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What is the best treatment for anemia in pregnant women in the third trimester: Ferric carboxymaltose or oral iron therapy?

Elif Ciler Eren[a,*], Yakup Karakurt[b], Sevil Sadri[c], Gamze Demirel[d]

[a] *Istanbul Medipol University, Faculty of Medicine, Department of Gynecology and Obstetrics, Istanbul, Türkiye*
[b] *Istanbul Medipol University, Faculty of Medicine, Department of Neonatology, Istanbul, Türkiye*
[c] *University of Health Sciences, Bursa City Hospital, Department of Hematology, Bursa, Türkiye*
[d] *Koc University, Faculty of Medicine, Department of Neonatology, Istanbul, Türkiye*

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Abstract

Aim: Iron deficiency anemia (IDA) is a significant health problem in pregnant women. We aimed to evaluate the effect of gestational IDA and to compare the results of iron therapy in pregnant women.

Materials and Methods: This retrospective cohort study of pregnant women in the third trimester analyzed the records of 63 women not taking any iron supplements, 70 women receiving intravenous ferric carboxymaltose therapy (FCM), and 73 pregnant women receiving oral iron therapy. It compared maternal and neonatal outcomes of the three groups.

Results: The mean age of the 206 pregnant women included in the study was 29.19±4.34 (19-44; min–max). Only 1% of anemic women received a blood transfusion in the postpartum period. There was no difference between the groups' mean age and gestational week. The median values of gravida and parity were the same in all 3 groups (Gravida=2, Parity=1). Maternal hemoglobin (Hb) value of the non-iron group was lower than that of the other groups ($p<0.001$). Although the mothers' Hb levels at birth were different, the newborns' Hb values were not affected ($p=0.547$). Neonatal height and weight were lower in the non-iron group than in the FCM and oral iron groups ($p=0.048$ and $p<0.001$, respectively). Neonatal head circumference, 1-minute Apgar, and 5-minute Apgar scores were similar in all three groups.

Conclusion: FCM is effective in pregnant women with IDA in late pregnancy and women undergoing this treatment deliver healthier newborns.

Introduction

During pregnancy, the need for iron increases significantly. Physiological changes in the mother, increasing demands of the fetus, and increased blood volume in the third trimester led to significant hematological changes [1,2]. IDA during pregnancy is a global health problem. It affects 6% to 30% of women in developed countries [3]. The prevalence of anemia in pregnant women in Türkiye has been reported to be 20% [4]. This condition is known to be associated with adverse physiological consequences for both the child and mother, including cardiovascular problems, decreased cognitive performance, decreased immune function, fatigue, and increased maternal depression, as well as preterm birth, low Apgar scores, fetal growth restriction, and neonatal infections in the child [5-8]. In addition, IDA has been associated with atonic postpartum hemorrhage after delivery and increases the need for peripartum red blood cell transfusions [9]. Anemia levels in pregnancy are considered as follows: In the first and third trimesters, Hb $<$ 11 g/dL, and in the second trimester, Hb $<$ 10.5 g/dL [10].

Oral iron is recommended as a first-line therapy due to its low cost and high efficacy [11]. However, it can often cause gastrointestinal side effects such as nausea, diarrhea, or vomiting [12,13]. Intravenous (IV) iron preparations are better for women who are unresponsive, incompatible with, or intolerant of oral iron [13,14]. For this reason, IV iron is increasingly recommended for pregnant women who have marked anemia or need rapid intervention [13]. Intravenous iron may bypass the risk of gastrointestinal side effects due to its route of administration [12]. IV iron supplementation reduces the need for postpartum blood transfusions, while ferric carboxymaltose (FCM) is a safe and effective alternative [15]. FCM is a dextran-free parenteral preparation that allows rapid administration of a

*Corresponding author:
Email address: dreliferen@hotmail.com (Elif Ciler Eren)

single weekly dose of iron.

In this study, we aimed to compare the neonatal and maternal outcomes of pregnant women who received anemia treatment through intravenous and oral iron with those of women whose anemia could not be corrected.

Materials and Methods

This retrospective cohort study was conducted with the approval of the Istanbul Medipol University Ethics Committee under the decision number E-10840098-722.02-2498.

This study included 212 pregnant women who applied to the obstetrics outpatient clinic of the same author between December 2019 and December 2020 and had anemia at the beginning of the third trimester (28 weeks and beyond). Hb < 11 g/dL was taken as the threshold for anemia. Four pregnant women with chronic diseases (diabetes mellitus, hypertension, cardiac disorders, etc.) and two pregnant women diagnosed with sickle cell anemia or thalassemia were excluded from the study. In addition, the study did not include pregnant women who had been receiving regular iron therapy since the beginning of their pregnancy and, pregnant women under 18 years of age. The first group consisted of 63 anemic pregnant women who did not want to take iron supplements, the second group consisted of 70 pregnant women whose anemia improved with FCM in the third trimester, and the third group consisted of 73 anemic pregnant women who regularly started taking oral iron in the last trimester.

Maternal age, gestational week at birth, prenatal hemogram parameters of pregnant women, gravida, parity, number of abortions, ectopic pregnancy, and type of delivery (Cesarean section (C/S) or vaginal) were recorded. Neonatal outcomes, birth weight, height, head circumference, 1-minute Apgar score, 5-minute Apgar score, and need for neonatal intensive care were recorded. In addition, baby cord blood was taken, and newborn hemogram values were checked. Neonatal and maternal outcomes of the three groups were compared.

Iron supplement protocols

Iron preparations of $^{+2}$ valent were preferred for oral iron treatment. Pregnant women with Hb levels below 9 received oral iron twice a day, while those with Hb levels between 9 and 11 received oral iron once a day. Pregnant women with Hb levels below 11 received FCM treatment in two doses, one week apart. According to the FCM protocol, the first dose of 500 mg in 150 ml saline was administered in 20 minutes and the second dose of 500 mg was administered one week later using the same procedure.

Statistical analysis

The NCSS (Number Cruncher Statistical System) 2007 software (Kaysville, Utah, USA) was used for statistical analysis by an expert. A power analysis was performed with G*Power software, version 3.1, to calculate the total sample size required to detect a newborn height effect of 0.36 with α=0.05 and power=0.8. Data were presented as mean and standard deviation (SD) or number of patients (%). The Shapiro–Wilk normality test was used to evaluate the distribution of variables. ANOVA test was used to compare continuous variables between three groups, and the student t test was used to compare two groups. Chi-square analysis was used to determine the relationship between categorical variables. The significance level was set at $p<0.05$.

Results

The mean age of the 206 pregnant women included in the study was 29.19±4.34 (19-44; min–max). The pregnant women received treatment for a minimum of five weeks and a maximum of twelve weeks. The median values of gravida and parity were the same in all three groups (Gravida=2, Parity=1). According to the mode of delivery, 112 women had a C/S. The most common cause of cesarean section was previous cesarean section (61.6%). There was no difference between the groups' mean age and gestational week at birth. The mother's Hb value at birth in the non-iron group was lower than that in the other groups (Table 1). The mothers' Hb values at birth in the oral iron group were significantly higher than those in the FCM and non-iron groups ($p=0.026$ and $p<0.0001$, respectively). Only 1% of anemic women received a blood transfusion in the postpartum period.

There was no difference in neonatal Hb values among all three groups. Neonatal height and weight values were lower in the non-iron group than in the FCM and oral iron groups. Newborn height did not differ between the FCM group and the oral iron group ($p=0.268$), but the birth weight of the newborn was higher in the oral iron group than in the FCM group ($p=0.034$). Although the newborn head circumference was higher in the group receiving iron treatment, no significant difference was observed ($p=0.128$). The 1-minute and 5-minute Apgar scores were similar in all three groups (Table 2). Three newborns in the FCM group, two in the oral iron group, and four in the non-iron group needed neonatal intensive care units.

Discussion

In the last months of pregnancy, when iron absorption is highest, successful treatment of iron deficiency anemia may prevent harm to both the mother and the child. This study demonstrated the efficacy of iron replacement therapy in the last trimester of pregnancy. FCM effectively increased Hb levels in pregnant women who could not take oral iron. However, we found that intravenous iron treatment was less successful than oral iron administration regarding Hb correction, although it is a shorter and more effective method. The main advantage of the IV forms is rapid recovery, but after 4-6 weeks, there is no difference between the oral and IV forms [6,16].

Numerous studies have shown that the incidence of preterm birth is higher in mothers with pregnancy IDA [17-20]. Allen et al. [21] suggested that gestational anemia increases corticotropin-releasing hormone (CRH) secretion by causing chronic tissue hypoxia. CRH regulates the onset of labor and high CRH has been associated with prematurity and preterm birth [22]. Low placental weight, an underweight baby, birth asphyxia, and stillbirths are

Table 1. The relationship between Non-iron, FCM, and Oral iron groups and the maternal outcomes.

	Non-iron	FCM	Oral iron	P value
	(N=63)	(N=70)	(N=73)	
Age*	29.3±4.6	28.8±4.1	29.3±4.3	0.832
Gestational Week at Birth*	38.48±1.43	38.19±1.46	38.19±1.46	0.426
Mother's Hb Value at Birth*	9.6±0.6	11.2±1.1	12.9±0.7	**<0.001**
Type of Delivery†				
C/S	28 (44.4)	47 (67)	37 (50.6)	**0.022**
Vaginal	35 (55.6)	23 (33)	36 (49.4)	

FCM= Ferric carboxymaltose, Hb= Hemoglobin, C/S= Cesarean section.

Values represent the number of patients (%) or mean± standard deviation unless stated otherwise. Boldface type indicates statistical significance.

*Analyzed using the chi-square test †Analyzed using the ANOVA test.

Table 2. Comparison of three different groups and the neonatal outcomes.

	Non-iron	FCM	Oral iron	P value
	(N=63)	(N=70)	(N=73)	
Neonatal Hb	18.2±1.9	18.7±1.7	18.4±1.9	0.547
Newborn Weight	3105.1±322.2	3440.7±340.1	3520.4±434.7	**<0.001**
Newborn Height	50.2±2.2	51.2±2.2	51.4±1.5	**0.048**
Newborn Head Circumference	34.5±0.7	35.6±0.5	36±0.8	0.128
1-Minute Apgar Score	8.6±0.5	8.6±0.5	8.7±0.6	0.164
5-Minute Apgar Score	9.7±0.4	9.6±0.5	9.8±0.6	0.076

FCM= Ferric carboxymaltose, Hb= Hemoglobin.

The values represent the mean±standard deviation. Boldface type indicates statistical significance.

Statistical analyses were performed by ANOVA.

among the adverse outcomes of maternal anemia in developing countries such as Bangladesh and Sudan [23-24]. However, this study did not find evidence suggesting that babies born to anemic mothers were more prone to complications such as preterm birth. In addition, although the mothers had different Hb levels at birth, it did not affect the Hb values of the newborns.

The prevalence of low-birth-weight infants ranges from 11.3% to 27% in anemic mothers [25]. Jung et al. [18] reported that low birth weight babies were observed twice more frequently in anemic pregnancies than in non-anemic pregnancies. Similarly, the present study found a significant positive association between maternal Hb level and low birth weight, consistent with previous studies [26]. In contrast, other studies did not find such association [20,27]. Another study in India reported that anemia was associated with preterm birth and low birth weight [28]. The height and weight of babies at birth can provide an idea about their size in adulthood. Correcting IDA in the mother can increase the chances of average birth weight and height.

Infants born to mothers with IDA may experience developmental delays. There is an increased risk of a low 1-minute Apgar score in infants of anemic women [18]. When iron therapy was administered to pregnant women, Apgar scores were found to be higher in newborns whose mothers received iron supplementation [3]. However, in our study, there was no correlation between Apgar scores and anemia. Although the mothers had different Hb levels at birth, it did not affect the Hb values of the newborns.

A study suggested that weight and head circumference, among anthropometric indicators of babies at birth are more likely to be influenced by maternal nutrition during pregnancy [29]. In the present study, neonatal height values of untreated anemic mothers showed significant differences between the oral iron and FCM groups. The neonatal height was lower in the untreated group than in the other groups. Although head circumference was lower in the non-iron group, there was no significant difference. Maternal diet may affect the baby's height, weight, and head circumference. According to Haugen et al. [30], maternal diet has a more negligible effect on the baby's height at birth than genetic and ethnic factors.

Anemia has been reported to increase maternal risks, such as C/S delivery, red blood cell transfusion, or death, and anemic mothers are more likely to be diagnosed with placental insufficiency or placental abruption [31-33]. In our study, the C/S delivery rate was higher in pregnant women treated with FCM. This was attributed to FCM group's high rate of previous C/S deliveries. We believe that this is not related to IDA.

The present study has some limitations, including its retrospective design, a small sample size of women, and including only the last trimester of pregnancy.

Conclusion

Anemia during pregnancy is associated with adverse effects on newborn and maternal life. Intravenous FCM is an important treatment modality for women in the late trimester or for pregnant women who cannot tolerate oral

therapy. It is a safe and quick method to raise iron levels in the third trimester. Prospective randomized studies should be conducted to determine the clinical impact of timely correction of iron levels on long-term maternal and neonatal outcomes.

Ethical approval

Istanbul Medipol University Ethics Committee approval was obtained (decision number: E-10840098-722.02-2498).

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