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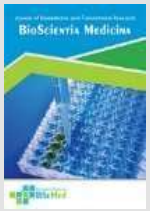

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The Role of Ferritin Levels on Vitamin D Status in Pregnant Women: An Observational Single Center Study at Hermina Hospital, Padang, Indonesia

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A B S T R A C T

Background: Vitamin D deficiency during pregnancy is associated with poor pregnancy outcomes. Research shows a complex interaction between iron and vitamin D. Pregnant women are susceptible to iron deficiency due to increased iron requirements during pregnancy. Ferritin reflects body iron stores and may decrease before serum iron. This study aims to analyze the relationship between ferritin levels and vitamin D status in pregnant women. **Methods:** This retrospective comparative cross-sectional analytical observational study involved pregnant women in the 1st, 2nd, and 3rd trimesters who underwent antenatal care at Hermina Hospital Padang from February to August 2023. Vitamin D (25(OH)D3) and ferritin were measured using enzyme-linked fluorescence assay (ELFA). Univariate and bivariate analysis used the Chi-square and odds ratio (OR) tests, with a significance of $p<0.05$. **Results:** Of 163 pregnant women (mean age 30.4 years), median ferritin levels were 25.85 ng/mL and 25(OH)D3 15.5 ng/mL. Low ferritin was found in 63.80% of subjects and sufficient vitamin D in 31.90%, insufficiency in 33.74%, and deficiency in 34.36%. There was no correlation between low ferritin and vitamin D insufficiency (OR=2.04; 95% CI 0.94-4.42; p=0.700). However, there was a significant correlation between low ferritin and vitamin D deficiency (OR=6.59; 95% CI 2.68-16.18; p=0.000). **Conclusion:** Pregnant women with low ferritin have a 6.59 times higher risk of experiencing vitamin D deficiency.

1. Introduction

Vitamin D deficiency has been recognized as a significant global public health problem, affecting various age groups and populations throughout the world. The prevalence of vitamin D deficiency is very high in pregnant women, with recent studies showing that this condition affects up to 80% of pregnant women in some geographic areas. This alarming level of deficiency raises serious concerns because of its potential impact on maternal and fetal health. Vitamin D, often referred to as the "sunshine vitamin", is an essential nutrient obtained primarily through exposure to sunlight and, to a lesser extent, through certain food sources such as fatty fish, egg yolks, and fortified foods. However, various factors contribute to the high prevalence of vitamin D deficiency in pregnant women. These factors include inadequate sun exposure due to an indoor lifestyle, use of sunscreen, darker skin pigmentation, poor diet, and increased need for vitamin D during pregnancy to support fetal growth and development.[1,2]

Vitamin D deficiency during pregnancy has been associated with a variety of adverse pregnancy complications, potentially affecting maternal and fetal

health. One of the most significant complications is an increased risk of gestational diabetes, a condition characterized by elevated blood sugar levels during pregnancy. Vitamin D deficiency impairs insulin secretion and increases insulin resistance, which contributes to the development of gestational diabetes. The consequences of gestational diabetes include an increased risk of preeclampsia, fetal macrosomia (large birth weight), and cesarean delivery. In addition, vitamin D deficiency has been implicated in the pathogenesis of preeclampsia, a serious condition characterized by high blood pressure and organ damage, usually occurring in the second half of pregnancy. Vitamin D plays an important role in immune system regulation and endothelial function, and deficiency can lead to endothelial dysfunction and inflammation, which are hallmarks of preeclampsia. Preeclampsia can cause serious complications for both mother and baby, including restricted fetal growth, premature birth, and, in severe cases, seizures and death of the mother. Vitamin D deficiency during pregnancy is also associated with an increased risk of preterm birth, defined as birth before 37 weeks of gestation. Vitamin D plays a role in maintaining healthy uterine muscles and regulating uterine contractions. Vitamin D deficiency can disrupt the function of the uterine muscles and cause premature labor. Premature birth can cause a variety of health problems for the newborn, including difficulty breathing, feeding problems, and developmental delays.[3,4]

In addition, vitamin D deficiency during pregnancy can negatively impact fetal growth and cause low birth weight. Vitamin D is essential for the absorption of calcium and phosphorus, minerals that are important for bone development and fetal growth. Vitamin D deficiency can inhibit the absorption of this mineral, leading to poor fetal growth and low birth weight. Babies with low birth weight have a higher risk of experiencing various health problems, including respiratory problems, infections and neurological problems. In vitro and animal studies have revealed a complex relationship between iron and vitamin D metabolism. Iron plays an important role in the synthesis of vitamin D-binding proteins, which are responsible for transporting vitamin D in the blood, and vitamin D receptors, which mediate the biological effects of vitamin D Therefore, iron deficiency can interfere with vitamin D activation and inhibit the body's ability to use vitamin D effectively. Iron deficiency is one of the most common nutritional deficiencies worldwide, especially among women of childbearing age, including pregnant women. During pregnancy, iron requirements increase substantially due to expansion of maternal blood volume, fetal growth, and placental development. If these increased iron requirements are not met, pregnant women may experience iron deficiency, which can have negative consequences for both mother and fetus.[5,6]

Pregnant women are a group that is very vulnerable to iron deficiency due to the large increase in iron requirements during pregnancy. Iron is needed for the production of hemoglobin, a protein in red blood cells that carries oxygen to body tissues. During pregnancy, the mother's blood volume increases significantly to support the growth of the fetus and placenta. This increase in blood volume requires the production of more hemoglobin, which in turn requires more iron. In addition, the developing fetus needs iron for its own hemoglobin production and to store iron for use after birth. The placenta, the organ that connects mother and fetus, also needs iron for growth and function. As a result, pregnant women's iron requirements increase significantly compared to non-pregnant women. If this increased iron requirement is not met through diet or supplements, pregnant women can experience iron deficiency. Iron deficiency during pregnancy has been associated with a variety of adverse pregnancy outcomes, including iron deficiency anemia, premature birth, low birth weight, and increased risk of maternal and infant mortality. Ferritin is an intracellular protein that functions as the main storage form of iron in the body. It is found in various tissues, including the liver, spleen, and bone marrow. Serum ferritin levels, the concentration of ferritin in the blood, reflect the body's iron reserves. When iron

stores are reduced, serum ferritin levels decrease, even before a decrease in serum iron levels occurs. Therefore, ferritin may serve as an early indicator of iron deficiency. Monitoring serum ferritin levels during pregnancy can help identify pregnant women at risk of iron deficiency. Early detection of iron deficiency allows early intervention, such as iron supplementation, to prevent negative consequences for mother and baby.[7-9] Considering the high prevalence of vitamin D and iron deficiencies in pregnant women, as well as the complex interactions between these two nutrients, this study aimed to investigate the relationship between ferritin levels and vitamin D status in a population of pregnant women.

2. Methods

This study used an analytical observational design with a retrospective comparative cross-sectional approach. The cross-sectional design allowed collecting data on exposure (ferritin levels) and outcome (vitamin D status) at the same time. The comparative approach allows comparison between groups with low and normal ferritin levels to see differences in the risk of vitamin D deficiency. The retrospective approach allows the use of existing data from medical records, making it more efficient and economical. The target population in this study was all pregnant women who underwent antenatal care (ANC) examinations at Hermina Hospital Padang, Indonesia, during the period February to August 2023. This hospital was chosen because it is one of the largest maternal and child health service centers and has a diverse population of pregnant women.

Sample selection was carried out using a purposive sampling technique. The inclusion criteria applied were pregnant women aged 18-40 years: This age range was chosen because it is a common reproductive age and includes the majority of pregnant women; Carrying out ANC examinations at Hermina Hospital Padang during the research period: This criterion ensures that the data collected comes from the same population and is relevant to the research objectives; Having complete data regarding ferritin and vitamin D levels: This criterion is important to ensure the validity and reliability of the data analyzed. Meanwhile, the exclusion criteria applied are: Having a history of chronic disease (diabetes mellitus, hypertension, kidney disease, liver disease): This chronic disease can affect the metabolism of iron and vitamin D, so it can be a confounding factor in the study; Taking iron or vitamin D supplements: Iron and vitamin D supplementation can affect the levels of these two substances in the body, which can interfere with the interpretation of research results.

This study has two main variables: Independent Variable: Serum ferritin levels. This variable is a factor that is thought to influence vitamin D status in pregnant women. Low ferritin levels are considered an indicator of iron deficiency. Dependent Variable: Vitamin D status. This variable is the outcome observed in the study. Vitamin D status was categorized into deficiency (<20 ng/mL), insufficiency (20-29 ng/mL), and sufficiency (≥30 ng/mL). Serum ferritin levels: Ferritin levels in blood serum are measured using the enzyme-linked fluorescence assay (ELFA) method. This method was chosen because it has high sensitivity and specificity in measuring ferritin levels. Vitamin D status: Levels of 25-hydroxyvitamin D (25(OH)D) in blood serum were measured using the ELFA method. 25(OH)D is the most stable vitamin D metabolite and is often used as an indicator of vitamin D status in the body. Data were collected retrospectively from the electronic medical records of pregnant women who met the inclusion and exclusion criteria. Electronic medical records were chosen because they provide more complete and accurate data compared to manual medical records. Data collected includes: Demographic data: Age, parity (number of pregnancies resulting in live births), economic status, and education level. This demographic data was collected to see whether there were differences in characteristics between groups with low and normal ferritin levels. Clinical Data: Trimester of pregnancy at ANC examination, serum ferritin levels, and 25(OH)D levels. This clinical data is the main data used to analyze the relationship

between ferritin levels and vitamin D status. Data collection was carried out by two researchers who had been previously trained. Researchers used standardized data collection forms to ensure data consistency and accuracy.

The collected data was analyzed using SPSS version 25 statistical software. Data analysis included: Univariate Analysis: This analysis was used to describe the characteristics of research subjects, distribution of ferritin and vitamin D levels, as well as the proportion of subjects with vitamin D deficiency, insufficiency, and sufficiency. Descriptive statistics used include mean, standard deviation, median, interquartile range (IQR), and percentage. Bivariate Analysis: This analysis is used to analyze the relationship between ferritin levels and vitamin D status. The Chi-square test is used to test differences in the proportion of subjects with vitamin D deficiency between groups with low and normal ferritin levels. Odds ratio (OR) with a 95% confidence interval (CI) was used to measure the strength of the association between low ferritin levels and vitamin D deficiency. A p-value <0.05 was considered statistically significant. This research has received approval from the ethics committee. All data collected is kept confidential and is only used for research purposes. The identity of the research subjects was not disclosed in the publication of the research results.

3. Results

Table 1 presents the characteristics of the study subjects, including age, ferritin levels, and 25(OH)D3 levels. The mean age of pregnant women in this study was 30.3 years with a standard deviation (SD) of 4.25 years. This suggests that most participants were around 30 years old, with considerable age variation in the sample. The median ferritin level was 25.85 µg/L with an interquartile range (IQR) of 18.52 µg/L. This means that half of the participants had ferritin levels below 25.85 µg/L and half above. The majority of participants (63.80%) had low ferritin levels (<30 µg/L), indicating a high prevalence of iron deficiency in this population. Median 25(OH)D3 level was 15.5 ng/mL with an IQR of 12 ng/mL. This showed that half of the participants had vitamin D levels below 15.5 ng/mL and half above. The distribution of vitamin D status was quite even, with 31.90% of participants having sufficient vitamin D levels (≥20 ng/mL), 33.74% experiencing insufficiency (12-19 ng/mL), and 34.36% experiencing deficiency (<12 ng/mL). This suggests that vitamin D insufficiency and deficiency are also significant problems in this population.

Table 1. Characteristics of study subject.

Variable	Frequency (%)	Mean (SD)	Median (IQR)
Age (years)		30.3 (4.25)	
Ferritin level			
Normal (≥30 µg/L)	59 (36.20)		
Low (<30 µg/L)	104 (63.80)		25.85 (18.52)
25(OH)D3 level			
Sufficient (≥20 ng/mL)	52 (31.90)		
Insufficient (12-19 ng/mL)	55 (33.74)		
Deficient (<12 ng/mL)	56 (34.36)		15.5 (12)

Table 2 presents the relationship between ferritin levels and vitamin D status in pregnant women. In the group with normal ferritin levels (≥30 µg/L), the majority of pregnant women had adequate vitamin D status (17.8%), followed by insufficiency (12.9%) and deficiency (5.5%). In the group with low ferritin levels (<30 µg/L), the proportion of pregnant women with vitamin D deficiency (28.8%) was higher than those with insufficiency (20.9%) and sufficiency (14.1%). A highly significant p-value (0.000) indicates a strong

relationship between low ferritin levels and an increased risk of vitamin D deficiency in pregnant women. Pregnant women with low ferritin levels have a higher chance of experiencing vitamin D deficiency compared to pregnant women who have normal ferritin levels.

Table 2. Relationship between ferritin level and vitamin D status.

Ferritin level	Vitamin D status			p-value
	Sufficient (≥20 ng/mL)	Insufficient (12-19 ng/mL)	Deficient (<12 ng/mL)	
Normal (≥30 µg/L)	29 (17.8%)	21 (12.9%)	9 (5.5%)	0,000
Low (<30 µg/L)	23 (14.1%)	34 (20.9%)	47 (28.8%)	

Table 3 shows the bivariate analysis of the test variables. There was no significant relationship between low ferritin levels and vitamin D insufficiency (p = 0.700). An odds ratio (OR) of 2.04 indicates that pregnant women with low ferritin levels are 2.04 times more likely to experience vitamin D insufficiency compared to pregnant women who have normal ferritin levels. However, because the confidence interval (CI) includes the value 1 (0.94 - 4.42), this result is not statistically significant. There is a significant relationship between low ferritin levels and vitamin D deficiency (p = 0.000). An odds ratio (OR) of 6.59 indicates that pregnant women with low ferritin levels have a 6.59 times higher risk of experiencing vitamin D deficiency compared to pregnant women who have normal ferritin levels. The confidence interval (CI) that does not include the value 1 (2.68 - 16.18) strengthens the statistical significance of this finding.

Table 3. Association between low ferritin level and vitamin D deficiency.

Outcome	Odds ratio (OR) 95%	Confidence interval (CI)	p-value
Vitamin D insufficiency	2,04	0.94 – 4.42	0.700
Vitamin D deficiency	6.59	2.68 – 16.18	0.000

4. Discussion

The results of this study indicate a significant relationship between low ferritin levels and vitamin D deficiency in pregnant women. Pregnant women with ferritin levels of less than 30 µg/L have a 6.59 times higher risk of experiencing vitamin D deficiency compared to pregnant women who have normal ferritin levels. These findings are consistent with several previous studies which also reported an association between iron deficiency and vitamin D deficiency in the general population and special groups, including pregnant women. Iron does play a role in protein synthesis, but its role in direct DBP and VDR synthesis is not fully understood. Vitamin D binding protein (DBP) is mainly synthesized in the liver and is responsible for transporting vitamin D in the blood. Although iron is important for protein synthesis in general, there is no strong evidence to show that iron deficiency directly interferes with DBP synthesis. Vitamin D receptor (VDR) is a nuclear receptor found in various body tissues. When vitamin D binds to VDR, this complex will activate or suppress the expression of certain genes. Iron does play a role in the regulation of gene expression, including genes involved in vitamin D metabolism. However, the effect of iron deficiency on VDR synthesis is still unclear. Iron deficiency can

increase the production of hepcidin, a hormone that regulates iron metabolism. Hepcidin is also known to inhibit the conversion of 25(OH)D to its active form, 1,25(OH)2D, thereby contributing to vitamin D deficiency. Iron deficiency can increase oxidative stress, which can damage cells and disrupt various biological processes, including vitamin metabolism. D. Iron can affect the composition of the gut microbiota, which plays a role in vitamin D metabolism. Changes in the gut microbiota resulting from iron deficiency can contribute to vitamin D deficiency. Although there is no direct evidence to suggest that iron deficiency disrupts the synthesis of DBP and VDR, iron still plays a role important in vitamin D metabolism through other mechanisms, such as hepcidin regulation, oxidative stress, and its effects on gut microbiota. Further research is needed to uncover the exact mechanisms by which iron deficiency contributes to vitamin D deficiency.[9-11]

Iron does play a role in the metabolism of vitamin D in the liver, especially in the hydroxylation process of vitamin D into its active form, 25-hydroxyvitamin D (25(OH)D). The enzyme 25-hydroxylase, which is mainly found in the liver, is responsible for catalyzing the first step in the activation of vitamin D. Iron acts as an important cofactor in this reaction. Cofactors are non-protein molecules required by enzymes to function properly. When the body lacks iron, the activity of the 25-hydroxylase enzyme can be impaired. This can cause a decrease in the production of 25(OH)D, which is the main form of vitamin D circulating in the blood and is used to assess a person's vitamin D status. Decreased 25(OH)D production can cause or worsen vitamin D deficiency. Vitamin D deficiency has been linked to a variety of health problems, including bone disorders, immune system disorders, and an increased risk of chronic disease. Several studies have shown a link between iron deficiency and decreased 25-hydroxylase enzyme activity. For example, a study in mice found that iron deficiency led to decreased expression of the 25-hydroxylase enzyme gene in the liver. Another study in humans showed that iron supplementation in individuals with iron deficiency can increase 25(OH)D levels. Iron has an important role in vitamin D metabolism in the liver, especially in the activation of vitamin D by the 25-hydroxylase enzyme. Iron deficiency can interfere with this process and contribute to vitamin D deficiency. Therefore, it is important to ensure iron adequacy, especially in groups at high risk of vitamin D deficiency, such as pregnant women.[12-14]

Iron deficiency can indeed trigger an increase in hepcidin levels, which in turn can worsen vitamin D deficiency. Hepcidin is a peptide hormone produced by the liver. Its main function is to regulate iron homeostasis in the body. Hepcidin works by inhibiting the absorption of iron in the intestine and the release of iron from stores in the liver and spleen. Hepcidin production is regulated by several factors, including iron levels in the body, inflammation, and erythropoiesis (red blood cell production). When iron levels are high, hepcidin production increases to reduce iron absorption and release. Conversely, when iron levels are low, hepcidin production decreases to increase iron absorption and release. In conditions of iron deficiency, the body tries to conserve the remaining iron. One way is to increase hepcidin production. This increase in hepcidin will further inhibit iron absorption in the intestine, thereby worsening iron deficiency. Apart from regulating iron metabolism, hepcidin can also inhibit the conversion of 25-hydroxyvitamin D (25(OH)D) into its active form, 1,25-dihydroxyvitamin D (1,25(OH)2D), in the kidneys. 1,25(OH)2D is the most active form of vitamin D and is responsible for most of the biological effects of vitamin D. Increased hepcidin levels in iron deficiency can inhibit the conversion of 25(OH)D to 1,25(OH)2D, thereby reducing the availability of active vitamin D and worsening of vitamin D deficiency. These findings have important implications in the treatment of iron and vitamin D deficiencies. In individuals with iron deficiency, iron supplementation can not only improve iron levels but can also reduce hepcidin levels and increase conversion 25 (OH)D becomes 1.25(OH)2D, thereby helping overcome

vitamin D deficiency.[15-17]

Several previous studies have reported an association between iron deficiency and vitamin D deficiency in various populations. A meta-analysis involving 15 cohort and cross-sectional studies found that iron deficiency was associated with an increased risk of vitamin D deficiency in adults. Another study in children also found that iron deficiency was an independent risk factor for vitamin D deficiency. In pregnant women, several studies have also shown an association between iron deficiency and vitamin D deficiency. A cross-sectional study of 200 pregnant women in India found that pregnant women with iron deficiency anemia have a 2.5 times higher risk of experiencing vitamin D deficiency compared to pregnant women without anemia. Another study of 150 pregnant women in Turkey reported that low ferritin levels were significantly associated with low 25(OH)D levels. Our study strengthens previous evidence regarding the association between iron deficiency and vitamin D deficiency in pregnant women. These findings have important implications in clinical practice. Given that vitamin D deficiency and iron deficiency are common health problems in pregnant women, early screening and intervention for these two conditions is essential to ensure optimal maternal and fetal health. Apart from the biological mechanisms described above, there are several other mechanisms that may play a role in the relationship between iron deficiency and vitamin D deficiency in pregnant women. First, iron deficiency can cause impaired thyroid function, which can affect vitamin D metabolism. Second, iron deficiency can cause oxidative stress, which can damage cells involved in vitamin D metabolism. Third, iron deficiency can affect the gut microbiota, which plays a role in vitamin D production.[17-19]

The findings of this study have important implications in clinical practice. First, pregnant women with low ferritin levels should have their vitamin D levels checked regularly. Second, pregnant women with iron deficiency must be given iron and vitamin D supplementation. Third, pregnant women must be given education regarding the importance of adequate iron and vitamin D intake during pregnancy. Although this study has provided strong evidence regarding the relationship between iron deficiency and vitamin D deficiency in pregnant women, further research is still needed to clarify the mechanisms underlying this relationship. In addition, intervention research is also needed to test the effectiveness of iron and vitamin D supplementation in preventing and treating vitamin D deficiency in pregnant women.[19,20]

5. Conclusion

This study shows that low ferritin levels are an independent risk factor for vitamin D deficiency in pregnant women. These findings have important implications for clinical practice and public health. Early screening and intervention for iron deficiency and vitamin D deficiency in pregnant women is essential to ensure optimal maternal and fetal health.

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