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Original Article

Impact of anemia on the six-month trend of anxiety and depression in women with threatened abortion: A case-control retrospective cohort study

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Abstract

Background: Anemia in pregnancy is associated with psychiatric symptoms and poor psychiatric symptoms, this study investigates the 6-month trends of anxiety and birth outcomes. Considering the controversies surrounding the impact of anemia on psychiatric symptoms**,** this study investigates the 6-month trends of anxiety and depression in anemic pregnant women with threatened abortion (TA).

Methods: A case-control retrospective cohort study conducted among 282 participants who enrolled in a registry of pregnant women with TA in Babol city from December 2022 to October 2023. Fifty individuals with anemia (hemoglobin < 11 g/dL) who were matched with 50 without anemia based on age, pregnancies, education, and gestational age, were included. The BSI-18 (Brief Symptom Inventory) was used to assess depression, anxiety, and psychological distress at the beginning, three and six-month follow-ups.

Results: The prevalence of anemia among women diagnosed with TA was found to be 17.7%. At the beginning, compared to normal individuals, anemic women had higher rates of depression (32% vs. 14%), anxiety (34% vs. 22%), and psychological distress (66% vs. 48%). Moreover, at 3- and 6-month follow-ups, the frequency of psychiatric symptoms in anemic women was significantly higher. The Generalized Estimating Equations model showed that although both groups had a decreasing trend of frequency anemic women experience a slower rate of decrease in psychiatric symptoms compared to non-anemic women.

Conclusion: Anemia in women with TA is associated with high rates of depression, anxiety, and psychological distress, as well as a slow recovery rate.

Keywords: Anemia; Threatened abortion; Depression; Anxiety; Psychological distress.

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At the first prenatal visit, hemoglobin levels are routinely measured, and tests for anemia are routinely carried out in pregnant women for general health assessment and diagnosis. According to the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), the diagnosis of anemia during pregnancy is confirmed when hemoglobin levels decrease to below 11 g/dl (1). Women of childbearing age are at higher risk for anemia due to menstruation, contraception, and pregnancy (2). Anemia is a major health problem affecting 25 to 50 percent of the world's population and affects almost 50 percent of pregnant women (3). A meta-analysis conducted in 2022 showed that the overall prevalence of anemia in pregnant women was 36.8% (95% CI: 31.5-42.4%) (4). Anemia can complicate pregnancy and may lead to complications in delivery (2). Anemia increases the risk of hypertension, diabetes, placental separation, and chorioamnionitis in pregnant women. Moreover, pregnant women with anemia may need blood transfusions and hospitalization in intensive care units (5).

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Besides the adverse outcomes of pregnancy, anemia can have mental health consequences for mothers during pregnancy or after delivery (6-8). One study demonstrated that during pregnancy, anxiety has a significant relationship with anemia (9). The evidence regarding the association of anemia with depression and anxiety in pregnant women is contradictory. In a study conducted in Korea in 2022, involving 4,067 pregnant women, the occurrence of anxiety and depression during pregnancy did not show a significant difference between individuals with and without anemia in the first trimester. However, anxiety and depression after childbirth were significantly higher in participants with anemia compared to those without anemia (10).

On the other hand, the results of a meta-analysis indicated a significant association between anemia during pregnancy and an increased risk of pregnancy and postpartum depression (11). Although pregnancy exposes women to high levels of psychological distress, the risk of TA, as a traumatic experience, increases psychological complications (12, 13). The uncertain pregnancy period in TA can increase the psychological distress of pregnant women (14) with adverse psychological outcomes such as anxiety, depression, post-traumatic stress disorder, and possibly suicide (15). In a study by Zhu et al. (2018), women with TA were significantly more exposed to depressive symptoms and anxiety compared to women without TA (16).

The prevalence of anemia in pregnancy is estimated at 14% in developed countries and 51% in developing countries (17). Therefore, the risk of abortion and anemia can add to anxiety (18), and these symptoms persist long after abortion (19). Although there are studies on the relationship between anemia and depression, this study is innovative in several ways. Firstly, to our knowledge, the relationship between anemia, depression and anxiety in pregnant women with threatened abortion has not been investigated. Secondly, the impact of anemia on the trend of depression and anxiety has not been considered in previous studies. Thus, considering the high prevalence of anemia in pregnancy with TA, the contradictory literature on the relationship between pregnancy anemia and psychological adverse outcomes, and the paucity of studies in this area, this retrospective cohort study was designed to investigate the frequency of psychiatric symptoms including depression, anxiety, and psychological distress in pregnant women with anemia during six months. Moreover, it aimed to assess alternations in psychiatric symptoms of anemic women with TA compared to non-anemic women.

Methods

The current case-control retrospective cohort study was part of a large longitudinal study of women with TA who enrolled at Babol Pregnancy Metal Health Registry (http://register.mubabol.ac.ir) (20). The sampling of TA patients was performed using the total population sampling method at Rouhani Hospital (Babol, Iran) from December 2022 to October 2023. During this period, 282 pregnant women with TA were included in the study. Inclusion criteria included the diagnosis of intrauterine pregnancy (based on ultrasound), gestational age under 20 weeks, bleeding and spotting, single pregnancy, at least primary school education, and having an internet-connected smartphone. Patients with severe psychiatric disorders such as bipolar or psychotic diseases, suicidal ideas, vaginal bleeding due to other causes, missed or unavoidable abortion, as well as those with an ectopic pregnancy diagnosis and previous history of anemia and blood problems, were excluded. The diagnosis of threatened abortion was based on the clinical examination of the obstetrician and gynecologist.

In this case-control retrospective cohort study, which was conducted to investigate depression and anxiety symptoms in two groups with and without anemia, the recorded data of 283 patients with TA was extracted and analyzed. The study was approved by the Ethics Committee of Babol University of Medical Sciences (IR.MUBABOL.REC.1401.158). First, we determined the population of patients with anemia who had hemoglobin levels of less than 11 g/dL. This group included 50 out of 282 participants. As the control group, 50 pregnant women with hemoglobin levels above 11, similar to the anemic group in terms of age, education, gestational age, and number of pregnancies, were selected.

For collecting data on women with TA, the principal researcher (the first author) selected the eligible women in the clinic and gynecological inpatient departments, and, after explaining the study, those who consented to participate were asked a complete demographic questionnaire including age, education, the number of pregnancies, and the gestational age. At the beginning of the study, 3 cc blood (EDTA) was collected from all the women for routine tests and measurement of hemoglobin levels. The samples were sent to the laboratory of Ayatollah Rouhani Hospital and tested using a cell counter. In order to assess depression, anxiety, and psychological distress symptoms, all patients answered the BSI-18 questionnaire three times: upon study entry and three and six months later.

Patients completed the BSI-18 questionnaire in the hospital on a paper form at the beginning of the study. The researcher informed the patients that they would receive a link to complete the BSI-18 questionnaire on their phones after three and six months. BSI-18 is an 18-item questionnaire that is scored on a five-point Likert scale [0=not at all, 1=slightly, 2=moderately, 3=completely, 4=severely].

This scale evaluates depression, anxiety, and somatization from psychological distress (total score) and overall psychological distress with GSI (Global Severity Index). The score of each sub-component is 0 to 24, and the total score is 0 to 72. In women, the cut-off point is ≥4 for depression, ≥6 for anxiety, and ≥5 for somatization. Also, the cut point of the total score for women is ≥13 (21). In this study, the authentic Persian version was used. The reliability coefficients and retest coefficients were 0.90 and 0.81, respectively (22).

Statistical analyses: Statistical analysis was conducted using SPSS software version 22. Descriptive statistics were presented as mean±standard deviation and percentage. Categorical variables were compared using chi-square tests. A Cochrane-Armitage test was used to compare the frequency of psychological distress in women at different times. To evaluate changes in depression and psychological distress symptoms in women with and without anemia complications, the GEE (Binary logistic Working Correlation Matrix, Unstructured) test was used at three measurement times. A value of P≤0.05 was used as the threshold for determining statistical significance.

Results

A total of 50 out of 284 pregnant women had hemoglobin levels below 11 g/dL, and therefore, the frequency of anemia among women with TA was 17.7%. Demographic characteristics of 100 participants in two groups of pregnant women with TA (50 with anemia and 50 without anemia) are presented in table 1. The mean age of all participants was 32.2±7.34 years, and 54% had higher education at the university level. 32% of pregnant women were experiencing their first pregnancy, 25% were having their second, 42% were having their third, and 26% were having their fourth or more. There were no significant differences between the anemic and non-anemic groups in terms of age, education, and number of pregnancies. Additionally, the average gestational age was not significantly different between the two groups (p<0.005). Table 2 compares the prevalence of depression, anxiety, and psychological distress symptoms between two groups of pregnant women with and without anemia. The study analyzed results at three-time points: baseline, 3-month, and 6-month follow-ups.

Table 1. Demographic characteristics in a population study (n=100)

Variables	With anemia N (%)	Without anemia N (%)	P-value
Age (years)			
≤ 35	30 (60)	29 (58)	0.841
>35	20 (40)	21 (42)	
Education			
Under diploma	24 (48)	22 (44)	0.692
University	26 (52)	28 (56)	
Gravid			
G1	15 (30)	17 (34)	
G2	10 (20)	15 (30)	0.529
G3	17 (34)	8 (16)	
G≥4	8 (16)	10 (20)	
Gestational Age (weeks) (Mean±SD)	12.24±5.69	11.66±4.91	0.587

Data are presented as mean±SD or n (%)

Table 2 compares the prevalence of depression, anxiety, and psychological distress symptoms between two groups of pregnant women with and without anemia. The study analyzed results at three-time points: baseline, 3-month, and 6-month follow-ups. The chi-square test was used to assess the trends of depression, anxiety, and psychological distress scores between the two groups at any time. The BSI-18 psychological distress frequency index showed a significant difference at all three-time points (T1, T2, T3). In other words, the frequency of psychological distress in the group

with anemia was significantly higher at the time of entering the study and at the three-month and six-month follow-up compared to the group without anemia.

Two groups of women with TA (with and without anemia) were analyzed separately for changes in psychological distress, depression, and anxiety symptoms using the Cochrane-Armitage test. The results showed that in both anemia and non-anemia groups, the frequency of depression and psychological distress and all its sub-components (anxiety, somatization, and GSI) decreased from the time of entering the study to the next three- and six-month follow-up points. Intergroup comparison of changes in depression, anxiety, and psychological distress symptoms in women with and without anemia complications during three measurement times was conducted by the GEE (Generalized Estimating Equations) test. In pregnant women with anemia, the prevalence of depression symptoms (32% vs. 14%), anxiety symptoms (34% vs. 22%), somatization (36% vs. 30%), and GSI (66% vs. 48%) was higher than those without anemia.

Moreover, all these subgroups had higher frequencies in the anemia group at the beginning of admission. Besides, the total psychological distress index (P=0.002) and all sub-components, depression symptoms (P=0.015), anxiety symptoms (P<0.001), somatization (P=0.041), and GSI (P=0.015) in pregnant women with anemia were significantly lower than women without anemia. All these differences were statistically significant.

Table 2. Comparison of the trend of depression and anxiety symptoms in two groups of pregnant women with and without anemia (n=100)

Time/Group	With Anemia N (%) (N=50)		Without Anemia N (%) (N=50)		*P-value Between Groups each time
	YES	NO	YES	NO	
Anxiety symptoms					
T1					
T2	17 (34)	33 (66)	11 (22)	39 (78)	0.181
T3	5 (10)	45 (90)	2 (4)	48 (96)	0.240
	4 (8)	46 (92)	2 (4)	48 (96)	0.410
****P-value (Within groups)**	0.001		<0.001		
Depressive symptoms					
T1	16 (32)	34 (68)	7 (14)	43 (86)	0.023
T2	14 (28)	36 (72)	6 (12)	44 (88)	0.046
T3	13 (26)	37 (74)	9 (18)	41 (82)	0.334
P-value	0.508		0.573		
Somatization					
T1	18 (36)	32 (64)	15 (30)	35 (70)	0.523
T2	5 (10)	45 (90)	2 (4)	48 (96)	0.240
T3	9 (18)	41 (82)	2 (4)	48 (96)	0.025
P-value	0.029		<0.001		
Psychological distress (Total BSI-18)					
T1	19 (38)	31 (62)	7 (14)	43 (86)	0.006
T2	9 (18)	41 (82)	1 (2)	49 (98)	0.008
T3	6 (12)	44 (88)	1 (2)	49 (98)	0.050
P-value	0.002		0.012		
Psychological distress (GSI)					
T1	33 (66)	17 (34)	24 (48)	26 (52)	0.069
T2	15 (30)	35 (70)	8 (16)	42 (84)	0.096
T3	18(36)	32 (64)	9 (18)	41 (82)	0.043
P-value	0.003		0.001		

Cut-off scores: depression≥4, anxiety ≥6, somatization≥5, total BSI-18≥ 13, and GSI≥ 0.5. *: chi score, **: Cochrane- Armitage test.

Discussion

In this study, the frequency of anemia in women with TA was 17.7%. In a similar study, the prevalence of anemia in women with TA under 20 weeks of gestation was reported as 18% (23). The results of a meta-analysis study demonstrated that the overall prevalence of anemia in pregnant women was 36.8% (95% confidence interval: 31.5-42.4%) (4). In another study in Pakistan, the prevalence of pregnancy-related anemia was 57.7% (24). In certain societies, 80% of pregnant women are anemic, and those with a higher risk are from low socio-economic groups and teenagers (25). There are several reasons for the lower level of anemia in these women with TA in the study than in some studies. First, socioeconomic status is an important factor in the prevalence of anemia in the pregnant population. Many studies have highlighted the role of socio-cultural and economic factors and eating habits in the prevalence of anemia (18, 26-28). Second, the difference in the gestational age of our study population and other studies can be responsible for the difference in the prevalence of anemia in other studies. In our study population, there were women with threatened abortion with an average gestational age of approximately 12 weeks. There is evidence that gestational age and, as a result, the time of anemia assessment during pregnancy, are important factors in the prevalence of anemia. Since the blood in the third trimester of pregnancy is thinner than in the second and first trimesters, the prevalence of anemia in the third trimester is higher than at other times of pregnancy.

In the present study, the frequency of symptoms of depression, anxiety, and mental disorders in anemic pregnant women with threatened abortion was about 1.5 to 2 times higher than those without anemia. Also, in the three-month and six-month follow-ups, the frequency of symptoms of depression, anxiety, and psychological distress in anemic women was significantly higher than those without anemia. In a similar study, it has been shown that anemia during pregnancy is a major risk factor for developing anxiety (10). In another review study (2017), the role of anemia in pregnancy anxiety has been highlighted (29). Although the mechanism of anemia's effect on increasing the prevalence of psychological symptoms is not elucidated, several assumptions are plausible. First, anemia may cause depression symptoms such as fatigue, irritability, anxiety, apathy, and inability to concentrate by alternating myelination and metabolism of neurotransmitters (7). Second, anemia and depression or anxiety may have common predisposing factors, as evidence suggests that elevated levels of glucocorticoid hormones, secondary to acute or chronic stress, are associated with both depression and anemia. Also, high levels of circulating steroids can lead to a decrease in neurogenesis and disruption of neural plasticity, thereby generating depression symptoms by disrupting the emotional and cognitive functions of the brain (30).

In this study, in both groups, the frequency of symptoms of depression, anxiety, and psychological distress gradually decreased during three months and six months. Still, the rate of decrease was slower in the anemic group. In a similar study, Ahmed et al. (2019) investigated depression and anxiety symptoms during a five-year postpartum period. They observed that approximately 70% of women experienced low to very low anxiety symptoms during the follow-up period, and the symptoms decreased (31). Another study reported that depression peaked at 4-6 weeks postpartum and then decreased at six months postpartum, while anxiety gradually decreased from a linear pattern from pregnancy to six months postpartum (32). Regarding the severity and trends of symptoms, in a study titled “The Relationship between Depression and Anemia in Healthy Adults”, it was demonstrated that depressed participants were significantly more likely to have anemia compared to non-depressed participants, and the rate of anemia increased with the severity of depression. This indicates a dose-response relationship (30). Our findings align with those of another study on beta-thalassemia patients. In their study, people with anemia suffered from higher levels of depression and anxiety, experienced a significant deterioration in their mental health, and had a slower recovery process in improving their quality of life (33).

The present study has clinical applications for medicine internists, obstetrics, and gynecologists. Based on the findings of this study, physicians should consider psychiatric problems in addition to medical and obstetrics issues in the treatment of anemia in pregnant women. Anemia can have comorbidity through psychiatric complications and slow down the spontaneous recovery of psychiatric symptoms. In addition, it seems necessary to screen pregnant women with anemia for psychiatric symptoms, especially in those with TA, up to 6 months after the diagnosis of anemia.

Apart from its many clinical applications, this study had strengths and weaknesses. The most important strength of this study was that, for the first time in Iran, a cohort study compared the alternations in depression and anxiety symptoms in two groups of anemic and normal pregnant women. One of the weaknesses of this study was that the reporting period of the cohort was 6 months; therefore, future studies should conduct a longer follow-up of one year or more. Also, in this study, the process of evaluating

patients' mental symptoms was conducted with a questionnaire. Specialized clinical interview diagnostic tools are recommended to report psychiatric symptoms in future studies. Another limitation of this study was that the anemia type that may affect the trend of depression and anxiety was not investigated. It is suggested that further studies investigate the impact of the anemia type on the trend of depression and anxiety. Finally, in this study, only the symptoms of depression, anxiety, and psychological distress in anemic women with TA were discussed. It is recommended that in future cohort studies, women without serious medical problems should be evaluated with a comprehensive examination of psychiatric symptoms.

Anemia increases the frequency of depression, anxiety, and psychological distress in pregnant women with threatened abortion. Although symptoms of psychological distress decrease in three months and six months after the onset of TA symptoms in both groups of TA patients with and without anemia, anemic women experience a slower rate of decrease in psychiatric symptoms compared to non-anemic women. This study recommends that internal medicine and obstetrics specialists pay special attention to psychiatric problems in addition to medical interventions in the treatment of anemia in pregnant women.

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Ethics approval: This study was approved by the ethics committee of Babol University of Medical Sciences, Babol, Iran with code IR.MUBABOL.REC.1401.158. All patients signed the free and informed consent form of this study.

Conflict of interests: None declared by the authors.

Authors' contribution: All authors contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

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