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Original Article

Comparative Evaluation of Efficacy, Safety, Cost Effectiveness and Acceptability of Ferric Carboxymaltose *versus* Iron Sucrose for Treatment of Iron Deficiency Anaemia in Pregnancy: A Multicenter Open Label Randomized Controlled Trial

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ABSTRACT

Objectives: To evaluate the efficacy, safety, cost-effectiveness, and patient acceptability of ferric carboxymaltose (FCM) versus iron sucrose complex (ISC) for treatment of iron deficiency anaemia (IDA) in pregnancy.
Methods: An open blind randomized controlled trial was conducted among pregnant women between 16-34 weeks of gestation with IDA and haemoglobin between >60 and <100 g/L, at two tertiary hospitals between November 2019 to December 2020. The participants were divided into two groups in a 1:1 ratio as FCM group and ISC group. Patients in the FCM group received 1000 mg of diluted IV FCM, whereas patients in the ISC group received 200 mg of IV ISC three times a week until their dosages were complete. The SPSS data processor was used to do the statistical analysis of the data. Mean and median of continuous data were analysed by Mann-Whitney or independent 't' tests, whereas categorical and quantitative data was analysed by using Chi-square/Exact Fischer's tests.
Results: Both groups of patients had similar characteristics. FCM and ISC groups had similar iron needs ($p = 0.3$). There were considerably fewer doses required in the FCM group compared with the ISC group [1.0 (IQR: 1-1) vs. 4 (IQR: 4-5; p value < 0.001)]. For the FCM group, the mean increase in Hb after 12 weeks was 3.26 gm% ($p < 0.001$). Satisfaction of both group of patients were similar. However, the patient felt more convenient with FCM as it needed only single visit. No significant side effects were seen in either group.
Conclusion: Treatment with ferric carboxymaltose in pregnancy is safe and effective, with a very good safety profile, and the added benefit of a large dosage being given in a single sitting. Further large-scale randomized trails are needed to find out the long-term effect on maternal and neonatal wellbeing of both forms of iron treatment.

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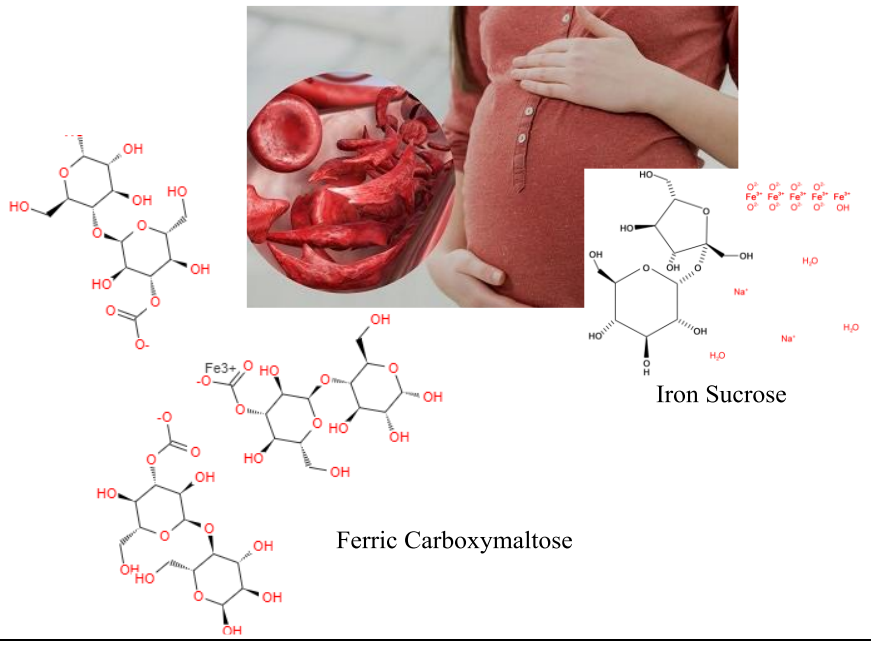
GRAPHICAL ABSTRACT



Introduction

In both developed and developing countries, iron deficiency anaemia (IDA) is prevalent. Increases in maternal and neonatal mortality due to iron deficiency anaemia have been reported by the World Health Organization (WHO) [1]. South Asians are more likely to suffer from anaemia than those in other regions of the world. Most maternal deaths globally are the result of anaemia, with India accounting for over 80% of these deaths [2].

Low dietary iron intake, poor iron bioavailability, phytate-rich diets, poor eating habits, chronic menstrual blood loss, and high infection rates, such as malaria and hookworm infestations, are all contributing factors to the high prevalence of anaemia in South Asian countries and including India [3]. Pregnancy exacerbates the problem since the demands rise of the foetus. Pregnancy-related increases in iron needs necessitate the use of prophylactic oral iron supplements. As a result of gastrointestinal side effects including bloating, diarrhoea, heartburn, nausea, constipation, and black stools, oral iron therapy has a very low compliance rate among pregnant women. In addition, some women might not be as responsive to oral iron treatment because they should be.

Oral irons are not ideal to treat moderate to severe anaemia, especially in the second and third trimesters. They must be administered intravenously for rapid replacement. Parenteral therapy can be used to avoid blood transfusions during pregnancy and the postpartum period [4]. Iron sucrose complex (ISC) is the most widely prescribed parenteral iron supplement for pregnant women with anaemia. It is safe and there is no need for a test dosage.

The drawback of iron sucrose is that it provides just a little amount of iron per serving. Only 200 mg a day or 600 mg per week if taken all is the maximum recommended daily dosage. Multiple sessions are required, which increases the overall cost of therapy. IV iron preparations now include Ferric Carboxymaltose (FCM), a dextran free iron and relatively a new ingredient. FCM can be used once a week to provide significant doses of iron (up to 1000 mg iron in 15 minutes) in a single dose. For instance, Froessler B. et al. [5] conducted a prospective observational study to evaluate the efficacy and safety of intravenous ferric carboxymaltose. FCM has also been studied for anaemia treatment in the postpartum period and other diseases with associated anaemia [5].

However, there is a lack of research on the FCM usage during pregnancy. Randomized trials comparing the safety and effectiveness of FCM and ISC in pregnancy have been conducted just a few times [6,7]. In this study, FCM and ISC were evaluated for the treatment of moderate to severe anaemia during pregnancy for their

efficacy, safety, cost-effectiveness, and patient acceptance.

Materials and Methods

Study design and setting

The Departments of Obstetrics and Gynaecology at Central Referral Hospital- Teaching Hospital of Sikkim Manipal Institute of Medical Sciences (SMIMS), Gangtok, and the Gauhati Medical College Hospital, India, conducted a prospective interventional open label randomised controlled research from November 2019 to December 2020. A committee of institutional ethics (SMIMS-IRPEC/398/19-086) gave its blessing to the inquiry. Participants in the research provided written and informed consent. Ethical norms were put out in the Helsinki Declaration and its revisions were fully adhered during the research.

Inclusion and exclusion criteria

The research included all pregnant women who had been diagnosed with iron deficiency anaemia and whose haemoglobin levels were between >60 and <100 g/L. Exclusions were chronic diseases including hepatitis and HIV, elevated serum creatinine levels, history of bad reaction to intravenous iron infusion, alcohol or drug usage within 10 days before to receiving antibiotics, hemochromatosis, or other iron store sickness, and significant cardiovascular disease.

Randomization and drug administration

By using a computer-generated block randomization table, participants, who met the inclusion criteria and had no exclusions, were divided into two groups in a 1:1 ratio between the FCM group and the ISC group.

Oral iron compliance and previous chronic sickness were all part of the patient's detailed medical history. In addition to physical and obstetric checks, a thorough investigation was conducted. The standard departmental practice of doing routine prenatal examinations was followed. The patient's haemoglobin, red cell indices such as MCV, MCH, MCH, MHC, Hb electrophoresis, serum ferritin, serum iron, the patient's total iron binding capacity (TIBC), and transferrin saturation were all examined in an effort to identify the source of their anaemia. The following formula was used to figure out how much iron was required [8]:

Iron need (mg) = total iron deficit (mg) = 2.4 x body weight (kg) x (target Hb (11) gm% actual Hb (gm%) + store iron (500 mg).

IV FCM was diluted in 200 ml, 0.9 percent normal saline and delivered over 15 to 30 minutes as an IV infusion to FCM patients who were found to have an iron shortage. After a week, if any further dosage was intended, it was be given. Three times a week, the ISC group got a total of 600 milligrams of ISC in 200 milliliters of NS for 30 minutes each time. Additional dosages were administered next week, as scheduled.

Monitoring and assessment

Before and after infusion, the patient's vitals were recorded and fetal heart rate monitoring was done. There were scheduled follow-up appointments for three, six, and twelve weeks after the start of therapy. Measurement of haemoglobin, RBC indices, and serum iron levels was done on a regular basis. Patients reported minor or major adverse events were noted at follow-up visits.

Outcome and safety measures

While the primary purpose of the trial was to improve haemoglobin (Hb) levels from baseline, additional objectives included changes in serum iron parameters, anaemia correction (defined as Hb less than 11.0 µg/dL), the length of time to anaemia correction, and the perinatal outcomes of pregnant women. Treatment cost analysis and patient acceptability were also assessed.

Statistical analysis

We estimated a minimum sample size that would be 24 per group based on an earlier retrospective study [9] comparing intravenous ferric carboxymaltose with iron sucrose for the therapy of iron deficiency anaemia in pregnancy, where Hb increased from 9.5 to 11.0 µg/dl, with a standard deviation of 11.9, and with non-inferiority limit change in mean Hb between the two groups was 10 µg/L and the projected mean difference as zero, alpha error 5%, and power of the study as 90%.

The SPSS data processor was used for statistical analysis of the data, which provided a summary

of statistics and their 95 percent confidence intervals (CI). It was used to analyse and compare the haematological outcomes parameters. Mann-Whitney or independent 't' tests were used to compare the mean and median of continuous data. Analysing the statistical significance of differences between categorical and quantitative data was done using Chi-square/Exact Fischer's tests. All statistical tests were conducted with a significance threshold of 0.05.

Results

One hundred and sixty pregnant women with iron deficiency anaemia in pregnancy between 16-34 weeks of gestation were assessed for inclusion of which 37 women were excluded from the study because they did not match the inclusion requirements, and another 25 women dropped out of participating because they did not want to be a part of the study. The remaining 98 women who met the requirements were divided into two equal groups, and then they were randomly assigned. FCM and ISC groups saw three and six patients withdraw their permissions following randomization, respectively. While one FCM patient and two ISC patients failed to show up for treatment. Each group of 43 women got the intervention and completed the requisite follow-up. The last 86 ladies were evaluated in this section. The randomization process can be seen in detail in Figure 1.

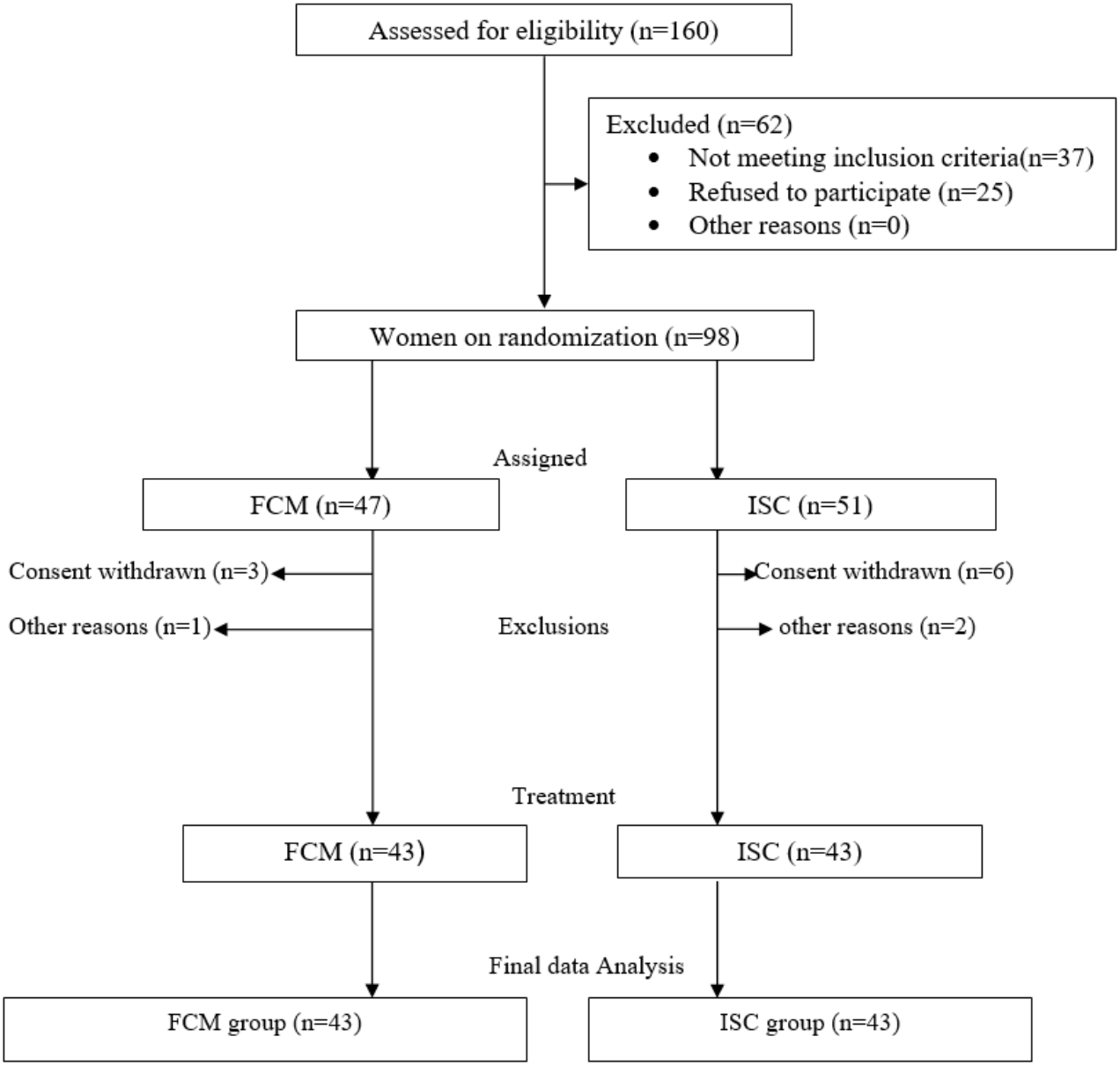


Figure 1: Consort flow diagram from randomization to analysis

Table 1 displays the demographic data and obstetrics profiles of the participants. For the FCM and ISC groups, the mean iron demand was almost the same (950.95±115.49 mg vs. 869.8±210.77 mg; P = 0.3). The FCM group required fewer doses to make up for the shortfall than the ISC group [1.0 (IQR: 1-1) vs. 4(IQR: 4-5); p value < 0.001).

Table 1: Baseline characteristics of the study participants

Characteristics	FCM group, n=43	ISC group, n=43	p value
Age, mean ±SD	33.05±3.34	31.16±5.95	0.074
POG, mean ±SD	26.77±6.00	27.26±5.26	0.689
Weight, mean ±SD	65.07±8.17	61.95±6.46	0.053
BMI, mean ±SD	24.15±.90	23.03±2.47	0.02
Gravida, median (IQR: Q1-Q3) Range: Minimum-Maximum	2(IQR:1-3) Range:1-4	2(IQR:1-3), Range:1-4	0.818
Parity, median (IQR: Q1-Q3) Range: Minimum-Maximum	1(IQR:0-1) Range:0-2	1(IQR:0-2), Range: 0-3	0.088
Type of anemia			
Moderate n(%)	39(49.4%)	40(50.6%)	0.999
Severe n(%)	4(57.1%)	3(42.9%)	
Baseline values			
Hb (Mean±SD)	8.21±.940	8.51±1.077	0.169
MCV (Mean±SD)	74.91±7.043	76.86±9.033	0.267
MCH (Mean±SD)	23.95±2.976	26.35±3.735	0.001
MCHC(Mean±SD)	31.12±1.499	33.02±2.087	<0.001
RDW (%) (Mean±SD)	20.23±2.256	20.63±3.317	0.520
S Iron (Mean±SD)	41.95±31.334	55.35±24.689	0.030
S ferritin (Mean±SD)	67.60±135.495	33.53±15.629	0.105
TIBC (Mean±SD)	496.51±70.01	466.63±58.808	0.035
Transferrin saturation (Mean±SD)	13.21±6.556	13.21±5.776	0.999

As a primary outcome, the 12-week increase in Hb was recorded. In the FCM group, the 12-week mean Hb increase was 3.26 gm percent (95% CI=3.088-3.43), compared with 1.77 gm percent (95% CI=1.562-1.987) in the ISC group (p value< 0.001) (Table 2).

Table 2: Primary outcome: increase in Haemoglobin at 12 weeks

Group	Hb-baseline, mean ±SD	Hb-12 week, mean ±SD	Mean difference (95% CI)	P-value	Cohen's D Effect Size
FCM group, n=43	8.21±.940	11.47±0.768	3.26(3.088-3.43)	<0.001	3.798
ISC group , n=43	8.51±1.077	10.29±0.568	1.77(1.562-1.987)	<0.001	2.067
*Cohen's D ≥ 0.8 implies large effect size					

Baseline and study-end haematological values are indicated in Tables 3 and 4, respectively. For the first three weeks, there was no discernible increase in haemoglobin levels, but after six weeks, the FCM group showed a considerable increase in haemoglobin levels compared with the ISC group. However, other blood parameters did not alter much over time. According to Table 4, the serum ferritin levels at baseline in the FCM group and the ISC group were 41.95(32.31-

51.60)±31.3 µg/L and 67.60(25.91-109.30)±135.49 µg/L, respectively. Despite the fact that ferritin levels rose in both groups during the course of the study, there was no difference in terms of statistical significance.

Each of the two groups of patients received the full dosage of the medication advised by the physician. There were no serious adverse events reported in either group. Five patients had minor side effect in FCM group (11.6%), which include Epigastric pain, nausea, headache, tingling in body, and rash. Similarly, seven patients in the ISC group (16.3%) had minor side effects.

Postpartum mode of delivery and baby weight, there was no significant difference. When we assessed satisfaction of both group of patients, there was similar level of satisfaction based on safety and cost. However, patient felt more convenience with FCM as it needed only single visit where was for ISC patient had to visit hospital 4-5 times when we assessed drug cost which was higher in FCM group (Table 5).

Table 3: Various blood markers in the FCM and ISC groups over the course of the research

Variables	FCM group, n=43	ISC group , n=43	P-value
Haemoglobin (g%)			
Baseline	8.21(7.92-8.50)±0.94	8.51(8.18-8.84)±1.08	0.169
3 weeks, mean ±SD	9.10(8.85-9.36)±0.83	9.21(8.93-9.50)±0.91	0.564
6 weeks, mean ±SD	10.37(10.16-10.57)±0.67	9.78(9.58-9.99)±0.66	<.00
12 weeks, mean ±SD	11.47(11.23-11.71)±0.77	10.29(10.11-10.46)±0.57	<.001
MCV (fl)			
Baseline [mean(95%CI)±SD]	74.91(72.74-77.07)±7.04	76.86(74.08 -79.64)± 9.03	0.27
3 weeks [mean(95%CI)±SD]	80.62(78.80-82.45)±5.93	82.00(79.60-84.39)±7.78	0.36
6 weeks [mean(95%CI)±SD]	86.93(85.12-88.75)±5.90	87.2(84.95-89.45)±7.31	0.85
12 weeks [mean(95%CI)±SD]	94.05(92.77-95.32)±4.15	93.31(90.80-95.82)± 8.16	0.6
MCH (pg)			
Baseline	23.95 (23.04 - 24.87)± 2.98	26.35 (25.20 - 27.50)± 3.73	0.001
3 weeks, mean ±SD	27.58 (26.78- 28.38)± 2.60	28.87 (27.84 - 29.90)± 3.36	0.05
6 weeks, mean ±SD	30.86(30.16 - 31.57)±2.29	31.38 (30.44-32.32)± 3.05	0.373
12 weeks, mean ±SD	33.85(33.15 -34.55)±2.27	33.50 (32.49-34.51)±3.27	0.57
MCHC (gm%)			
Baseline	31.129(30.65-31.58)±1.50	33.02 (32.38-33.67)±2.09	<0.001
3 weeks, mean ±SD	33.119(32.93-33.28)±0.57	33.54(33.15 -33.93)±1.27	0.047
6 weeks, mean ±SD	34.59(34.28-34.91)±1.02	35.11(34.79-35.44)±1.06	0.022
12 weeks, mean ±SD	35.89 (35.58-36.20)±1.02	36.13(35.93-36.34)±0.68	0.189
RDW (%)			
Baseline	20.23(19.54-20.93)±2.26	20.63(19.61-21.65)±3.32	0.52
3 weeks, mean ±SD	17.41(16.91-17.91)±1.62	18.07(17.38-18.76)± 2.24	0.122
6 weeks, mean ±SD	15.40(14.95-15.84)±1.44	16.57(15.35-17.79)±3.96	0.073
12 weeks, mean ±SD	13.03(12.70-13.37)±1.09	13.82 (13.29-14.34)±1.70	0.013

Table 4: Different time points during the research period in the FCM and ISC groups were used to measure serum iron concentrations

Variables	FCM group, n=43	ISC group , n=43	P-value
S Iron (µg%)			
Baseline	41.95(32.31-51.60)±31.33	55.35 (47.75-62.95)±24.69	0.03
3 weeks, mean ±SD	73.49(65.45-81.53)±26.13	73.16(66.79-79.53)±20.69	0.948
6 weeks, mean ±SD	98.81(92.38-105.24)±20.89	95.91(87.17-04.64)±28.37	0.591
12 weeks, mean ±SD	126.99(119.53-134.45)±24.23	128.62(119.18-138.07)±30.68	0.785
S ferritin (µg%)			
Baseline	67.60(25.91- 109.30)±135.49	33.53(28.73- 38.34)±15.63	0.105
3 weeks, mean ±SD	83.86(57.20-110.51)±86.62	67.06(63.66-70.46)±11.04	0.211
6 weeks, mean ±SD	120.39(89.16-151.62)±101.49	95.29(92.36-98.23)±9.54	0.11
12 weeks, mean ±SD	138.28(124.77-151.80)±43.92	137.75(133.45-142.06)±14.00	0.94
TIBC (µg/L)			
Baseline	496.51(474.97-518.06)±70.01	466.63(448.53- 484.73)±58.81	0.035
3 weeks, mean ±SD	393.90(380.96-406.84)±42.04	394.09(383.23-404.94)±35.27	0.982
6 weeks, mean ±SD	324.75(316.75-332.75)±25.99	317.89(308.12- 327.66)±31.74	0.276
12 weeks, mean ±SD	271.96(266.62-277.31)±17.36	267.15(260.89-273.41)±20.35	0.241
Transferrin saturation (%)			
Baseline	13.21(11.19-15.23)±6.56	13.21(11.43-14.99)± 5.78	0.999
3 weeks, mean ±SD	22.33(21.30-23.36)±3.35	24.28(22.88- 25.68)±4.55	0.026
6 weeks, mean ±SD	33.47(31.32- 35.61)±6.96	34.85(32.77-36.92)±6.74	0.352
12 weeks, mean ±SD	43.91(40.82-47.00)± 10.04	44.51(42.30-46.72)±7.18	0.753

Table 5: Iron requirement and other outcomes

Variables	FCM group, n=43	ISC group , n=43	P-value
No of doses of iron, median (IQR: Q1-Q3) Range: Minimum-Maximum	1(IQR:1-1)	4(IQR:4-5)	<0.001
Iron requirement (mg),mean ±SD	950.95±115.49	869.8±210.77	0.3
Cost of treatment (INR), mean ±SD	5941.33±341.97)	5056±822.76	<0.001
Mode of delivery			
LSCS, n (%)	18(41.9)	20(46.51)	0.664
Vaginal delivery, n(%)	25(58.1)	23(53.49)	
Baby birth weight (kg),mean ±SD	3.27±0.322	3.21±0.252	0.361
Side effects, n(%)	5 (11.6%)	7 (16.3)	0.534
Satisfied with			
Safety, n (%)	42(97.67)	41(95.35)	0.557
Cost, n (%)	40(93.02)	38(88.37)	0.458
Convenience, n (%)	39(90.7)	16(37.21)	<0.001

Discussion

Preterm delivery and low birth weight infants have been related to anaemia during pregnancy, as have maternal health complications. Although the consequences of mild to moderate iron deficiency anaemia may not be so dangerous, maternal mortality and morbidity in both underdeveloped and developed countries can be enhanced by severe iron deficiency anaemia in pregnant women.

In the great majority of cases, oral iron supplements can successfully treat iron deficiency anaemia during pregnancy. Iron supplementation is well tolerated by most people, although up to 40% may experience adverse effects that are dose-related [11,12].

The standard treatment for parenteral iron therapy has been iron sucrose, in pregnant women who cannot tolerate iron oral preparations. However, the main disadvantage with iron sucrose is limited dose per setting which needs patients to visit clinic multiple times to take the required amount, while FCM can be administered in a larger amount at a single visit only [9].

Pregnant women in their second and third trimesters can now get the benefits of FDA-approved ferric carboxymaltose. Ferric carboxymaltose during pregnancy is a controversial topic with only a few studies examining the molecule [9]. Hb levels rose at the conclusion of the research with FCM and ISC, but FCM had the extra benefit of a big iron dosage at one time, which meant that patients did not require as many doses, and they were more comfortable since they did not have to apply it several times. In our study, we observed that three weeks after therapy began, the FCM group had significantly greater Hb levels than the ISC group. FCM recorded 3.26 gm percent rise of Hb as against 1.77 gm percent in ISC (p-value< 0.001).

Pregnant patients with iron deficient anaemia were evaluated between intravenous FCM and oral iron by Breymann C. *et al*. [12]. In both groups, haemoglobin levels rose at a similar rate, but the improvement was significantly different. Anaemia correction in the FCM group was faster and more efficient than in the oral group [Hb ≥ 11.0 g/dL; 84% to 70%; OR: 2.06; 95% CI 1.07, 3.97; P = 0] within a shorter time period (median 3.4 vs. 4.3 weeks). Oral iron therapy was found to be useless in the second and third trimesters of pregnancy, while FCM was found to be safe and beneficial for expecting mothers and their unborn babies. Our research also revealed that FCM induced a quick increase in haemoglobin with a good safety record.

Serum ferritin levels influence the amount of iron in the body. After receiving FCM infusion, patients with anaemia and women with iron deficiency, but no anaemia were shown to have higher ferritin levels [5,13]. In our investigation, we found that the serum ferritin levels of the FCM and ISC groups were comparable at the beginning and conclusion of the 12-week trial. Despite the fact that FCM increases iron storage quickly, it is likely that over the long run, ISC is just as effective in replacing iron stores.

Ferric carboxymaltose has been shown to be safe and tolerable in a number of studies including a variety of patient groups, as well as in a meta-analysis of 14 randomised trials involving more than 3000 patients. For the treatment of postpartum anaemia, ferric carboxymaltose has been widely studied [15]. Breastfeeding infants of moms who received FCM have not been proven to have any safety concerns.

In the current study, the FCM group had a considerably greater medication cost than the ISC group. The ISC group, on the other hand, had higher travel expenses and lost workdays as a result of numerous hospital visits, which were not taken into account in this study. As a result of the requirement for several hospital visits, the overall cost of therapy may have been greater. Previous research [16, 17] has shown that FCM therapy is significantly less expensive than ISC treatment when it comes to the therapy's cost.

Pregnant women tolerate ferric carboxymaltose better than iron sucrose, according to our study. Both groups saw no major side effects from the therapy. There was no evidence of an anaphylactic or anaphylactoid reaction.

Strength of the present study is that pregnant women's acceptance of therapy with ferric

carboxymaltose was examined in this study in addition to safety and effectiveness. Data on side effects that were recorded during and after treatment are reliable, according to reliable sources. In the majority of prior studies, Ferric carboxymaltose was utilized in an inpatient setting, but we treated the patient at outpatient setting and monitored him for two hours after the injection.

Limitation of the present study were small sample size. No data on haematological parameters or ferritin levels were assessed in relation to the neonatal outcome. Anaemia's effect on mental well-being or the treatment's advantages were not explored which are further potential research areas on this subject.

Conclusion

FCM is a safe and effective treatment option for iron deficiency anaemia in the second and the third trimester of pregnancy and is well tolerated with excellent safety profile. Large dosage administration per sitting, early Hb increase, less total doses required, reduced hospital visits for patients, and overall cost savings are some of the FCM advantages.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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