RESEARCH ARTICLE

Ferric Carboxymaltose for the Treatment of Anemia during Antenatal and Postpartum Period: Expert Opinion

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Abstract

Iron therapy is a cornerstone for treating iron-deficiency anemia (IDA) in pregnancy and in the postpartum period. Oral iron is the first choice of iron preparation around the globe. However, intolerating gastrointestinal side effects with oral iron seriously affect the compliance. Intravenous (IV) iron, such as ferric carboxymaltose (FCM) is a useful alternative to oral iron for treatment of IDA. Use of FCM in the second and third trimesters of pregnancy and in postpartum anemia (PPA) is associated with a significant rise in hemoglobin (Hb) and replenishment of iron stores. With increasing use of FCM in IDA of pregnancy and PPA, there is a need for a unified approach. With this context, nearly 250 experts from the field of obstetrics and gynecology (ObGy) discussed the current evidence and their experiences with FCM use. After a series of expert meetings on an online platform, key opinions were formulated for the use of FCM in management of IDA in these subgroups. This paper brings out current evidence along with expert opinions for the use of FCM in the management of IDA in pregnancy and postpartum periods.

Keywords: Antenatal care, Ferric carboxymaltose, Iron-deficiency anemia, Postpartum anemia, Pregnancy.

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Introduction

Anemia affects 1.62 billion individuals worldwide and is more prevalent in Africa (57.1%) and Southeast Asia (48.2%). Estimated global anemia prevalence in pregnant and nonpregnant women is 41.8 and 30.2%, respectively.[1] Analysis of data from the National Family Health Survey 5 (NFHS5) in India observed anemia in 52.2% of pregnant and 57.2% of nonpregnant women.[2] Increased iron demands during pregnancy predispose to IDA that has the highest burden in the Asia-Pacific region.[3] Anemia or iron deficiency during pregnancy increases the risk of peripartum blood transfusions (BTs) necessitating rigorous and early iron supplementation during the antenatal period.[4] Besides the burden of anemia in pregnancy, PPA is common in the Indian setting with some studies reporting PPA prevalence of over 75%.[5] Along with acute blood loss, IDA in pregnancy and inadequate iron supplementation during the postpartum period are significant determinants of PPA.[6] Despite advances in anemia interventions, the anemia burden is substantial during pregnancy and postpartum period.[5,7] Anemia during pregnancy adversely affects both mother (headache, fatigue, weakness, depression, preeclampsia, placenta previa, and cesarean delivery) and fetus (intrauterine growth restriction, low Apgar scores, low birth weight, and neonatal and perinatal death).[8,9]

Conventionally, iron supplementation, either oral or parenteral, is recommended for the correction and treatment of IDA and iron stores.[10] Nearly 70% of women report gastrointestinal (GI) intolerance (nausea, constipation, diarrhea, indigestion, and metallic taste) with oral iron that affects compliance.[11] Thus, intravenous (IV) iron formulations such as iron sucrose and FCM may be preferred which can be administered from the second trimester onward.[12] A faster rise in hemoglobin (Hb) and better replenishment of iron stores are achieved with IV iron. Given the need for multiple infusions with iron sucrose, a preference may

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be given to FCM as the total required dose can be administered in a single infusion.[13] Multiple studies identify excellent efficacy and equivalent safety of FCM in comparison with oral iron and iron sucrose.[14–16] As FCM is used widely in the second and third trimesters of pregnancy and is also recommended in PPA,[17,18] there is a need for a unified consensus for the use of FCM in pregnancy and PPA. Through this paper, we attempt to review the existing evidence and provide the expert opinion on the optimum use of FCM in the management of IDA in pregnancy and PPA in routine clinical practice.

Approach to the Development of Expert Opinions

In formulating the key expert opinions, 250 Indian experts in the field of ObGy participated. A core group of 25 experts was formed, wherein each expert had over 20 years of experience in the field of ObGy. Two national-level advisory meetings comprising of 12 and 13 core group experts in each meeting were conducted on an online platform. Two experts presented the most updated and extensive evidence related to the use of FCM in pregnancy and PPA. This was followed by the focused discussion led by moderator with key questions among the experts and the identification of key expert opinions and consensus was made. Each expert from the core group then conducted regional advisory meetings involving approximately 10 experts from respective regions. Based on the evidence and expert practices, key opinions were formulated in all the regional meetings. After collating discussion from all advisory meetings, expert opinions were finalized. The final expert opinions were reviewed and approved by all the experts who participated in the meetings.

Expert Opinions

FCM for Iron-deficiency Anemia in Pregnancy

First-trimester Anemia

In India, anemia is common in females. Estimates from Andhra Pradesh indicate nearly 50% of women being anemic (32.4% mild, 14.9% moderate, and 2.2% severe).[19] Given such a significant prevalence of anemia in Indian women, the majority of them are expected to enter pregnancy in an anemic state. This is supported by the observations from Shobeiri and colleagues reporting 45% of women being anemic in the first trimester of pregnancy itself.[20] Identifying the first-trimester anemia is essential so as to plan the investigative and treatment strategies. In the first trimester of pregnancy, anemia is defined by the level of Hb <11 gm/dL.[21]

Iron-deficiency anemia is the commonest cause of anemia in pregnancy. Women with severe anemia (Hb <7 gm/dL) in the first trimester of pregnancy should be assessed for the cause of anemia. Hemoglobinopathies are an important cause of anemia. A study from Chauhan and Prasad from Mumbai, India, identified thalassemia trait (81.66%) as the most common hemoglobinopathy followed by sickle-cell disease (13.3%), 1.66% each of HbD, HbE, and Hb beta thal/HbF combination. The Hb ranged from 5.7 to 13.0 gm/dL.[22] This indicates hemoglobinopathy may even be observed with mild anemia. Therefore, Hb electrophoresis should be performed in all women suspected of any hemoglobinopathy, especially in women belonging to a high prevalence zone for hemoglobinopathies.

Expert opinion: Anemia in the first trimester is common and should be evaluated to determine its cause. Hb electrophoresis may be performed in women with severe anemia or in women clinically suspected of hemoglobinopathy. IV iron administration is contraindicated in the first trimester.

Second- and Third-trimester Anemia

Hb threshold for starting iron therapy: During the second trimester, Hb concentration drops by 0.5 gm/dL. Accordingly, The Federation of Obstetric and Gynaecological Societies of India (FOGSI) defines anemia in the second trimester for Hb <10.5 gm/dL.[18] However, the World Health Organization (WHO) does not differentiate the Hb threshold by trimesters and advised <11 gm/dL as a definition for anemia in pregnant women.[21] In our opinion, taking different threshold by trimester may not be particularly essential and Hb <11 gm/dL should define the anemia in all pregnant women irrespective of the trimester.

Expert opinion: Irrespective of the trimester, a Hb threshold of <11 gm/dL should be used to start iron therapy in pregnancy.

Cause of anemia: differentiating IDA from beta-thalassemia trait: Though IDA is the most common anemia, nutritional vitamin B12 deficiency may also lead to megaloblastic anemia. This is important in the Indian context as the majority of women are vegetarians who are prone to vitamin B12 deficiency. Evidence indicates nearly 35–40% of women may have macrocytic anemia and may be more common, especially in those with severe anemia.[23,24] In patients with severe anemia, a simple tool to identify the beta-thalassemia trait (β-TT) is the Mentzer index. Mentzer index is the ratio of mean corpuscular volume to red blood cell count (MCV/RBC count). A value <13 may indicate thalassemia trait and that >13 points toward IDA. This index offers the highest reliabilities for differentiating β-TT from IDA.[25] Also, the red cell distribution width (RDW) can be a helpful parameter in such differentiation. Zafar et al. observed significantly higher RDW in women with IDA compared to women who had IDA and β-TT and β-TT alone.[26] If indicated by these parameters, women should undergo Hb electrophoresis screening for hemoglobinopathies.

Expert opinion: Evaluate the cause of anemia, especially in severe cases. Megaloblastic or dimorphic anemia can be encountered frequently. Mentzer index or RDW can help in the early differentiation of IDA from β-TT. Hb electrophoresis should be considered if indicated by these parameters or suspected strongly on clinical assessment.

Choice of iron: FCM vs oral vs iron sucrose: The choice between oral and parenteral iron may be determined by multiple factors. The Anemia Mukt Bharat Guidelines 2018 advise daily oral iron for 6 months in patients with mild to moderate anemia. However, parenteral iron should be considered in women who have an intolerance to oral iron or those who present late in the pregnancy. For severe anemia, guidelines advised preference to parenteral iron.[27] Three formulations of iron, i.e., oral iron, iron sucrose, and FCM, are commonly used for treating IDA. Evidence with the use of FCM in IDA of pregnancy (Tables 1 and 2) clearly indicates its superior efficacy in raising Hb concentration than oral iron or iron sucrose, better tolerability than oral iron, and ease of

Table 1: Clinical studies with FCM use in IDA of pregnancy

Author (year)	*Country*	*Group/s*	*Dosing*	*GA (weeks)*	*Follow-up*	*Change in Hb (g/dL)*	*Change in ferritin (µg/L)*
Christoph et al. (2012)[14]	Switzerland	FCM ($n = 103$) vs IS ($n = 103$)	FCM: 1000 mg/week, repeated in 13 women IS: 400 mg/week in two infusion 48 hours apart	FCM: 13–40 IS: 8–39	FCM: 28.4 days IS: 41.2 days	FCM: 1.54 IS: 1.17	NR
Myers et al. (2012)[28]	United Kingdom	FCM ($n = 44$) IHD ($n = 48$)	Max dose of 1000 mg of both treatments	Second or third trimester	6 weeks	2 weeks: 1.73 vs 1.34 4 weeks: 2.57 vs 2.34 6 weeks: 3.01 vs 3.2	NR
Pels et al. (2015)[29]	Netherlands	FCM ($n = 64$) vs Control ($n = 64$)	FCM: 1000 mg/week to raise Hb >9.7 Control: continued oral iron	34	Till delivery	FCM: 8.4–10.7 Control: 8.4–10.8	NR
Froessler et al. (2014)[30]	Australia	FCM ($n = 65$)	FCM: 15 mg/kg	24–40 (median 35)	6 weeks	Hb ≥9.5: 10.2–12.0 Hb 9–9.4: 9.2–10.8 Hb <9: 8.3–11.0	6.3–194
Aporta Rodriguez et al. (2016)[31]	Spain	FCM ($n = 96$)	FCM: 1000 mg (up to 20 mg/kg)	First (median 11): 4.2% Second (median 26): 29.5% Third (median 35): 66.3%	First and second trimesters: 20–40 days; third trimester: 7–14 days	Overall: 8.5–11 First trimester: 8–11.6 Second trimester: 8.6–11.7 Third trimester: 8.6–10.2	Increase from 5.5–85.5
Breymann et al. (2017)[32]	Switzerland	FCM ($n = 123$) vs FS ($n = 124$)	FCM: *Weight ≥66 kg:* 1000 mg f/b 500 mg at 1 week for Hb 8–9 and 1000 mg only for Hb >9 to <11 *Weight <66 kg:* 3 × 500 mg within 2 weeks for Hb 8–9 and 2 × 500 within 2 weeks for Hb >9–<11 FS: 100 mg twice daily	16–20: 10 vs 7% 20–<33: 85 vs 89% ≥33: 5 vs 4%	12 weeks	3 weeks: 1.23 vs 0.96 6 weeks: 1.75 vs 1.32 12 weeks: Figure NA Achievement of Hb >11 gm/dL: 84 vs 70% Time to achieve Hb > 11 gm/dL: 3.4 vs 4.3 weeks	Significantly higher rise with FCM than FS at each visit
Shim et al. (2018)[33]	Korea (Korean subgroup from FER-ASAP trial)	FCM ($n = 46$) vs IS ($n = 44$)	FCM: 1000–1500 mg iron IS: 200 mg iron/day	16 to <20: 6.7 vs 4.5% 20 to <33: 88.9 vs 90.9% ≥33: 4.4 vs 4.5%	12 weeks	No significant difference in Hb change in two groups except at 9 months Achievement of Hb > 11 gm/dL: 93.3 vs 85.7%	Significantly higher rise with FCM than FS at each visit
Froessler et al. (2014)[34]	Australia	FCM for ID and IDA ($n = 863$)	FCM: 20 mg/kg, majority received 1000 mg	30–37 weeks	6 weeks	ID only: 0.51 Mild IDA: 1.53 Moderate IDA: 0.98 Severe IDA: 2.15	Increased from 7 (preinfusion) to 137 (6 weeks)
Naqash et al. (2018)[16]	India	FCM ($n = 100$) vs IS ($n = 100$)	FCM: 1000 mg, repeated if required on 8th and 15th day IS: 200 mg infusion, repeated alternate days as required	Second trimester: FCM 8% and IS 9% third trimester: FCM and IS 39% each	4 weeks	FCM: 7.82–13.2 IS: 7.64–11.59	Significant increase with FCM than IS
Khalafallah et al. (2018)[35]	Australia	FCM ($n = 83$) vs IPM ($n = 82$) vs FS ($n = 81$)	FCM: 1000 mg single infusion IPM: 1000 mg single infusion FS: 325 mg daily till delivery	Median 27 in all three groups	4 weeks and Predelivery	4 weeks: 0.89 vs 0.87 vs 0.46 Predelivery: 1.46 vs 1.55 vs 0.98	4 weeks: 148.5 vs 170 vs 4.03 Predelivery: 90.4 vs 99.6 vs 7.31

Jose et al. (2019)[15]	India	FCM ($n = 50$) vs IS ($n = 50$)	FCM: 1000 mg, repeated if required on 8th and 15th day IS: 300 mg infusion, twice weekly, repeated alternate days as required	FCM: 27.5 IS: 26.4	12 weeks	FCM: 2.96 IS: 2.21	FCM: 7.9–187.5 IS: 9–145.5
Wani et al. (2019)[36]	UAE	FCM ($n = 1001$)	FCM single dose—500/1000/1500 mg	Second or third trimester	—	500 mg: 9.91–11.4 1000 mg: 9.4–11.1 1500 mg: 8.7–11.1 Hb rise ≥2 gm/dL: 41.4%	NR
Oskovi-Kaplan et al. (2020)[37]	Turkey	FCM ($n = 72$) vs Control ($n = 72$)	FCM: 1000 mg fb 500 mg (<70 kg) or 1000 mg (>70 kg) after 1 week	Second or third trimester	—	Baseline Hb: 8.2 At birth: 11.1 vs 9.1	NR

FCM, ferric carboxymaltose; FS, ferrous sulfate; GA, gestational age; Hb, hemoglobin; ID, iron deficiency; IDA, iron-deficiency anemia; IHD, iron hydroxy dextran; IPM, iron polymaltose; IS, iron sucrose; NR, not reported

Table 2: Adverse effect profile of FCM alone and in comparison with iron sucrose and oral iron

Author (year)	*Total AE*	*Local site reaction*	*Systemic reaction*	*GI disorders*	*Nausea ± vomiting*	*Headache*	*Tingling sensation*	*Arthralgia*	*Epigastric pain/ heartburn*	*Constipation*	*Hyperphosphatemia*
Christoph et al. (2012)[14]	FCM: 7.8% IS: 10.7%	FCM: 2.9% IS: 2.9%	FCM: 4.9% IS: 7.8%	NR	NR	NR	NR	NR	NR	NR	NR
Myers et al. (2012)[28]	NR	NR	1 case each in FCM and IHD	NR	NR	NR	NR	NR	NR	NR	NR
Froessler et al. (2014)[30]	FCM: 20%	8%	NR	NR	1.5%	6%	NR	NR	NR	NR	NR
Breymann et al. (2017)[32]	FCM: 49% FS: 40%	FCM: 3% FS: 0	NR	FCM: 2% FS: 13%	FCM: 2% FS: 5%	FCM: 6% FS: 1%	NR	NR	FCM: 0 FS: 4%	FCM: 0 FS: 2%	NR
Shim et al. (2018)[33]	FCM: 60% FS: 63.6%	NR	NR	FCM: 35.6% FS: 31.8%	FCM: 2% FS: 9%	FCM: 7% FS: 0	NR	NR	FCM: 0 FS: 7%	FCM: 0 FS: 7%	NR
Froessler et al. (2018)[34]	FCM: 11%	4%	NR	NR	2%	3%	NR	1%	NR	NR	NR
Naqash et al. (2018)[16]	FCM: 1% IS: 6%	NR	NR	NR	IS: 3	IS: 2	IS: 3	IS: 1	NR	NR	NR
Khalafallah et al. (2018)[35]		NR	FS: 10%	FS: 55%	FCM: 6.3%* IPM: 11.5%* FS: 22%	NR	NR	NR	FS:	NR	NR
Jose et al. (2019)[15]	—	FCM: 2%	NR	NR	NR	NR	NR	NR	IS: 4%	NR	FCM: 4% IS: 6%
Wani et al. (2019)[36]	0.7%	NR	Yes	NR	NR	NR	NR	NR	NR	NR	NR

*Combined flu-like symptoms with bone ache and nausea; NR, not reported; Clinically relevant adverse effects have been captured

administration over iron sucrose. The rise in Hb can be 3–4 gm/dL after a single FCM infusion of 1000 mg. In addition, serum ferritin levels are significantly increased with FCM than those observed with iron sucrose or oral iron.[28–37] Thus, compared to oral iron or IV iron sucrose, FCM is a better choice of iron supplementation for IDA in pregnancy.

Expert opinion: IV FCM may be preferred over oral iron and IV iron sucrose for all severities of anemia in the second and third trimesters of pregnancy.

Dose and administration of FCM: Ferric carboxymaltose allows controlled release of the iron within the reticuloendothelial cells by virtue of it macromolecular ferric hydroxide carbohydrate complex. This helps in preventing the release of large amounts of iron in the systemic circulation.[38] The dose of FCM depends on the total iron requirement. Ganzoni's formula provides an estimation of iron requirements including stores.[39] Total iron dose = {(body weight) [kg] × (target Hb − actual Hb) [g/L]} × 0.24 + iron stores [mg], where 0.24 is a correction factor that takes into account the patient's blood volume, estimated at 7% of body weight and Hb iron content; which is 0.34%. Alternatively, anemia severity and weight can be taken into consideration to roughly estimate the dose requirement. In their pioneering RCT, Breymann et al.[32] considered a dose of FCM based on weight and anemia severity as shown in Table 3. Infusion of 1000 mg dose should be diluted in 250 mL of 0.9% normal saline and should be infused in 15 minutes. For a 500 mg dose, dilution may be done in 100 mL of 0.9% normal saline and may be infused within 10 minutes. Ferric carboxymaltose administration is performed in a day-care setting under the supervision of a gynecologist.

Expert opinion: Ganzoni's formula should be used to calculate total iron requirements. In a single sitting, the maximum FCM dose should be 1000 mg. If required, the next dose can be repeated after a week's time. In a hospital setup, infuse 1000 mg diluted in 250 mL and 500 mg diluted in 100 mL of 0.9% normal saline over 10–15 minutes under the supervision of a gynecologist.

Optimal timing of FCM administration: The goal of iron therapy is to avoid progression beyond low iron stores to impaired Hb production or frank IDA. During the second and third trimesters, the total iron need is just above 1000 mg.[40] At any week of gestation, the desirable Hb concentration is ≥11 gm/dL. Anemia in the early duration of pregnancy is known to result in low birth weight.[41] We believe IDA should be corrected to optimal Hb levels before 24 weeks of pregnancy to optimize the outcomes. With this consideration, FCM in a dose of 1000 mg administered during 12–24 weeks can provide a substantial improvement in iron status. Some experts believed FCM may be administered in the late second or early third trimester. If administered in the third trimester, it should be done at least 2 weeks before the expected date of delivery (EDD).

Table 3: Dosing of FCM by Breymann et al.[32]

Weight (kg)	*Hb levels (g/dL)*	*FCM dose (mg)*
≥66	8 to <9	1,000 followed by 500
	9 to <11	1,000 only
<66	8 to <9	3 × 500 weekly
	9 to <11	2 × 500 weekly

Expert opinion: Correction of IDA early in the pregnancy is highly desired. Administration of FCM may be done from week 12 to at least 2 weeks before the EDD. Correction of anemia with FCM administration before 24 weeks may help improve the ID and iron stores.

FCM administration in hemoglobinopathy: In patients who present with severe anemia or do not respond to initial oral therapy, it is imperative to assess for hemoglobinopathies. Ideally, iron administration is contraindicated in any hemoglobinopathy because of expected iron overload. However, in the Indian context where IDA is hugely prevalent, all hemoglobinopathies should be assessed for IDA and iron stores. A multicenter evaluation from Mohanty et al.[42] reported IDA without hemoglobinopathy in 27% of pregnant women, whereas IDA prevalence was 55.9% among beta-thalassemia carrier pregnant women. Another evaluation in 22 pregnant and 18 nonpregnant women with sickle-cell disease reported that 63 and 50%, respectively, had scanty or no iron in the bone marrow.[43] It indicates that iron may be required for managing pregnant women with hemoglobinopathies. The United Kingdom guidelines on the management of iron deficiency in pregnancy recommend iron therapy in women with hemoglobinopathy if their serum ferritin levels are <30 µg/L.[13] We consider FCM may be used in women with severe anemia or those who fail to respond to oral iron within 4 weeks of treatment. In women with hemoglobinopathy presenting in the third trimester, a single FCM infusion (based on requirements) may be offered if serum ferritin criteria <30 µg/L.

Expert opinion: With constant supervision and follow-ups, FCM may be considered in pregnant women with hemoglobinopathy having serum ferritin levels <30 µg/L with severe anemia (Hb <7 gm/dL) and failed response to initial oral iron therapy even after 4 weeks. Ferric carboxymaltose may also be optional for IDA for such women who present in the third trimester of pregnancy.

BT vis-à-vis FCM in pregnancy: The 10 commandments for the transfusion practice in medicine state that transfusion should only be used when the benefits outweigh the risks and there are no appropriate alternatives, and laboratory tests should not be the sole deciding factor for transfusion.[44] BT in pregnancy should only be done in emergencies such as hemorrhage. During ANC, a trial of FCM is to be given before BT in women presenting with severe anemia. Achieving the predelivery Hb of >11 gm/dL is advantageous to all women. In women with severe anemia and in labor, BT should be initiated immediately. Studies from India identify that postpartum hemorrhage (PPH) is the major indication for BT in obstetric practice.[45,46]

Expert opinion: In pregnant women with severe anemia (Hb <7 gm/dL) who are not in labor, a trial of FCM should be given before initiating BT. Postpartum hemorrhage and women with severe anemia (Hb <7 gm/dL) in labor or cardiac compensation are indications for BT in obstetrics.

FCM for IDA in Postpartum Period

Prenatal anemia and delivery blood loss are important determinants of PPA.[47,48] The estimated prevalence of PPA in developing countries is 50–80%.[49] Blood loss of more than 250–300 mL at delivery can result in rapid depletion of iron stores.[50] Postpartum anemia is associated with impaired quality of life, reduced cognitive abilities, emotional instability, and depression.[49] Being a significant health problem, adequate treatment of PPA is essential to improve the general health of women after delivery.

Defining PPA: The UK guidelines define PPA when Hb is <10 gm/dL.[13] The International Society for Blood Transfusion defines PPA with Hb <10 gm/dL.[14] The WHO[51] and South Australian Perinatal Practice Guidelines[52] also define PPA as Hb <10 gm/dL. However, the International Federation Gynecology and Obstetrics (FIGO) defined PPA with Hb <11 gm/dL.[10] Some researchers advise the definition of PPA as Hb <11 gm/dL at 1 week and <12 gm/dL at 8 weeks postpartum.[49] Given most women may not achieve the desired levels of Hb predelivery, they are expected to have lower iron reserve despite normal Hb in the third trimester. Therefore, we consider PPA should be defined by Hb levels <11 gm/dL.

Expert opinion: Hb levels <11 gm/dL should be the cutoff to define PPA.

Ferric carboxymaltose vs oral iron and iron sucrose for PPA: Oral iron therapy should be continued till 6 weeks after delivery to meet the demands and replenish the stores in the postpartum period.[10] In comparison with oral iron, a meta-analysis of 15 RCTs reported that the use of IV iron is associated with increased Hb concentrations at weeks 1, 2, and 3; have higher ferritin levels at weeks 1, 2, 4, and 6 in the postpartum period. At week 6, the rise in the IV iron group was almost 1 gm/dL higher than that seen in the oral iron group. At the same time, the rates of constipation and dyspepsia reported being significantly lower in the IV iron group. Thus, IV iron is a much better-suited option for PPA.[53] Table 4 provides a summary of studies assessing the efficacy and safety of FCM compared to oral iron and iron sucrose in the management of PPA.[54–62] Ferric carboxymaltose is found to be more efficacious than oral iron in raising the Hb and achieving better iron stores. Compared to iron sucrose, FCM had a better and more sustained effect on the Hb. The rise in Hb of 1 gm/dL or more was evident after a week of administration and was sustained over 6 weeks. Replenishment of iron stores as indicated by the rise in ferritin levels was rapid and better with FCM than iron sucrose and oral iron. The tolerability of FCM was better than both oral iron and iron sucrose.

Expert opinion: Ferric carboxymaltose should be the choice of iron supplementation in PPA to rapidly and effectively correct iron deficiency, improve iron stores, and raise Hb to optimal levels.

Administration of FCM in the postpartum period: Postdelivery, hemodynamic stabilization occurs over 24–48 hours. In normal vaginal delivery, determine the Hb levels after 24 hours and at least 48 hours after cesarean delivery. Ferric carboxymaltose may be considered from any time after 24–48 hours till the discharge of the patient. An attempt should be made to administer FCM, while the patient is still in the hospital in the postpartum period. The dose of FCM depends on the requirement of iron calculated from Ganzoni's formula, as stated above.

Ideally, all iron requirements should be substituted with FCM administration only without the need for further use of oral iron. In one study from Switzerland, Becuzzi et al.[58] assessed oral iron (for mild anemia) alone vs FCM (500 mg single dose) followed by oral iron (for moderate anemia). There was no difference in Hb levels but serum ferritin was significantly higher in the combination group (57.7 ± 49.3 µg/L vs 32.9 ± 20.1 µg/L). They also observed that 20% of women in the oral iron alone group and 52% of women in the combination group did not even start oral treatment. Though the results on ferritin levels are encouraging, we believe that the correction of anemia with FCM alone can rapidly improve Hb and replenish iron stores effectively. Considering the GI intolerance with oral iron, FCM should remain an optimal choice for PPA. As half of the women did not start oral iron treatment probably because of the sense of having received an FCM dose that is not desirable in routine management.

Expert opinion: Ferric carboxymaltose dose calculated as per Ganzoni's formula should be administered at any time after 24–48 hours of delivery till discharge. An attempt should be made to administer FCM while the patient is in hospital in the postpartum period. All iron requirements should be met with FCM dosing and the use of oral iron after an initial lower dose of FCM should be avoided.

BT in PPA: Postpartum hemorrhage is an important cause of maternal morbidity after delivery. A systematic review of 120 studies involving 3,815,034 women observed prevalence of PPH (≥500 mL blood loss) and severe PPH (≥1000 mL blood loss) to be 6 and 1.86% of all deliveries, respectively.[63] BT is necessary for women with anemia with signs of shock or acute hemorrhage with signs of hemodynamic instability. Also, severe anemia (Hb <7 gm/dL) with symptoms of hemodynamic alterations may be offered BT.[18] In general, IV iron may reduce the risk of allogenic BT as identified in a systematic review.[64] A randomized trial of IV iron (iron polymaltose) vs blood for acute postpartum anemia (IIBAPPA) is underway with primary outcomes of change in Hb, ferritin, and C-reactive protein levels at day 7 postpartum.[65] These data indicate in select women; IV iron such as FCM can be an alternative to BT, especially in women at high risk of transfusion-related reactions. However, this requires further evaluation in prospective studies.

Expert opinion: BT should be offered to women with signs of shock after PPH or have hemodynamic instability. BT may also be offered to women with severe anemia and signs of hyperdynamic circulation. IV iron such as FCM may be an alternative to BT in selected patients with PPA, especially those who are at increased risk of transfusion-related reactions.

Other Considerations

Safety

Evidence from various studies as summarized in Tables 2 and 4 identifies that FCM is overall safe and well-tolerated. In general, hypersensitivity reactions including anaphylactic shock are very rare. Majorly, injection site reaction, myalgia, and tingling sensation are the reported AEs with FCM. Rates of these AEs are comparatively lower than iron sucrose. The risk of systemic reactions may be related to the infusion of FCM. A network analysis of 21 studies identifies that FCM is well tolerated and is associated with minimal risk of AEs.[66] Therefore, it should not be too fast or too slow. Ideally, a 500 or 1000 mg dose of FCM should be diluted in 100 or 250 mL normal saline and be administered over 10–15 or 15–20 minutes, respectively.

With FCM, there is a risk of hypophosphatemia.[67] However, the reduction in phosphate levels is asymptomatic and transient and is related to the degree of baseline phosphate levels. Van Wyck et al.[54] reported a decrease in phosphate levels with both IV and oral iron treatment. It indicates that a reduction in phosphate level is intrinsic to iron therapy. A greater decrease in phosphate with IV iron probably reflects better efficacy of IV iron in either stimulating erythropoiesis, replenishing iron stores, or both.

Table 4: Comparison of FCM to other oral iron formulation in PPA

Author (year)	*Country*	*Groups*	*Dosing*	*Follow-up*	*Change in Hb (g/dL)*	*Change in ferritin (µg/L)*	*Adverse events (%)*
Vsn Wyck et al. (2007)[54]	USA	FCM ($n = 182$) vs FS ($n = 179$)	FCM: 1000 mg single dose (repeated weekly as required, max 2500 mg) FS: 325 mg three times daily	6 weeks	Hb rise 2 or more: 96.4 vs 94.1% Median time to raise Hb by 2: 7 vs 14 days Hb >12 at 6 weeks: 90.5 vs 68.6%	FCM: Increased FS: No increase	GI disorders: 6.3 vs 24.2 Constipation: 3.4 vs 11.2 Pruritus, rash, or both: 5.2 vs 2.2 Headache: 5.7 vs 2.8 Increase AST: 0.6 vs 2.8
Seid et al. (2008)*[55]	USA	FCM ($n = 143$) vs FS ($n = 148$)	FCM: 1000 mg (repeated weekly to max dose of 2,500) FS: 325 mg thrice daily	6 weeks	Hb change: 4.0 vs 3.4 Achievement of Hb >12 at 6 weeks: 91.4 vs 66.7% With baseline Hb <8: 78.9 vs 43.5% Hb rise >3: 91.4 vs 64.6% Time to reach Hb 12: 14 vs 27 days	225.9 vs 2.7	Total: 10.6 vs 21.8 Urticaria: 2.8 vs 0.7 Constipation: 0 vs 10.9 Nausea: 1.4 vs 2 Muscle cramps/Dysgeusia: 1.4 vs 0 each Increased ALT: 0.7 vs 4.1 Increased AST: 0.7 vs 2
Breymann et al. (2008)[56]	Switzerland	FCM ($n = 227$) vs FS ($n = 117$)	FCM: 3 weekly doses of 1000 mg maximum FS: 100 mg twice daily, 12 weeks	12 weeks	FCM: 3.37 FS: 3.29	FCM: 39.9–161.2 FS: 32.4–43.3	AE rate: 26 vs 22.2 Constipation: 0.4 vs 6.8 Injection site reactions: 2.2
Pfenniger et al. (2012)[57]	Switzerland	FCM ($n = 105$) vs IS ($n = 105$)	FCM: 1000 mg (max 15 mg/kg) IS: 2 × 200 mg at 2 days' interval	8 days	FCM: 1.29 IS: 0.93	—	Total: 5 vs 6% local burning and pain at the infusion site: 1.9 vs 3.8
Becuzzi et al. (2014)[58]	Switzerland	FCM + FS ($n = 75$) vs FS ($n = 150$)	FCM: 500 mg single dose f/b FS 80 mg iron per day FS: 80 mg iron per day	6 weeks	FCM + FS: 10.1–13.3 FS: 9.1–13.3	FCM + FS: 26.9–57.7 FS: 29.5–32.9	
Rathod et al. (2015)[59]	India	FCM ($n = 100$) vs IS ($n = 100$) vs FA ($n = 100$)	FCM: 1000 mg once a week (repeated if required) IS: 300 mg (repeated on alternate days as required) FA: 100 mg daily	6 weeks	FCM: 7.71 ± 1.17 to 12.11 ± 0.84 IS: 8.05 ± 1.07 to 11.40 ± 1.17 FA: 8.23 ± 1.01 to 10.36 ± 1.39 *Severe anemia subgroup* FCM: 6.39 ± 0.61 to 11.25 ± 0.64 IS: 6.55 ± 0.46 to 9.88 ± 0.62 FA: 6.6 ± 0.33 to 8.36 ± 0.73	FCM: 35.52 ± 20.22 to 142.22 ± 58.74 IS: 38.39 ± 19.79 to 102.32 ± 48.73 FA: 37.01 ± 18.06 to 51.20 ± 21.49	Total: 1 vs 9 vs 51 Vomiting: 0 vs 0 vs 17 Diarrhea/constipation: 0 vs 0 vs 34 Transient hypotension: 0 vs 3 vs 0 Arthralgia/tingling sensation: 1 vs 6 vs 0
Damineni and Thunga (2016)[60]	India	FCM ($n = 45$) vs FA ($n = 45$)	FCM: single dose 1000 mg FA: 100 mg twice daily for 6 weeks	6 weeks	FCM: 3.22 FA: 2.27 Hb rise >3: 48.88 vs 17.77%	—	Constipation: 0 vs 11.1 Epigastric pain: 0 vs 8.88 Nausea: 0 vs 17.77 Noncompliance to oral iron: 7/45 (15.5)
Mishra et al. (2017)[61]	India	FCM ($n = 595$)	As per requirement 1500 mg: 309 1000 mg: 214 500 mg: 92	3 weeks	8.97 ± 1.05 to 11.34 ± 0.90	18.30 ± 16.39 to 104.10 ± 32.46	Total: 5.7 Local: 2.6 Systemic: 3.1
Sharma et al. (2017)[62]	India	FCM ($n = 60$) vs IS ($n = 60$)	FCM: 1000 mg IS: 1000 mg (600 mg max per week)	2 weeks	FCM: 7.528 ± 0.60 to 10.46 ± 0.69 IS: 7.528 ± 0.9999999 to 9.2 ± 0.50	FCM: 66.5 ± 33.91 to 292.41 ± 29.04 IS: 64.48 ± 35.26 to 181.35 ± 38.66	Headache: 1.6 vs 1.6 Pain at injection site: 1.6 vs 1.6 Fever: 1.6 vs 0 Tingling sensation: 0 vs 1.6

Expert opinion: Ferric carboxymaltose is safe and well tolerated, and adverse events are mainly limited to infusion-related local site reactions. Though the risk of systemic hypersensitivity and anaphylactic reactions is rare, it should be administered under supervision in a hospital or a day-care setting as per recommended dissolution and infusion rate.

Cost

Evidence on the cost-effectiveness of FCM establishes that FCM infusion is less costly than iron sucrose infusion. Compared to iron sucrose, FCM also offers savings of 30–44% per patient per treatment cycle.[68] In a cost-effectiveness analysis of FCM in pregnancy, Al-Shaghana et al.[69] reported FCM as an effective cost-saving treatment in comparison with red cell transfusion in women who did not respond to oral iron.

Expert opinion: Ferric carboxymaltose is a cost-effective option compared to oral iron and iron sucrose. Wider use may lead to a reduction in per infusion costs of FCM.

Conclusion

Iron-deficiency anemia in pregnancy and postpartum period impacts maternal and fetal/neonatal health adversely. Along with oral iron, IV iron is recommended in the treatment of IDA. Ferric carboxymaltose is an effective, safe, well-tolerated, and cost-effective option for treating IDA in pregnancy and the postpartum period. Optimally, FCM should be used within 12–32 weeks of pregnancy. In PPA, FCM may be administered after 24 hours of delivery. Within 6 weeks of FCM treatment, one can expect a rise in Hb by nearly 3–4 gm/dL with a significant rise in ferritin and replenishment of iron stores. Ferric carboxymaltose infusion should be preferred to oral iron and iron sucrose to rapidly increase the Hb and sustain the iron stores. With a recommendation from Anemia Mukt Bharat guidelines, FCM may be a choice for all severities of anemia in pregnancy and in the postpartum period.

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