ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Importance of Micronutrient Deficiency in the Etiology of Anemia in the First Trimester of Pregnancy: a Cross-Sectional Study

Gebeliğin İlk Trimesterinde Anemi Etiyolojisinde Mikrobesin Eksikliğinin Önemi: Kesitsel Bir Çalışma

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ABSTRACT

Aim: *Anemia is a common pregnancy complication, with iron, folate, and vitamin B12 deficiencies being the most frequent causes. This study aimed to evaluate the role of micronutrient deficiencies in the etiology of anemia during the first trimester of pregnancy.*

Material and Method: *Between January 2023 and January 2024, 271 pregnant women aged 18–50 years who presented to the Obstetrics and Gynecology Outpatient Clinic of a tertiary university hospital were included in this study. Demographic data and hemoglobin, serum iron, total iron binding capacity (TIBC), ferritin, folate, and vitamin B12 levels were obtained retrospectively from medical records. According to the Centers for Disease Control and Prevention (CDC), 1st trimester hemoglobin <11 g/dl and hematocrit <33% were considered as anemia, ferritin <15 ng/ml as iron deficiency, serum folate <3 ng/ml, and vitamin B12 <200 pg/ml as a deficiency.*

Results: *In total, 107 (39.5%) pregnant women had anemia. Pregnant women with and without anemia were similar in terms of age, gravidity, parity, abortion, gestational week, infant birth weight, APGAR scores at 1 and 5 min, folate levels, and vitamin B12 deficiency levels. Those with anemia had significantly lower serum iron (p=0.006) and ferritin levels (p<0.001), and higher TIBC levels (p<0.001) than those without anemia. Ferritin was <15 ng/ml in 61.7% (n=66) of those with anemia (p<0.001). Vitamin B12 deficiency was present in one of the three pregnant women with anemia. There were only four pregnant women with folate deficiency, and none of them had anemia.*

Conclusion: *Providing adequate micronutrient support before and during pregnancy prevents anemia. Therefore, pregnancy follow-up protocols should emphasize regular screening for micronutrient deficiencies.*

Key words: *anemia; iron deficiency; ferritin; folate; vitamin B12 deficiency*

ÖZET

Amaç: *Anemi, gebelikte sık görülen bir komplikasyondur ve en sık anemi sebepleri demir, folat ve B12 vitamini eksiklikleridir. Bu çalışmanın amacı, gebeliğin ilk üç ayında anemi etiyolojisinde bu mikro besin eksikliklerinin rolünü değerlendirmektir.*

Materyal – Metod: *Çalışmaya Ocak 2023 ile Ocak 2024 arasında üçüncü basamak bir üniversite hastanesi Kadın Hastalıkları ve Doğum Polikliniği'ne başvuran 18–50 yaş arası 271 gebe dâhil edildi. Hastalara ait demografik veriler ve hemoglobin, serum demiri, total demir bağlama kapasitesi (TDBK), ferritin, folat ve B12 vitamini düzeyleri retrospektif olarak tıbbi kayıtlardan elde edildi. Hastalık Kontrol ve Önleme Merkezlerine (CDC) göre, 1. trimester hemoglobin <11 g/dl ve hematokrit <%33 anemi, ferritin <15 ng/ml demir eksikliği, serum folat <3 ng/ml ve vitamin B12 <200 pg/ml olması eksiklik düzeyi olarak kabul edildi.*

Bulgular: *Anemisi olan 107 (%39,5) gebe kadın vardı. Anemisi olan ve anemisi olmayan gebeler yaş, gravida, parite, abortus, doğum haftası, bebek doğum ağırlığı, 1. ve 5. dakikadaki APGAR skorları, folat düzeyleri ve B12 vitamini eksikliği düzeyi açısından benzerdi. Anemisi olanların serum demir (p=0,006) ve ferritin düzeyleri (p<0,001) anemisi olmayanlara göre anlamlı olarak daha düşük, TDBK düzeyleri daha yüksekti (p<0,001). Anemisi olanların %61,7'sinde (n=66) ferritin <15 ng/ml idi (p<0,001). Anemisi olan her üç gebeden birinde B12 vitamini eksikliği mevcuttu. Folat eksikliği olan sadece dört gebe vardı ancak hiçbirinin anemisi yoktu.*

Sonuç: *Gebelik öncesi ve sırasında yeterli mikro besin desteği sağlanması, anemiyi önlemek için kritik öneme sahiptir. Bu nedenle, gebelik takip protokollerinde mikro besin eksikliklerinin düzenli taranmasına daha fazla önem verilmelidir.*

Anahtar kelimeler: *anemi; demir eksikliği; ferritin; folat; vitamin B12 eksikliği*

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Introduction

Anemia is one of the most common complications of pregnancy and can have serious consequences on both maternal and fetal health. According to World Health Organization (WHO) data, the prevalence of anemia during pregnancy is approximately 36% worldwide, and this rate is higher, especially in low- and middle-income countries[1]. Anemia during pregnancy has been associated with significant complications, including maternal mortality, premature delivery, low birth weight, and intrauterine growth retardation. Anemia not only directly affects maternal health but may also have permanent adverse effects on fetal development[2].

The most common causes of anemia during pregnancy include iron, folic acid, and vitamin B12 deficiencies[3]. Iron deficiency is the most common cause of anemia in pregnancy due to increased blood volume, and this need increases even more with placental development and fetal growth in the first trimester[4]. These deficiencies are more common when appropriate nutrition and prenatal care are inadequate[5].

Iron deficiency constitutes 50–75% of anemia during pregnancy and may have serious consequences for both the mother and fetus when left untreated[6]. Inadequate iron intake may lead to problems such as fatigue, increased risk of infection, and complications during labor for the mother. In fetuses, the risk of intrauterine growth retardation and premature birth increases. Folate and vitamin B12 deficiencies also play important roles in developing anemia. Folic acid deficiency may lead to severe developmental problems, such as neural tube defects in the fetus, while vitamin B12 deficiency may lead to megaloblastic anemia[7]. Low socioeconomic conditions and malnutrition increase the prevalence of these deficiencies; therefore, prenatal care should be strengthened in at-risk groups[8].

In this study, we aimed to evaluate the role of iron, folate, and vitamin B12 deficiencies in the etiology of anemia in the first trimester of pregnancy and to contribute to the development of more effective prevention strategies to reduce the risk of anemia in pregnancy by early diagnosis of micronutrient deficiencies.

Materials and Methods

Patients and Data Collection

This study included 271 pregnant women aged 18–50 who presented to the Obstetrics and Gynecology Outpatient Clinic of a tertiary university hospital between January 2023 and January 2024.

Medical records were retrospectively accessed for demographic data, including age, gravida, parity, abortion, comorbidity, and medication. The first-trimester hemoglobin, iron, total iron binding capacity (TIBC), ferritin, folate, and vitamin B12 levels were also recorded.

Pregnant women with unavailable 1 st-trimester hemoglobin, serum iron, TIBC, ferritin, folate, and vitamin B12 levels in the medical records, those with additional systemic diseases, smokers during pregnancy, those with obstetric vaginal bleeding during pregnancy, and those using any iron and/or vitamin preparation were excluded. In addition, 58 pregnant women with additional systemic diseases and 19 pregnant women taking medications were excluded.

Terms and Definitions

According to the Centers for Disease Control and Prevention (CDC), 1 st-trimester hemoglobin <11 g/dl and hematocrit <33% anemia[9], ferritin <15 ng/ml[9], serum folate <3 ng/ml[10] and vitamin B12 <200 pg/ml[11] are considered deficiency levels.

Ethics Committee Approval

This study was approved by the Non-Interventional Clinical Research Ethics Committee of Kafkas University Faculty of Medicine (01/10/2024, 80576354–050–99/535) and complied with the recommendations of the Declaration of Helsinki for human biomedical research.

Statistical Analysis

The Windows SPSS program (version 24.0) was used for statistical analyses. When appropriate, categorical variables are presented as numbers with corresponding percentages and were assessed using the chi-square test or Fisher's exact test. Continuous variables were expressed as median (minimum-maximum) or mean ± standard deviation using the Kolmogorov-Smirnov test and assessed using Student's t-test or Mann-Whitney U test. Spearman correlation analysis determined the relationship between hemoglobin levels and serum iron, ferritin, folate, and vitamin B12 levels. Statistical significance was set at p <0.05. Prism software (version 8, GraphPad Software, San Diego, California, USA) was used for the analysis and graphical data.

Results

Demographic and laboratory data of the total cohort

The mean age of the 271 pregnant women in the first trimester was 33.31±5.43 years. Median gravida was 2 (1–8), median parity was 1 (0–6), and median abortion was 0 (0–3). 15.9% (n=43) were preterm, 84.1% (n=228) were term; 5.2% (n=14) were <2500 grams, 93% (n=252) were 2500–4000 grams and 1.8% (n=5) were >4000 grams. The median hemoglobin level was 11.90 (6.6–16.1), and 39.5% (n=107) had a hemoglobin level <11 g/dl. The median serum iron was 71 (12–278) µg/dL, median TIBC was 321 (25–754) µmol/L, and median ferritin was 15 (2–199) ng/ml, respectively. Ferritin levels were <15 ng/ml in 47.2% (n=128) of pregnant women. The median folate level was 8.20 (1.91–24.8) ng/ml, and four pregnant women (1.5%) had folate levels <3 ng/ml. The median vitamin B12 levels were 240 (12–1146) pg/ml, and 33.6% (n=91) had vitamin B12 levels <200 pg/ml. Detailed data are presented in Table 1.

***Table 1.** Demographic and laboratory data of the total cohort*

	Total cohort (n=271)
Age (mean ± SD)	33.31±5.43
Gravida (median (min-max))	2 (1–8)
Parity (median (min-max))	1 (0–6)
Abortion (median (min-max))	0 (0–3)
Birth week (n, %)	
<37 weeks	43 (15%.9)
37–42 weeks	228 (84%.1)
>42 weeks	0 (0%)
Infant birth weight (n, %)	
<2500 gram	14 (5%.2)
2500–4000 gram	252 (93%)
>4000 gram	5 (1%.8)
1st minute APGAR score (median (min-max))	8 (2–10)
5th minute APGAR score (median (min-max))	9 (8–10)
Hemoglobin (median (min-max))	11.90 (6.6–16.1)
Hemoglobin <11 g/dl (n, %)	107 (39%.5)
Serum iron (median (min-max))	71 (12–278)
TIBC (median (min-max))	321 (25–754)
Ferritin (median (min-max))	15 (2–199)
Ferritin <15 ng/ml (n, %)	128 (47%.2)
Folate (median (min-max))	8.20 (1.91–24.8)
Folate <3 ng/dl (n, %)	4 (1%.5)
Vitamin B12 (median (min-max))	240 (12–1146)
Vitamin B12 <200 pg/dl (n, %)	91 (33%.6)

TIBC: total iron binding capacity.

Comparison of pregnant women with and without anemia

There were 107 pregnant women with anemia and 164 pregnant women without anemia. Pregnant women with and without anemia were similar in terms of age, gravidity, parity and abortion, gestational week, infant birth weight, APGAR scores at 1 and 5 min, folate levels, and B12 deficiency levels. Those with anemia had significantly lower serum iron (58(12–278) µg/dL vs 76 (13–227) µg/dL; p=0.006) and ferritin levels (10(2–199) ng/ml vs 18 (2–184) ng/ml; p<0.001) and higher TIBC levels (351(25–754) µmol/L vs 301 (103–635) µmol/L; p<0.001). Ferritin was <15 ng/ml in 61.7% (n=66) of those with anemia and 37.8% (n=62) of those without anemia and was significantly lower in those with anemia compared to those without anemia (p<0.001). Vitamin B12 levels were significantly lower in patients with anemia than in those without (225(78–663) pg/ml vs 249.5 (12–1146) pg/ml; p=0.020). Among the pregnant women with anemia, 39.2% (n=42) had only iron deficiency, 0.9% (n=1) had only vitamin B12 deficiency, and 24.2% (n=26) had both iron and vitamin B12 deficiency (Figure 1). Detailed data are presented in Table 2.

Comparison of pregnant women according to ferritin level

Age, gravidity, parity, abortion, gestational week, infant birth weight, and APGAR scores at 1 and 5 min were similar according to ferritin levels. Hemoglobin was <11 g/dl in 51.6% (n=66) of those with ferritin <15 ng/ml and 28.7% (n=41) of those with ferritin >15 ng/ml (p<0.001). Median folate (7.45 (1.91–24.2) ng/ml vs 9 (2.6–24.8) ng/ml; p=0.018) and vitamin B12 (225(78–519) pg/ml vs 246 (12–1146) pg/ml; p=0.007) levels were significantly lower in patients with ferritin <15 ng/ml than in those with ferritin >15 ng/ml. Vitamin B12 deficiency was present in 40.6% (n=52) of patients with ferritin levels <15 ng/ml and 27.3% (n=39) of patients with ferritin levels >15 ng/ml (p=0.020).

Table 2. *Comparison of pregnant women with and without anemia*

	Pregnant women with anemia (n=107)	Pregnant women without anemia (n=164)	p
Age (mean ± SD)	33.71±5.90	33.05±5.11	0.333
Gravida (median (min-max))	2 (1–8)	2 (1–8)	0.079
Parity (median (min-max))	1 (0–6)	0 (0–5)	0.090
Abortion (median (min-max))	0 (0–3)	0 (0–3)	0.282
Birth week (n, %)			
<37 weeks	15 (14%)	28 (17%.1)	0.615
37–42 weeks	92 (86%)	136 (82%.9)	0.615
>42 weeks	0 (0%)	0 (0%)	*
Infant birth weight (n, %)			
<2500 gram	6 (5%.6)	8 (4%.9)	1.0
2500–4000 gram	98 (91%.6)	154 (93%.9)	0.627
>4000 gram	3 (2%.8)	2 (1%.2)	0.386
1st minute APGAR score (median (min-max))	8 (7–9)	8 (2–10)	0.723
5th minute APGAR score (median (min-max))	9 (8–10)	9 (8–10)	0.279
Hemoglobin (median (min-max))	10.3 (6.6–11.0)	12.8 (11.1–16.1)	<0.001
Serum iron (median (min-max))	58 (12–278)	76 (13–227)	0.006
TIBC (median (min-max))	351 (25–754)	301 (103–635)	<0.001
Ferritin (median (min-max))	10 (2–199)	18 (2–184)	<0.001
Ferritin <15 ng/ml (n, %)	66 (61%.7)	62 (37%.8)	<0.001
Folate (median (min-max))	7.84 (4–24.8)	8.44 (1.91–24.2)	0.452
Folate <3 ng/dl (n, %)	0 (0%)	4 (2%.4)	0.156
Vitamin B12 (median (min-max))	225 (78–663)	249.5 (12–1146)	0.020
Vitamin B12 <200 pg/dl (n, %)	39 (36%.4)	52 (31%.7)	0.419

TIBC: total iron binding capacity.

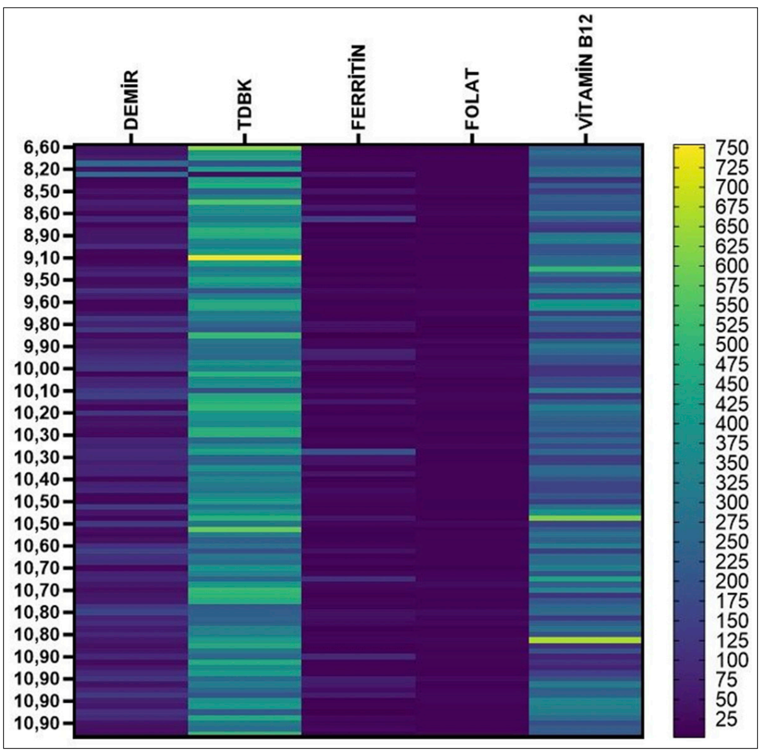

Figure 1. *The relationship between hemoglobin levels and iron, iron-binding capacity, folate and vitamin B12 in pregnant women with anemia.*

Comparison of pregnant women with and without vitamin B12 deficiency

Pregnant women with and without vitamin B12 deficiency were statistically similar in age, gravidity, abortion, gestational week, infant birth weight, APGAR scores at 1 and 5 min, hemoglobin, serum iron, TIBC, ferritin, and folate levels. The ferritin level <15 ng/ml was significantly higher in those with vitamin B12 deficiency than in those without vitamin B12 deficiency (n=52 (57.1%) vs n=76 (42.2%); p=0.020). Parity count was significantly higher in patients with vitamin B12 deficiency than in those without vitamin B12 deficiency (1(0–6) vs 0 (0–5); p=0.036).

Comparison of pregnant women with and without folate deficiency

The mean age of the four pregnant women with folate deficiency was statistically significantly lower than those without folate deficiency (26.75±2.63 years vs 33.41±5.41 years; p=0.015). Gravida, parity, gestational week, birth weight, infant birth weight, 1st and 5th minute APGAR scores, hemoglobin, serum iron, TIBC, ferritin, and vitamin B12 levels were similar in folate-deficient and non-folate-deficient women. The number of abortions was significantly higher in patients without folate deficiency than in those with folate deficiency (0(0–3) vs 1 (0–1); p=0.029).

Spearman Correlation Analysis Results

Spearman correlation analysis revealed a statistically significant positive correlation between hemoglobin levels and vitamin B12 (r=0.167, p=0.006), serum iron (r=0.167, p=0.006), and ferritin (r=0.216, p<0.001).

Discussion

This study examined the contribution of micronutrient deficiencies, including iron, vitamin B12, and folic acid, to the etiology of anemia in the first trimester of pregnancy. Anemia was detected in 40% of the pregnant population evaluated in our study, and iron deficiency was the most common etiology. In addition, 30% of pregnant women with anemia have low vitamin B12 levels. Folic acid deficiency was present in only four pregnant women, none of whom had anemia.

The prevalence of 1st trimester anemia during pregnancy varies among countries. It has been reported to be 27.8% in Türkiye[12], 18.2% in the USA[13], 15.9% in Sri Lanka[13], 10.6% in Jordan[14] and 31.8% in Ethiopia[15]. A systematic review by the WHO shows that it varies between 24–44% in low-income and middle-income countries[16]. In our study, the prevalence of anemia in the first trimester was 40%. The higher prevalence of anemia compared to the literature may be because the region where the study was conducted was rural and economically less developed, with malnutrition and limited access to health services.

In young pregnancies, it may be difficult for the body to meet the increased iron demand owing to ongoing growth and development. However, factors such as decreased body iron stores or chronic diseases may increase the risk of anemia in older pregnant women[17]. It has been reported that the prevalence of anemia is lower in pregnant women between the ages of 18–35 years and increases in pregnant women aged >35 years, which has negative effects on maternal complications and neonatal outcomes[17,18]. In our study, pregnant women aged <20 years and those aged >35 years were compared regarding anemia, but no significant difference was found (p=0.976). As socioeconomic status, dietary habits, access to health services, and pregnancy follow-up were similar in both age groups, factors other than age may have significantly affected the prevalence of anemia.

Each pregnancy depletes maternal iron stores, and the risk of anemia may increase during the subsequent pregnancy. Studies have shown that high gravida and parity trigger the development of anemia during pregnancy. A study conducted in Ethiopia found that the risk of anemia was higher in women who gave birth at intervals of less than two years[15]. In a study conducted in Türkiye, the anemia rate was 42.3% in women who had four or more live births[12]. In Ghana, it was shown that the risk of anemia was significantly increased in women who had many births compared to those who had fewer births[16]. In our study, we could not conclude that gravida, parity, or number of abortions were associated with anemia. The fact that gravida, parity, and number of abortions were not found to be associated with anemia in our study may have weakened the relationship because of insufficient sample size, different diagnostic criteria for anemia, or the effect of regional nutrition and health conditions.

Smoking can impair iron absorption by causing oxidative stress, reduce the oxygen-carrying capacity of hemoglobin, and lead to malnutrition, which can interfere with iron absorption and micronutrients, such as folic acid, increasing the risk of anemia. Several studies have shown that smoking increases the risk of anemia during pregnancy. In a study conducted in India, anemia was found in 72% of pregnant smokers and was associated with iron deficiency[19]. In another study, the prevalence of anemia in smoking women was 27.6%[15]. To obtain more reliable results related to micronutrient deficiency in the etiology of anemia, pregnant women who smoked were excluded from our study.

The prevalence of anemia in women with chronic diseases in the first trimester of pregnancy is quite high, ranging up to 40% in women with chronic kidney disease[18], around 25% in women with thyroid disorders[20], 30–50% in autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis[18], and 30–60% in chronic infections such as diabetes and HIV[18,20]. These systemic diseases decrease erythropoietin production and cause anemia by disrupting iron metabolism. In our study, to obtain more reliable results regarding micronutrient deficiency in the etiology of anemia, pregnant women with systemic diseases and taking medication were not included.

Iron deficiency is the primary cause of anemia in the first trimester of pregnancy due to increased blood volume, and fetal growth demands that low iron stores cannot meet[13]. This condition is prevalent in areas with malnutrition, intestinal parasites, and a low socioeconomic status[18]. Also, heightened pregnancy inflammation disrupts iron metabolism and contributes to iron deficiency anemia[19]. The reported prevalence rates are 18.2% in the USA[13], 16.64% in Türkiye[21], 19.4% in China[13], 72% in India[19], and 27.6% in Ethiopia[15]. A systematic review and meta-analysis found that iron supplementation in the first trimester reduced the prevalence of anemia and improved pregnancy outcomes, highlighting the importance of early detection and management of iron deficiency[16]. Our study identified iron deficiency in three out of five pregnant women with anemia, likely due to nutritional deficiencies in the economically underdeveloped rural study area.

Vitamin B12 deficiency is recognized as one of the main causes of anemia during pregnancy. Vitamin B12 plays a vital role in DNA synthesis and erythrocyte maturation. Its deficiency leads to megaloblastic anemia, impaired erythropoiesis, and reduced oxygen transport capacity. This deficiency decreases maternal energy levels and negatively affects the neurological development of the fetus[13,15]. Therefore, early dietary adjustments and micronutrient supplements play key roles in protecting maternal and fetal health[15]. Studies reported that vitamin B12 deficiency was 74% in India[15], 12.4% in the UK[13], 46.5% in Ethiopia[18], 33% in Türkiye[13] and 22.2% in Brazil[13]. These rates vary depending on geographical factors and dietary habits. According to data in the literature, vitamin B12 deficiency was found in one out of every three pregnant women with anemia.

Folic acid is essential for DNA synthesis, cell division, and fetal development, with increased demand during pregnancy due to increased cell division, particularly during placental and fetal growth. Insufficient folic acid can hinder erythrocyte maturation, causing megaloblastic anemia and fetal developmental issues such as neural tube defects. Consequently, the WHO recommends a daily supplement of 400 µg folic acid for all pregnant women to prevent anemia and neural tube defects[22,23]. This deficiency is more prevalent in patients with malnutrition and low socioeconomic status. Studies have reported varying anemia rates among pregnant women with folic acid deficiency: 44% in India[24], 23%[22], 28.9%[23] in Ethiopia, and 25%[25] in Nepal. In a domestic study, the prevalence of anemia during pregnancy was 27.1%, primarily due to folic acid deficiency[12]. The fact that only four pregnant women with folic acid deficiency were identified in our study and anemia was not observed in these women may be due to the insufficient sample size, prevalence of folic acid supplementation practices in the region, or predominance of other causes of anemia, which may have led to the inability to determine the role of folic acid deficiency in the etiology of anemia.

The most important limitation of our study was its retrospective and single-center design. This may limit the generalizability of the findings. In addition, although most people in the region where the study was conducted were engaged in animal husbandry as a source of livelihood, anemia was detected in two out of every five pregnant women. The most common causes of anemia were iron and vitamin B12 deficiencies. The strength of our study is that to examine the role of micronutrient deficiencies in the etiology of anemia, we selected the cohort only from healthy pregnant women who were not on medication and had no additional systemic diseases. Thus, our findings provide more reliable conclusions regarding the association between anemia and micronutrient deficiencies.

Conclusion

Adequate micronutrient supplementation before and during pregnancy is critical for preventing anemia development. In particular, micronutrient deficiencies such as iron, folic acid, and vitamin B12 adversely affect maternal health during pregnancy and threaten healthy fetal development. Therefore, the early recognition of these deficiencies and appropriate supplementation will contribute to maternal health status and favorable birth outcomes. Thus, assessing micronutrient deficiencies during pregnancy and integrating interventions for these deficiencies into pregnancy follow-up protocols should be considered effective approaches for maternal and fetal health.

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