SERUM FERRITIN LEVEL AS a MARKER OF EARLY SPONTANEOUS PRETERM LABOR

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Abstract

Objective: The present study aims to evaluate the role of serum ferritin level in predicting early spontaneous preterm labor.

Patients and method: A cross section study was carried out on one hundred pregnant women attended emergency department of Obstetrics and Gynecology department of Ismailia general hospital. Selected women were divided into two groups: 50 patients started labor between 28 and 36 weeks gestation (study group) and 50 pregnant women started labor after they completed 37 weeks gestation (control group). Maternal serum ferritin, serum iron and complete blood count were assessed.

Results: The mean serum ferritin in the study group was significantly higher when compared to that of the control group (35.84±34.1 and 12.64±11.7ng/dl respectively, P<0.0001). The mean serum Ferritin regarding gestational age was highest (47.87 ±44.11 ng/dl) at preterm cases delivered at 28 weeks of gestation. The lowest mean serum Ferritin was found in the control group (12.64 ±11.70 ng/dl). There was significant negative correlation between mean serum Ferritin and gestational age (P<0.006). Srum Ferritin levels was classified into 25th percentile (≤8 ng/ml), 50th percentile (12 ng/ml), 75th percentile (30 ng/ml), 90 percentile (60 ng/ml), and >90th percentile (>60 ng/ml). At 25 percent, the incidence of PTL was 23.5%, and at> 90th percentile the incidence of PTL was 88.87%. The incidence of Full term labor in the control group falls from 76.4% at 25th percentile to 11.1% at >90th percentile.

Conclusion: High serum ferritin level is associated with premature delivery and serum ferritin level may consider as a marker for preterm labor. In cases with high serum ferritin, prophylactic treatment and early intervention may be considered to prevent preterm birth and to improve pregnancy outcome.

Key Words: serum ferritin, preterm labor

Introduction

Spontaneous preterm labor complicates 5-11% of all pregnancies and is a leading cause of neonatal morbidity and mortality [1, 2]. It is responsible for 75% of neonatal deaths [3, 4]. The clinical criteria for diagnosis of preterm labor (PTL) are inaccurate until labor is well established. Over diagnosis is common due to inclusion of false labor pains, vaginal discharge and vaginal bleeding [5].

The physiologic mechanism that initiates PTL has not been substantially identified. Placental ischemia and acute inflammation are the most common two pathologies that have been implicated. Compelling clinical and experimental evidence has demonstrated an association between intrauterine infection and preterm delivery [6,7].

It has been postulated that infection is a major etiologic agent in pathogenesis of preterm labor (PTL) and preterm rupture of membrane (PROM). Chronic infection of the genito-urinary tract is an important and treatable factor associated with PTL, it accounts for 25-40% of cases [8, 9, 10].

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Serum Ferritin is a high molecular weight glycoprotein, which can be observed in the range of 20-120 ng/ml in healthy women in fertility ages and is the main protein for iron storage. It is an intracellular protein that stores iron and releases it in a controlled fashion. Serum ferritin is also released by infiltrating leukocytes in response to acute and chronic infection so it increases during infection and inflammation [11]. Serum ferritin is considered to be an acute phase reactant during inflammation [12].

In pregnancy, serum ferritin concentrations is maximum at 12-16 weeks gestation, and then falls with advancing gestation to reach the nadir at third trimester [13, 14]. Although ferritin is an intracellular protein that is mainly localized in cytoplasm, trace amount are also found in serum and other biological fluids. Ferritin serves to store iron in a non-toxic form to deposit it in a safe form and transport it to areas where it required [15].

Ferritin hetero-polymers are formed from L and H subunits, H ferritin chains are transitionally activated through cytokines such as TNFα [16, 17]. Several reports have indicated that ferritin is degraded in response to bacterial infections, the presence of an antitumor agent or in response to iron deficiency. Serum ferritin levels are increased by inflammation, suggesting that ferritin may modulate inflammation or immunity [18, 19].

Previous studies showed great variation in serum ferritin level in preterm labor. Therefore, we aimed to assess the role of measuring serum ferritin level in predicting early spontaneous preterm labor.

Patients and methods

A case control study was carried out on one hundred pregnant women attended emergency ward of Obstetrics and Gynecology department of Ismailia General Hospital in the period from January 2011 to December 2011.The study was approved by the research ethics committee of Faculty of medicine, Suez Canal University and an informed written consent was obtained from all participants in the study.

A sample size was calculated based on serum ferritin concentration in patients with preterm labor [20]. Assuming α=0.05 and power = 0.80, a total sample size was 100 pregnant classified into two groups; the study group, included 50 pregnant women who started spontaneous labor between 28 and 36 weeks of gestation and the control which included 50 women started labor >37 weeks of gestation.

All patients were presented with singleton pregnancy and labor was diagnosed by presence of confirmed 4 or more regular uterine contraction in 20 minutes or 8 or more in 1 hour and each should last for more than 40 seconds [21] and cervical dilation at least 3 cm [22]. Exclusion criteria were Hb<10.5 g/dl or diagnosed iron overload (Hemochromatosis), preexisting chronic infectious diseases, uterine malformation, uterine masses, preeclampsia, eclampsia, diabetes mellitus, alcoholism, chronic liver diseases, chronic impairment of renal function, malignancy, multiple pregnancy, polyhydraminos, preterm rupture of membranes, and fetal anomalies.

Thorough medical and obstetric history was done to all women. Laboratory investigations were evaluated including urine analysis, blood glucose, C reactive protein (CRP), complete blood count and serum iron. Serum Ferritin was assayed in all patients and control groups' participants by U131 MA GIWGLL1 FERRITIN quantitative test system. This is a solid phase enzyme linked immunosorbent assay (ELISA) Kit was purchased from Immunospec Corporation, Canada.

Statistical analysis

Statistical analysis was done with the statistical package for social science (SPSS) version 16. Quantitative data was expressed as means ±SD and qualitative data was expressed as numbers and percentages. Student`s T- test was used to test significance of difference for quantitative variables and Chi-square was used to test significance for qualitative variables. A probability value (p-value) < 0.05 was considered statistically significant. Correlation between serum ferritin and gestational weeks was done. Significance of correlation was decided based on 'r' & 'p' values.

Results

A total of 100 women were enrolled in our study among them, 50 patients were recruited in the study group and 50 pregnant women were recruited in control group. The mean ages of study and control group of women were 26.35 ±4.6 and 24.26 ±3.6 years respectively. 30% of study group and 36% of control group were nullipara, there were no statistically significant differences in age or parity between the two groups. The mean hemoglobin (Hb) level of the study group was 12.3mg/dl and ranged from 11.3 to 14.2mg/dl and that of the control group was 11.7mg/dl ranging from 10.8 to 14.4 mg/dl, this difference was statistically insignificant.

The mean serum Ferritin in the study group was 35.84 ±34.1 ng/dl while in control group it was 12.64 ±11.7 ng/dl (P<0.0001, table 1). We analyzed the value of

mean serum Ferritin regarding gestational age. It was highest (47.87 ±44.11 ng/dl) at preterm cases delivered at 28 weeks of gestation. The lowest mean serum Ferritin was found in the control group (12.64 ±11.70 ng/dl), table 2. There was significant negative correlation between mean serum Ferritin and gestational age (P<0.006) as shown in figure 1.

We classified serum Ferritin levels into 25th percentile (≤8 ng/ml), 50th percentile (12 ng/ml), 75th percentile (30 ng/ml), 90 percentile (60 ng/ml), and >90th percentile (>60 ng/ml) ( ). At 25 percent, the incidence of PTL was 23.5%, and 50th percentile the incidence of PTL was 54.5%, and 75th percentile the incidence of PTL was 45% and 90th percentile The incidence of PTL was 86.67% and at >90th percentile, the incidence of PTL was 88.8%. The incidence of Full term labor in the control group falls from 76.4% at 25th percentile to 11.1% at >90th percentile as shown in figure 2. Using 40 ng/ml as a cut off point the odds ratio, sensitivity, specificity, PPV and NPV were 12.3, 34 %, 96 %, 89.47 %, and 59.25 % respectively.

Discussion

In this study, we aimed to assess serum Ferritin level as a marker of early spontaneous preterm labor. The mean serum Ferritin showed highly significant difference between the study group when compared to the control group (35.8, 12.6 ng/ml respectively, P<0.0001). Our finding agreed with the recent study of Movahedi et al., 2012 [20]. They found a higher serum ferritin level in women who delivered before 37 weeks compared to those who delivered after 37 weeks of gestation (26.7 ng/ml, 19.8 ng/ml respectively, P <0.001).

A similar correlation was detected in another recent study carried out by Singh and colleagues and included 40 women with PTL and 40 delivered at term. It showed that the mean serum Ferritin level among study and control group were 169.9 and 68.5 µg/dl respectively. There was statistically significant difference (P<0.001). This study concluded the Ferritin emerged as the best marker for prediction of PTL [23].

Our results are in accordance with that of Ramsey et al., 2002 they studied the women serum Ferritin in 182 women who had spontaneous preterm delivery and 182 term control subjects, and revealed that mean serum Ferritin in preterm labor group was 43 ng/ml and in full term group was 28ng/ml, the difference was significant [24].

Our study agree with an older and large study that include 1162 gravidas were followed prospectively from entry to prenatal care, Scholl found that serum Ferritin of patients who got PTL in the 3rd trimester was 23 ng/ml and that was significant higher than others who got full term labor. He concluded that high serum Ferritin concentration in the 3rd trimester is associated with preterm delivery [25].

For a long period ferritin was considered only as an iron storage protein that correlates with body iron stores and give account about degree and type of anemia so old studies carried out in 1980th and early 1990th considered serum ferritin level only as an indicator of iron stores and anemia and didn't consider it as acute phase reactant since maternal anemia also can cause PTL, they reported a significant association between low ferritin level and incidence of PTL. In our study we excluded the complex relation between anemia, serum ferritin and preterm labor through measuring Hb level and serum iron in study and control groups and exclude any patient with Hb <10.5 mg/dl or abnormal serum iron.

H ferritin chains are transcriptional activated through cytokines as TNF [16]. Ferritin is also profoundly affected by acute or chronic inflammation, conditions under which it may raise 10-100 fold [26]. Therefore, our study showed that high serum ferritin level is a risk factor for preterm birth possibly because these reflect an acute phase reaction to subclinical infections that are closely associated with preterm delivery.

The present study was planned to assay the serum ferritin level in women with PTL to explore whether serum ferritin levels which may be raised in any infective process in most cases of preterm labor and delivery, subclinical intrauterine infection, histologic evidence of inflammation in the decidua, fetal membranes, or umbilical cord is relatively common [27].

We classified serum Ferritin level into five categories (percentiles), the incidence of PTL increased from 23.5% at 25th percentile to 88.8% at >90th percentile so there is was marked increase in incidence of PTL with increasing serum ferritin level while the incidence of labor at full term in the control group falls from 76.4% at 25th percentile to 11.1% at >90th percentile. Goodarzi and Bashardoost, 2009 classified serum ferritin into six percentiles, and reported the incidence of preterm labors was 3.6% in group with ferritin level lower than 8.6 ng/ml. In the second group (ferritin level of 8.6-12.5ng/ml) 10.7% of women experienced preterm labors. Finally, the incidence of preterm labors in other groups was 21.4%, 23.2%, 28.6% and 12.5%, respectively. Therefore, with increasing ferritin levels, the incidence of preterm labors was increased [28].

The relation between elevated maternal second trimester serum ferritin concentrations and preterm delivery was studied by Xlao et al., it was found that women

with ferritin concentration in the highest percentile (>96 ng/ml) experienced a 2.7 fold increased risk for delivery before 34 completed weeks, compared with concentrations <26.0 ng/ml [29].

Goel and coworkers agreed with our finding regarding the cut of point. they studied 100 subjects 76 delivered at term and 24 had PTL found that serum ferritin levels of > 30 µg/dl at 26 weeks and > 40 µg/dl at 34 weeks were found to have a reasonable sensitivity (62% and 75% respectively) and specificity (45% and 67% respectively) for predicting preterm delivery [30] while The study of Movahedi et al. [20] found that a serum ferritin level of 22.5 ng/ml yielded the best combination of 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 and concluded that this is the optimal cut-off value.

Several studies reported different cut of point of serum ferritin in PTL with reasonable sensitivity, specificity, PPV and NPV. Our study revealed great variation in serum ferritin in cases of PTL according to the gestational age, so cut of point need further and larger studies in early and late preterm labor.

From this study, it may be concluded that serum ferritin level may be considered as an important parameter for detecting preterm labor. In the cases of high level of high serum ferritin, treatment may be instituted to prevent preterm birth. High serum ferritin level is associated with premature delivery. So timely detection and intervention could easily prevent high serum ferritin related adverse pregnancy outcome.

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Table (1) :
Mean serum ferritin level and serum iron in case and control groups:

Parameters	Cases n=50	Controls n=50	P value
Serum ferritin Mean ± SD Range	5.84 ± 34.1 3 – 120 ng/ml	12.64 ± 11.7 3 – 62 ng/ml	<0.0001*
Serum iron Mean ± SD Range	169.37 ±50.42 90 – 284 µ/dl	173.87±56.58 95–280 µ/dl	>0.05**

n= number of subjects; unpaired Student's 't' test was done as test of significance;
* = Significant
** = Insignificant

Table (2) :
Mean serum ferritin level in different gestational ages:

Gestational age (GA)	N = 100	Serum ferritin
Preterm cases:		
28 wks	8	47.87±44.11
29 wks	9	36.22±31.42
30 wks	0	
31 wks	6	36.33±32.4
32 wks	5	36.60±38.39
33 wks	8	35.87±37.30
34 wks	11	34.81±26.88
35 wks	2	25.00±14.14
36 wks	1	16.00
Full term controls: > 37 wks	50	12.64 ±11.70

n= number of subjects, Results are expressed as mean ± SD

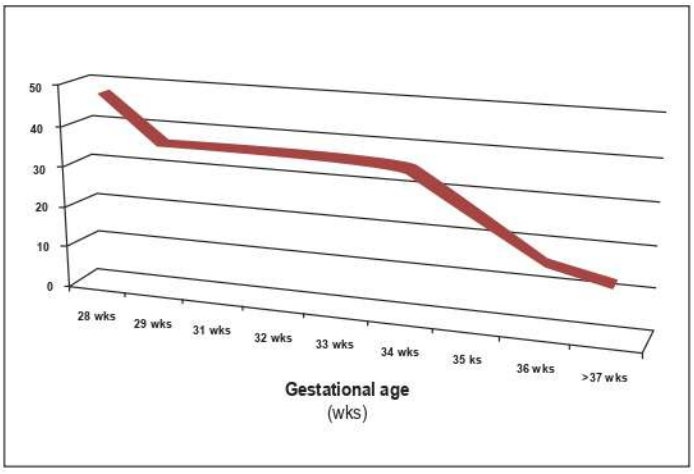

Figure 1: Shows negative statistically significant correlation between serum ferritin and gestational age

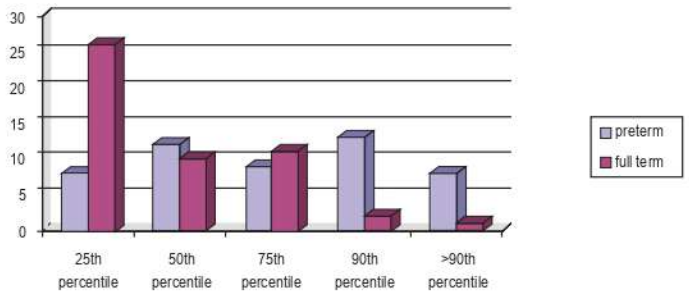

Figure 2: Incidence of full term and preterm labor according to the level of serum ferritin