Comparison of the Anaemia and Transfusion Rates of Pregnant Women Treated with Intravenous *versus* Oral Iron in the Third Trimester

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ABSTRACT

Objective: To evaluate and compare the blood transfusion requirements during delivery in third-trimester pregnant women with iron deficiency anaemia (IDA) who were treated with intravenous (IV) ferric carboxymaltose (FCM) *versus* those treated with oral iron supplementation.

Study Design: Comparative study.

Place and Duration of the Study: Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkiye, from January 2017 to December 2022.

Methodology: Pregnant women with haemoglobin (Hb) levels <10 g/dL in their third trimester were included. One group (n = 50) received IV FCM, while the other group (n = 96) received oral iron therapy. Key outcome measures included Hb levels at delivery and the need for a postpartum blood transfusion. Inclusion criteria were third-trimester pregnancy with IDA, and exclusion criteria included haematological or chronic systemic diseases and high-risk pregnancies.

Results: The mean initial Hb levels in the third trimester of pregnancy in the FCM group and oral iron group were 8.31 ± 0.96 g/dL and 9.29 ± 1.20 g/dL, respectively (p <0.001). The mean Hb levels in the delivery room were 11.09 ± 1.38 and 9.44 ± 1.16 g/dL, respectively (p <0.001). The rates of postpartum erythrocyte transfusion requirement were 6% (n = 3) and 18.75% (n = 18), respectively (p = 0.037).

Conclusion: IV FCM administration to pregnant patients with IDA during the third trimester was found to be more effective than oral iron treatment in reducing blood transfusion rates.

Key Words: *Anaemia, Ferric carboxymaltose, Pregnancy, Iron deficiency, Intravenous iron.*

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INTRODUCTION

Anaemia is a global health problem that affects pregnant women.[1] Anaemia is the most common haematological disease encountered during pregnancy, affecting approximately 16% of pregnancies in the United States and 38% of pregnancies worldwide. It maintains a high prevalence rate (up to 62%) in many countries.[2] The World Health Organization (WHO) reported that in Turkiye, the incidence rate of anaemia among pregnant women was 28%.[3]

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The definition of anaemia in pregnancy changes with the trimester period as follows: A haemoglobin (Hb) level <11 g/dL or haematocrit (Hct) level <33% in the first and third trimesters and an Hb level <10.5 g/dL or Hct level <32% in the second trimester. In the postpartum period, anaemia is defined by the WHO as an Hb level <10 g/dL.[4,5]

Although anaemia in pregnancy has many causes, such as vitamin B12 and folate deficiencies, thalassaemia, inflammatory disorders, haemolysis, and blood loss, the most common cause is iron deficiency and the increased iron requirement during pregnancy due to the developing foetus and increased maternal blood volume during pregnancy.[6,7]

Anaemia in pregnancy can increase the risks of maternal and foetal morbidity and mortality, including preterm delivery and other adverse outcomes.[8] According to WHO data, anaemia is responsible for 40% of maternal deaths worldwide.[9,10] The maternal mortality rate escalates with the severity of iron deficiency anaemia (IDA). The factors that cause anaemia are associated with heightened incidence rates of cardiovascular failure, increased

susceptibility to haemorrhagic shock, increased infection rates, and compromised wound healing.[11] A correlation has been reported between low maternal Hb levels and adverse outcomes for neonates. Maternal Hb levels <9.0 g/dL especially increase the risks of preterm birth, intra-uterine growth retardation, and intra-uterine foetal death.[12] For this reason, pregnant women should be checked and treated for prepartum anaemia.

Oral and intravenous (IV) iron administration are the most preferred prophylaxis and treatment options. Oral iron preparations are recommended as the first choice of prophylaxis and treatment for anaemia in pregnancy owing to their low cost and easy accessibility. In cases in which oral iron cannot be tolerated and treatment response is inadequate, the second choice is to use IV iron.[13,14] IV iron is a safe and effective preparation for use during pregnancy. Intravenous administration of iron effectively elevates haemoglobin (Hb) levels within a relatively brief period, resulting in a reduction in hospital visits. Consequently, this intervention can be deemed cost-effective when considering its broader implication.[15]

This study intended to compare IV FCM and oral iron supplementation for treating third-trimester IDA. Despite baseline differences in haemoglobin levels and sample sizes, statistical controls were applied. Anaemia severity was classified to enhance result interpretation: Mild (Hb 10 – 10.9 g/dL), moderate (Hb 7 – 9.9 g/dL), and severe (Hb <7 g/dL).

The objective of this study was to evaluate and compare the effectiveness of IV FCM and oral iron supplementation in improving haemoglobin levels and reducing the need for blood transfusions during delivery in third-trimester pregnant women with IDA.

METHODOLOGY

In this retrospective comparative study, pregnant women in their third trimester (28 – 32 weeks) whose Hb levels were <10 g/dL and who were followed up in the outpatient maternity clinic of Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Istanbul, Turkiye, between January 2017 and December 2022 were selected. Pregnant women diagnosed with IDA and treated with IV FCM were included in one group (FCM group). Third-trimester pregnant women diagnosed with IDA who refused to take IV FCM and received oral iron therapy instead were included in the other group (oral iron group). This study was performed in line with the principles of the Declaration of Helsinki and approved by the Clinical Research Ethics Committee of the Health Sciences University Bakirkoy Dr. Sadi Konuk Training and Research Hospital (Approval Number: 2022-24-13). Informed consent was obtained from all participants.

The inclusion criteria for the study group were defined as pregnant participants who started anaemia treatment in the 32nd week of gestation, had an Hb level below 10 g/dL, had no haematological or chronic systemic disease, and had an uncomplicated pregnancy. The women who met the inclusion criteria for the control group (uncorrected anaemia at the time of delivery) were those with low-risk, singleton pregnancies, Hb levels less than 10 g/dL, and no thalassaemia or chronic illnesses. Participants with high-risk pregnancy, thalassaemia, haematological diseases, and chronic disease diagnoses were excluded from the study. Anaemia severity was classified as mild (Hb 10 – 10.9 g/dL), moderate (Hb 7 – 9.9 g/dL), and severe (Hb <7 g/dL).

Patients whose medical records were available in the hospital's electronic system were retrospectively evaluated. Significant differences in intrapartum and postpartum anaemia severity, blood transfusion requirement, hospitalisation duration, and complications between the two groups were examined. Evaluations were recorded in the third trimester (28 – 32 weeks) (visit 3), from the 38th week until the application for birth (visit 4), and in the first 24-hour postpartum. Demographic data and laboratory values (age, parity, education, first-admission Hb / Hct levels, prepartum and postpartum Hb / Hct levels, erythrocyte count, and fresh-frozen plasma transfusion history) were obtained from the hospital database system.

An algorithmic approach as utilised in the clinic for the management of pregnant women with anaemia is demonstrated in Figure 1.

Statistical analyses were performed using the SPSS version 17.0 software. The normality of the variables was assessed using histogram visualisations and the Kolmogorov-Smirnov statistical test. Descriptive analysis results were reported as measures, including mean, standard deviation, median, minimum, and maximum values. Pearson's Chi-square test was used to compare categorical variables. Mann-Whitney U test was performed to assess groups that showed no normal distributions (i.e., nonparametric). Statistical significance was attributed to results with p-values <0.05.

RESULTS

In total, 146 patients who met the study's inclusion criteria were assigned to the study and control groups. FCM was administered to 50 participants, and oral iron was administered to 96. The mean age was 29.1 ± 5.62 years in the FCM group and 28.45 ± 6.10 years in the oral iron group. The median value of parity was shown to be similar in both groups. There were no documented adverse reactions to FCM and oral iron therapy among the patients. The groups were comparable in terms of age, gravidity, and parity (p = 0.562, Table I). No difference was observed between the groups in terms of education levels.

Of the pregnant women, 106 had caesarean section and 40 had vaginal delivery. In the FCM group, the caesarean rate was 52%, whereas in the oral iron group, the caesarean rate was 83.33%. The caesarean rate was statistically significantly higher in patients who received oral iron compared to patients who received FCM. There was no statistically significant difference in the postpartum complication rates (Table I).

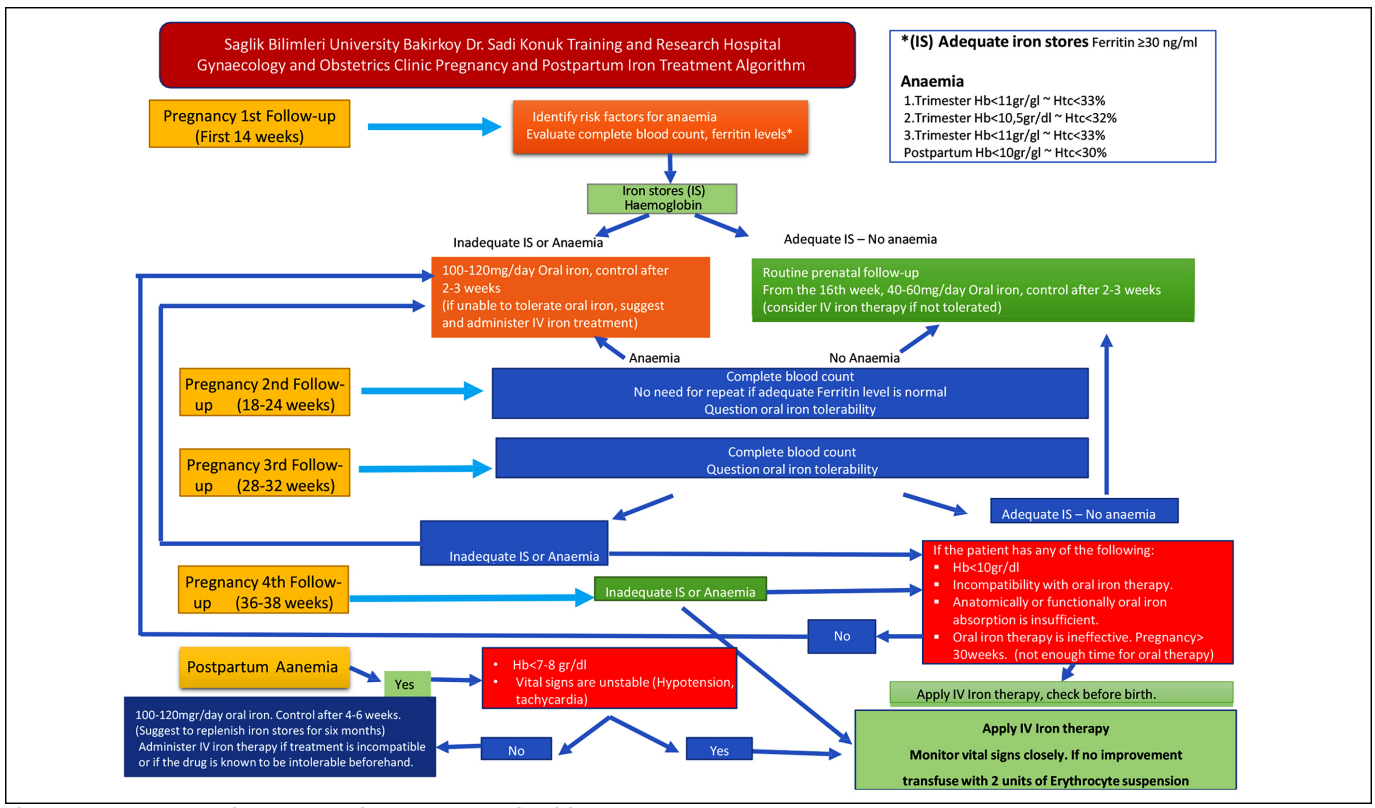

Figure 1: Pregnancy and postpartum iron treatment algorithm.

Table I: Distribution by demographic characteristics.

	Treated anaemia with FCM* (n = 50)	**Treated anaemia with oral iron (n = 96)**	**p†**
Age (years) (Median (IQR))	28 (25 – 33)	29 (23 – 33)	0.56
Parity (n§) (Median (IQR))	2 (1 – 2)	2 (1 – 3)	0.45
Birth method (n, %)			<0.001
Vaginal delivery	24 (48%)	16 (16.67%)	
Caesarean section	26 (52%)	80 (83.33%)	
Postpartum complication			0.39
No complications	44 (88%)	90 (93.75%)	
Atonia	1 (2%)	3 (3.13%)	
Dysuria	1 (2%)	1 (1.04%)	
Endometritis	1 (2%)	0 (0.00%)	
HELLP syndrome	1 (2%)	0 (0.00%)	
Hysterectomy	1 (2%)	2 (2.08%)	
Rest placenta	1 (2%)	0 (0.00%)	

*Mann-Whitney U test (Median (IQR)) and Chi-square test. *Ferric carboxymaltose †p-value <0.05, which is given in bold, is considered significant. §Number.*

Table II: Comparison of outcomes by treatment route.

	Treated anaemia with FCM* (n = 50)	**Treated anaemia with oral iron (n = 96)**	**p†**
Gestational age at birth (weeks)	38.57 (38 – 39.86)	38.36 (37.71 – 39.14)	0.07
Hb levels prior to treatment (g/dL)	8.3 (7.5 – 8.9)	9.2 (8.35 – 10.15)	<0.001
Hb levels prior to delivery (g/dL)	11.25 (10.1 – 12.1)	9.2 (8.6 – 10.15)	<0.001
Postpartum Hb levels in the sixth hour (g/dL)	10.3 (9.5 – 11)	8 (7.45 – 8.55)	<0.001
Hct levels prior to treatment	27.67 (24.4 – 28.9)	28.75 (26.3 – 31.2)	<0.001
Hct levels prior to delivery	34.1 (32.3 – 36.2)	29.25 (27.65 – 31.45)	<0.001
Postpartum haematocrit levels	32.3 (30 – 33.5)	25.35 (24.05 – 27)	<0.001
Postpartum erythrocyte replacement			0.03
No	47 (94%)	78 (81.25%)	
Yes	3 (6%)	18 (18.75%)	

*Mann-Whitney U test (Median (IQR)) and Chi-square test. *Ferric carboxymaltose. †p-values <0.05, which are given in bold, are considered significant..*

Several postpartum complications were observed in the IV iron group, including retained placenta, dysuria, and haemolysis, elevated liver enzyme levels, and low platelet levels (HELLP) syndrome. Retained placenta refers to the retention of placental fragments in the uterus after delivery, which can lead to postpartum haemorrhage and infection. Dysuria, or painful urination, may occur due to urinary tract infections or trauma during delivery. In one patient in the IV iron group who was followed up with a diagnosis of preeclampsia at 38 weeks and delivered, HELLP syndrome occurred at 24-hour postpartum.

The higher number of complications in the IV iron group may be attributed to the more severe anaemia and associated health conditions that necessitated the use of IV iron therapy. These patients were likely at higher risk for complications due to their baseline health status.

The mean gestational age at birth was 38.85 ± 1.35 years in the FCM group and 38.44 ± 1.14 years in the oral iron group ($p = 0.07$) (Table II). Before treatment, the initial mean Hb/Hct level was 8.31 ± 0.96 g/dL / 27.01 ± 2.82 in the FCM group and 9.29 ± 1.20 g/dL / 28.98 ± 3.29 in the oral iron group. Pre-treatment Hb and Hct values were statistically higher in anaemic pregnant women using oral iron than in pregnant women who received FCM ($p <0.001$, Table II).

The mean Hb/Hct levels in the delivery room were 11.09 ± 1.38 g/dL / 33.98 ± 3.54 in the FCM group and 9.44 ± 1.16 g/dL / 29.84 ± 3.36 in the oral iron group. In the FCM group, mean Hb / Hct levels at the sixth hour after delivery were 10.23 ± 1.28 g/dL / 31.5 ± 3.50 in the FCM group and 8.09 ± .93 g/dL / 25.81 ± 2.91 in the oral iron group. Prepartum and postpartum Hb and Hct values were statistically higher in anaemic pregnant women who underwent FCM than in the oral iron group ($p <0.001$).

The main outcome of this study was that the number of patients who needed postpartum erythrocyte transfusion was 3 (6%) in the FCM group and 18 (18.75%) in the oral iron group (Table II). The oral iron group required considerably more postpartum maternal blood transfusions than the FCM group ($p = 0.03$).

Patients with severe or moderate anaemia (Hb <7 g/dL) and significant clinical symptoms such as fatigue, dizziness, and haemodynamic instability were primarily referred for blood transfusions in both IV FCM and oral iron groups. Patients with significant blood loss during and after delivery and also after bleeding due to complications underwent erythrocyte transfusion in accordance with the above criteria.

In the IV FCM group, no significant adverse reactions were reported. Commonly observed minor side effects included mild injection site reactions, which resolved spontaneously without further intervention. In the oral iron group, gastrointestinal side effects, such as nausea, constipation, and abdominal discomfort were frequently reported. These side effects led to lower adherence to the treatment regimen in some patients.

A Post-hoc power analysis was conducted using the G Power 3.1.9.7 software developed by Franz Faul in Germany. The analysis assumed an effect size of $d = 0.901$. The study's power was determined to be 99% based on the calculated effect size and a margin of error of 5%.

DISCUSSION

This study aimed to compare the effectiveness of IV FCM and oral iron supplementation in treating IDA during the third trimester of pregnancy. The results demonstrated that IV FCM is significantly more effective in increasing haemoglobin levels and reducing the need for blood transfusions during delivery compared to oral iron.

IV FCM led to a more substantial increase in haemoglobin levels compared to oral iron.[16] The mean haemoglobin levels at delivery were 11.09 ± 1.38 g/dL in the IV FCM group and 9.44 ± 1.16 g/dL in the oral iron group, indicating a significant improvement in the IV FCM group ($p <0.001$). This can be attributed to the rapid replenishment of iron stores provided by IV FCM, bypassing the gastrointestinal absorption issues associated with oral iron.

In a study conducted by Oskovi-Kaplan *et al*., a comparison of the postpartum blood transfusion needs of second- and third-trimester pregnant women with IDA was made between the FCM group and the untreated anaemic groups.[17] Similar to this study, less postpartum maternal blood transfusion was reported in the FCM group. The lower transfusion requirement in the FCM group compared with the untreated group is not surprising. In contrast to the Oskovi-Kaplan *et al*.'s study, this study's control group incorporates a cohort that used oral iron supplementation.

The higher rate of caesarean section in the oral iron group (83.33%) compared to the IV FCM group (52%) may be attributed to iron deficiency anaemia, as haemoglobin levels in the oral group were significantly lower than in the IV group. There are no criteria for anaemic patients to be delivered by caesarean section. A study by Drukker *et al*. found that iron deficiency anaemia at delivery was associated with an increased risk of caesarean delivery and adverse maternal and neonatal outcomes in otherwise healthy women. The findings of this study suggest that the higher caesarean section rates observed in the oral iron therapy group may be due to the adverse effects of iron deficiency anaemia during labour.[18]

The higher number of postpartum complications observed in the IV iron group can be justified by the severity of anaemia in these patients. The patients in the IV iron group had more severe anaemia initially, as indicated by their significantly lower haemoglobin levels compared to the oral iron group. This severe anaemia may have predisposed these patients to a higher risk of complications during and after delivery.

IV FCM was generally well tolerated, with no significant adverse reactions reported, aside from minor injection site reactions that resolved spontaneously.[19] In contrast, the oral iron group experienced more frequent gastrointestinal side effects, such as nausea, constipation, and abdominal discomfort, which negatively impacted treatment adherence. These findings are consistent with previous studies that have highlighted the better tolerability of IV iron formulations.

Hepcidin, a key regulator of iron homeostasis, inhibits iron absorption when its levels are elevated.[20] Oral iron therapy can increase hepcidin levels, further reducing iron absorption and efficacy.[21] This explains the limited effectiveness of oral iron in this study and highlights the advantage of IV FCM, which bypasses gastrointestinal absorption issues.

The authors acknowledge that pre-treatment haemoglobin levels were significantly lower in the IV FCM group compared to the oral iron group. Despite this baseline difference, post-treatment haemoglobin levels were significantly higher in the IV FCM group. This finding indicates that IV FCM is more effective in increasing haemoglobin levels compared to oral iron supplementation. The significant improvement in the IV FCM group, even with initially lower Hb levels, underscores the superior efficacy of IV FCM in treating iron deficiency anaemia. These results suggest that IV FCM can achieve better outcomes in patients with more severe anaemia, highlighting its practical advantage in clinical settings.

The innovation of this study lies in its comparative analysis of IV FCM *versus* oral iron supplementation for treating IDA during the third trimester of pregnancy. While previous studies have explored the efficacy of these treatments individually, this study directly compares their effectiveness in a real-world clinical setting, taking into account the severity of anaemia and associated maternal outcomes. Additionally, this study highlights the practical implications of using IV FCM, such as improved adherence due to fewer gastrointestinal side effects, and provides new insights into the management of anaemia in high-risk pregnant populations. By addressing the limitations of oral iron therapy and demonstrating the benefits of IV FCM, this study contributes to the optimisation of anaemia management protocols during pregnancy.

This study's retrospective design limits the ability to perform randomisation and blinding, which may introduce selection bias. Additionally, the disparity in sample sizes between the groups and the reliance on existing medical records limit the control over potential confounders. Future prospective, randomised controlled trials are recommended to validate these findings and minimise bias.

CONCLUSION

This study demonstrated that IV FCM is a more effective and better-tolerated option than oral iron for treating IDA in the third trimester of pregnancy. These findings support the use of IV FCM to improve maternal outcomes and reduce the need for blood transfusions during delivery.

ETHICAL APPROVAL:
This study was performed in line with the principles of the Declaration of Helsinki and approved by the Health Sciences University Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (Approval Number: 2022-24-13).

PATIENTS' CONSENT:
Informed consent was obtained from all patients before conducting the study.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
MCD: Writing of the original draft, interpretation of data, and discussion of results.
IYD: Conception, study design, and acquisition of data.
OA: Drafting and critical revision of the manuscript.
SY: Proofreading and final approval of the manuscript.
GUE: Data analysis and statistical evaluation.
ME: Literature review and acquisition of data.
All authors approved the final version of the manuscript to be published.

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