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The Diagnostic Value of Cervicovaginal and Serum Ferritin in Relation to Spontaneous Preterm Birth: Observational Study

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ABSTRACT

Background: Preterm labor is a major cause of neonatal complications. Some researchers have demonstrated that increased serum ferritin level and cervicovaginal ferritin concentrations is associated with preterm labor.

Objective: The aim of the current work was to detect the role of serum and cervicovaginal ferritin concentrations in mid gestation in predicting preterm labor in patients with no well-known risk factors for preterm delivery.

Patients and methods: This prospective cohort observational study included a total of 100 pregnant women with singleton pregnancies between 20 and 24 gestational weeks, attending at the Department of Obstetrics and Gynecology, Menoufia University Hospital between March 2017 to March 2019. Cases were distributed between 2 groups; Group 1 delivered full-term and group 2 delivered preterm. Cervicovaginal and serum ferritin was measured for them. All cases were followed up till delivery.

Results: There is a strong relation between spontaneous preterm delivery and increased levels of serum and cervicovaginal ferritin when measured at gestational age 20–24 weeks. Serum ferritin level ≥110.5 ng/mL gave sensitivity 86.7% and specificity 94.1% in preterm delivery prediction. Cervicovaginal ferritin level ≥25.5 ng/mL gave sensitivity 86.7 % and specificity 64.7% in preterm delivery prediction.

Conclusion: It could be concluded that increased serum and cervicovaginal ferritin concentrations in mid gestation are dependable markers for predicting preterm delivery

Keywords: cervicovaginal ferritin, preterm delivery, serum ferritin, spontaneous preterm delivery

INTRODUCTION

Preterm delivery (PTD) is a large healthcare problem worldwide, its incidence increases in middle-income and high-income societies that can cause major short-term and long-term medical and developmental problems in infants [(1)]. Also, suspected preterm delivery is the largest cause of pregnant women hospital admission [(2)].

It is, therefore, vital to understand the basic mechanisms of preterm labor (PTL) because even if existing preventive interventions were fully scaled, fewer than 20% of preterm births would be prevented [(3)].

Ferritin is an iron storage protein. It is an acute phase reactant. Ferritin level increases in inflammation and infection. Some researchers have demonstrated that increased serum ferritin level is associated with preterm labor [(4)].

Some researchers had considered cervicovaginal ferritin as a predictor for preterm labor with using other parameters in order to get better results [(5-6)].

The aim of the current work was to detect the role of serum and cervicovaginal ferritin concentrations in mid gestation in predicting preterm labor in patients with no well-known risk factors for preterm delivery.

PATIENT AND METHODS:

This prospective cohort observational study included a total of 100 pregnant women with singleton pregnancies, between 20 and 37 years age, average body weight, and between 20 and 24 gestational weeks, attending at the Department of Obstetrics and Gynecology, Menoufia University Hospital, Shibin El-kom, Menoufia, Egypt. This study was conducted between March 2017 to March 2019.

Ethical approval:

Written informed consent of all the subjects was obtained after counseling and explanation of the benefits and unexpected risks of any procedure. **The study protocol was reviewed and approved by the local ethics committee at Menoufia University hospital.**

Exclusion criteria: Women with multiple pregnancies, hypertension, smoking, polyhydramnios, placenta previa, diabetes mellitus, chronic underlying diseases, known short cervix or uterine malformation, and previous preterm delivery or surgery of the cervix.

The included subjects were distributed between two groups; **Group (1)** consisted of 85 pregnant women who delivered at full term and **Group (2)** consisted of 15 pregnant women who delivered preterm.

All women were subjected to complete history taking**,** general examination, and abdominal examination. Obstetrical US was done for each case.

Local (vaginal) examination: Sterile speculum was used before any pelvic examination to obtain a cervicovaginal sample.

Measurement of cervicovaginal ferritin:

Before local pelvic examination a pipette was used to obtain mucous sample from external os and

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posterior fornix which immediately put in eppendorf tubes then in an ice-box and transferred to laboratory to be stored at −20°C and cervicovaginal ferritin was measured within one month.

Measurement of serum ferritin:

In all cases we used ethyl alcohol swab for skin sterilization and disposable plastic syringe to obtain 5 cm venous blood sample. A serum separator tube was used and samples were left to clot for 2 h at room temperature before centrifugation for 20 min. The supernatant was used for assaying. Grossly hemolyzed samples were excluded.

Statistical analysis:

All data were tabulated & analyzed by SPSS V.20 (statistical package for the social science) using the mean, standard deviation and chi-square test Chi-square test was done to assess association between qualitative variables. Standard student "t test", test of significance of the difference between two means: **ROC** curve for detection of validity and cut off point in comparison to sure diagnostic test. Spearman correlation for non parametric correlation between non parametric continuous variables P- value: level of significance

-P>0.05: Non significant (NS).
-P< 0.05: Significant (S). -
P<0.01: Highly significant (HS).

RESULTS

This study was conducted on 100 pregnant women at 20–24 weeks of gestation, 85 of them delivered at full term (37:39 weeks). 15 of them delivered preterm (33-36 weeks).

Table (1): Represents the demographic and clinical characters associated with both groups. No statistical difference was detected regarding the maternal age between term and preterm groups as the P value was 0.35. High statistical difference was detected as regarding parity as the P value is 0.001. No statistically significant differences regarding body mass index with the P value is 0.3. No statistically significant difference as regarding the mode of delivery with P value is 0.33. There was high statistical significant difference as regarding the mean gestational age at time of delivery in weeks with P value is <0.001.

Table (1): Demographic and clinical characters associated with preterm and full-term delivery.

	Term delivery N=85	**Preterm delivery N=15**	**Test of significance**
Age /years Mean±SD	28.11 ± 4.5 (20.0-37.0)	26.93 ± 4.4 (20.0-35.0)	t=0.93 P=0.35
Parity.			
P0	3(3.5)	5(33.3)	MC P=0.001**
P1	46(54.1)	6(40.0)	
P2	29(34.1)	3(20.0)	
P3	7(8.2)	1(6.7)	
Maternal BMI (kg/m^2) mean ±SD (Min-Max)	25.11±1.9 (21.0-27.0)	24.53±1.9 (21.0-27.0)	t=1.03 P=0.3
Spontaneous vaginal delivery.	34(40.0)	4(26.7)	χ^2=0.96 P=0.33
Cesarean section.	51(60.0)	11(73.3)	
Gestational age at time of delivery (weeks) Mean±SD (Min-Max)	38.8±0.49 (37.0-39.0)	35.2±0.94 (33.0-36.0)	t=22.6 P<0.001**

*χ^2=Chi-Square test t: Student t test MC: Monte Carlo test P: Probability *statistically significant if P <0.05 ** High statistically significant if P<0.01*

Table (2) Represents a high +ve correlation between both serum and cervicovaginal ferritin levels measuring 0.83. **Figure (1)**

Table (2): Correlation between serum and cervicovaginal ferritin in the studied group.

	Serum ferritin.	
	R	P
Cervicovaginal ferritin.	0.83	<0.001**

r: Pearson correlation coefficient
P: Probability *statistically significant if P <0.05
** High statistically significant if P<0.01

Figure (1): Correlation between serum and cervicovaginal ferritin.

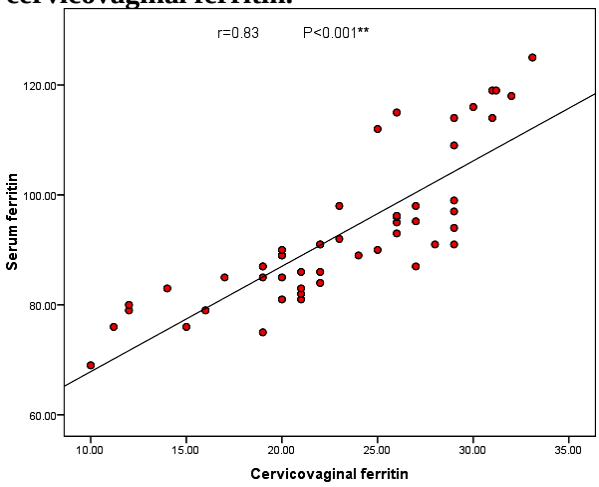

Table (3): shows that mean of serum ferritin concentrations in the term patients was 89.04 ± 9.7 **(**ng/ml) and the range was 69–119 **(**ng/ml), while in the preterm group patients the mean was 116.27 ± 4.9 **(**ng/ml) and the range was 109–125 **(**ng/ml). The *P* value was less than 0.001. It shows a high statistically significant difference As regards the mean cervicovaginal ferritin concentration in the term patients it was 22.0 ± 5.4 and the range was 10–31, while in the preterm patients the mean was 29.84 ± 2.7 and the range was 25–33.1. The *P* value was less than 0.001. It shows a high statistically significant difference.

Table (3): Serum and cervicovaginal ferritin results associated with preterm and full-term delivery

	Term delivery N=85 Mean±SD	**Preterm delivery N=15 Mean±SD**	**Test of significance**
Serum ferritin (ng/ml)	89.04±9.7 (69.0-119.0)	116.27±4.9 (109.0-125.0)	t=10.6 P<0.001**
Cervicovaginal ferritin (ng/ml)	22.0±5.4 (10.0-31.0)	29.84±2.7 (25.0-33.1)	t=5.5 P<0.001**

t: Student t test
P: Probability *statistically significant if P <0.05
** High statistically significant if P<0.01

Table (4) shows the area under the ROC curve (AUC) for serum ferritin is 0.97, the cutoff value 110.5 ng/ml with sensitivity 86.7%, Specificity 94.1% and **95% CI** 0.94-1.0. Also shows the area under the ROC curve (AUC) for cervicovaginal ferritin is 0.91, the cutoff value 25.5 ng/ml with sensitivity 86.7%, Specificity 64.7% and **95% CI** 0.84-0.98**. (Figure 2-3)**

Table (4): ROC curve of serum and cervicovaginal ferritin in detection of preterm and term delivery.

	AUC	**P value**	**95% CI**	**Cut off Point**	**Sensitivity (%)**	**Specificity (%)**
Serum ferritin	0.97	<0.001	0.94-1.0	≥110.5	86.7	94.1
Cervicovagina l ferritin	0.91	<0.001	0.84-0.98	≥25.5	86.7	64.7

AUC: Area under curve

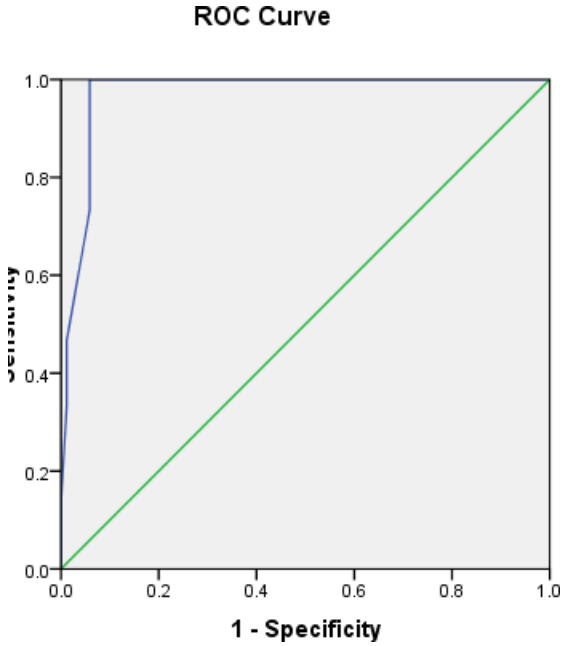

Figure (2): ROC curve for serum ferritin.

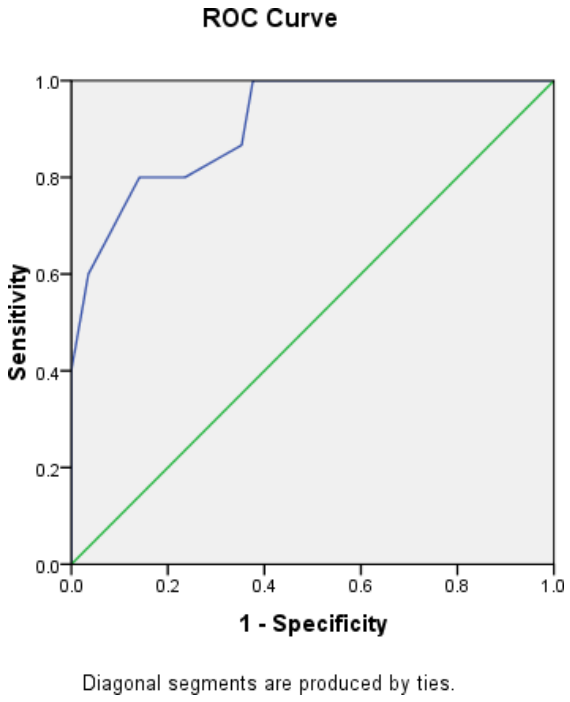

Figure (3): ROC curve for Cervicovaginal ferritin

In table 5: Serum and cervicovaginal ferritin are significant predictors for preterm delivery as an increase by one unit of serum ferritin value increases the preterm delivery risk by 1.277 and an increase by one unit of cervicovaginal ferritin value increases the preterm delivery risk by 1.108. 85% of preterm delivery can be predicted by serum and cervicovaginal ferritin.

Table (5): Logistic regression to detect predictors of preterm delivery.

Predictors	B	P	Odds ratio	95.0% C.I. for odds ration	
				Lower	Upper
Parity	2.115	0.194	8.290	0.342	201.137
Gravidity	-2.585	0.125	0.075	0.003	2.042
Serum ferritin	0.244	0.019	1.277	1.041	1.566
Cervicovaginal ferritin	0.103	0.04	1.108	1.002	2.110
Constant=-26.961, Model Chi-Square =61.18 ,P=0.002 Percent predicted = 85.0%					

DISCUSSION

WHO has categorized the preterm delivery according to the gestational age at birth, with birth before 28 weeks considered to be extremely preterm; between 28 and 32 weeks very preterm; between 32 and 34 weeks moderately preterm; and between 34 and 37 weeks late preterm [(7)] .

In current study serum and cervicovaginal ferritin concentrations were studied as predictors for preterm delivery in 100 women and there was a positive association between both serum and cervicovaginal ferritin measuring 0.83.

Our study is consistent with Cetinkaya ***et al.*** where 91 pregnant women diagnosed with threatened preterm labor and 83 pregnant women as a control group. They found that serum ferritin concentrations were significantly higher in the study groups when compared the control group[(8)] .

It is also consistent with the study done by **El-Shahawy *et al.*** where study group included 30 patients with established PTL between 30 to 34 weeks. Control group included 30 patients with uncomplicated pregnancies between 30 to 34 weeks. They found that the median serum ferritin concentration in preterm labor group and control group was 150 (100-150)ng/ml and 20 (15- 25)ng/ml respectively. There was statistically significant difference between both groups in serum ferritin concentration as the p value was 0.0001[(9)].

This study agrees with the research done by **Broumand *et al.*** where 300 singleton pregnancies at of 22–24 weeks gestational age included and mean serum ferritin concentration was 58.98 ± 25.7 in term or near-term group versus a mean of 99.4 ± 28.7 in preterm group, which was a statistically different ($P < 0.001$). Cervicovaginal ferritin level in term near-term delivery group was statistically different from before 32 weeks delivery group ($P = 0.02$) [(10)].

It is not consistent with the study done by **Valappil *et al.*** 50 pregnant women with PROM and 50 with preterm labor. They found no significant difference in the ferritin values between the control group and spontaneous preterm labor group as indicated by a p-value of 0.180. They carried out their study on preterm labor women during labor that may be the cause of difference [(11)].

It is also not consistent with the study done by **Abdel-Malek *et al.*** where they found the cutoff value of serum ferritin between the two groups was 31ng/ml with sensitivity 92.8%, specificity 99.4%. Different sample size, different gestational age of the studied group, women with haemoglobin level <10.5g/dl were excluded or may be different kits may be the cause of difference [(12)].

It is also consistent with the study done by **Movahedi *et al.*** that the serum ferritin concentration can give a suitable discrimination in predicting PTD, but disagree regarding that the serum ferritin levels > 22.5 ng/ml was the optimal cut-point, resulted in the best combination with a sensitivity of 78.3% and a specificity of 83.0%[(13)] .

This study agrees with the study done by **Singh *et al.*** where a study was performed on 40 patients coming with preterm onset of labor followed by delivery in the Biochemistry Department, GB Pant Hospital. They found that serum ferritin has a high diagnostic value in predicting preterm labor [(14)].

CONCLUSION

It could be concluded that increased serum and cervicovaginal ferritin concentrations in mid gestation are dependable markers for predicting preterm delivery; also the presence of a good positive correlation between both supports this evidence. Trial of using combination between ferritin levels and sonographic scales to get a higher sensitivity and specificity may lead to improvement of maternal or neonatal outcomes significantly.

Strength of the study:

Our study is promising for prediction of PTL with easily available and applicable toll for early prediction of PTL in early pregnancy; accordingly, such pregnant women will need close monitoring for PTL so we could advise rest and medication to improve maternal and neonatal outcomes.

Limitations of the study:

There were some limitations in our study as small sample size, and does not include high-risk pregnant women and including only singleton normal pregnancies.

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Ibrahim Saif Elnasr: project development, data collection and analysis, manuscript writing and submission

Hesham Ammar: statistical analysis and manuscript writing.

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REFERENCES

1-Romero R, Erez O, Maymon E, Pacora P (2017): Is an episode of suspected preterm labor that subsequently leads to a term delivery benign? Am J Obstet Gynecol., 216:89-94.

2- Hernandez W, Francisco R, Bittar R *et al.* (2017): Effect of vaginal progesterone in tocolytic therapy during preterm labor in twin pregnancies: Secondary analysis of a placebo- controlled randomized trial. Journal of Obstetrics and Gynaecology Research, 43: 1536- 1542.

3- Tsikouras P, Anastasopoulos G, Maroulis V *et al.* (2018): Comparative Evaluation of Arabin Pessary and Cervical Cerclage for the Prevention of Preterm Labor in Asymptomatic Women with High Risk Factors.International journal of environmental research and public health ,15: 791-797.

4- Shetkar N and Pyati A (2017): Study of serum high sensitive C - reactive protein and ferritin in preterm labor. International Journal of Clinical Biochemistry and Research, 4: 213-215.

5- Ramsey P, Tamura T, Goldenberg RL *et al.* (2002): National Institute of Child Health and Human Development, Maternal-Fetal Medicine Units Network. The preterm prediction study: elevated cervical ferritin levels at 22 to 24 weeks of gestation are associated with spontaneous preterm delivery in asymptomatic women. Am J Obstet Gynecol ., 186:458-463.

6- Leitich H (2005): Secondary predictors of preterm labour.BJOG: An International Journal of Obstetrics & Gynaecology , 112.1: 48-50.

7- Khambalia A, Collins C, Roberts C *et al.* (2015): High maternal serum ferritin in early pregnancy and risk of spontaneous preterm birth. British Journal of Nutrition, 114: 455- 461.

8- Cetinkaya S, Ozaksit G, Biberoglu E *et al.* (2017): The value of acute phase reactants in predicting preterm delivery. The Journal of Maternal-Fetal & Neonatal Medicine , 30.24: 3004-3008.

9- El-Shahawy H, Hendawy S, Hassanin A *et al.* (2017): Estimation of Serum Ferritin Level in Preterm Labour. Egyptian Journal of Hospital Medicine , 68.3: 1469-1474

10-Broumand F, Saeidkar S, Behrouzlak T *et al.* (2014): The diagnostic value of cervicovaginal and serum ferritin levels in midgestation time to predict spontaneous preterm delivery. Niger Med J., 55:321-327.

11-Valappil S, Varkey M, Areeckal B *et al.* (2015): Serum Ferritin as A Marker for Preterm Premature Rupture of Membranes–A Study From A Tertiary Centre in Central Kerala. Journal of clinical and diagnostic research , 9: BC09 –BC12.

12-Abdel-Malek K, El-Halwagi M, Hammad B *et al.* (2018): Role of maternal serum ferritin in prediction of preterm labour. Journal of Obstetrics and Gynaecology, 38: 222-225.

13- Movahedi M, Saiedi M, Gharipour M *et al.* (2012): Diagnostic performance and discriminative value of the serum ferritin level for predicting preterm labor. J Res Med Sci ., 17:164-166.

14-Singh B, Goswami B, Gupta N *et al.* (2011): Potential biochemical markers for preterm labor: a pilot study in north India. Indian J Clin Biochem ., 26:41-45.