

Original Article

Relationship Between Gestasyonel Depression and Iron Deficiency Anemia In Pregnancy: A Case-Control Study

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Abstract

Background: Iron deficiency may occur due to increased need and inadequate compensation of losses in pregnancy. Anemia may contribute to the emergence of depression and may lead to increased frequency.

Aim: The aim of this study was to evaluate whether iron deficiency anemia (IDA) is related to the risk of pregnancy depression and whether that risk differs in different stages of pregnancy.

Method: A total of 408 pregnant women took part in the study. Possible depression was assessed using the Edinburgh postnatal depression scale (EPDS). Pregnant women were divided into two groups according to the presence of anemia.

Results: IDA frequency was found as 13%. Eighteen (34.0%) pregnant women in the anemic group scored ≤ 12 points which were considered the cutoff value for depression on the EPDS. Eighty-one (22.8%) pregnant women in the non-anemic group scored ≤ 12 points which were considered the cutoff value for depression on the EPDS. According to our study, there is a risk of depression in pregnant women with IDA, especially in the second trimester ($p=0.007$).

Conclusion: In our study, a possible depression was determined in pregnant at about a quarter, especially in the second trimester this rate has been determined more frequently. As the tissues deteriorate in oxygenation and changes occur in the release of neurotransmitters, predisposition to depression emerges in IDA. Symptoms such as tiredness, fatigue and concentration impairment during anemia may contribute to the intensity of depression. Therefore IDA in pregnancy is important to prevent and control it.

Keywords Iron deficiency anemia, depression, pregnancy, women's health, nursing/midwifery

Introduction

Depression was found in approximately 10-16.4 % of pregnant women (Eke Saccone and Berghella, 2016; Okagbue et al., 2019), and depression occurs more commonly during the second and third trimesters (Beard et al., 2005; Virit et al., 2008; Okagbue et al., 2019). The disruption of cognitive functions during depression in pregnancy may inhibit one's capacity for self-care, including inadequate nutrition, smoking, and poor antenatal clinic attendance, which may directly impair the development of the fetus and may lead to adverse pregnancy complications and perinatal outcomes,

such as premature delivery, preeclampsia and lower birth weight (Field, 2011).

Depression during pregnancy is also important because of the potential increase in suicide attempts and an increased risk of postpartum depression (Grote et al., 2010; Grigoriadis et al., 2013). Although clinical guidelines ensure the screening and treatment of depression during pregnancy, these guidelines generally fail to recognize and treat the associated, non-psychiatric comorbidities (Committee on Obstetric Practice, 2015; MacQueen et al., 2016).

Iron is essential for the function of all cells through its roles in oxygen delivery, electron

transport, and enzymatic activity. Cells with high metabolic rates require more iron and are at greater risk for dysfunction during iron deficiency. Iron requirements during pregnancy increase dramatically, as the mother's blood volume expands and the fetus grows and develops. Thus, pregnancy is a condition of impending or existing iron deficiency, which may be difficult to diagnose because of limitations to commonly used biomarkers such as hemoglobin and ferritin concentrations. Iron deficiency is associated with adverse pregnancy outcomes, including increased maternal illness, low birthweight, prematurity, and intrauterine growth restriction (Georgieff 2020).

Maternal- fetal iron status has been linked to a number of neurocognitive and mental health disorders, in part by the timing of iron deficiency during pregnancy. Therefore, anemia during pregnancy and after pregnancy may be one of the causes of depression by altering inflammatory cytokines (Corwin et al., 2003). Some studies have shown that health problems such as anemia, IDA in particular, are associated with the development and management of depression (Vahdat et al., 2007; Chen et al., 2013; Yilmaz et al., 2017). In a study conducted with the EPDS, Beard et al., (2005) showed that there is a strong correlation between a pregnant woman's iron level and their depression, stress, and cognitive function scores in the postpartum period. In a similar study, Corwin et al., (2003) found that women with low hemoglobin levels in the first week after birth had a higher risk of developing postpartum depression. Another study, showed that if serum ferritin was about 1 µg, the risk of PPD would increase by 3.98 times (Albacar et al., 2011). Yilmaz et al., (2017) found that the total EPDS score was significantly higher in anemic 3rd-trimester pregnant women anemic group compared with the non-anemic group. A similar study also has shown that iron supplementation may improve symptoms of depression (Murray-Kolb and Beard 2007).

Despite the links between iron deficiency and depression, the number of studies examining the relationship between peripartum iron deficiency and depression is few in the literature, and limited number of studies have been done in Turkey. Anemia, which is common in pregnant women, is a prevalent healthcare problem worldwide, including in Turkey. IDA is the most common type of anemia during the second and third trimesters and is a common complication of pregnancy (Mei et al., 2011; Vural Ozcan and

Sancı, 2016). In Turkey, IDA affects 40% of pregnant women Turkey (Demir Kocaman and Dilek, 2011). Cıtlı et al., (2014), in Turkey, the prevalence of iron deficiency in pregnant women in 1, 2 and 3 trimesters reported 22.0%, 27.5%, and 22.4%, respectively. Iron sufficiency is essential for oxygen delivery to the maternal-placental-fetal unit to support the increased oxygen consumption demand of pregnancy. The major reasons to maintain an iron sufficient state during pregnancy are to protect the health of the mother, improve pregnancy outcomes and foster fetal development (Georgieff, 2020).

The level of anemia during pregnancy varies based on preexisting iron levels and prenatal iron support, and it can be affected by the pregnant mother's eating habits. As the oxygen supplied to tissues decreases during anemia, vital events where oxygen is used—such as enzyme synthesis, protein synthesis, etc.—cannot take place; disorders in neurotransmitter and hormonal systems may develop, which can lead to the emergence of depression (Kim and Wessling-Resnick 2015; Georgieff, 2020). Nutritional deficiencies related to iron deficiency anemia may play a role in disrupting the function of neurotransmitters during pregnancy (Dennis and Ross 2006; Georgieff, 2020). Because IDA is common in Turkish pregnancies and because it may play an important role in the pathogenesis, course, and management of depression, it is vital to understand the relationship between iron levels and depression during pregnancy (Wisner et al., 2013).

Our study aims to evaluate whether IDA in pregnancy is associated with of risk depression during pregnancy.

Methods

Study design: Study is a comparative study. The study was completed with pregnant women matching the inclusion criteria who applied at the Pregnancy Clinic of University Medical Hospital in the central Anatolian city of Turkey. The study was evaluated and approved by the local ethics committee. The study was approved by the Medical Research Ethics Committee of Local (approval no. 2014-06/01). All participants gave their written, informed consent at the hospital interview, and their written consent was confirmed verbally.

Participants: The sample size was calculated as 408 pregnant women in order to provide 95% confidence and a margin of error from 5–20%

(Fleiss Levin and Paik, 2003). Every fifth patient who applied to the outpatient clinic between August 2014 and January 2015 was invited to the study and asked for routine blood tests to be used in the study. During the specified period, researchers interviewed a total of 772 pregnant women. Eligible participants were pregnant women 18 years and older with a single pregnancy, performing prenatal care visits and blood tests. Participants had to meet the following exclusion criteria:

- To have pre-pregnancy anemia
- To have surgical intervention or bleeding during pregnancy
- To have anemia due to causes other than iron deficiency
- To have iron support during pregnancy
- To have thyroid diseases
- To have hereditary erythrocyte diseases, like thalassemia, or hemoglobin structure disruption
- To have depression before pregnancy and using antidepressants
- To have malignancies
- To smoking, alcohol, or substance abuse
- To have active infections
- To have systemic diseases such as diabetes mellitus, hypertension (including pre-eclampsia or eclampsia), or hyperemesis gravidarum (eclampsia)
- No pregnancy must have been preplanned

Of the 772 women interviewed, 98 did not agree to participate, 148 did match the exclusion criteria, 64 did not perform the blood tests, and 54 did not fill the questionnaires correctly. These women were excluded from the study, leaving 408 pregnant women who met the criteria and agreed to participate.

EPDS and personal information form were applied to pregnant women after the blood count was completed. According to the EPDS results, pregnant women who had depressive symptoms and were willing to treat were referred to psychiatry. Counseling was provided by a physician for pregnant women who were anemic.

Data collection tools: Researchers recorded sociodemographic information for each participant, including obstetric information (such as gestational week and number of pregnancies) and variables such as hematological parameters (complete blood count, iron, iron-binding capacity, serum transferrin saturation, folate and ferritin).

Laboratory Investigations: Blood samples were taken, with the laboratory requests being made by

the physician after having explained the reason for the blood samples to the participant. Venous blood samples were taken into hormone tubes containing EDTA hemogram and gel. Hemogram examination was performed with a Coulter LH 780 hematology analyzer. Folic acid was measured with a DxC 800. The results were recorded in data form. The Centers for Disease Control and Prevention (CDC) define IDA during pregnancy as when the hemoglobin (hb) level is above 11 g/dL during the first and third trimesters and above 10.5 g/dL in the second trimester (CDC, 1989). This study used the CDC's criteria to determine whether a participant had IDA.

The Edinburgh Postpartum Depression Scale:

This scale was developed by Cox Holden and Sagovsky, in 1987. The scale was adapted to Turkish in 1996 by Engindeniz Kuzey and Kultur. The EPDS consists of 10 questions, each of which contributes from zero to three points. Higher scores indicate more severe depression symptoms, and scores of 12 or higher indicate a high likelihood of depression. The Cronbach alpha coefficient of the EPDS is 0.79. In our study, the Cronbach alpha coefficient was found to be 0.82, suggesting that the scale has a good reliability coefficient.

Statistical analysis: Statistical analysis was performed with SPSS Statistics 17.0. The mean, standard deviation, and frequency were reported as descriptive statistics. The relationship between continuous variables was examined using Pearson's correlation analysis. The difference in the distribution of individuals with and without depression and those with and without IDA was examined using a chi-squared test. Analysis of variance was used to assess whether there was any difference in hematologic parameters and psychiatric-scale scores between trimesters. Post-hoc comparisons for significant variables were made with the Bonferroni test for homogeneous variances and the Tamhane test for inhomogeneous variances. The homogeneity of variances was assessed by the homogeneity test of the Levene variances. In statistical tests, p values below 0.05 were considered significant.

Results

Characteristics of the pregnant women

Table 1 shows the descriptive characteristics of pregnant women with and without anemia in pregnancy. At the end of the measurements the subjects were divided into two groups according to presence of IDA; IDA group n=53 and non-IDA

group n=355. IDA was detected in 53 participants (13%) and not detected in 355 participants (87%). There was no statistically significant difference in terms of age, education status, marital status, and pregnancy numbers for those with and without IDA in each trimester. IDA was detected in 20 participants (11.3%) in their second trimester and 25 participants (16.4%) in their third trimester. IDA was detected in 46 participants (13.7%) and not detected in 289 participants (86.3%) of those with anemia symptoms. The mean weeks of pregnancy was 24.37 ± 9.28 . The mean for those with IDA was 25.76 ± 8.74 compared to those without IDA at 24.15 ± 9.35 .

Symptoms of anemia were compared between groups (Table 2). There was a significant difference between these groups with respect to frequency of fatigue ($\chi^2 = 5.69$, $p = 0.017$), dizziness ($\chi^2 = 6.39$, $p = 0.012$), palpitation and breathlessness ($\chi^2 = 4.66$, $p = 0.031$), and pica ($\chi^2 = 9.76$, $p = 0.001$). These symptoms were significantly more common in the IDA group than in the non-IDA group.

Depression states and IDA of pregnant women

There was no difference in EPDS scores between those with IDA and those without IDA (for without IDA group ($t = -1.136$, $p = 0.257$). In our study, 18 (%34) pregnant scored ≥ 12 points which is considered the cutoff value for depression risk on the EPDS, for IDA group. A statistically no

significant difference was found in terms of IDA frequency, but the p value was at the trend level ($\chi^2 = 3.12$, $p = 0.077$) (Table 3).

EPDS total score averages were compared according to trimesters of pregnant women with and without IDA (Table 4). The chi-squared test was used to investigate whether there was a difference in the frequency of depression for anemic and non-anemic women based on their trimester. It was found that depression frequency increased in patients who had anemia and were in their second trimester ($\chi^2 = 7.183$, $p = 0.007$, odds ratio = 3.49, 95%-confidence interval = 1.34–9.05). There was no difference in the frequency of depression between the anemic and non-anemic groups in other trimesters. Also, correlation analysis showed no correlation between depression scores and anemia of pregnant women ($r=0.056$, $p=0.257$).

Hemoglobin, mean erythrocyte volume, hematocrit, serum iron, iron-binding capacity, transferrin saturation, and EPDS scores were compared between trimesters (Table 5). Iron-binding capacity varied statistically significantly between groups ($F(2,344) = 27.22$, $p < 0.001$). Hemoglobin ($p = 0.116$) and hematocrit ($p = 0.055$) were not significantly different but were at trend-level differences. Hemoglobin and hematocrit levels were lower in 2 nd trimester than in other trimesters.

Table 1. Descriptive characteristics of pregnant with and without iron deficiency anemia in pregnancy (n=408)

Characteristics	With IDA** (n=53)		Without IDA (n=355)		Test value t^* / χ^2	p
	n	%	n	%		
Age	27.28+4.77		27.01+4.59		-0.41	0.683
Education						
Primary school	6	14.0	37	86.0	0.831	0.842
Middle school	15	14.9	86	85.1		
High school	23	12.9	155	87.1		
College	9	10.5	77	89.5		

Income state						
1000-1500 TL	26	49.1	229	64.5		
1500-3000 TL	26	49.1	113	31.8	6.201	0.045
>3000 TL	1	1.9	13	3.7		
Marriage Duration						
	5.15+4.70		5.05+4.29		-0.16	0.874
Number of pregnancies						
	1.85+0.74		1.89+1.05		0.29	0.770
Trimester						
1st trimester	8	10.1	71	89.9		
2nt trimester	20	11.3	157	88.7	2.628	0.269
3rd trimester	25	16.4	127	83.6		

*t test, Chi-square testi χ^2 : chi-square, **IDA: Iron Deficiency Anemia

Table 2. Distribution of symptoms associated with anemia according to anemia status in pregnancy (n=408)

	IDA				Test value* χ^2	p
	without IDA (n=355)		with IDA (n=53)			
	n	%	n	%		
Anemia Symptoms	289	86.3	46	86.7	0.91	0.340
Fatigue	207	58.3	40	75.5	5.69	0.017
Tiredness	234	65.9	33	62.3	0.27	0.602
Dizziness	100	28.2	24	45.3	6.39	0.012
Amnesia	118	33.2	21	39.6	0.84	0.360
Palpitation breathlessness	114	32.1	25	47.2	4.66	0.031
Pica	19	5.4	9	17.0	9.76	0.002

* χ^2 = chi-square

Table 3. Comparison of depression scores of groups with and without iron deficiency anemia (n=408)

	with IDA (n=53)	without IDA (n=355)	Test value* t / χ^2	p
EPDS**	8.90 ± 4.90	8.05 ± 5.08	-1.14	0.257
EPDS	<12 points 35 (66.0 %)	274 (77.2%)	3.12	0.077
	≥12 points 18 (34.0 %)	81 (22.8%)		

*t test, Chi square test, χ^2 : Chi square, EPDS**: Edinburgh Postpartum Depression Scale

Table 4. Comparison of the EPDS total point averages by cutoff point according to trimesters with and without IDA (n=408)

		Anemia						* χ^2	p	
		with IDA		without IDA		Total				
		n	%	n	%	n	%			
1st trimester	EPDS**	<12	56	78.9	5	62.5	61	77.2	1.096	0.295
		≥12	15	21.1	3	37.5	18	22.8		
		Total	71	100.0	8	100.0	79	100.0		
2nd trimester	EPDS	<12	122	77.7	10	50.0	132	74.6	7.183	0.007
		≥12	35	22.3	10	50.0	45	25.4		
		Total	157	100.0	20	100.0	177	100.0		
3rd trimester	EPDS	<12	96	75.6	20	80.0	116	76.3	0.225	0.635
		≥12	31	24.4	5	20.0	36	23.7		
		Total	127	100.0	25	100.0	152	100.0		

*Chi square test. χ^2 : Chi square, **EPDS: Edinburgh Postpartum Depression Scale

Table 5. Comparison of hematologic values and depression scores between trimesters

	1st Trimester (n=79)	2nd Trimester (n=177)	3rd Trimester (n=152)	Test value F	p
Hemoglobin	12.28±1.26	11.98±0.94	12.12±1.23	2.17	0.116
Hematocrit	36.86±3.37	35.99±2.80	36.67±3.37	2.93	0.055
MCV	85.67±7.78	87.82±6.68	87.68±7.74	2.60	0.076
Serum ferritin levels	79.97±58.40	78.73±46.30	77.11±46.69	0.076	0.927
Iron binding capacity	445.94±110.28	488.24±86.10	545.88±90.04	27.22	<0.001
Transferrin saturation	17.88±9.79	16.83±10.45	15.06±10.20	1.84	0.160
Folat	13.41±4.54	12.89±4.63	13.28±5.03	0.381	0.684
EPDS	7.62±5.38	8.27±5.06	8.34±4.90	0.581	0.560

ANOVA. MCV Mean erythrocyte volume, EPDS: Edinburgh Postpartum Depression Scale. Post-hoc comparison of iron binding capacity: 1st Trimester <2nd Trimester, $p = 0.005$, 1st Trimester <3rd Trimester, $p < 0.001$; 2nd Trimester <3rd Trimester, $p < 0.001$.

Discussion

According to our knowledge in our country, a study investigating the relationship between anemia and depression was found only in third trimester pregnant women. No research has examined comparing particularly trimesters the association between iron deficiency anemia and perinatal depression in the Turkish pregnant population. Therefore, this study is pioneering for our country. In this study, possible depression was found in about a quarter of pregnant mothers, especially those in the second trimester where the frequency of depression increased, and IDA could be an important risk factor for the progress of in pregnancy and postpartum in depression.

In Turkey, the rate of depression during pregnancy varies between 5 and 51%, depending on the study

and the region (Karacam and Ancel 2009; Copoglu Kokacya and Demircan, 2015; Yilmaz and Gulumser, 2015). Methodological differences between studies and socioeconomic differences between regions may be the cause of this wide variance. In a systematic review, the prevalence of depression in pregnancy was reported as 7.4%, 12.8%, and 12% in the first, second, and third trimesters, respectively (Gavin et al., 2015). In a study conducted in Turkey, it was reported that depression was seen at the rate of 22% in the first trimester, 32% in the second trimester, and 36% in the third trimester (Karatayli et al., 2010). In similar studies conducted in other countries, depression during pregnancy occurred at rates of 16% to 51.4% in the first trimester, 5.7% to 20.4% in the second trimester, and 4.9% to 15% in the

third trimester (Andersson et al., 2003; Marcus et al., 2003).

In Turkey, studies using the Beck Depression Inventory showed rates of depressive symptoms in pregnancy at 27.3% (Karacam and Ancel, 2009). In a study using the EPDS, the prevalence of depressive symptoms in pregnancy was 28.6% (Golbasi Kelleci and Kisacik, 2010). In another study, the depression rate reported using the EPDS was between 11.2% and 17% (Karatayli et al., 2010). Yilmaz et al., (2017) found as 25.3% the frequency of depression in 3rd trimester pregnant women.

In our study, the depression rate all of pregnant women calculated with the EPDS was 24.3%. The rate of depression we found is consistent with the literature. In some of the studies cited above, depression and anxiety symptoms were found to be more frequent in the first and third trimesters than in the second trimester. In this study, the prevalence of depression was 22.8% in the first trimester, 25.4% in the second trimester, and 23.7% in the third trimester. Depression rates in this study were higher than other studies done using the EPDS.

Iron deficiency may occur due to increased need and inadequate compensation of iron losses during pregnancy. The World Health Organization has estimated the prevalence of IDA in pregnant women to be between 14% and 51% in developed and developing countries, respectively. Anemia prevalence in pregnant women in Turkey is 40.2% which is defined as a severe public health problem (WHO, 2008).

Demir Kocaman and Dilek, (2011), determined iron deficiency anemia rates according to trimesters, as 26%, 33.5% and 53%, respectively. The frequency of IDA in our study group was found as 13.0%. The lower frequency IDA in our study, may be due to that the hospital where the study was done, is located in a developed city of Turkey and to take place in a relatively better socio-economic level. It may also depend on the low sample size.

It is known that there is a relationship between iron deficiency anemia and mood disorders or maternal mental status (Corwin et al., 2003; Leung and Kaplan, 2009). An inadequate intake of iron can cause hypoxia to develop due to a decrease in oxygen in tissues. As a result, vital events such as enzyme synthesis and protein synthesis, especially when oxygen is needed, cannot take place. It is

also thought that nutritional disorders in pregnancy provide a basis for depression by affecting neurotransmitter and hormonal systems independently (Bodnar and Wisner, 2005). Symptoms such as tiredness, nervousness, fatigue, and concentration impairment caused by anemia may also contribute to depressive symptoms (Beard et al., 2005; Leigh and Milgrom, 2008).

Studies have shown that iron deficiency causes an increase in postpartum-depression symptoms. Beard et al., (2005) found a strong association between iron levels and depression, stress, and cognitive functions in South African mothers during the postpartum period. They also found high EPDS scores. found that women with low hemoglobin levels in the first week Corwin Murray-Kolb and Beard (2003) after birth had a higher risk of developing postpartum depression. By contrast, a study conducted in China found no relationship between iron deficiency anemia and postpartum depression (Leung and Kaplan, 2009). Contrary to studies in the literature regarding IDA increasing the risk of postpartum depression, the studies on the contribution of IDA to peripartum depression are very few in the international literature, (Corwin Murray-Kolb and Beard (2003); Yilmaz et al., 2017; Dama et al., 2018), and no studies have been found comparing particularly trimesters the association between iron deficiency anemia and perinatal depression in Turkish literature. A study investigating the relationship between anemia and depression was found only in third trimester pregnant women. Yilmaz et al., (2017) found that total EPDS score of pregnant women with low hemoglobin levels in third trimester was significantly higher in the anemic group compared with non-anemic group. Dama et al., (2018) found that, in pregnant women in the second or third trimester, a link exists between IDA and prenatal depression; this study is the only one in the literature that is similar to our study. Similarly, in our study, we found that the frequency of depression increased in pregnant women with IDA and in the second trimester. Our findings that IDA could be an important risk factor for the progress of peripartum depression is novel.

It is important to prevent and control IDA as it can lead to physical symptoms and depression. During the medical evaluation of a pregnant woman, it may be useful to evaluate psychosocial factors in addition to the physical factors and risk factors that may cause IDA. Iron supplementation during pregnancy is an effective approach to control IDA. Women's increased awareness of nutrition during

the pregnancy period may not be capitalized on by health care providers. The role of midwives in nutrition education during pregnancy is being increasingly recognized. Midwives were reported to share belief in the importance of nutrition during pregnancy and the significant role they should play in educating women about nutrition (Arrish Yeatman and Williamson, 2014).

In regions where anemia is a serious public health problem in pregnant women, WHO recommends an average of 60 mg of element daily iron supplementation (WHO, 2017). A national iron-supplementation program for pregnant women was implemented in Turkey in 2007. Iron supplementation is intended to be routine in Turkish prenatal care. However, there is not enough awareness or evaluation of common mental disorders in Turkey's primary healthcare. The results of the present study indicate that there is a need to improve the quality of primary healthcare for pregnant women during prenatal care.

One of the limitations of this study is the fact that the EPDS is a self-assessment scale. For a more reliable diagnosis, psychiatric examination may be more useful because of the contribution of anemia symptoms. Another limitation is the fact that the study sample was chosen from patients who applied to the hospital, making it difficult to generalize to patients who do not or cannot choose primary healthcare.

Conclusion: The literature includes limited number of similar studies conducted by the same measuring instruments with the present study. The present study is one from the first to assess the relationship between according to trimesters iron deficiency anemia and depression during pregnancy in Turkey. In this study, possible depression was determined in about a quarter of pregnant women, especially those in the second trimester where this rate occurred more frequently. In the second trimester, the rate of depression in the anemic group was found to increase. IDA could, therefore, be an important risk factor for the progress of peripartum depression. However, hemoglobin and hematocrit levels of pregnant women were lower in the second trimester than in other trimesters. Pregnancies are currently evaluated in terms of iron deficiency, but they should also be evaluated in terms of depressive symptoms. Nurses and midwives have an important role to play in educating pregnant women especially in iron

deficiency anemia about nutrition during pregnancy. The nurses and midwives should assess nutritional status as a changeable risk factor, must do the necessary nutrition training, watch and follow carefully.

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