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ORIGINAL ARTICLE

Efficacy, tolerability, and safety of intravenous ferric carboxymaltose compared with oral ferrous sulfate for the treatment of iron deficiency anemia during the antepartum period

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ABSTRACT

Objective: This study aims to compare the efficacy, safety, and tolerability of intravenous ferric carboxymaltose to oral ferrous sulfate in pregnant women (gestation weeks 14–21) with antepartum anemia.

Material and Methods: A retrospective cohort study was conducted in a tertiary hospital comparing intravenous 1000 mg ferric carboxymaltose treatment during pregnancy (120 patients) to oral ferrous sulfate (100 mg) 2x1 treatment until delivery (120 patients) for the treatment of iron deficiency anemia in pregnancy. The patients' responses to treatment were assessed by measuring hemoglobin, hematocrit, and ferritin levels on the 60th day, 120th day, and postpartum 1st day following the initiation of the therapeutic intervention.

Results: There were no significant differences between the groups in terms of gestational age, parity, delivery patterns, or antepartum hemoglobin and hematocrit levels. On the 60th and postpartum first day of treatment, the IV ferric carboxymaltose group had significantly higher hemoglobin and hematocrit levels than the oral ferrous sulfate group ($p<0.05$). Ferritin levels improved rapidly on the 60th day of IV treatment. However, there was no significant difference in hemoglobin, hematocrit, or ferritin levels on the 120th day.

Conclusion: Intravenous ferric carboxymaltose proves to be safe and well-tolerated in the management of antepartum iron deficiency anemia. While short-term intravenous iron therapy leads to a quicker elevation of hemoglobin, hematocrit, and ferritin levels in women with antepartum anemia compared to oral ferrous sulfate therapy, over the long term, the levels tend to equalize.

Keywords: Antepartum iron deficiency anemia, ferric carboxymaltose, ferrous sulfate, intravenous treatment, oral treatment.

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INTRODUCTION

Anemia represents a significant global health concern, impacting newborns, pregnant and postpartum women, as well as adolescent girls. The burden of anemia is disproportionately borne by non-educated individuals and impoverished rural households residing in low- and middle-income countries. Globally, the prevalence of anemia among pregnant women aged 15–49 is reported at 36.5%.[1] The primary contributors to anemia encompass dietary iron deficiency, thalassemia, sickle cell trait, and malaria.[2] Iron deficiency anemia can manifest with symptoms such as fatigue, headache, dizziness, shortness of breath, palpitations, decreased cognitive function, and depression.

A singleton gestation imposes a need for roughly one gram of iron on expectant mothers. This augmented demand stems from heightened red cell mass, fetal-placental growth, and enlargement of maternal blood volume. Anemia poses a significant risk factor for both maternal and fetal morbidity. This will lead to adverse fetal, neonatal, and newborn outcomes such as preterm labor, fetal growth restriction (FGR), postpartum hemorrhage, cardiac hypertrophy, recurrent infections, and puerperal sepsis.[3,4]

The World Health Organization (WHO) suggests that all women receive daily oral iron supplements along with folic acid.[5] According to the Pregnancy Iron Support Program Guide issued by the Ministry of Health on January 31, 2007, in Türkiye, the use of appropriate daily iron supplements containing elemental iron (40–60 mg) is recommended from the beginning of the 4th month of pregnancy (second trimester) throughout the pregnancy, for a total duration of nine months, including six months postpartum.[6] Although numerous iron preparations are available for addressing iron deficiency anemia during pregnancy, oral forms are notable for their pronounced gastrointestinal side effects such as GI discomfort, vomiting, diarrhea, and a metallic taste in the mouth.[7] IV iron treatment shows better tolerability, fewer adverse effects, and rapid improvement in desired hemoglobin (Hb) levels compared to oral iron preparations.[8] Ferric carboxymaltose (FCM) is one of the modern intravenous iron formulations frequently employed in the management of iron deficiency during pregnancy. Hence, we conducted a retrospective cohort study at our tertiary research hospital to assess the tolerability, efficacy, and safety of a single dose of 1000 mg intravenous ferric carboxymaltose (FCM) in comparison to oral ferrous sulfate (FS).

MATERIAL AND METHODS

We conducted a retrospective cohort study at the Istanbul Health Sciences University Kanuni Sultan Suleyman Training and Research Hospital, a tertiary referral center, from November 2020 to November 2023. The study included patients referred to our outpatient clinics in the Department of Obstetrics and Gynecology and diagnosed with antepartum anemia based on their biochemical investigations. This investigation targeted women aged ≥18 years who encountered iron deficiency anemia (IDA) within the antepartum period, precisely in the second trimester (gestational weeks 14–21). Patients with serum ferritin levels ≤40 (μg/L) and IDA (Hb levels of 8.0–10.4 g/dL for gestation weeks 14–21) were included in the study. Pregnant women with severe postpartum vaginal bleeding, iron intolerance, a history of peripartum blood transfusions, myelosuppressive therapy, asthma, pulmonary thromboembolism, alcohol consumption, malabsorption syndrome, or renal-hepatic infections were excluded from the study. We followed the Helsinki Declaration guidelines and received clinical and ethical approval from the institutional review board (Approval number: KAEK/2023.11.171). Each participant provided written informed consent before enrollment.

An electronic medical database of the hospital was used to determine patients in the second trimester who had received either IV ferric carboxymaltose (total dosage 1000 mg) or oral ferrous sulfate (100 mg capsules taken twice daily; total dosage 200 mg) treatment until delivery during the antepartum period for the treatment of IDA. Demographic data, including age, BMI, gravida, parity, pre-treatment hemoglobin (Hb) levels, pre-treatment hematocrit (Hct) levels, and delivery type, were obtained from the patients' records. On the 60th day, 120th day, and postpartum 1st day of the treatment, the levels of hemoglobin (Hb), hematocrit (Hct), and ferritin were documented for both groups. Additionally, any treatment-emergent adverse events were recorded for efficacy, safety, and tolerability assessment.

The primary objective was to compare the effectiveness of the IV FCM and oral ferrous sulfate (FS) treatment for IDA during the antepartum period by measuring Hb and Hct levels from baseline. The secondary objective was to assess the tolerability of FCM and FS usage during pregnancy.

The data analysis was conducted using IBM Statistical Package for the Social Sciences version 20 (SPSS Inc., Chicago, IL, USA). Mean±standard deviations were provided for continuous variables, and percentages along with numerical values were presented for categorical variables. The normal distribution of groups was assessed using the Kolmogorov-Smirnov test, and based on the distribution results, comparisons of means were performed using either the Mann-Whitney U or Student's t-test. The Chi-square test and Fisher's exact test were employed to compare categorical variables. A p-value<0.05 was considered statistically significant in the results.

RESULTS

Routine assessment of hemoglobin levels during outpatient clinic admissions revealed values within the range of 8 to 11 g/dl for the enrolled patients. The oral iron supplementation (FS) group had an average age of 27.1±6.1 years, while the intravenous ferric carboxymaltose (IV FCM) group exhibited an average age of 27.7±7.0 years. There were no statistically significant differences observed between the groups regarding gravida, parity, or mode of delivery. The demographic and characteristic features of the patients are outlined in Table 1.

The mean pretreatment hemoglobin (Hb) levels for patients in the FS group were determined to be 10.1±1.2 g/L, with hematocrit (Htc) levels averaging 30.4±2.6 g/L. In contrast, the IV FCM group's mean pretreatment Hb levels were 10.3±1.2 g/L, and Htc levels averaged 30.6±2.7 g/L. The pretreatment Hb and Htc values among the groups showed no statistically significant differences.

Table 1: Characteristic and demographic features of the patients

	Group 1 Oral treatment (n=120)	Group 2 Intravenous treatment (n=120)	p
Age (year)	27.1±6.1	27.7±7.0	0.410
BMI (kg/m^2)	22.2±1.6	22.9±1.8	0.186
Gravida	2.2±1.1	2.3±1.2	0.110
Parity	2.0±1.1	2.1±1.1	0.097
Hb before treatment (g/dL)	10.1±1.2	10.3±1.2	0.060
Htc before treatment (%)	30.4±2.6	30.6±2.7	0.642
Mode of delivery, n (%)			0.786
Vaginal delivery	41 (34.1%)	43 (35.8%)	
Cesarean section	79 (65.9%)	77 (64.2%)	

BMI: Body mass index; Hb: Hemoglobin; Htc: Hematocrit.

Table 2: Hemoglobin, hematocrit, ferritin values on day 60, day 120 and postpartum day 1 of treatment

	Group 1 Oral treatment (n=120)	Group 2 Intravenous treatment (n=120)	p
Hb on day 60 of treatment (g/dL)	10.2±1.1	11.3±1.3	0.032
Htc on day 60 of treatment (%)	33.4±3.1	36.0±2.8	0.041
Ferritin on day 60 of treatment (μg/L)	91.7±80.8	398.1±186.8	0.012
Hb on day 120 of treatment (g/dL)	11.8±0.6	11.6±0.8	0.452
Htc on day 120 of treatment (%)	36.6±2.2	36.9±2.3	0.332
Ferritin on day 120 of treatment (μg/L)	198.4±76.5	236.7±89.9	0.090
Hb on postpartum day 1 of treatment (g/dL)	9.1±0.6	9.3±0.7	0.026
Htc on postpartum day 1 of treatment (%)	27.3±1.8	29.8±2.8	0.009
Ferritin on postpartum day 1 of treatment (μg/L)	28.5±20.6	33.8±29.7	0.156

Hb: Hemoglobin; Htc: Hematocrit

On the 60th day of treatment, the average Hb value in the FS group was determined to be 10.2±1.1 g/L, with a mean hematocrit value of 33.4±3.1 g/L. In the IV FCM group, the Hb average was 11.3±1.3 g/L, with a mean Htc value of 36.0±2.8 g/L. Upon comparing ferritin levels between the two groups on the 60th day of treatment, a statistically significant difference favoring the IV FCM group (398.1±186.8) was observed compared to the FS group (91.7±80.8) (p=0.012).

On the 120th day of treatment, there was no statistically significant difference between the groups in terms of hemoglobin (Hb), hematocrit (Htc), and ferritin levels (Table 2). However, on the postpartum 1st day, there was a significant difference in Hb and Htc levels among groups, favoring the IV FCM group. On the postpartum 1st day of treatment, the average Hb value in the FS group was determined to be 9.1±0.6 g/L, with a mean hematocrit value of 27.3±1.8 g/L. In the IV FCM group, the Hb average was 9.3±0.7 g/L, with a mean Htc value of 29.8±2.8 g/L.

No serious side effects were detected in either group. In the IV FCM group, 2 patients (1.6%) experienced headaches during the infusion of the drug, while flushing occurred in 9 women (7.5%). Four women (3.4%) reported a sensation of trembling, and 3 women (2.5%) mentioned feeling fatigued. However, none of these effects were persistent or progressive. No hemodynamic issues were observed during or after the infusion. Sixty-one patients (51%) in the FS group reported experiencing side effects. These side effects were generally related to the gastrointestinal system, such as dyspepsia and constipation. Thirty-two women (27%) reported a change in taste or a metallic taste sensation, while twenty-nine (24%) women reported constipation (Table 3). Despite these symptoms, patients adapted to the medication and completed the treatment. When comparing the groups regarding side effects, the rate of complaints related to side effects was significantly higher in the oral FS group (p<0.05).

Table 3: Treatment related side effects

	Group 1 Oral treatment (n=120)	Group 2 Intravenous treatment (n=120)	p
Fatigue	0	3 (2.5%)	
Constipation	29 (24%)	0	
Flushing	0	9 (7.5%)	
Trembling	0	4 (3.4%)	0.008
Change in taste	32 (27%)	0	
Headache	0	2 (1.6%)	
Total	61 (51%)	18 (15%)	

DISCUSSION

IDA is a major health problem affecting approximately 40% of women worldwide. Due to the elevated fetal iron requirements, ferritin levels decrease in approximately 30–50% of pregnant women throughout gestation.[9] IDA and acute bleeding are the main causes of anemia during the antepartum and postpartum periods.[10] IDA during pregnancy is associated with maternal and neonatal morbidity and mortality. To prevent complications and reduce the morbidity and mortality rates due to IDA, the National Institute for Health Care Excellence (NICE) recommends screening for hematological pathologies through a full blood count at 28 weeks of gestation, as well as at any point during pregnancy if anemia is suspected.[11] The Network for the Advancement of Patient Blood Management, Haemostasis, and Thrombosis (NATA) consensus statement advocates for the routine antenatal administration of oral iron (30–60 mg/day) and folic acid (400 μg/day) to mitigate the risk of low birth weight and IDA during pregnancy.[12] However, the gastrointestinal adverse effects of oral iron salts often impede the compliance of pregnant women with treatment. IV iron supplements are another route for treating IDA during pregnancy. It is usually administered in the second or third trimester, as there is no available data for first-trimester use. In this study, we aimed to compare the efficacy, tolerability, and safety of intravenous FCM over oral FS for treating IDA during pregnancy.

Many randomized controlled trials have compared the efficacy and safety of IV FCM with oral FS during pregnancy.[13–16] These studies consistently demonstrate that FCM is superior at rapidly increasing hemoglobin (Hb) levels without resulting in group 3 or 4 adverse outcomes. Additionally, this statement is supported by systematic reviews in the literature favoring IV iron preparations compared to oral forms in terms of efficacy, safety, and quality of life.[8,17] Both meta-analyses illuminate that intravenous iron formulations significantly enhance hemoglobin levels within 4 weeks following the initiation of treatment. Consistent with the literature, our results demonstrate that IV FCM is superior to oral FS in terms of rapidly improving hemoglobin levels and replenishing iron stores. Additionally, IV FCM exhibits fewer adverse effects compared to the oral FS group.

There is a significant reluctance to use intravenous iron preparations due to the high risk of anaphylactoid reactions. However, ferric carboxymaltose offers various advantages over other parenteral iron preparations. It does not contain dextran and does not react with dextran antibodies, hence eliminating the risk of anaphylactic reactions observed with iron dextran.[18] Additionally, ferric carboxymaltose possesses favorable characteristics compared to iron sucrose (VenoferTM, Vifor International, StGallen, Switzerland), including lower pH, lower osmolarity, and higher single-dose administration.[19] Its safety profile allows for short-term administration in outpatient facilities. Common adverse effects, such as metallic taste, flushing, and burning at the injection site, are observed at a rate of 0.5% for doses up to 200 mg.[20] It is well known that oral iron medications cause gastrointestinal side effects.[21] Gastrointestinal side effects are believed to be dose-dependent and occur more frequently at higher doses. Up to 30% of women treated with oral iron report gastrointestinal side effects.[22] Ferric carboxymaltose is well-tolerated by patients in single-dose administrations.[16] Consistent with findings from other studies, our study also supports a higher frequency of gastrointestinal disturbances in the iron sulfate group, while the incidence of side effects in the parenteral ferric carboxymaltose group was lower. Outside of a clinical trial setting, non-adherence to oral iron therapy is reported to be 10% after two weeks, 25% after one month, and 32% after two months.[23,24] Given these high rates of non-adherence, many patients are exposed to symptoms associated with anemia and increased interventions such as transfusions. In this study, ferric carboxymaltose provided clinical improvement in anemia without the need for prolonged adherence to oral iron therapy.

The interpretation of this study is subject to some limitations. One of the limitations was the retrospective nature of this study. Another limitation of this study is the lack of comprehensive records, the quality of the documents, and the inherent recollection bias associated with retrospective data collection. Additionally, we refrained from incorporating fetal outcomes in this study due to potential variations in the quality of available documents, which could introduce inconsistencies or errors in the data analysis.

CONCLUSION

In conclusion, our findings further support the evidence that IV FCM is both safe and efficacious for the treatment of IDA during pregnancy. In patients with intolerance to oral iron and a limited timeframe before delivery, IV FCM may be considered as an option. IV FCM could provide an alternative approach for managing IDA during the antepartum period, offering a safety profile comparable to oral formulations.

Statement

Acknowledgments: We thank all our study subjects for participating in this study.

Ethics Committee Approval: The Kanuni Sultan Suleyman Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 30.11.2023, number: KAEK/2023.11.171).

Author Contributions: Concept – MG, OK; Design – MG, OK; Supervision – MG, OK; Resource – OK; Materials – OK; Data Collection and/or Processing – MG; Analysis and/or Interpretation – OK; Literature Search – MG; Writing – MG, OK; Critical Reviews – MG, OK.

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REFERENCES

1. World Health Organization. The global health observatory data repository. Explore a world of health data. 2023. Available at: https://www.who.int/data/gho. Accessed Aug 6, 2024.
2. Global Health Metrics (2019) Anaemia—Level 1 Impairment. The Lancet, 393, R2.
3. Nair M, Churchill D, Robinson S, Nelson-Piercy C, Stanworth SJ, Knight M. Association between maternal haemoglobin and stillbirth: A cohort study among a multi-ethnic population in England. Br J Haematol 2017;179:829–37.
4. Tangeda PR, Patil S, Shastri N, Noorali SN. Maternal myocardial performance in second trimester of pregnancy with iron deficiency anaemia. J Clin Diagn Res 2016;10:CC16–8.
5. WHO. Guideline: Daily iron and folic acid supplementation in pregnant women. Geneva: World Health Organization, 2012. Available at: https://iris.who.int/bitstream/handle/10665/77770/9789241501996_eng.pdf. Accessed Aug 6, 2024.
6. Türkiye Cumhuriyeti Sağlık Bakanlığı. Gebelerde demir destek programı uygulaması genelgesi 2007/6. 2007. Available at: https://www.saglik.gov.tr/TR-11100/gebelerde-demir-destek-programi-uygulamasi-genelgesi-2007--6.html. Accessed Aug 6, 2024. [In Turkish]
7. Chawla S, Singh A, Jhamb D, Anupama CH. A randomised controlled trial to compare injection ferric carboxymaltose and oral iron in treating iron deficiency anemia during pregnancy. J Obstet Gynaecol India 2022;72:492–6.
8. Govindappagari S, Burwick RM. Treatment of iron deficiency anemia in pregnancy with intravenous versus oral iron: Systematic review and meta-analysis. Am J Perinatol 2019;36:366–76.
9. Benson AE, Shatzel JJ, Ryan KS, Hedges MA, Martens K, Aslan JE, et al. The incidence, complications, and treatment of iron deficiency in pregnancy. Eur J Haematol 2022;109:633–42.
10. Anemia in pregnancy: ACOG practice bulletin, number 233. Obstet Gynecol 2021;138:e55–e64.
11. National Institute for Health Care Excellence. Antenatal care 2021. Available at: https://www.nice.org.uk/guidance/ng201. Accessed Apr 27, 2023.
12. Muñoz M, Peña-Rosas JP, Robinson S, Milman N, Holzgreve W, Breymann C, et al. Patient blood management in obstetrics: Management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. Transfus Med 2018;28:22–39.
13. Jose A, Mahey R, Sharma JB, Bhatla N, Saxena R, Kalaivani M, et al. Comparison of ferric Carboxymaltose and iron sucrose complex for treatment of iron deficiency anemia in pregnancy- randomised controlled trial. BMC Pregnancy Childbirth 2019;19:54.
14. Vanobberghen F, Lweno O, Kuemmerle A, Mwebi KD, Asilia P, Issa A, et al. Efficacy and safety of intravenous ferric carboxymaltose compared with oral iron for the treatment of iron deficiency anaemia in women after childbirth in Tanzania: A parallel-group, open-label, randomised controlled phase 3 trial. Lancet Glob Health 2021;9:e189–98.
15. Khalafallah AA, Hyppa A, Chuang A, Hanna F, Wilson E, Kwok C, et al. A prospective randomised controlled trial of a single intravenous infusion of ferric carboxymaltose vs single intravenous iron polymaltose or daily oral ferrous sulphate in the treatment of iron deficiency anaemia in pregnancy. Semin Hematol 2018;55:223–34.
16. Breymann C, Milman N, Mezzacasa A, Bernard R, Dudenhausen J; FER-ASAP investigators. Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: An international, open-label, randomized controlled trial (FER-ASAP). J Perinat Med 2017;45:443–53.
17. Rogozińska E, Daru J, Nicolaides M, Amezcua-Prieto C, Robinson S, Wang R, et al. Iron preparations for women of reproductive age with iron deficiency anaemia in pregnancy (FRIDA): A systematic review and network meta-analysis. Lancet Haematol 2021;8:e503–12.
18. Burns DL, Mascioli EA, Bistrian BR. Parenteral iron dextran therapy: A review. Nutrition 1995;11:163–8.
19. Venofer: Iron sucrose injection USP. Full prescribing information. Available at: https://www.venofer.com/pdfs/venofer-prescribing-information.pdf. Accessed Aug 6, 2024.
20. Perewusnyk G, Huch R, Huch A, Breymann C. Parenteral iron therapy in obstetrics: 8 years experience with iron-sucrose complex. Br J Nutr 2002;88:3–10.
21. Crichton R, Danielson B, Geisser P. Iron therapy. Bremen, Germany: Uni-Med Verlag; 2005.
22. al-Momen AK, al-Meshari A, al-Nuaim L, Saddique A, Abotalib Z, Khashogji T, et al. Intravenous iron sucrose complex in the treatment of iron deficiency anemia during pregnancy. Eur J Obstet Gynecol Reprod Biol 1996;69:121–4.
23. Hallberg L, Ryttinger L, Sölvell L. Side-effects of oral iron therapy. A double-blind study of different iron compounds in tablet form. Acta Med Scand Suppl 1966;459:3–10.
24. Bonnar J, Goldberg A, Smith JA. Do pregnant women take their iron? Lancet 1969;1:457–8.