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Original Research Article

## Efficacy and safety of ferric carboxymaltose in Indian pregnant women with iron deficiency anemia

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### ABSTRACT

**Background:** Iron deficiency anemia (IDA) is a significant problem worldwide particularly in women. The aim of the study was to evaluate the effectiveness of intravenous ferric carboxymaltose (FCM) in Indian pregnant women with anemia.

**Method:** This was a single centre, prospective, observational, open label, clinical study at real life scenario with 4 weeks follow up. Fifty pregnant women with IDA and visiting to the Radhakrishna multispecialty hospital, Bangalore, for antenatal care were enrolled for the study. IV FCM was given as per the standard protocol. Change in the laboratory parameters such as hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), packed cell volume (PCV) level at baseline and after 4 weeks of completion of parenteral iron therapy was recorded and fatigue score was assessed. The pregnant women were monitored for the adverse events.

**Results:** All pregnant women received a single IV infusion of FCM 1000 mg. A significant increase in the hemoglobin of  $2.37 \pm 0.51$  g/dl ( $p < 0.001$ ) was noted at 4 weeks, MCV rise of  $19.89 \pm 21.94$  ( $p < 0.001$ ) was noted at 4 weeks, MCHC rise was of  $2.56 \pm 5.65$  and PCV rise was of  $4.45 \pm 2.67$  ( $p < 0.011$ ) at over 4 weeks. Significant improvement in fatigue score was observed at 4 weeks after single FCM infusion. No adverse effects were observed in any pregnant woman throughout the duration of the study.

**Conclusions:** This real-life observational study highlights IV FCM is effective in management of IDA in pregnant women and well tolerated.

**Trial registration number:** CTRI/2021/02/030874

**Keywords:** IDA, FCM, Hemoglobin, MCV, MCHC, PCV

### INTRODUCTION

Anemia is a common health problem worldwide during pregnancy with a prevalence of 41.8%.<sup>1,2</sup> The national family health survey (NFHS)-5 data shows 57.2% Indian women in the age group of 15 to 49 years are anaemic, a rise from 49.7% in comparison with NFHS-4 was noted.<sup>3</sup> The most common cause of anemia in pregnancy is iron deficiency (ID).<sup>4</sup> IDA is prevalent in Indian pregnant women, around 47% of women suffer from iron deficiency anemia during pregnancy.<sup>5</sup> If IDA remains untreated during pregnancy it can lead to maternal morbidity and perinatal morbidity.<sup>4</sup> Therapy for ID includes mainly

dietary modification, oral iron supplementation and in selected cases intravenous (IV) iron and blood transfusion.<sup>6</sup> Oral iron therapy is mainstay in treating IDA in pregnancy however, tolerability is major limiting factor.<sup>7</sup> Also, oral iron therapy is not adequate to treat moderate to severe anemia and also in pregnant women who are reporting late in second and third trimester. There are limitations of oral iron therapy with adverse effects like constipation, dysgeusia and nausea. Poor adherence is a common cause for failure to respond to oral iron therapy.<sup>8</sup> A major drawback of oral iron is compliance owing to poor tolerability and side effects. The GI adverse effects of oral iron may further exacerbate the pregnancy associated GI

disturbances which includes indigestion, constipation, nausea, vomiting, and reflux esophagitis.<sup>9</sup> Parenteral iron therapy is the treatment of choice in these patients and reduces need for blood transfusions in the antenatal and postpartum period.<sup>10</sup> There are many IV iron preparations like: Iron sucrose (ISC), iron polymaltose, and FCM. Among the various preparations of parenteral iron supplementation FCM was found to be superior to all other parenteral iron supplementation products.<sup>11-13</sup> FCM is a stable and robust complex formulated as a colloidal solution.<sup>14</sup> It has a neutral pH (5.0-7.0) and physiological osmolarity which makes it possible to administer its higher single doses over shorter time periods (single dose up to 1000 mg over 15 min) than other parenteral preparations. It is dextran free, therefore negligible risk of anaphylaxis or serious hypersensitivity reactions.<sup>15</sup> Safety pharmacology studies highlighted favourable cardiovascular, central nervous, respiratory, and renal tolerability.<sup>14</sup> All these properties make IV FCM an attractive alternative in terms of safety, efficacy, convenience, and resource utilization.<sup>16</sup> There are published literatures highlighting role of FCM for treatment of anemia in the postpartum period and other diseases with associated anemia.

There is limited data of clinical use of FCM in Indian pregnant women at real life scenario and the objective of present study was to evaluate the efficacy and safety of IV FCM in Indian pregnant women with anemia in real-life scenario.

## METHODS

### Study design

This was a single centre, prospective, open label, 4 weeks' observational study in a real-world scenario at the Radhakrishna multispecialty hospital, Bangalore, India from February 2021 to April 2021.

### Patient characteristics

Pregnant women aged >18 years of age, between 16 to 36 weeks of gestation with hemoglobin between 6 g/dl to 10 g/dl and not responding to oral iron or oral iron therapy not tolerable or oral iron therapy is inappropriate based on clinical judgement of investigator and provided informed consent were part of this study.

Pregnant women with anemia due to causes other than IDA; any chronic infections like hepatitis and HIV; serum transaminases more than 1.5 times the upper limit of normal; serum creatinine level of more than 2.0 mg/dl or history of allergic reaction to intravenous iron infusion were excluded from study.

### Treatment characteristics

FCM was used as per the institution's protocol and locally approved prescribing information. The iron requirement is

calculated with Ganzoni's formula and FCM (Injection Orofer FCM, Emcure pharmaceuticals Ltd., Pune, India) was administered. Individualized iron dosage with a maximum dose of 1000 mg (20 mg/kg body weight) in a single infusion over at least 15 min was administered.

### Outcome measure

Routine antenatal investigations were done according to the standard departmental protocol. Investigations specific to anemia included hemoglobin (Hb), MCV, MCH, MCHC. Fatigue measurement was done by a linear analogue scale assessment (LASA) that recorded scores between 0 (no fatigue) and 10 (worst possible fatigue).

### Ethical consideration

Ethical clearance was obtained from an independent ethics committee at Bangalore and the trial was registered with clinical trial registry of India (CTRI) CTRI/2021/02/030874.

### Statistical analysis

The laboratory parameters from baseline after 4 weeks, change in hemoglobin levels, MCV, MCH, MCHC, change in fatigue levels, safety outcome was analysed. Data were presented as number (%) or mean  $\pm$  SD/median (min-max) as appropriate. Baseline categorical variables were compared between the groups using Chi-square/Fisher's exact test and continuous variables were compared using student's t test/Wilcoxon rank sum test.

## RESULTS

Total 50 pregnant women matching inclusion and exclusion criteria and provided written consent completed the study. All pregnant women received a single IV infusion of FCM 1000 mg over 15 minutes.

A significant increase in mean hemoglobin of 2.24 g/dl ( $p < 0.001$ ) over 4 weeks was observed.

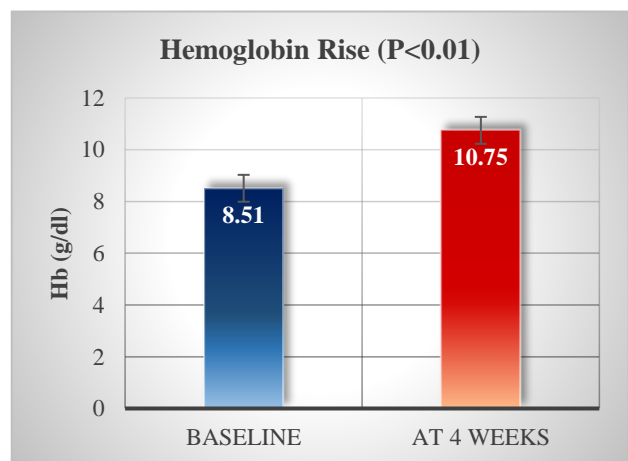
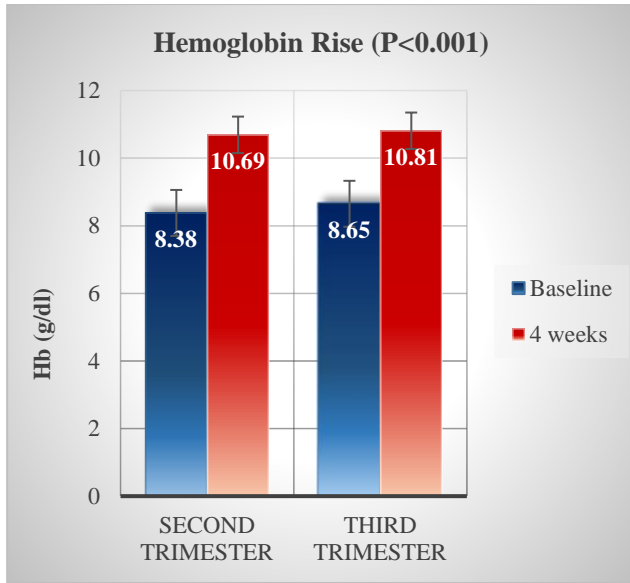


Figure 1: Increase in hemoglobin.



**Figure 2: Significant increase in Hb levels in 2<sup>nd</sup> and 3<sup>rd</sup> trimester.**

Significant increase in hemoglobin was noted in both, 2<sup>nd</sup> and 3<sup>rd</sup> trimester of pregnancy. Increase in Hb in second trimester observed was 2.31 g/dl (p<0.001) and increase in Hb in second trimester observed was 2.16 g/dl (p<0.001).

A significant rise in Hb was observed at 4 weeks' treatment irrespective of gravida status (Table 1).

Table 2 shows significant increase in all the age group. In age group of women > 20 years, the mean values of 4 weeks Hemoglobin (g/dl) is higher with a difference of 2.37 g/dl was statistically significant with a p=0.015, whereas this rise in hemoglobin was 2.28 g/dl at 4 weeks' treatment in age group 21-25 years, 2.18 g/dl at age group 26-30 years, 2.26 g/dl in age group 31-35 years.

Table 3 shows mean rise of lab parameters in all pregnant women at 4 weeks of the treatment. There was a significant increase in all haematological parameters like MCV (mean increase 19.89, p<0.001), MCHC (mean increase 2.56, p<0.011), PCV (mean increase 4.45, p<0.001)

**Table 1: Significant increase in Hb irrespective of gravid status.**

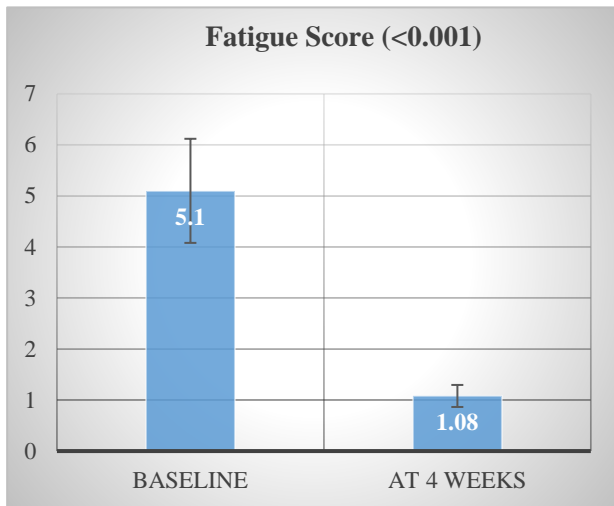
Pregnancy category	N	Hb measured at	Hb levels (g/dl),	Rise in Hb (g/dl)	P value
			Mean ± SD	Mean difference ± SD	
Primi	15	Baseline	8.31±0.77	2.4±0.48	<0.001
		4 weeks	10.71±0.57		
Second	25	Baseline	8.6±0.58	2.13±0.35	<0.001
		4 weeks	10.72±0.53		
Third	10	Baseline	8.58±0.8	2.29±0.59	<0.001
		4 weeks	10.87±0.45		

**Table 2: Increase in Hb in all age groups.**

Age group (Years)	N	Hb measured at	Hb levels (g/dl)	Rise in Hb (g/dl)	P value
			Mean ± SD	Mean difference ± SD	
18-20	3	Baseline	8.47±0.81	2.37±0.51	0.015
		4 weeks	10.83±0.67		
21-25	14	Baseline	8.52±0.58	2.28±0.4	<0.001
		4 weeks	10.8±0.51		
26-30	18	Baseline	8.44±0.58	2.18±0.41	<0.001
		4 weeks	10.62±0.48		
31-35	15	Baseline	8.57±0.91	2.26±0.56	<0.001
		4 weeks	10.83±0.56		

**Table 3: Hematological parameters after 4 weeks of FCM treatment.**

Parameters	Duration	No. of pregnant women	Mean ± SD	Mean difference ± SD	P value
MCV, (fL)	Baseline	47	52.52±23.56	19.89±21.94	<0.001
	4 weeks	47	72.4±4.75		
MCHC, (g/dl)	Baseline	35	31.45±5.04	2.56±5.65	<0.011
	4 weeks	35	34.01±1.24		
PCV, (%)	Baseline	50	26.72±2.78	4.45±2.67	<0.001
	4 weeks	50	31.17±1.82		



**Figure 3: Improvement in fatigue score.**

Significant improvement in fatigue score was observed at 4 weeks after single FCM infusion (1.08,  $p<0.001$ ) (Figure 3).

No adverse effects were observed in any pregnant women throughout the duration of the study.

## DISCUSSION

Anemia during pregnancy is a major global health concern affecting half of pregnant women. IDA is easily preventable. Parenteral iron therapy can reduce chances of morbidity and mortality during pregnancy and timely intervention can reduce burden over health sector by reducing complications during delivery due to anemia.

It is well known fact that iron deficiency anemia is more prevalent in low socioeconomic class and community with poor literacy, due to nutritional deficiencies, phytate rich diet, frequent infections like malaria, intestinal worms, less interval between to pregnancies.<sup>17</sup>

This study analysed hemoglobin, MCV, MCHC, and PCV level before and after 4 weeks of completion of parenteral iron therapy. Pregnant women after receiving FCM had reported hemoglobin rise of  $2.37\pm 0.51$  g/dl, MCV rise of  $19.89\pm 21.94$  fL, MCHC rise of  $2.56\pm 5.65$  g/dl and PCV  $4.45\pm 2.67\%$ .

IDA causes fatigue and reduced quality of life. Our study highlights significant improvement of fatigue score in 4 weeks.

Gupte et al assessed the efficacy and safety of FCM in Indian pregnant women with moderate-to-severe anemia.<sup>18</sup> In their retrospective real-world evidence analysis, Gupte et al reported that the dosage of FCM injection varies from 500 to 2000 mg depending on iron requirement with a mean dose of 1057 mg.<sup>18</sup> Our study demonstrated demonstrates that significant increase in hemoglobin in all

subsets of pregnant women in 4 weeks with single infusion of FCM 1000 mg. All the pregnant women in our study reported significant increase in hemoglobin in 4 weeks' duration.

Anemia Mukht Bharat Indian operational guidelines of an intensified national iron plus initiative (I-NIPI) provides anemia management protocols including pregnancy.<sup>19</sup> As per the guidelines, parenteral iron including FCM can be considered as the first line, if anemia is detected late in pregnancy and compliance is likely to be low. Also, FCM is considered as a second-line treatment if no improvement is seen after the first level of treatment (oral iron supplements). In moderate (7-9.9 g/dl) and severe anemia (5.0-6.9 g/dl), FCM is considered as first-line treatment.<sup>20</sup> Interestingly, in our study a pregnant woman with severe anemia reported a significant increase in hemoglobin of 4.23 g/dl.

The present study further strengthens the evidence of efficacy and safety of FCM in anemia, particularly in Indian pregnant women. The limitations of the present study are that not all hematological parameters data were available and lack of control group. Despite these limitations, this study supports clinical efficacy and excellent safety of FCM in pregnant Indian women with anemia.

## CONCLUSION

This prospective observational study at real life scenario highlights 1 gm IV infusion of FCM is effective in treating IDA in pregnant Indian women. High dose of IV FCM is well tolerable. IV FCM is important for treatment of IDA in pregnancy in resource limited situation.

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*Conflict of interest: None declared*

*Ethical approval: The study was approved by the Institutional Ethics Committee*

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