensively studied, the particular chemical and biological properties of the various ferritins are still attracting researchers; thereby new lines of research are developing in many different fields. The easy production of recombinant ferritins and their genetic manipulation, joined to the efficient self-assembly, has been exploited in an increasing variety of fascinating nanomaterial applications, and in fact ferritin seems to be the most popular protein for nanotechnologists [8].

Serum ferritin and preterm labor

Various biochemical markers have been developed to predict preterm labour. These markers include foetal fibronectin in the cervicovaginal secretions [9], human chorionic gonadotropin in the cervicovaginal secretions [10], maternal serum corticotropin-releasing hormone (CRH) [11], maternal serum alpha-fetoprotein (AFP) at 11–13 weeks. [12] This might be explained by the status of an acute phase reaction to subclinical infections that are commonly associated with preterm labour. [13] It has been hypothesized that subclinical maternal infection is responsible for both the elevated maternal serum ferritin levels and for spontaneous preterm PROM. 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 [11].

Aim of the study: To evaluate the value of serum ferritin level as predictors in preterm labor

Patients and method:

Study design and setting A prospective cross-sectional study, conducted at the department of Obstetrics and Gynecology at Al-Elwiya maternity teaching hospital, from the first of Feb 2019 to the end of July 2019. The sample collected from the pregnant ladies who visited the outpatient clinic.

Sample collection: Two hundred and sixteen pregnant ladies between the age 18-40 years, with gestational age between (30-34) weeks (based on the last menstrual period and early U/s scan). Full history was taken from the ladies, with general obstetrical, medical and surgical history, and full general physical and obstetrical examination was carried to all respondents. We sent the respondents for U/s to confirm the gestational age, Hb and PCV%, S. iron, S. ferritin, and other investigations according to the patient's condition. The pregnant ladies with no sign and symptoms of anemia and their Hb ≥11g/dl was included in the study. The sample were sent for S. iron, S. ferritin.

Statistical analysis: All patients' data entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 23 used in this study. Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Multiple contingency tables conducted and appropriate statistical tests performed, Chi-square used for categorical variables (Fishers exact test used when expected variable was less than 20% of total) and t-test used to compare between two means. One-way ANOVA analysis used to compare between more than two means. In all statistical analysis, level of significance (p value) set at ≤ 0.05 and the result presented as tables and/or graphs.

Results

No statistical association were found between the studied groups regarding Hb level (P=0.2), while significant increase in hematocrit in full-term were found (P=0.001) (table 1)

Table 1: Association between Hb and hematocrit with gestational age

	gestational age		P value
	Preterm	Full-term	
	Mean±SD	Mean±SD	
Hb (g/dl)	11.8±0.5	11.9±0.8	0.2
Hematocrit (%)	36.4±2.6	37.7±3.1	0.001

The mean level of iron in preterm was (75.2±23.9) and (73.6±27.6) for full-term women with no significant differences (P=0.2). S. ferritin were highly significant decrease in full term than that in preterm (P<0.001) (table 2)

Table 2: Association between S. Iron and S. ferritin with type of term

	Type of gestational age		P value
	Preterm Mean±SD	**Full-term Mean±SD**	
Iron level (Mg/dl)	75.2±23.9	73.6±27.6	0.6
S. Ferritin level (ng/ml)	72.54±15.78	23.88±18.82	<0.001

Table 3 show that the level of the serum ferritin declined with progression of the gestational age in preterm labor, and the mean gestational age at delivery time was below the 36 weeks.

Table 3: level of serum ferritin according to GA in preterm labor

GA at time of sample collection	No. of patients	No. of patients who delivered preterm	S. Ferritin level (Mean±SD)	Mean od GA at delivery (Mean±SD)
30 wks	32	18	117.6±28	31.8±1.2
31 wks	27	7	105.9±12.2	32.4±2.4
32 wks	48	20	94.5±21	33.1±0.9
33 wks	60	35	77.1±22.9	33.2±0.6

34 wks	33	20	63.7±13.2	35.2±0.7
Total	200	100	-	-

Table 4 show that Hb in preterm [in primigravida was (12±0.6) and decrease in multigravida (11.7±0.5) but with no significant association (p=0.3)], and Hb in full-term [in primigravida was (11±0) and increase in multigravida (12±0.8) with no difference (P=0.5)

For s. ferritin: in preterm [in primigravida the level was (21.35±11.63) and increase in multigravida (23.33±16.63) with no difference (P=0.7), and in full-term [hb was (25±4.18) and decrease to (23.59±20) with no significant differences were found (p=0.08)

Table 4: Relation between S. Hb and S. ferritin with gestational age

	gestational age					
	Preterm Mean±SD		**P value**	**Full-term Mean±SD**		**P value**
	Primigravida	Multigravida		Primigravida	Multigravida	
	Mean±SD	Mean±SD		Mean±SD	Mean±SD	
Hb (g/dl)	12±0.6	11.7±0.5	0.3	11±0	12±0.8	0.5
S.Ferritin level (ng/ml)	21.35±11.63	23.33±16.63	0.7	25±4.18	23.59±20	0.08

Validity of the test to diagnose preterm was assessed by using cutoff value of S. ferritin at 34.2 ng/L and the AUC was (80.0%) show that sensitivity was (91.0%), specificity (95.0%), NPV (94.8%), PPV (68.0%) and the accuracy of the test was (93.0%), all these were found in (table 5 and figure 1)

Table 5: Validity test of the S. Ferritin

Cutoff value of S. ferritin	Sensitivity	Specificity	NPV	PPV	Accuracy
34.2 (ng/L)	91.0%	95.%	94.8%	68.0%	93.0%

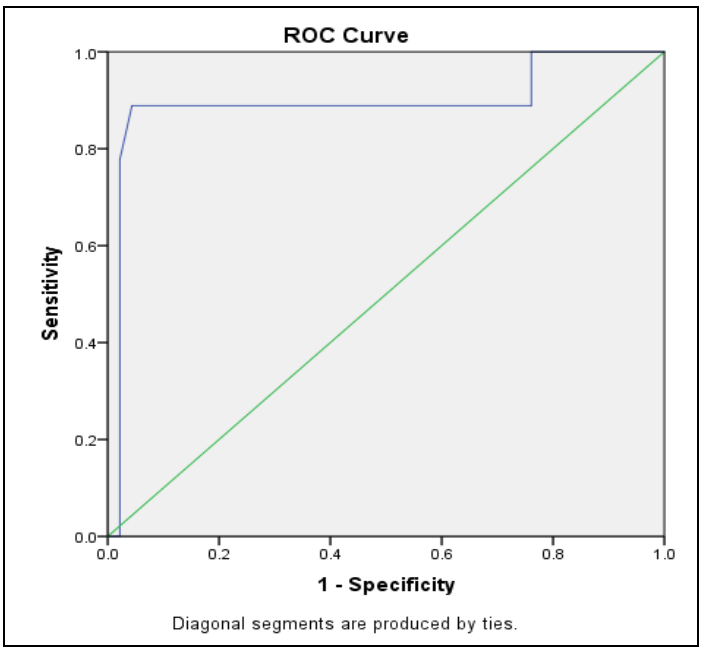

Fig 1: ROC curve for serum level of S. ferritin in patients with preterm.

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 [14]. 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 [15]. Most pregnant women have vaginal discharges that are either physiologic or pathologic. The challenge to the clinician is to separate the vaginal infections with potentially serious input for pregnancy from annoying but not serious secretions, irritation and pruritus. Infectious vaginitis is usually caused by yeast, such as Trichomonas vaginalis, bacterial vaginosis, gonorrhoea, Chlamydia trachomatis, Mycoplasma, Group B streptococcus or herpes. Normal vaginal secretions consist of water, electrolytes, epithelial cells, microbial organisms, fatty acid and carbohydrate compounds Vaginal pH, glycogen content and amount of secretion influence the quantity and type of organisms present in the vagina. Lactobacilli restrict the growth of other organisms by producing lactic acid, thus maintaining a low pH. These organisms also produce hydrogen peroxide, which is toxic to anaerobes. The normal vaginal bacterial population assists in inhibiting the growth of pathologic vaginal organisms. If the normal vaginal ecosystem is altered, there is a greater chance of proliferation of pathogenic organisms [13]. Serum ferritin initiate to decrease normally from the beginning of second trimester and its level in maternal serum at time of labor reach one third the value of infant cord sample. When there is physiologic stress in acute or chronic infection the level of ferritin can elevate markedly, also increase with tissue damage or if there is liver disease or cancer. Ferritin in these cases reflects a status of an acute phase reaction rather than being an indicator of nutritional status [12]. The current study shed the light on the level and role of serum ferritin in preterm labor. The level of ferritin was significantly increased in patients with preterm labor (p<0.001). Scholl TO, found that increased level of serum ferritin in pregnant women, especially at 28 weeks of gestation, acute phase for chorioamnionitis and subclinical infection reactant and preterm delivery. In the same study, high ferritin value has not been reported to be significant. [56] In a study by Xiao R *et al*. when study [15].

In a control case study conducted by Tamura *et al*., At the 24th week of gestation, 94 pregnant women were sampled in 94 pregnant women. These cases were determined on the basis of spontaneous labor at 32 weeks or less (n = 31) with two control groups, one spontaneously administered at 33-36 weeks (n = 32) and the other spontaneously at 37 weeks or more (n = 31). There was a negative correlation between ferritin levels and gestational age at birth. Increased serum ferritin levels are closely associated with the risk of subclinical infection and premature birth reported [16].

But it is not in agreement with Cekmez Y, when he found that serum ferittin can be used as a marker of PPROM but cannot be used as a marker for spontaneous preterm labour. A cut off value of 35.5 mg/l of serum ferritin may be used for predicting PPROM cases [17]. Moreover it is not in agreement with that revealed by Weintraub *et al*., who reported that there is no significant different in mean serum ferritin regarding patients with preterm and full-term labor. This difference may be due to difference in sample size collection and difference in exclusion or inclusion criteria between the studies [18].

In this study, no significant differences were found between females of primigravide and multigrade with respect to Hb and ferritin levels. This means that women's gravity and parity do not affect Hb and ferritin levels. These results are consistent with Abdel-Malek K *et al*. [11] But not according to Da Silva and others. Who found that the risk of preterm birth was significantly higher among very young immigrants. This discrepancy may be due to the fact that their target group in the primitive were mothers under 18 years [19]. Also, current study results are in agreement but better than those reported in previous Iranian study carried by Movahedi *et al*., when they noticed that increased serum ferritin concentrations during the second trimester were predictive of preterm delivery, and the validity test in his study was sensitivity of 78.3% and specificity of 83% this lower results in their study was due to difference in serum ferritin cut off value (serum ferritin of more than 22.5 ng/ml was the optimal cut-point), while in the present study the cutoff point was (34.2 ng/L) [12].

Limitation of the study

1. Small sample size with short period of the study
2. Single center study
3. The test for markers were done by different person

Conclusion

Elevated serum ferritin level during the third trimester may be of use in prediction of preterm labour.

No conflicts of interest

Source of funding: self

Ethical clearance: was taken from the scientific committee of the Iraqi Ministry of health

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