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A study on safety and efficacy of ferric carboxymaltose in anaemic patients during pregnancy

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Abstract
Aims & Objectives: The purpose of the study was to assess the safety and efficacy of Ferric Carboxymaltose (FCM) in anaemic patients during pregnancy in the department of Obstetrics and Gynaecology at Rajah Muthiah Medical College & Hospital (RMMCH), a 1400 bedded multi-specialty tertiary care teaching hospital.
Methodology: This is a Prospective Observational Study conducted on total of 41 pregnant anaemic patients who were included in the study of 3 months period. In our study, the majority of the subjects falls in the age group 24-29 (37%) with a mean gestational age 34 ± 2 weeks and the average weight of the patients is 58 ± 3 kilograms.
Results: Outcome of our study shows a significant increase in the mean Hb level and mean ferritin levels. At pre-infusion stage the mean Hb level and mean ferritin levels of 41 patients were recorded as 8.58 ± 0.37 and 78.21 ± 26.41 respectively. Whereas Hb and Ferritin levels increased to 10.85 ± 0.57 and 151.46 ± 16.21; 11.82 ± 0.55 and 195.78 ± 6.94; 11.87 ± 0.58 and 204.07 ± 5.56 after 3 weeks of post infusion, at delivery and at 6 weeks of post infusion respectively. As part of our study, DDD/41 patients were calculated according to the DTC (Drugs and Therapeutic Committee-guide) with reference from WHO Recommended ATC Classification and found that DDD/41 patients were 1.6g.
Conclusions: Our study suggests that therapeutic doses of FCM IV can be recommended for treatment of IDA during pregnancy. It is simple to use and causes significant increase in Hb and ferritin levels. It does not affect the health of the mothers as well as babies. Only a mild and quickly reversible local adverse reaction such as pain and rash at injection site were recorded from patient case sheet and patient interview.

Keywords: Ferric carboxymaltose, anaemia, haemoglobin, ferritin

Introduction
Anemia [1] is a condition that develops when the cells in your body will not get enough oxygen due to lack of RBC or Hemoglobin in your blood. Hemoglobin present in RBC's helps in binding oxygen to the cells, so too few or abnormal RBC's or low Hemoglobin can cause anemia.

Iron deficiency anemia (IDA) [2]: Hemoglobin is responsible for carrying oxygen to your tissues, which is present in your RBC's. The amount of iron present in your body estimates the amount of Hb present.
The most common type of anemia is the iron deficiency anemia which occurs due to insufficient mineral iron in your body. The body doesn't get the amount of oxygen it needs if there isn't enough iron in your blood stream. In many cases people don't know they have iron deficiency anemia, they experience the symptoms for years without even knowing the cause.
The most common cause of iron deficiency anemia in pregnancy is because of loss of iron in the blood due to heavy menstruation. Iron deficiency anemia can also be caused by poor diet or certain intestinal diseases that affects the absorption of iron into the body.
Doctors normally use iron supplements or changes to diet to treat the condition.

Symptoms [3]
At first, symptoms of iron deficiency anemia can be mild and may not even notice them.
The symptoms include:
- General fatigue
- Weakness

- Pale skin
- Tongue swelling or soreness
- Brittle nails
- Fast or irregular heart beat
- Tingling or crawling feeling in the legs
- Headaches
- Dizziness
- Shortness of breath

Causes of iron deficiency anemia [4]

Various causes of Iron deficiency anemia include:

1. Insufficient iron intake:

Inappropriate iron intake over an extended amount of time either due to malnutrition or food malpractice can cause a shortage in your body. Meat, eggs, & some green leafy vegetables are foods rich in iron. Additional supplement of iron is needed in the diet of pregnant women and young children as it is essential during times of growth and development.

2. Menstruation blood loss or pregnancy

The most common cause IDA in women of childbearing age are heavy menstrual bleeding and blood loss during childbirth.

3. Internal bleeding

Medical conditions such as ulcers in stomach, polyps in the colon or intestines or colon cancer can cause internal bleeding, which can lead to IDA. Regular use of Aspirin like pain relievers can also cause bleeding in the stomach.

4. Inability to absorb Iron

Absorption of iron can also be interfered by certain disorders or surgeons that affect the intestines. For example: Celiac disease, Intestinal surgery such as gastro bypass may limit the amount of iron absorbed by the body.

Iron deficiency anaemia during pregnancy [5]

In Obstetrics and Perinatal care the common problem is Anemia. Nutritional deficiencies, parasitic and bacterial diseases and inborn RBC disorders such as thalassemia are main reasons for anemia in pregnancy. Iron deficiency is the main cause of anemia in obstetrics. Stages of Iron deficiency are depletion of iron stores, iron deficient erythropoiesis with anemia and iron deficiency anemia, the most pronounced form of iron deficiency. Various conditions such as uterine or placental bleeding, gastrointestinal bleedings and peripartum blood loss can aggravate pregnancy anemia.

Some of the risk factors caused by anemia for the mother and fetus are intrauterine growth retardation, prematurity, fetoplacental miss ratio and higher risk for peripartum blood transfusion.

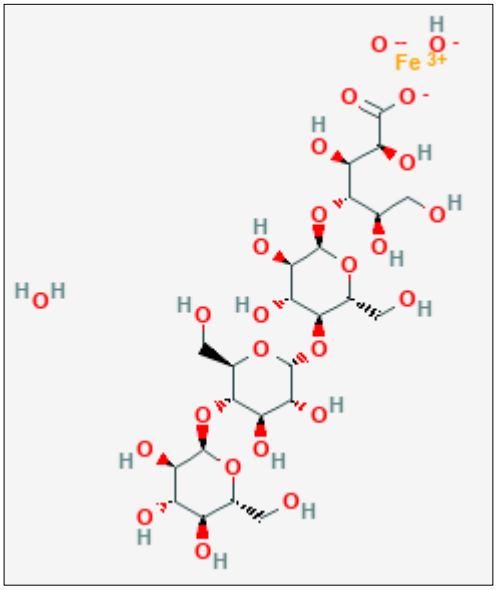
Treatment for iron deficiency anemia during pregnancy [6]

During pregnancy there is a need of increase in iron in the body due to which prophylactic oral therapy is given to all pregnancy women with normal lab values. Throughout pregnancy oral iron preparations can be used whereas IV iron therapy is recommended during the 2nd and 3rd trimesters.

Conditions during pregnancy that require intravenous iron therapy [7]

- Insufficient response to oral iron treatment.
- Patient non-compliance with oral iron treatment.
- Intolerance to oral iron treatment (gastrointestinal adverse effects)
- Presence of severe anemia.(Hb ≤9 g\dL)
- Presence of risk factors like Coagulation disorders, placenta previa.
- Situations where anemia should be treated urgently.

Ferric Carboxymaltose [8]



a) Chemical name: Iron Dextri-Maltose
b) Molecular formula: $C_{24}H_{44}FeO_{25}^-$
c) IUPAC Name: (2S,3S,4S,5R)-4-[(2R,3R,4R,5S,6R)-5-[(2R,3R,4R,5S,6R)-3,4-dihydroxy-6-(hydroxymethyl)-5-[(2R,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyoxan-2-yl]oxy-3,4-dihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-2,3,5,6-tetrahydroxyhexanoate
d) Molecular weight: 788.436 g/mol
e) Mechanism of Action: Ferric carboxymaltose is a colloidal iron (III) hydroxide in complex with carboxymaltose, a carbohydrate polymer that release iron.
f) Pharmacokinetics

Absorption

Maximum serum concentration (Cmax) was 37 µg/mL to 333µg/mL when a single dose of 100 to 1000 mg of iron was given to iron deficient patients. These levels were obtained 15 minutes to 1.21 hours of post dose (Tmax).

Route of elimination

Renal elimination of iron was negligible.

Adverse effects [9]

Nausea (2.2%), Hypertension (1.8%), Flushing (1.6%), Dizziness (1.5%), Vomiting (1.4%), Pruritus (1.2%), Rash (0.8%), Headache (0.5%), Hypotension (0.4%), Constipation (0.2%).

Defined daily dose [10]

Defined Daily Dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults.

- It is a technical unit of measurement, established by convention, based on review of the available information

of the doses recommended by the manufacturer, published drug trials and expert recommendations, and medical practice in a selection of countries.

- Defined Daily Dose provides a unit of measurement that is independent of price and formulation, making it possible to assess trends in consumption of medicines and to perform comparisons between population groups and health-care systems.
- DDDs have not been established for topical medicines, vaccines, general/local anesthetics, contrast media and allergen extracts.
- The DDD method should only be used in settings where reliable procurement, 0inventory or sales data have been recorded. DDD method can be used in calculation of;
- Consumption in units (tablet/capsules)
- Consumption in monetary value
- Cost per DDD
- Cost per course of treatment.

Steps

- Find out the total amount of medicines used or procured in one year in terms of the number of units (tablets, capsules, injections) and the strength (mg, g (gm), IU).
- To calculate the total quantity consumed in one year in terms of mg/g/I.U. and by multiplying the number of units (tabs, caps, inj.) by the strength of dose of the drug.
- Then divide the total quantity by the assigned DDD for that medicine.
- Then divide the total quantity by the number of patients (if known) or by the population [13].

Methodology

Study type: Prospective observational study.

Study place: The study will be conducted in Department of obstetrics and gynaecology, Rajah Muthiah Medical College and Hospital, Annamalai University, Annamalai Nagar, Tamil Nadu, which is a 1400 bedded multi-speciality tertiary care teaching hospital located in rural South India.

Study recruitment procedure

The recruitment of subjects was carried out with the help of physician who has the knowledge of the patient's medical history.

- The selected subjects (n=41) are the patients who were referred to or admitted in the department of OBG at RMMCH and the follow up taken for the period of 3months.
- The study procedure will be completely explained to the patients and informed consent will be obtained from them.

Patients included in the study are selected based on Inclusion and exclusion criteria.

Inclusion criteria

- Antenatal patients who are suffering with iron deficiency anaemia.

Exclusion criteria

- Patients without any other medical/obstetric complications.
- Patients who are not willing to participate in the study.
- Patients suffering from other types of anaemia or comorbidity conditions.

Study Method

- The Study will be conducted in departmemt of obstetrics and gynaecology at RMMCH, a 1400 bedded multi-specialty tertiary care teaching hospital.
- Approval from the Hospital authorities and Institutional Human Ethics Committee.
- The study method involves selection of patients based on the inclusion and exclusion criteria.
- Interpretation of results.
- Report writing.
- Conclusion of report.

Collected data will be stored in department library for future reference in the form of thesis book.

Results and Discussions

Table 1: Age wise distribution of subjects

S. No.	Age (Years)	No. of Subjects	Percentage
1.	19 – 23	14	34%
2.	24 – 29	15	37%
3.	30 – 35	7	17%
4.	36 – 41	5	12%

The Total number of 41 subjects were enrolled in the study, the age wise distribution of patients are as follows: Majority of the subjects falls in age group 24 - 29(37%) followed by 19 - 23(34%), 30 – 35(17%), 36 – 41(12%).

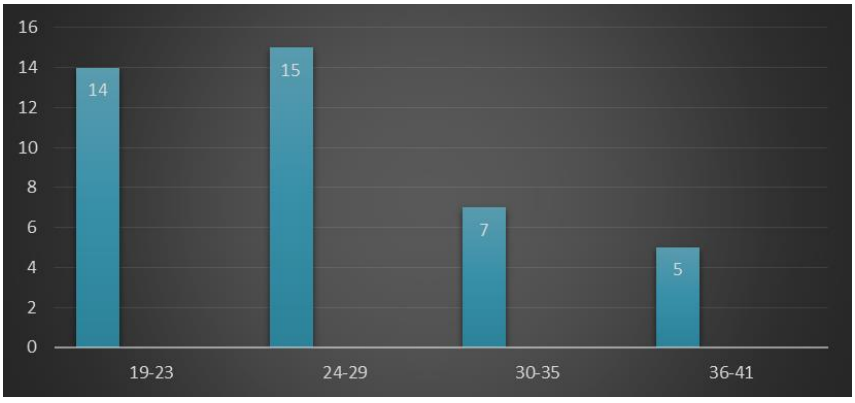


Fig 1: Age wise distribution of subjects

Table 2: Demographic profile of pregnant women

S. No.	Demographic Data	Mean ± Sd
1.	AGE(years)	26 ± 6
2.	WEIGHT(kgs)	58 ± 3
3.	GESTATIONAL AGE (weeks)	34 ± 2
4.	PULSE RATE (beats/min)	86 ± 3

All the patients are in gestational age 34 ± 2 weeks and the average weight of the patients is 58 ± 3 kilograms. There is no significant changes in maternal cardio respiratory parameters.

Table 3: Mean haemoglobin levels [11] across the testing period of the study

	Pre-infusion	3 weeeks post infusion	After delivery	6 weeks post infusion
Haemoglobin	8.58 ± 0.34	10.85 ± 0.57	11.82 ± 0.55	11.87 ± 0.58

Significant increase in mean Hb levels is observed. On pre-infusion stage the mean Hb levels are observed after the administration of FCM 500mg/10ml. In Pre infusion state, the mean Hb levels of 41 patients were observed as 8.58±0.37, whereas after 3rd week of treatment the significantly increased by 10.85 ± 0.57, followed by delivery time the level of Hb increased to 11.82 ± 0.55 and after the 6th week of treatment it raised to 11.87 ± 0.58.

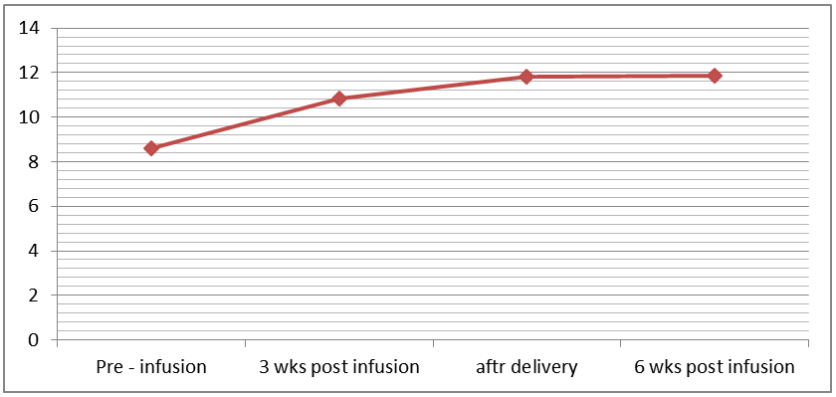


Fig 2: Mean haemoglobin levels across the testing period of the study

Table 4: Mean ferritin levels [12] across the testing period for women in study

	Pre infusion	3 weeks post infusion	After delivery	6 weeks post infusion
Ferritin	78.21 ± 26.41	151.46 ± 16.21	195.78 ± 6.94	204.07 ± 5.56

In that respect is likewise a significant increase observed in mean ferritin levels after administration of FCM 500mg/10ml. At pre-infusion stage the mean ferritin levels of 41 patients were recorded as 78.21 ± 26.41 whereas after 3 weeks of post infusion and delivery it was increased to 151.46 ± 16.21 and 195.78 ± 6.94 respectively and at 6 weeks of post infusion it raised to 204.07 ± 5.56.

Drug	ATC CODE	Prescribed Strength	Assigned DDD	Total Quantity consumed (mg)	Total DDDs/ Assigned DDD	DDD/41 Patients
Ferric Carboxymaltose	BO3AC	500 mg	0.3 g	20500 mg	68.3 g	1.6 g

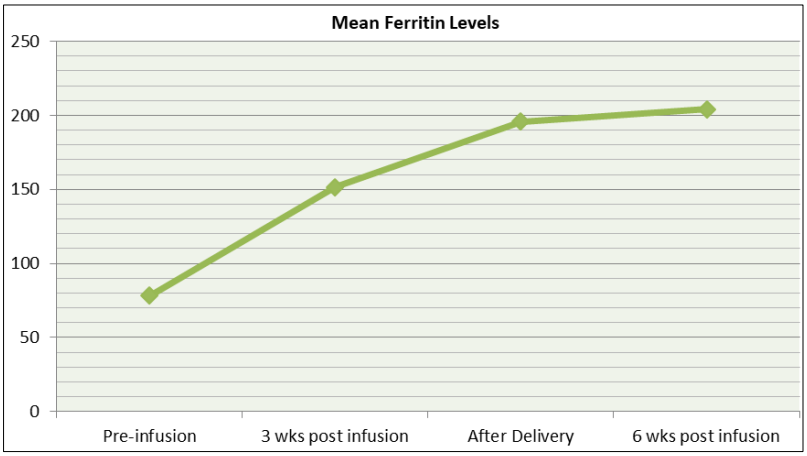


Fig 3: Mean ferritin levels across the testing period for women in study

Defined daily dose [14]

No. of units of ferric carboxymaltose used during study period = 41 ampoules

Total quantity consumed during trial period = 41 x 500 mg
= 20500 mg
= 20.5 g

Assigned Defined Daily Dose = 0.3 g

$\frac{\text{Total quantity consumed}}{\text{Assigned DDD}}$ = $\frac{20.5\text{ g}}{0.3\text{ g}}$
= 68.3 g/41 patients
= 166.6 g/100 patients

Table 5: Daily defined dose

Drug	ATC Code	Prescribed Strength	Assigned DDD	Total Quantity consumed (mg)	Total DDDs/ Assigned DDD	DDD/41 Patients
Ferric Carboxymaltose	BO3AC	500 mg	0.3 g	20500 mg	68.3 g	1.6 g

As part of our study, DDD/41 patients were calculated according to the DTC (Drugs and Therapeutic Committee-guide) with reference from WHO Recommended ATC Classification and found that DDD/41 patients are 1.6 g.

Conclusion

Anaemia is a common problem in obstetrics and perinatal care. Any haemoglobin [15] below 10.5 g/dL can be regarded as true anemia regardless of gestational age. In addition to the general consequences of anaemia, there are specific risks during pregnancy for the mother and the fetus such as intrauterine growth retardation, prematurity, feto-placental miss ratio, and higher risk for peripartum [16] blood transfusion. Oral iron preparations [17] can be used throughout pregnancy, whereas IV iron therapy is recommended during the 2nd and 3rd trimesters. Actually, IV iron therapy [18] should be the first choice in the presence of serious anemia and risk factors, and in emergency situations, because IV therapy is more effective and rapid than oral therapy for resolving anemia. Moreover, oral iron preparations have increased rates of gastrointestinal adverse events when used for long course. Hence, IV iron compounds [19] are the preferred treatment options for severe anemia during pregnancy.

In our study, the majority of the subjects falls in the age group 24-29 (37%) with a mean gestational age 34 ± 2 weeks and the average weight of the patients is 58 ± 3 kilograms. There are no significant changes in maternal cardio respiratory parameters.

Outcome of our study shows a significant increase in the mean Hb level and mean ferritin levels. At pre-infusion stage the mean Hb level and mean ferritin levels of 41 patients were recorded as 8.58 ± 0.37 and 78.21 ± 26.41 respectively. Whereas levels increased to 10.85 ± 0.57 and 151.46 ± 16.21 ; 11.82 ± 0.55 and 195.78 ± 6.94 :11.87 ± 0.58 and 204.07 ± 5.56 after 3 weeks of post infusion, delivery and 6 weeks of post infusion.

Only a mild and quickly reversible local adverse reactions such as pain and rash at injection site were recorded from patient case sheet and patient interview. Hence, no definite conclusion about safety can be drawn from the results of this small group.

In our study, the quantum of use of FCM as DDD is higher than the assigned DDD. Hence, the use of FCM was more in our hospital. However, the sample size too low to make a clear cut conclusion.

Our study suggests that therapeutic doses of FCM IV can be recommended for treatment of IDA during pregnancy. It is simple to use and causes significant increase in Hb and ferritin levels. It does not affect the health of the mothers as well as babies.

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