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Maternal Serum Ferritin Concentrations as a Predictor of Preterm Labour

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Abstract

Objectives: The objective of this research was to assess as a predictor of Preterm labour, the usefulness of serum ferritine levels. Data Sources: This research was a case-control study performed from May 2020 to February 2021 by the department of gynaecology and obstetrics at the Benha University Hospital. Study selection: 90 pregnant women of 28 to 35 weeks in premature work or with premature work risk factors (history of previous preterm, vaginal bleeding in pregnancy, moderate to severe anemia, short cervix, cervical incompetence, previous cervical surgery, submucosal uterine fibroid, substance abuse during pregnancy) Findings: the ROC curve indicates that serum ferritin level off point 220 ng/ml was chosen with a sensitivity equal to 61.54%, a specificity of 92.19%, a positive PPV of 76.2%, a negative predictive value (NPV) of 85.5%, and an accuracy of 70 percent. Conclusion: The optimum cut-off was significantly increased in serum ferritin concentrations linked with spontaneous preterm delivery and serum ferritin levels of more than 220 ng/mL.

Keywords: Serum ferritin, preterm labour, pregnancy.

1. Introduction

Preterm work is a regular uterine contraction with intact membranes with 2cm or more of cervical dilation seen for 2hours before the 37 full weeks of gestation [1].

According to the World Health Organization (WHO), 15 million infants are born too early each year and over one million children are dying each year because of preterm birth problems. Preterm work refers to work between the beginning of foetal viability and the 37 weeks of gestation. It accounts for about 10% of all births and 75% of perinatal death [2].

Preterm care is seen not only as the primary cause of newborn death, but also, even later in the child's life, as the risk factor for behavioural disorders. About 12.8% of US pregnancies lead to preterm delivery, 3.66% to < 34 weeks of gestation. In 6% to 10% of births occur in developed nations [3].

In many nations, the share of prematurely born infants has increased in the last 20 years. The rise in prevalence may be related to changes in incidences of twin or multiple pregnancies, better prenatal care and enhanced preterm labour diagnosis by the broader use of ultrasonography in gestational age estimates [4].

Pre-employment pathophysiology is still substantially unknown. There is nevertheless evidence that subclinical infections, intrauterine infection and chronic inflammation are major risk factors that induce premature labour and premature membrane breakup (PROM) [5].

Microorganisms generate prostaglandins in instances of infection. The effect of prostaglandins is uterine contraction and also contributes to cervical softening [6] Placental tissue is a type of ferritin (placental isoferritin) and in many populations this ferritin has been linked to pregnancy levels [7]. Subclinical maternal infection was believed to be both responsible for high motherly serum ferritin and spontaneous premature PROM [8].

Ferritin maintains iron in soluble and non-toxic form and has been shown, as a diagnostic marker, to be linked with a range of acute phase responses, including inflammatory disorders [9].

Some researchers have found a link between high amounts of serum ferritin and premature labour [10]. This research will therefore investigate the connection between premature delivery and a potential marker of infection, i.e. ferritin.

2. Patients and Methods

This study is a case-control study conducted at obstetrics and gynecology department at Benha University Hospital from May 2020 to February 2021.

Study population: 90 pregnant women their gestational ages ranging from 28 to 35 weeks in preterm labour or with risk factors of preterm labour (history of previous preterm, vaginal bleeding in pregnancy, moderate to severe anemia, short cervix, cervical incompetence, previous cervical surgery, submucosal uterine fibroid, substance abuse during pregnancy) were selected for this study. We classified patients into 2 groups:

Preterm group: included pregnant women who had preterm labour.

Fullterm group: included pregnant women who had full term labour (baby was born between 37 weeks and 41 weeks and 6 days).

Inclusion criteria: Age: 20-35 years old and gestational age between 28 to 35 weeks.

Exclusion criteria: Multiple pregnancies, ruptured membranes, polyhydramnios, congenital fetal malformation, intra uterine fetal death (IUFD) and patients with: Diabetes mellitus, hypertensive heart disease, pre-eclampsia – eclampsia, liver disease, renal disease and cough, fever, dyspnea, loss of smell or taste.

All patients enrolled in this study had the following:

Verbal consent: was obtained from the pregnant women on whom the study was performed and they were informed about the objectives of the study.

Complete history taking: Personal history: Name, age, occupation, residence, and special habits of medical importance. Obstetric history: Gravidity and parity, full details about the course of previous deliveries, history of abortion and history of cerclage. Menstrual history: Menarche, rhythm of cycle, quantity of flow, first day of last menstrual period (LMP), expected date of delivery (EDD) and gestational age (GA) and late first trimester or early second trimester U/S to confirm gestational age (GA). Past medical history: Hypertensive disorders, diabetes mellitus, cardiac problems and thyroid disorders. Past surgical history: Previous uterine scars or surgery. Family history: Diabetes mellitus and hypertensive disorders. History of present illness: Analysis of any complains (onset, course, duration, precipitating factors, what increases and what decreases it) and obstetric symptoms: Warning symptoms (genital bleeding, watery discharge, pain, and decrease fetal kicks), symptoms suggestive of urinary tract infection, pregnancy-induced hypertension, and diabetes mellitus.

Physical examination: General examination: vital data (pulse, blood pressure and temperature). Abdominal examination: Scar of previous operations, size of the uterus (fundal level) and uterine contractions frequency/ duration/ intensity. Vaginal examination: Cervical dilatation, effacement, consistency and position. The presence and amount of uterine bleeding should be assessed. Condition of the fetal membranes (intact or ruptured), and in case of PPROM assessment of color of liquor and presence of cord prolapse.

Clinical criteria for diagnosis of PTL: Regular painful uterine contractions + cervical dilation and/or effacement: Regular painful uterine contractions: 4 every 20 minutes or 8 every 60 minutes. Document cervical change: cervical effacement of at least 80% or dilatation > 2 cm.

Investigations in the form of: Ultrasonography for: Fetal viability, gestational age: biparietal diameter (BPD), femur length (FL), head circumference (HC), amount of liquor, position of the placenta, cervical length, liquor abnormalities and congenital fetal malformation. Complete blood picture, serum ferritin estimation and follow up the outcome.

Method of estimation of serum ferritin: Samples were collected by venipuncture technique, centrifugated and stored at (-20 Co). The Ferritin Quantitative Test is based on a solid phase enzyme-linked immune sorbent assay (ELISA).

Data Management and Analysis: Statistical presentation and analysis of the present study was conducted, using the mean, standard Deviation, unpaired student t-test, chi-square and tests by (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

3. Results

Maternal age between the two groups showed that the mean maternal age in preterm group was 27.5 years while it was 26.2 years in full-term group, there was no statistically significant difference between the two groups, P-value >0.05. Previous preterm between the two groups showed that 20 women of preterm group had previous preterm labour while 13 women of full-term group had previous preterm labour. There was statistically significant difference between the two groups, P-value >0.05. Table (1).

Serum ferritin was elevated in the preterm group in comparison with fullterm group, mean serum ferritin in preterm group was 254.62 ng/mL while it was 110.81 ng/mL in fullterm group, there was a statistically significant difference, P-value <0.05. Table (2) Figure (1).

The ROC curve shows the serum ferritin level cut off point 220 ng/ml was selected providing sensitivity equal to 61.54%, specificity of 92.19%, positive predictive value (PPV) of 76.2%, negative predictive value (NPV) of 85.5 %, and accuracy 70% Table (3).

Results derived from the ROC curve show the cervical length cut off point ≤26 mm was selected providing sensitivity equal to 76.9%, specificity of 92.2%, positive predictive value (PPV) of 80%, negative predictive value (NPV) of 90.8%, and accuracy 94% Table (4).

A comparison between the results derived from ROC curve between serum Ferritin and cervical length in preterm and full-Term Table (5).

Table (1) Characteristics of patients with preterm labor and fullterm.

variable	Preterm group n=26	Fullterm group n=64	t	P-value
Age	27.5 ±4.31	26.2 ±4.81	1.192	0.236
Previous Abortion			1.134	0.287
Yes (n=34)	12.2% (n=11)	25.5% (n=23)		

No (n=56)	16.7% (n=15)	45.6% (n=41)		
Previous preterm			32.168	<0.001
Yes (n=33)	22.2% (n=20)	14.44% (n=13)		
No (n=57)	6.66% (n=6)	56.7% (n=51)		
Hb (gm/dl)	10.64 ±1.20	10.40 ±1.16	0.208	0.835
Submucous fibroid	1.1% (n=1)	5.5% (n=5)	0.467	0.494
Yes (n=6)	27.8% (n=25)	65.6% (n=59)		
No (n=84)				
Vaginal bleeding in early pregnancy			0.014	0.907
Yes (n=18)	5.6% (n=5)	14.4% (n=13)		
No (n=72)	23.3% (n=21)	56.7% (n=51)		
Delivery time Wks.	32.92 ±2.24	38 ±0.78	15.998	<0.001

Table (2) Comparison between Preterm and Fullterm as regard Ferritin.

	Ferritin n= 18-115 ng/mL						T-test	
	Range			Mean	±	SD	T	P-value
Preterm	33	-	520	254.62	±	165.19	6.006	<0.001
Fullterm	32	-	322	110.81	±	63.05		

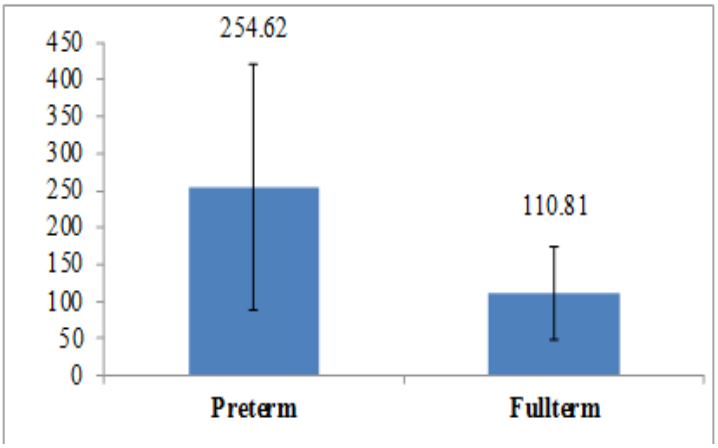

Fig. (1) difference between Preterm and Fullterm as regard Ferritin.

Table (3) The results derived from the ROC curve show the accuracy of Ferritin by sensitivity and specificity at cut off predictive value in prediction of preterm labour.

ROC curve in prediction of preterm labour as regard Ferritin n= 18-115 ng/mL					
Cut off	**Sens.**	**Spec.**	**PPV**	**NPV**	**Accuracy**
>220	61.54	92.19	76.2	85.5	70

Table (4) ROC in prediction of preterm labour as regard cx length.

Cut off	Sens.	Spec.	PPV	NPV	Accuracy
≤26	76.9	92.2	80	90.8	94.0

Table (5) ROC curve between Ferritin and cervical length in prediction of preterm labour.

	Cut off	Sens.	Spec.	PPV	NPV	Accuracy
Ferritin n=18-115 ng/ml	>220	61.54	92.19	76.2	85.5	70
Cervical length n>25mm	≤26	76.9	92.2	80	90.8	94.0

4. Discussion

In the absence of congenital abnormalities, preterm work is the most significant consequence for pregnancy, increasing newborn morbidity and death. Premature delivery represents 75 percent of perinatal mortality and responsible for 50% of long-term morbidity. Approximately 30%–35% of preterm birth are caused by medical indication, about 40–45% by spontaneous work, and about 25–30% by early membrane breakdown [11].

Ferritin plays a key function in hosting protection against bacterial invasion by sequestering iron, which is a necessary ingredient for bacterial development. Placental isoferritin, which is a placental ferritin type, was expressed as syncytiotrophoblast and deciduum macrophages [12].

This research was performed from May 2020 to February 2021 at Benha University Hospital. The population of the research included 90 pregnant women, split in two groups: the full-term population (n=64) and the preterm population (n=26). The findings indicated that serum ferritin levels were substantially higher in the preterm group compared to the full-term group, because the p value was <0.0001.

Our research is in agreement with the study performed at the Obstetrics and Gynecology Department, Menoufia University Hospital between March 2017 and March 2019 by Ibrahim Saif Elnasr et al., (13) per 100 pregnant women between 20 to 24 weeks of gestation, 85, of whom were born at full term (37:39 weeks). Of these, 15 were premature (33-36 weeks) and there were no significant differences in maternal age between term and premature group as the mean age for the term was 28.11, and 26.93 for the premature group was 0.35. In terms of the average gestational age at time of birth, there was a large statistically significant difference in terms of 38.8 and 35.2 P was <0.001 in a preterm group.

Our research revealed, for both groups the length of the cervix was 10 women, 9 of whom had short cervix, while 1 had full-time work; the P-value >0.05 was statistically significantly different. The cervical length cut-off point = 26 mm has been chosen with sensitivity equal to 76,9 percent, 92,2 percent specificity, 80 percent PPV, 90,8 percent negative predictive value (NPV), and 94 percent accuracy.

Naim A. et al. [14] conducted this research to evaluate the usefulness of cervical changes as a predictor of preterm labour for 154 women at the Maimonides Medical Center, 20 of whom experienced preterm labour at 13 percent. Cervical length < 3 cm before 16 weeks of gestation is strongly linked with a preterm birth sensitivity of 72%, 86% species, 78% negative predictive value 92%. In our short cervix study, the predictive value is better than the predictor serum ferritin as it is low and can be carried out on routine antenatal care. Comparison of the results between Serum Ferritine and the cervical length that serum ferritine provides sensitivity at cut-off point 220 ng/ml equal to 61.54%, 92.19% specificity, 76.2% positive predictive value (PPV), 85.5% negative prediction value (NPV), 70% predictive accuracy while <26 mm cervical longitude provides sensitivity equals

Several studies have examined the relationship of serum ferritin with premature birth. In the research by Movahedi et al. [2], 222 single-ton pregnancies were referred to in Isfahan as University Hospital clinics. In terms of serum ferritin concentration, preterm delivery group (n = 69) and delivery group (n = 153) were compared. The mean concentration of the women preterm delivered is greater than that of the preterm ferritine (26.7±5.5 ng/ml) vs (19.8±3.6 ng/ml) p-value < 0.001. The cutoff value for serum ferritin in this research was 22,5 ng/mL, with 78,3 percent sensitivity and 83 percent specificity.

This is in line with a research by Nandini M D et al [15]. Group 1 (preterm delivery, case group) and group 2 of 100 pregnant women split into two groups (term delivery, control group). Study findings revealed substantially higher levels of serum ferritin in preterm labour, ranging from 4.4 µg/dl to 841.2 µg/dl and from 9.8 µg/dl to 67 µg/dl, respectively, in preterm and control individuals. The mean ferritin serum levels of 81,29 µg/dl were higher in the study group compared with 28,57 µg/dl in the control group and the P value was statistically significant (0.0062).

Our trial coincides with Cetinkaya et al., [16] where 91 pregnant women have risked premature work and 83 pregnant women have been diagnosed as a control group. They observed that serum ferritin concentrations in the study groups were substantially greater in comparison to the control group

Beta et al. [17] conducted a case-control research, comprising 30 spontaneous delivery cases before to 34 weeks and 90 matching tests after 37 weeks, which investigated the potential usefulness of blood ferritin levels in the first quarter of pregnancy for predicting spontaneous pre-term work. The research showed that serum ferritin was unlikely to be helpful in screening for spontaneous early preterm work at 11 to 13 weeks of gestation, because a comparison of two groups in respect of serum ferritin was not statistically different (p value = 0.725).

Another case-control research was conducted to examine the link between serum ferritin and premature labour. Serum samples were collected at 24 weeks gestation, case definition was based on a spontaneous birth at 32 weeks or less(n=32) and spontaneous delivery at 37 weeks or longer(n=31). The serum ferritin levels were negatively related to gestational age (p-value = 0.34), and the study found that higher serum ferritin levels are predictive of early spontaneous preterm delivery in the second trimester, possibly reflecting an acute phase reaction to

subclinical infections that are closely linked to premature employment.

El-Shahawy etal. [18] also demonstrated that preterm ferritin levels at 30-34 weeks and ferritin levels over 55 ng/mL were substantially higher than uncomplicated pregnancy levels at the same gestation age with a sensitivity of 96.7 and a specificity of 96.7% were a predictor of early birth.

This contradicts with the Adathila Sanoop A. et al research [19]. Their goals were to compare the levels of ferritin in 50 PPROM patients, 50 spontaneous preterm labour and 50 hemoglobin-associated pregnant women at the same gestational age. The mean ferritin levels between the control unit and the spontaneous preterm labour group were not statistically significantly affected by a p-value of 0.180.

The strengths and limitations of our research. One strength of this study was the fact that more confusing variables were compared with other studies, which were readily available and useful tools for predicting early PTL pregnancy, other strengths included a precise assessment of gestational age, exclusion of preliminary work-related medical conditions.

5. Conclusion

The optimum cut-off point is high serum ferritin concentrations linked with spontaneous preterm birth and serum ferritin levels more than 220 ng/ml.

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