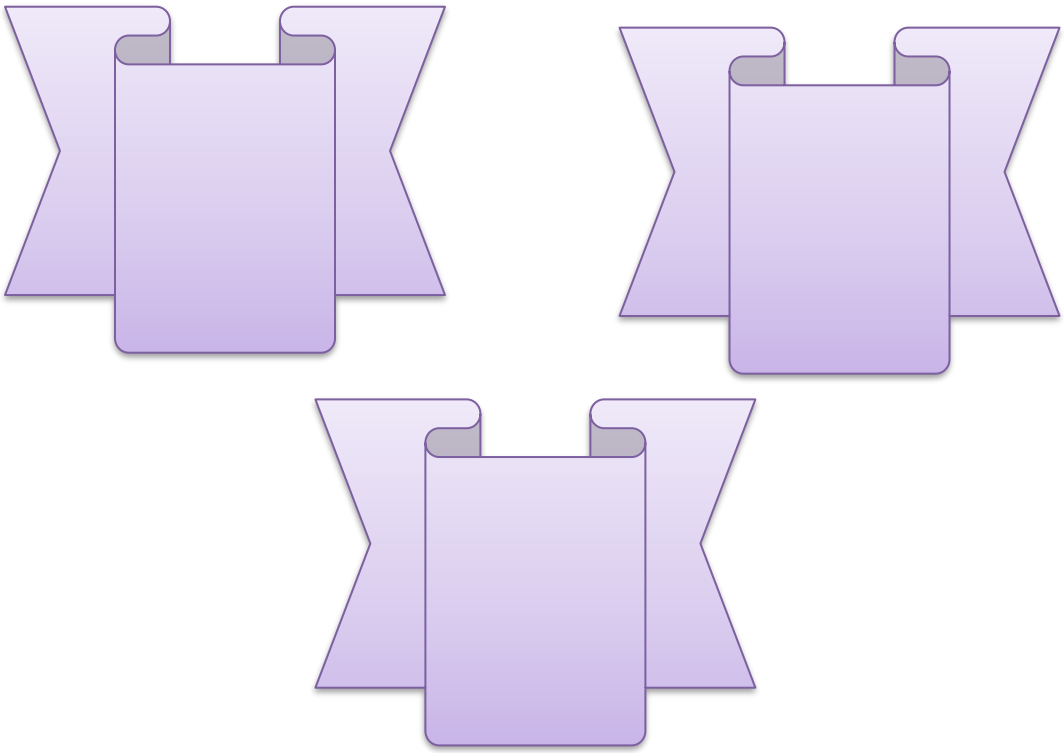
International Journal of Medical Arts

Volume 5, Issue 3, March 2023

https://ijma.journals.ekb.eg/



Print ISSN: 2636-4174

Online ISSN: 2682-3780

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main Subject [Gynecology and Obstetrics]

Original Article

Association Between Vitamin D Deficiency and Serum Ferritin and Preterm Labor: A Case Control Study

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Article information

Received: 19-03-2023

Accepted: 05-05-2023

DOI: 10.21608/IJMA.2023.201191.1645.

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Citation: Atia AH, Mohammed MA, Mohammed MF, Radwan MS. Association Between Vitamin D Deficiency and Serum Ferritin and Preterm Labor: A Case Control Study. IJMA 2023 March; 5 [3]: 3100-3105. doi: 10.21608/IJMA. 2023.201191.1645.

ABSTRACT

Background: One of the main factors contributing to prenatal morbidity and death is preterm birth. There have been some investigations describing the connection between vitamin D deficiency and serum ferritin during gestation and increasing the incidence of preterm birth.

Aim of the work: To assess the connection between maternal blood ferritin levels, vitamin D insufficiency, and premature labour.

Patients and Methods: A Case Control trial involved 200 women divided into two groups; research group of 100 women, preterm labor was clearly apparent between 28 and 37 weeks of pregnancy. 100 women in the control group had straightforward pregnancies and gave birth to healthy babies at full term [≥37 to 40 weeks]. All women subjected to history taking, clinical assessment, ultrasound and laboratory tests [as a complete blood count, a serum ferritin level, a vitamin D level, a serum creatinine level, and a random blood sugar reading].

Results: The median of Vitamin-D in research group [14.58 ±7.26] was substantially lower than control group [37.15 ±11.43], while the median of the ferritin in research group [237.15 ±149.32] was statistically higher than the control group [48.64 ±25.11]. Our Receiver operating curve [ROC] findings showed that serum ferritin cutoff value is more than 85 and the area under curve [AUC] is 0.714 with sensitivity of 94% and specificity of 70%. Also, Vit. D cutoff value is less than 25 and the AUC is 0.723 with sensitivity of 67.3% and specificity of 82%.

Conclusion: The present study recommends the use of serum ferritin and vitamin D as a marker of preterm labor. It assisted in the development of a cutoff value of ≤20 nmol/L of serum 25 [OH] D and ≥85 ng/ml of serum ferritin for the predicting of premature labor.

Keywords: Preterm Labor; Vitamin D Deficiency; Serum Ferritin

INTRODUCTION

One of the main factors contributing to prenatal morbidity and death is preterm birth. An estimated million infants every year suffer complications from premature delivery. It is responsible for over 70% of newborn fatalities and 50% of long-term neurological outcomes [1]. Many babies that survive have severe morbidities including syndrome of respiratory distress, bronchopulmonary dysplasia, intra-ventricular hemorrhage, retrolental fibroplasia, and developmental issues [2].

Ferritin, which plays a crucial part in maintaining the balance of iron in the body, is also released by invading leukocytes in response to both acute and chronic infections. Increased serum ferritin concentration and premature birth have been linked in a number of earlier studies. Increased ferritin values might be an acute stage response to a subclinical genital tract infection or inflammatory condition. infection-related tissue damage leading to elevated blood ferritin levels that serve as an acute stage reactant [3].

A fat-soluble metabolite called vitamin D is important for normal human development and growth as well as the correct control of numerous bodily functions. Efficiency of vitamin D is seen as a widespread and challenging public health issue, particularly for pregnant women. Pregnancy complications including diabetes mellitus, preeclampsia, and small for gestation age have all been connected to maternal vitamin D deficit [4]. Investigations have shown that having insufficient vitamin D at pregnancy increases the likelihood of having a baby who is born prematurely. **Wagner *et al.*** [5] revealed that Preterm births were 3.81 times more likely to occur in pregnant women with blood vitamin D levels below 20 ng/ml compared to those with values over 40 ng/ml. **Bodnar *et al.*** [6] revealed that When 25-hydroxyvitamin D levels in blood rose to about 36 ng/mL and subsequently plateaued, the risk of preterm delivery dramatically reduced.

We aimed to assess the connection between maternal blood Ferritin levels, vitamin D insufficiency, and premature labour.

PATIENTS AND METHODS

Between May 2019 and December 2022, a case control Investigation was done in the Departments of Obstetrics and Gynecology at El. Mahala EL Kobra Hospital and Al-Azhar University Hospital.

In the current research, 200 women were separated into two groups. Among the study group, 100 women had preterm labor that had been confirmed to have started between 28 and < 37 weeks of pregnancy. The other 100 women in the control group had straightforward pregnancies and gave birth to healthy babies at full term [about ≥37]. The hallmark of preterm labor is regular uterine contractions that begin before 37 weeks of pregnancy and cause changes to the cervix, such as effacement and dilation [7]. This study involved women with singleton pregnancy and hemoglobin > 10 gm%. We excluded women with iron overload status, birth defects of the uterus and an ineffective cervix, repeated pregnancies, polyhydramnios, preterm rupture of membranes, chronic comorbidity, pre-eclampsia and eclampsia, fetal congenital malformations, and morbid obesity [BMI ≥35 kg/m^2].

All women subjected to history taking, clinical assessment, ultrasound and laboratory tests [as a complete blood count, a serum ferritin value, a vitamin D level, a serum creatinine level, and a random blood sugar reading]. Measurement of serum ferritin level: All women between the ages of 28 and 36 weeks had three milliliters of venous blood collected from the antecubital vein utilizing a disposable plastic syringe and allowed to clot for 30 minutes. After centrifuging the sample, serum was isolated and stored at -20 °C until the test. The ELFA method was used to assess the serum ferritin values [8]. Measurement of vitamin D level: The total amount of 25-hydroxy [25-OH] vitamin D [vitamins D2 and D3] in serum was determined for all samples using the 25-hydroxy [25-OH] vitamin D ELISA. The kit name: We followed the manufacturer's recommendations for using the 25-hydroxy [25-OH] Vitamin D ELISA from Calbiotech, Inc. At the laboratory of the obstetrics and gynecology department, blood samples [5 ml] were drawn by venipuncture into test tubes without any additives, clotting was permitted, and then the serum was separated by centrifugation for ten minutes at 5.000 g. Transported serum was frozen at -20 °C.

Statistical analysis: SPSS version 20 was used for analysis. Mean and standard deviations were used to describe numerical variables; frequency and percentages for categorical

variables. For comparing variables, t test and chi square test were used. ROC curve was used to calculate diagnostic statistics. P value < 0.05 is considered significant.

RESULTS

In this investigation, 200 pregnant women participated. The median age of the research group was 23.81 ± 7.35 and the control one was 26.24 ±5.61 years. The study group's average gestation period was 32.64 ± 3.11 weeks, which was statistically reduced than the control group's average gestational age of 38.17 ±1.25 weeks [p-value< 0.001]. Regarding age, parity, and abortion, there was no significant variation between the two groups [Table 1].

The median of Vitamin-D in research group [14.58± 7.26] was significantly lower than control group [37.15± 11.43] [p < 0.001], while the median of the ferritin in research group [237.15± 149.32] was statistically substantially greater than the control group [48.64± 25.11] [p-value <0.001]. Also, the mean of the WBCs in research group [9.42± 1.85×10^3/mm^3] was statistically substantially greater than the control group [8.16 ±1.37 ×10^3/mm^3] [p-value <0.001]. However, there was no substantial variation between both groups regarding hemoglobin and RBS [Table 2].

Regarding mode of delivery, the cesarean section [CS] mode was more prevalent in the control group [59%] and in the study group the vaginal mode was more prevalent [62%] that was statistically substantial variation [p-value=0.003] [Table 3].

The mean of the Neonatal body weight in study group [2275.18± 282.44 gm] was statistically substantially lower than the control group which [3164.29±417.53 gm] [p-value <0.001]. The median of the Apgar Score in research group [7.15±2.73] was statistically substantially lower than the control group which [9.28±0.46] [p-value <0.001]. The newborns in the research and control group were 71 [71%], 64 [64%] males and 29 [29%], 36 [36%] females respectively with no statistically substantial variation between two groups [p-value>0.05] [Table 4].

The threshold value for serum ferritin and vitamin D in predicting preterm labor was determined using the ROC method. Our ROC findings showed that serum ferritin cutoff value is more than 85 and the AUC is 0.714 with sensitivity of 94% and specificity of 70%. Also, Vit. D cutoff value is less than 25 and the AUC is 0.723 with sensitivity of 67.3% and specificity of 82% [Table 5].

Table [1]: Comparison of the demographic information between the two groups

		Research group [n=100]	Control group [n=100]	t test	P value
Age [year]	Mean ± SD Range	23.81±7.35 21-33	26.24±5.61 24-37	1.547	0.123
Gestational age [week]	Mean ± SD Range	32.64±3.11 30-35	38.17±1.25 37-40	16.499	**< 0.001***
Parity	Mean ± SD Range	2.53±1.72 2-5	2.28±1.31 1-4	-1.156	0.249
Abortion	Mean ± SD Range	2.16±1.02 0-3	1.92±0.85 0-2	-1.808	0.072

Table [2]: Comparison between both groups regarding laboratory results

		Research group [n=100]	Control group [n=100]	t test	P value
Hemoglobin [gm/dl]	Mean ± SD Range	10.83±2.16 10-12.2	11.17±2.41 10.5-12.7	1.051	0.295
Random blood sugar [mg/dl]	Mean ± SD Range	84.13±32.91 65-129	76.26±44.73 74-118	-1.417	0.158
White blood cells [×10^3/mm^3]	Mean ± SD Range	9.42±1.85 7.4-11.8	8.16±1.37 7.1-11.3	-5.473	**< 0.001***
Serum ferritin [ng/ml]	Mean ± SD Range	237.15±149.32 64-627	48.64±25.11 27-183	-12.450	**< 0.001***
Vitamin D [nmol/L]	Mean ± SD Range	14.58±7.26 4-28	37.15±11.43 12-53	16.668	**< 0.001***

Table [3]: Comparison between groups regarding mode of delivery

		Research group [n=100]	Control group [n=100]	X^2 test	P value
Mode of delivery	Vaginal Cesarean	62 [62%] 38 [38%]	41 [41%] 59 [59%]	8.784	**0.003***

Table [4]: Comparison between groups regarding neonatal outcome

		Study group [n=100]	Control group [n=100]	t / X^2 test	P value
Neonatal weight [gm]	Mean ± SD Range	2275.18±282.44 1700-2600	3164.29±417.53 2600-3400	17.640	**< 0.001***
Apgar Score	Mean ± SD Range	7.15±2.73 6-10	9.28±0.46 8-10	7.694	**< 0.001***
Neonatal Sex	Mean ± SD Range	71 [71%] 29 [29%]	64 [64%] 36 [36%]	1.111	0.292

Table [5]: Receiver operating characteristics of serum ferritin and Vitamin D as a predictor for preterm labor

Parameters	Cutoff value	AUC	Sensitivity	Specificity	P value
Serum Ferritin	≥ 85	0.714	94%	70%	**0.008***
Vitamin D	≤ 25	0.723	67.3%	82%	**0.001***

AUC: Area Under a Curve

DISCUSSION

Preterm birth is the most severe obstetrical condition in the world, yet its multifaceted and mostly unidentified etiology has made prevention difficult and ineffectual [6].

Uncertainty exists about the connection between maternal Fe status and the probability of preterm birth. The risk of preterm delivery has been linked to both low and high maternal Fe levels. The most current Cochrane and systematic review of intervention investigations revealed no substantial impact of Fe supplement in pregnancy on the probability of preterm birth, despite several randomized investigations of Fe supplementing in pregnancy reporting a reduce in preterm deliveries. On the other hand, a number of observational investigations have shown a link between increasing levels of serum ferritin [an indicator of Fe storage] in the 2nd trimester and a greater incidence of sPTB [Spontaneous preterm birth] [9].

Poor vitamin D level during pregnancy is connected to negative pregnancy outcomes including preterm birth and a poor neonatal outcome [10].

This investigation examined the relationship between maternal blood ferritin levels, vitamin D insufficiency, and premature labor.

The current study shows that median of Vit D in study group [14.58 ± 7.26] was substantially lower than control group [37.15 ± 11.43] [p < 0.001], while the median of the ferritin in research group [237.15±149.32] was statistically substantially greater than the control group [48.64±25.11] [*p*-value <0.001]. Also, the median of the WBCs in research group [9.42±1.85×10^3/mm^3] was significantly greater than the control group [8.16±1.37 ×10^3/mm^3] [*p*-value <0.001]. However, there was no substantial variation between both groups as regards Hemoglobin and RBS.

Our findings are corroborated by **Abd El Hameed *et al.*** [11] revealed that Mothers in the preterm group had considerably lower blood vitamin D levels than full-term moms, with a median of 4.48 ±2.5 against 24.9 ±13.7. **Bodnar *et al.*** [6] revealed that in contrast to their findings, the average vitamin D level across research groups was 82.7 nmol/L, with a standard deviation of 31.5 nmol/L and an average of 85.7 nmol/L. The fact that they only evaluated vitamin D across women who were expecting twins and that it was an interventional trial may be the cause of this discrepancy.

In a meta-analysis investigation by **Qin *et al.*** [12] a total of 11 investigations out of 237 studies; 6 investigations were done in the USA, 2 in Spain, and one each in Australia, China, and Canada. According to this meta-analysis, pregnant women with low vitamin D values have a higher risk of giving birth prematurely. The odds ratio is 1.29, with a 95% confidence interval between 1.16 and 1.45. Vitamin D

supplementation at pregnancy decreases the likelihood of low birth weight [<2.5 kg] by 52%, according to a Cochrane Review. Similar to this, a meta-analysis of 24 observational investigations by **Wei *et al.*** [13] They discovered a link between preterm birth and maternal blood vitamin D levels less than 50 nmol/l.

Khambalia *et al.* [14] revealed that the acute-phase response results in higher serum ferritin values, and the inflammatory process linked to sPTB is seen as early as the 1st trimester of gestation. Previous research on the relationship between high ferritin levels and preterm delivery has shown mixed results [15, 16]. There has only been one previous research that examined blood ferritin values in the 1st trimester in a small sample of 30 subjects and 90 as controls, and it did not detect any substantial variations in the percentage of women with ferritin values. Early preterm vs term delivery groups' 75th percentile [36.7 vs. 25.6%, P=0251] [17].

Premature deliveries, lower birth weight, greater perinatal mortality in the kids, enhanced morbidity, infections, and a significant share of maternal fatalities [due to ante-partum and post-partum bleeding] are all linked to low hemoglobin status in pregnancy.

The present research demonstrates the application of the Receiver Operating Curve [ROC] to establish the cutoff values for serum ferritin and vitamin D for the prediction of preterm labor. According to our ROC data, the serum ferritin cutoff value is more than 85, and the AUC has a sensitivity of 94% and a specificity of 70%. Also, the Vit. D cutoff value is less than 25, and the AUC has a sensitivity of 67.3% and a specificity of 82%. Its AUC is 0.723.

Khambalia *et al.* [14], revealed that the subcategory of moderate-to-late sPTB and serum ferritin values in the 75th percentile [43 mg/l] were linked to higher likelihood of sPTB [37 weeks] [34–36 weeks]. In this investigation, early sPTB was only substantially related with serum ferritin concentrations above the greater threshold [90th percentile; 68 mg/l]. This is consistent with a few investigations that discovered a link between levels of 30 mg/l and premature delivery [16]. Inconsistent findings across investigations may be caused by differences in research populations, the intensity of sPTB, the percentage of women in certain categories of exposure and/or result, and the kinds of confounders included in adjusted analyses. Earlier researches were mostly cross-sectional and only measured serum ferritin at the end of pregnancy or at delivery [18].

Regarding **Bodnar *et al.*** [6], 8.6% of preterm births occurred before 37 weeks, whereas 2.1% occurred before 34 weeks [weighted sample]. Sixty one percent [621/1126] of preterm births occurred spontaneously. Mothers with blood 25-hydroxyvitamin D levels of <50, 50-74.9, and 75 nmol/L, respectively, had a preterm birth rate of 11.3%, 8.6%, and 7.3% [p <0.01].

An interesting Cochrane database systematic review by **De-Regil *et al.*** [19] indicated that, vitamin D supplementation with calcium during pregnancy is associated with increased risk of preterm labor. This elevates the issue of the timing of vitamin-D support and the route of administration.

This review had been updated in 2019 by **Palacios *et al.*** [20] and concluded that, vitamin-D supplement when used alone potentially reduce the risks of preeclampisa, diabetes, low birth weight and postpartum hemorrhage. Luckily, vitamin D alone did not increase the risk of preterm birth. However, and regardless of its critical importance, the issue of Vitamin-D supplementation is out of the scope of this article. Future studies are warranted

Conclusion: The present study recommends the use of serum ferritin and vitamin D as a probable marker of preterm labor. It assisted in the development of a cutoff value of ≤ 20 nmol/L of serum 25 [OH] D and ≥ 85 ng/ml of serum ferritin for predicting of premature labor. However, due to small sample size, the results must be treated cautiously and large-scale future studies are recommended to validate the results.

Conflict of Interest and Financial Disclosure: None.

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International Journal of Medical Arts

https://ijma.journals.ekb.eg/
Print ISSN: 2636-4174
Online ISSN: 2682-3780