

# Intravenous Ferric Carboxymaltose Compared to Oral Iron in the Treatment of Iron Deficiency Anaemia in Pregnancy

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**Abstract:** *Background:* Iron deficiency Anaemia (IDA) in pregnancy is a global phenomenon and causes significant maternal morbidity and mortality worldwide. Effective management of IDA in pregnancy is currently lacking. Ferric Carboxymaltose (FCM) is a newer treatment option which is both effective and well tolerated. *Objectives:* To compare the efficacy and tolerance of FCM with oral iron in the treatment of IDA in pregnancy. *Materials and Methods:* This is a prospective study carried out over a period of 12 months in the department of Obstetrics and Gynaecology, Gauhati Medical College and Hospital, Guwahati, India. Pregnant women (n=100), between 12-36 weeks with IDA were randomised 1:1 to FCM (500 mg iv in 250 ml NS) or oral iron (200 mg elemental iron per day orally) for 6 weeks. *Results and observations:* Rise in mean Hb and mean serum ferritin levels after 3 weeks and 6 weeks was more in FCM Group than Oral Group. The difference was statistically significant. Also, treatment with FCM led to fewer gastrointestinal adverse events. *Conclusion:* During the second and third trimesters, FCM has improved efficacy than first line oral iron treatment and is well tolerated in pregnant women.

**Keywords:** Ferric carboxymaltose, Oral iron, Haemoglobin, Serum ferritin, Gastrointestinal

## 1. Introduction

Anaemia in pregnancy is one of the most frequent problems in Obstetrics. It is one of the major contributing factors in maternal mortality and morbidity in third world countries and according to the WHO, contributes to 20% maternal deaths [1]. In India, nearly two-thirds of all pregnant women are affected. WHO defines anaemia in pregnancy as the haemoglobin concentration of less than 11gm/dl and a haematocrit of less than 33%. Using 11gm/dl as a cut-off for the definition of anaemia is probably too high for India and hence Federation of Obstetrics and Gynaecological Societies of India (FOGSI) has suggested a cut off of haemoglobin of 10gm/dl for India [2].

The main cause of anaemia in pregnancy is found to be iron deficiency, about 95% [3], making Iron Deficiency Anaemia (IDA), the commonest cause of anaemia during pregnancy. Iron deficiency in pregnancy has been defined by the National Academy of Sciences Panel On Nutrition and Pregnancy as ferritin levels lower than 12 ng per ml. Many women have low or empty iron stores already at the start of pregnancy. During pregnancy, there is an increased demand for iron, required to support maternal haemoglobin mass expansion, as well as the growing foetus and placenta. Dietary iron intake does not compensate for this strongly increased iron demand. Consequently, the risk of iron deficiency and, ultimately, iron deficiency anaemia increases during pregnancy. This is further aggravated by blood loss associated with delivery.

Peri-partum iron deficiency anaemia (IDA) is associated with significant maternal, foetal and infant morbidity. However, iron deficiency is potentially both preventable and

treatable. For many decades, the mainstay treatment of IDA has been oral iron and red blood cell (RBC) transfusions. However, oral iron supplementation can lead to significant gastrointestinal side effects. The risks of RBC transfusion, anaphylactic and allergic reactions and risks of transmissible diseases are well described and should be avoided whenever possible[4]. Intravenous iron formulations offer an alternative approach in the presence of moderate or severe anaemia, intolerance of or non-adherence to oral iron and malabsorption states. However, Intravenous Iron either risks anaphylaxis [5] when using iron dextran or requires multiple injections of low doses when using previously available non-dextran-containing agents like iron sucrose [6,7].

Ferric Carboxymaltose is a newer dextran-free iron formulation with a near neutral pH, physiological osmolarity and increased bioavailability which allows for a single dose, short 15 minute infusion time and higher dosing (up to 1000 mg)[8]. To date, there are few clinical studies using ferric carboxymaltose in pregnant women. However, it has been previously shown that ferric carboxymaltose does not cross the placental barrier in an in vitro dual perfusion model[9] and its use is approved in the second and third trimesters of pregnancy. Hence, to determine whether large-dose intravenous FCM administration is an effective iron therapy, we conducted a prospective study to compare the efficacy and tolerance of intravenous ferric carboxymaltose with that of oral iron in the management of patients with anaemia during pregnancy.

## 2. Materials and Methods

This is a hospital based study carried among anaemic, pregnant patients in Gauhati Medical College and Hospital,

Guwahati, Assam from June 2016 to May 2017. This is a prospective and interventional study based on comparison and observation. The study protocol was approved by the Institutional Ethical Committee. 100 antenatal patients who fulfilled the inclusion criteria were randomly selected for the study. The inclusion and exclusion criteria taken for the study have been mentioned below.

**Inclusion criteria**

Pregnant women, with period of gestation from 12 weeks to 36 weeks and serum haemoglobin levels between 7- 9.9gm %, willing to participate in the study.

**Exclusion criteria**

- a) Women with anemia not linked to iron deficiency i.e. anaemia due to haemoglobinopathies or haemolyticanaemias.
- b) Women with hypersensitivity or intolerance to iron derivatives.
- c) Women with signs of infection or evidence of chronic diseases like renal or hepatic dysfunction, heart diseases, malaria or tuberculosis.
- d) Women who had recent blood transfusion.
- e) Women with irregular follow up.

Written and informed consent was taken from each patient after explaining the benefits and risks associated with the study. A structured case record form was used to record the detailed particulars of the patient. One group of 50 patients (Group F) was given 500 mg IV ferric carboxymaltose in 250 ml NS. Patients were observed for next 1 hour for any side effects such as burning sensation at injection site, swelling at injection site, pruritis, nausea, vomiting, chills or rigor, etc. The other group of 50 patients (Group O) was given oral iron sulphate tablets containing 100 mg of elemental iron twice daily for 6 weeks. After drug administration, patients were asked to come for follow up 3 weeks & 6 weeks after treatment.

**Follow up**

The primary outcome was assessed by measuring haemoglobin & serum ferritin levels 3 weeks & 6 weeks after treatment and a comparison of the safety and efficacy between the two groups was made. Secondary outcome measures were to observe for any adverse effects and need of blood transfusion.

**Statistical analysis**

Data were compared by using Mann - Whitney U test for numerical variables and Fischer's exact test for categorial variables. A p value < 0.05 was considered significant. Friedman's ANOVA followed by Dunn's posthoc test was used for multiple comparisons in Hb level and serum ferritin level between the groups.

**3. Results and Observations**

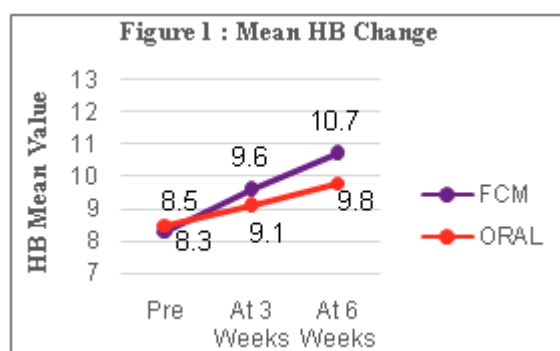
A total of 100 anaemic pregnant women were included in the study; 50 received FCM injection and 50 were given oral ferrous sulphate tablets. All the cases in both the groups were well matched with respect to the demographics. The pre treatment mean Hb level and mean serum ferritin level were comparable in both the groups and the difference was found to be statistically insignificant.

**Table 1:** Distribution of patients

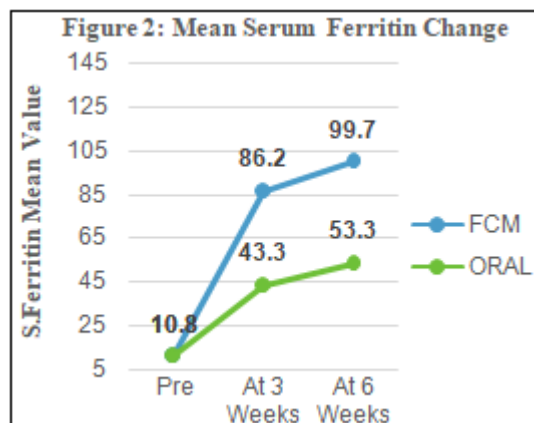
Parameter	Group F	Group O	p value
Age (years)	23.92 ±3.77	23.76 ±4.04	0.71
Pre treatment mean Hb level (g/dl)	8.39 ±0.78	8.52 ±0.77	0.37
Pre treatment mean serum ferritin level (ng/ml)	10.84 ±1.31	10.87 ±1.06	0.72

**Efficacy**

The pre treatment Hb levels in both the groups were comparable (Mean ± S.D. for F group 8.39 ±0.78 gm/dl and O group 8.52 ± 0.77gm/dl; p value = 0.37). Significant rise in Hb levels were noted in both the treatment groups. However, rise in mean Hb level after 3 weeks and 6 weeks was more in Group F (9.63 ± .81 gm/dl and 10.73± .86 gm/dl) than Group O (9.16 ± .85 gm/dl and 9.82 ± .92 gm/dl) respectively. This difference between the two groups at 3 weeks and 6 weeks was found to be statistically significant (p value= .0096 and <.0001) respectively.



Similarly, though increase in ferritin levels was seen with both treatment groups, a significantly greater increase in serum ferritin was seen with FCM treatment compared to oral iron. The mean and standard deviation of pre treatment serum ferritin levels in both the groups were comparable i.e. 10.84 ±1.31 ng/ml for F Group and 10.87 ± 1.06 ng/ml for O Group (p value =0.72). Rise in mean serum ferritin level after 3 weeks and 6 weeks was more in Group F (86.27± 10.12 ng/ml and 99.76 ±16.32 ng/ml) than Group O (43.34± 8.36 ng/ml and 53.34± 7.31 ng/ml) respectively. This difference between the two groups at 3 weeks and 6 weeks was found to be statistically significant (p value= <.00001 and <.00001) respectively.



Thus, FCM was found to be much more effective than oral iron sulphate in increasing serum ferritin and Hb levels and

thus, in correcting iron deficiency anaemia during pregnancy.

**Table 2:** Changes in Hemoglobin level with treatment

Hb Levels					
	Pre Treatment	At 3 weeks	P value	At 6 weeks	P value
FCM	8.39 ± 0.78	9.63 ± .81	<.00001	10.73 ± .86	<.00001
Oral	8.52 ± .77	9.16 ± .85	0.0002	9.82 ± .92	<.00001
P value	0.37	0.0096		<.00001	

**Table 3:** Changes in Serum ferritin levels with treatment

Serum Ferritin Levels					
	Pre Treatment	At 3 weeks	P value	At 6 weeks	P value
FCM	10.84 ± 1.31	86.27 ± 10.12	<.00001	99.76 ± 16.32	<.00001
Oral	10.87 ± 1.06	43.34 ± 8.36	<.00001	53.34 ± 7.31	<.00001
P value	0.72	<.00001		<.00001	

### Safety and tolerability

No major side effects were noted in any of the treatment group. However, 16 patients (32%) in Group O had nausea and vomiting whereas only 3 patients (6%) in Group F complained of nausea and vomiting and this was statistically significant (p value=.0009). 9 patients (18%) in Group O also complained of heartburn whereas none of the patients in Group F had similar complains and this was found to be statistically significant (p value=.0026). Thus, gastrointestinal side effects are significantly more in the oral iron group which often decreases patient compliance. Other side effects noted were headache (1 patient in F Group), burning sensation at the injection site (4 patients in F Group), pruritus (2 patients in F Group) and chills/rigor (1 patient in F Group). None of these side effects were noted in O Group, however the difference was found to be statistically insignificant (p value >.05 in all four conditions).

**Table 4:** Comparison of adverse effects of both FCM & Oral Group

Adverse Effect	No. of cases F Group	Percentage %	No. of cases O Group	Percentage %	P value
Nausea/Vomiting	3	6	16	32	0.0009
Heart Burn	0	0	9	18	0.0026
Headache	1	2	0	0	1
Burning sensation at injection site	4	8	0	0	0.1174
Pruritis	2	4	0	0	0.4949
Chills / rigor	1	2	0	0	1

### Need of blood transfusion

30 patients in the F Group and 28 patients in the O Group delivered during the course of study. 4 patients out of 30 (13.33%) in the F group and 9 patients out of 28 (32.14%) in the O Group required blood transfusion. More patients required blood transfusion in the O group, however the difference was not statistically significant (p value = 0.11).

**Table 3:** Comparison of need of blood transfusion in both groups

Need of blood transfusion	No. of Cases F Group	No. of Cases O Group	P value
Yes	4	9	0.11
No	26	19	

## 4. Discussion

Our study shows that IV FCM is effective and well tolerated in pregnant women in the second and third trimester of pregnancy. Though significant improvement in haemoglobin was seen in both the groups, FCM improved Hb levels to a significantly greater extent than oral iron. Similarly, rise in serum ferritin levels was significantly greater with IV FCM. The findings of our study have been consistent with other studies.

In a prospective study conducted by Froessler et al [10] intravenous ferric carboxymaltose infusion significantly increased Hb values (p < 0.01) above baseline levels in all women. Increased Hb values were observed at 3 and 6 weeks post infusion and up to 8 weeks post-infusion. Ferritin values also increased significantly after the infusion. Of the 29 (44.6%) women interviewed, 19 (65.5%) women reported an improvement in their well-being and 9 (31%) felt no difference after the infusion. No serious adverse effects were found and minor side effects occurred in 13 (20%) patients [7]. No adverse effect on fetus was found.

Breyman et al [11] conducted a randomised controlled trial in 2016 comparing IV FCM with oral ferrous sulphate (FS). Significantly more women achieved anaemia correction with FCM than FS and within a shorter time frame. FCM treatment significantly improved vitality and social functioning prior to delivery. Recently, Maheshwari et al in 2017 [12] conducted a prospective randomised controlled trial in 300 pregnant women in Muzaffarnagar Medical College. Efficacy, safety and cost effectiveness of oral iron sulphate, IV iron sucrose and IV FCM was compared. Regarding efficacy, all three groups were statistically significant. However, maximum improvement in haematological parameters was seen with IV FCM.

In addition to haematological effectiveness, a number of other benefits of FCM over oral iron was demonstrated. For some patients, a single dose of FCM may correct IDA with no repeated administration required. This increases patient's compliance and dramatically reduces health care costs.

FCM was well tolerated in pregnant women in second and third trimester. The safety profile was found to be consistent with what has been previously reported. No serious adverse effects were noted in any of the treatment groups. However, as expected treatment with FCM led to significantly lesser gastrointestinal side effects and this is likely to improve adherence to therapy.

To date few prospective controlled studies have been performed comparing IV FCM with first line oral iron. This is the first prospective study reporting on ferric carboxymaltose infusions in pregnancy in North East India. The key finding of our study is that in women presenting with IDA in second and third trimester, FCM injections prior to delivery significantly increased haemoglobin levels and improved iron stores.

## 5. Conclusion

The data from this prospective study is consistent with other studies that ferric carboxymaltose infusion in second and third trimester of pregnancy is more effective and well tolerated than routinely used oral ferrous sulphate. No unexpected safety concerns were noted. Thus, during late pregnancy when rapid correction of anaemia is warranted in a shorter time, FCM becomes more appropriate option than oral iron.

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