

# **Ferric Carboxymaltose Utilization in Treating Iron Deficiency Anemia among Obstetricians**



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# Background and Objective of the Survey

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Ferric carboxymaltose (FCM) utilization in treating iron deficiency anemia (IDA) among obstetricians is becoming increasingly common due to its efficacy, safety profile, and convenience, particularly in the management of pregnant women with iron deficiency.

Pregnancy is a period of increased iron demand, and iron deficiency anemia is a prevalent condition among pregnant women worldwide. FCM offers several advantages in the treatment of IDA during pregnancy. Its high molecular weight and stable iron-carbohydrate complex allow for rapid intravenous administration of large iron doses in a single infusion session, reducing the need for multiple visits and enhancing patient compliance.

Obstetricians often prefer FCM over oral iron supplements in pregnant women with severe iron deficiency or intolerance to oral iron therapy due to gastrointestinal side effects. FCM bypasses the gastrointestinal tract, avoiding issues such as poor absorption, constipation, and gastric irritation commonly associated with oral iron supplementation.

## **The objective of the survey is:**

To evaluate ferric carboxymaltose utilization in treating iron deficiency anemia among obstetricians

# Methodology of the Survey

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A survey was conducted to evaluate ferric carboxymaltose utilization in treating iron deficiency anemia among obstetricians. A total of 50 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Iron Balance: An Overview
- Iron Requirements during Pregnancy
- Benefits And Risks of Iron Supplementation During Pregnancy
- Pregnancies in Iron-Sufficient Populations
- Approach to Iron Administration in Pregnancy
- Ferric carboxymaltose
- Clinical studies evaluating the efficacy of FCM
- Clinical and experimental information on the safety profile of FCM
- Quality of life in patients treated with FCM

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

# Literature Review

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## Introduction<sup>1</sup>

Anemia with a hemoglobin (Hb) concentration no lower than 10 g/dL at term, occurs in nearly all pregnancies, and in the majority of cases reflects a physiologic process (discussed below) rather than a deficiency state or underlying hematologic disorder. Significant anemia in pregnancy (defined as a Hb concentration <11 g/dL in the first trimester or <10 g/dL in the second and third trimesters) occurs with a prevalence ranging between 2% and 26%, depending upon the population studied. Anemia is a major contributor to maternal and fetal morbidity and mortality, particularly in less developed countries. Of the pathologic causes of anemia in pregnancy, anemia due to iron deficiency (IDA) is the most common, particularly in more developed countries, where contributions from other anemia-producing disorders such as malaria or hemoglobinopathies are less significant.

Anemia in pregnancy, and particularly IDA, is both a long-standing scholarly interest and an element of my practice as a hematologist. In preparing for this review, PubMed searches using the terms “pregnancy” and “iron deficiency” were performed. A date range was not specified, but the focus was on papers 2015 and later. Specific searches for subtopics included “hepcidin”, and “guidelines”. Approximately 71 reports, reviews, or studies new to the author were identified through this process.

The effects of ID on red cell production occur in the context of what is usually called the *physiologic anemia of pregnancy*. This is a phenomenon that is conserved across mammalian species, and it is hypothesized that the physiologic anemia of pregnancy serves the purpose of enhancing placental perfusion by reducing maternal blood viscosity and facilitating oxygen and nutrient delivery to the fetus by expanding the erythrocyte mass. Beginning approximately the sixth week of pregnancy, the plasma volume increases disproportionately to the erythrocyte mass, reaching a maximum value at approximately 24 weeks’ gestation. At maximum, the plasma volume is 40%50% higher than at the start of pregnancy.

Since the parameters used to identify anemia in clinical practice (the hematocrit (Hct), the blood Hb concentration, and the circulating erythrocyte count) are expressed as concentrations based on whole blood volume, the expanded plasma volume causes them to decrease and hence produces “anemia”. While Hb concentration, Hct, and to a lesser degree erythrocyte count, are the anemia indicators used in practice, these parameters are only surrogates for the actual definition of anemia: a reduction in erythrocyte mass per unit body weight. By this criterion, the physiologic anemia of pregnancy is not actually anemia: a 15%–25% increase in the erythrocyte mass occurs in pregnancy but is concealed by the dilutional effect of the increase in plasma volume. This is driven by an increase in serum erythropoietin concentrations during the late second and early third trimesters and is facilitated or potentially limited by iron availability. Pregnant women using iron supplementation have a greater increase in erythrocyte mass than women not using supplemental iron, and women with compromised iron stores at outset of pregnancy will have a limited increase in erythrocyte mass. The upper limit of erythrocyte mass increase in the presence of adequate iron is, however, regulated through erythropoietin control and is not raised by increased iron availability: pregnant women in the Bantu tribe, who have both an iron-rich traditional diet and a genetic predisposition to increased dietary iron absorption, do not increase Hb concentration or Hct with supplementation.

As a result of the reset balance between plasma volume and erythrocyte mass, it is generally considered that a Hb concentration <11 g/dL in the late first trimester and <10 g/dL in the second and third trimesters should be investigated for a cause other than the physiologic anemia of pregnancy.

Maternal plasma volume generally decreases during the final weeks of pregnancy, and consequently the Hct, Hb, and circulating erythrocyte count increase. The maternal blood volume generally returns to prepregnancy levels within one to six weeks after delivery and maternal erythropoiesis increases late in gestation and returns to normal by about one month after delivery.

### **Iron Balance: An Overview<sup>1</sup>**

A detailed discussion of the regulation of iron balance is outside the scope of this review, and the reader is referred to recent reviews. Iron content in the human body is carefully regulated and is normally maintained at about 40 mg/kg in women and about 50 mg/kg in men. Since humans are unable to excrete excess iron in a regulated manner, iron balance is controlled at

the levels of iron absorption by enterocytes in the duodenum, and of iron mobilization from liver parenchyma and macrophages. These processes are regulated by hepcidin, a small peptide produced in the liver. Hepcidin binds to a cellular iron export protein, ferroportin, causing its internalization. When hepcidin levels are increased, iron is retained in enterocytes or macrophages and is not available for red cell production. When hepcidin is decreased, either because of ID or by increased erythropoiesis, absorbed iron in the enterocytes or stored iron in macrophages are mobilized into the circulation.

Absorption of dietary iron is also affected by the iron source and duodenal conditions, such as pH. The proportion of iron absorbed from heme iron and non-food sources such as iron salts or saccharates is approximately 10% 15% of elemental iron, while less than 2% of elemental iron from vegetable sources is absorbed. ID may double the percent iron absorption from any given source.

Iron is transported from the enterocyte to the plasma iron transport protein transferrin. The amount of iron bound to transferrin and in circulation is approximately 0.2 mg/kg under normal circumstances. Storage iron resides in macrophages of the spleen, bone marrow, or liver, and in liver parenchymal cells (5–6 mg/kg in women, 10–12 mg/kg in men). Macrophage iron is largely derived from recycling of senescent erythrocytes while liver parenchymal cells receive or release iron from or to transferrin. The largest pool of iron in the body is in circulating erythrocytes and erythroid precursors in the bone marrow (approximately 28 mg/kg in women and 32 mg/kg in men). Nearly all of this erythrocyte iron is in the form of Hb.

### **Iron Requirements during Pregnancy<sup>1</sup>**

It is generally considered that a normal singleton pregnancy carried to term requires a transfer of 500–800 mg of maternal iron. It is estimated that the demand for absorbed iron increases from 0.8 mg/day in early pregnancy to 7.5 mg/day in late pregnancy, with an average requirement over the entire course of pregnancy of 4.4 mg/day. In a study of healthy pregnant women in Denmark, the 5th percentile Hb value of subjects receiving supplementation with 66 mg elemental iron/day was consistently higher than that of the subjects receiving placebo. Differences were small in the first trimester (0.1 mg/dL Hb higher) and gradually increased into the second (0.1–0.4 mg/dL Hb higher) and third trimesters (0.3–0.9 mg/dL Hb higher) and the postpartum period (1 mg/dL Hb higher). The relatively small difference in the first trimester likely reflects a high incidence of ID or marginal iron stores in both groups and the steadily



increasing gap reflects the increasing iron requirements of pregnancy that are not being met in the placebo group. In a large review of premenopausal women, only 20% had presumed iron reserves of >500 mg (defined as a serum ferritin concentration >70 µg/L), and would potentially be able to go through pregnancy without iron supplementation. This is consistent with an earlier study in which women who received or did not receive iron supplementation during pregnancy underwent bone marrow evaluation after delivery. Only 16% of women not supplemented with oral iron had stainable iron in bone marrow aspirates after delivery at term, although their mean Hb concentration (10.9 g/dL) was in the expected range for the third trimester.

## **Benefits And Risks Of Iron Supplementation During Pregnancy<sup>2</sup>**

### **Physiologic Considerations**

Pregnancy poses a large risk of negative iron balance to a woman. Compared with the nonpregnant state, iron demands are greatly amplified for two reasons. First, the fetoplacental unit requires a large amount of iron for its own growth and development during gestation. One gram of iron needs to be accreted by the mother during pregnancy—of which 360 mg is transferred from the mother to the fetus, particularly during the third trimester when growth is most rapid—in order to maintain a content of 75 mg of iron per kg body weight of the fetus. The pregnant woman expands her own plasma and blood volumes to maintain proper circulation and oxygen delivery to her own organs as well as to the placenta. The blood volume expansion consumes 450 mg of the 1 g of additional iron required during pregnancy. Decreasing hepcidin concentrations during pregnancy indicate the pregnant woman's need to absorb more iron for both her own hemoglobin synthesis as well as for transport across the placenta to the highly metabolic and growing fetus. Iron deficiency is generally acknowledged as a greater risk than iron overload during human pregnancy.

The goals of maintaining iron sufficiency during pregnancy are to reduce maternal morbidity, promote fetal health, and to set up the newborn with adequate nutrient stores for early postnatal life. Increasing evidence supports the concept that postnatal iron status at 9 months of age depends on proper fetal iron loading during pregnancy. The risk of postnatal iron deficiency in infants is reduced when neonatal iron stores are normal following gestation, delayed cord clamping is practiced, and postnatal growth rate is not excessive. It is also likely that proper

loading of the newborn via the maternal–fetal route reduces the need for excessive early iron supplementation of the infant postnatally in certain iron-sufficient populations.

### Pregnancies in Iron-Deficient Populations

There is little debate that iron-deficient women have an increased risk of adverse pregnancy outcomes, that is, those that affect the woman, her fetus, or, consequently, her offspring. Most studies utilize hemoglobin as the biomarker for iron status because of the ubiquitous availability of this measurement and because iron deficiency is the most common cause of anemia in most populations. However, anemia and iron deficiency are not synonymous, which makes interpreting the outcomes of these studies problematic. Anemia at various time points in pregnancy is associated with an increased risk of preterm birth, birth weight <2,500 grams, and low weight for gestational age. In most studies, supplementation of anemic women with iron during pregnancy reduces the rate of iron-deficiency anemia and nonanemic iron deficiency at term, and in some studies, it reduces the risk of adverse outcomes, suggesting that supplementation in this population is beneficial.

Table 1. Interpretation and risk–benefit analysis of maternal iron supplementation during pregnancy based on whether hemoglobin or ferritin was used as the primary biomarker to assess iron status and the information added by a second biomarker

<i>Primary marker</i>	<i>Literature interpretation</i>	<i>Biochemical interpretation with second biomarker</i>	<i>Agreement between literature and biochemical finding?</i>	<i>Low hepcidin (likely response to therapy)</i>	<i>Estimate of risk-benefit of routine supplementation<sup>a</sup></i>
<b><i>Hemoglobin</i></b>					
<i>Low</i>	Iron-deficiency anemia	Low ferritin: iron-deficiency anemia	Low ferritin: yes	Low ferritin: yes	B >> R

<i>Normal</i>		Normal ferritin: anemia of inflammation	Normal ferritin: unknown because total- body iron is unmeasur able	Normal ferritin: no	Unknown, but R > B because iron will not be absorbed in high hepcidin state
		High anemia of inflammation	ferritin: unknown because total- body iron is unmeasur able	High ferritin: no	
	Iron sufficient	Low low-iron state	ferritin: no	Low ferritin: yes	B > R
		Normal ferritin: iron sufficient	Normal ferritin: yes	Normal ferritin: no	Unknown
		High iron overload	ferritin: no	High ferritin: no	R > B
<i>High</i>	Iron sufficient	Low polycythemia by volume contraction or other non-iron-	ferritin: nonanemi a iron deficienc y	Low ferritin: yes	R > B

<b>Ferritin</b>		related condition			
		Normal ferritin: polycythemia by volume contraction or other non-iron-related condition	Normal ferritin: iron overload	Normal ferritin: no	$R > B$
		High ferritin: iron overload	High ferritin: iron overload	High ferritin: no	$R > B$
		Low hemoglobin: iron-deficiency anemia	Low hemoglobin: partly	Low hemoglobin: yes	$B \gg R$
		Normal hemoglobin: nonanemia iron deficiency	Normal hemoglobin: yes	Normal hemoglobin: yes	$B > R$
		High hemoglobin: polycythemia by volume contraction or other non-iron-related condition	High hemoglobin: no	High hemoglobin: no	$R > B$

<i>Normal</i>	Iron sufficient	Low hemoglobin: anemia of inflammation	Low hemoglob in: no	Low hemoglobin : no	R > B
		Normal hemoglobin: iron sufficient	Normal hemoglob in: yes	Normal hemoglobin : no	Unknown
		High hemoglobin: polycythemia by volume contraction or other non-iron- related condition	High hemoglob in: no	High hemoglobin : no	R > B
<i>High</i>	Iron sufficient	Low hemoglobin: anemia of inflammation	Low hemoglob in: no	Low hemoglobin : no	R > B
		Normal hemoglobin: iron overload	Normal hemoglob in: no	Normal hemoglobin : no	R > B
		High hemoglobin: iron overload	High hemoglob in: no	High hemoglobin : no	R > B

Abbreviations: B, benefit; R, risk.

<sup>a</sup>Estimate of whether the risk (R) of adverse outcomes or the benefit (B) associated with iron supplementation is greater, given each combination of iron markers.

A minority of clinical studies that assessed outcomes as a function of iron status used iron-specific biomarkers as opposed to or in conjunction with hemoglobin concentrations. Iron-specific markers can be problematic for routine screening for analytic and interpretative reasons. The limited availability of the analytic equipment needed to measure specific iron parameters—especially serum ferritin, percent total iron-binding capacity saturation, soluble

transferrin receptor, or hepcidin—is a major hurdle, particularly in low-resource countries. An ideal biomarker would index the risks of negative iron balance before physiologic consequences are present. Serum ferritin, which typically indexes iron stores, could theoretically serve this purpose since there are no known consequences of low iron stores, per se, as long as adequate iron is available to support hematopoiesis, tissue-level iron proteins (e.g., cytochromes), and iron transport to the fetus. However, ferritin acts as an acute-phase reactant to infection and inflammation, which undermines its effectiveness as a screening tool. Nevertheless, a meta-analysis of pregnancy outcomes as a function of iron stores demonstrated that low iron stores, particularly during the first trimester, are associated with a greater risk of low birth weight, prematurity, and small size for dates.

Clinical studies have also assessed maternal iron status exclusively as a function of dietary iron intake during pregnancy. This approach has potential drawbacks, including the inherent variability of dietary recall and, more importantly, the question of whether dietary intake is tightly linked to actual iron accretion. This linkage can be tenuous because multiple inflammatory events during pregnancy could result in relatively less absorption of dietary iron due to activation of hepcidin by proinflammatory cytokines, including interleukin-6. Furthermore, dietary iron intake gives no information about the distribution of iron between mother and fetus. Nevertheless, a meta-analysis of studies of maternal iron intake in iron-deficient populations shows that iron supplementation of iron-deficient populations is beneficial. Neurobehavioral pathologies in offspring related to low maternal iron intake during critical periods of pregnancy include increased risks of schizophrenia and autism.

Overall, clinical studies support iron supplementation of pregnant women with iron deficiency defined by any of the three biomarker approaches (i.e., hemoglobin, serum ferritin, or dietary intake). Little discordance exists among the three biomarkers, except in the case of active inflammatory processes.

The role of inflammation in confounding iron status assessments is important. Inflammation activates hepcidin and thereby countermands the normal increase in iron accretion mediated by low hepcidin concentrations during pregnancy. Hepcidin increases iron in the storage pool, as evidenced by high serum ferritin concentrations, while shortchanging iron availability for hemoglobin synthesis by reducing intestinal iron absorption. Chronic inflammation results in reduced total-body iron during pregnancy and less iron availability for the fetus, yet the

condition may be interpreted as iron overload or iron sufficiency if ferritin is the only biomarker used by the clinician to assess iron status.

Although chronic low-grade inflammation may be relatively common in austere settings, the most common inflammatory condition worldwide during pregnancy is malaria. Worldwide, approximately 35 million pregnant women are at risk of *Plasmodium falciparum* malaria each year. The vast majority of populations at risk for malaria live in regions where iron deficiency is endemic. Iron supplementation in areas where both iron deficiency and malaria are endemic must be viewed within the context of the 2006 landmark study on Pemba Island, Tanzania, that found that universal, daily supplementation with iron and folic acid increased the risk of hospitalization and death in young children. Subsequent cross-sectional studies seemed to support this association in pregnant women, finding a lower prevalence of placental malaria among women with iron-deficiency anemia. In vitro studies have provided apparent mechanistic support of these findings, demonstrating that red blood cells taken from both anemic children and anemic pregnant women support a lower rate of *Plasmodium* growth than nonanemic red blood cells. Iron supplementation without treatment of malaria leads to increased parasite growth in red blood cells from both children and women.

However, two recent randomized placebo-controlled trials have not supported a harmful link between healthy iron status and the risk of malaria in pregnant women. The trials demonstrate the importance of treating the malaria first and then addressing iron status. In the first study, 1,500 HIV-uninfected pregnant Tanzanian women with serum ferritin concentrations  $>12\text{ }\mu\text{g/L}$  and hemoglobin concentrations  $>85\text{ g/L}$  were enrolled before 27 weeks' gestation and were randomized to 60 mg of daily iron as ferrous sulfate or to placebo. All women received monthly prenatal health checks that included malaria screening, intermittent presumptive treatment for malaria, and antimalarial treatment if needed. Iron supplementation was not associated with an increased risk of placental malaria or other adverse events, and while iron did not increase birth weight, hemoglobin concentration and iron status as measured by serum ferritin concentration were greater among women in the iron-supplemented group. Although this study was conducted in an urban setting with a relatively low risk of malaria, a subsequent study in a malaria-endemic area of rural Kenya had similar findings. In that randomized placebo-controlled trial, daily supplements of 60 mg iron as ferrous fumarate given to pregnant women between the ages of 15 and 46 years, with no other inclusion criteria, did not increase the risk of maternal malaria and were associated with greater birth weight, lower risk of premature

birth, longer length of gestation, and higher maternal and infant iron stores 1 month after birth when compared with placebo.

After the Pemba study, all iron supplementation trials in malaria-endemic areas have included a malaria control component for ethical reasons. These findings support the current World Health Organization (WHO) recommendation for universal daily supplementation with 30 to 60 mg elemental iron during pregnancy in regions where the prevalence of anemia is 20% or higher, with a stipulation in malaria-endemic areas that supplementation should be given in conjunction with “adequate measures to prevent, diagnose and treat malaria”.

### Pregnancies in Iron-Sufficient Populations

Further controversy with respect to the accurate diagnosis of iron status and subsequent iron supplementation surrounds the routine iron supplementation of apparently iron-sufficient (i.e., non-iron-deficient) women during pregnancy. The US Preventive Services Task Force stated that there was insufficient evidence to advocate routine iron supplementation during pregnancy. A similar statement from the European Food Safety Authority concluded that iron supplementation during pregnancy should be reserved for those at risk for or with documented iron deficiency. The controversy stems from the difficulty in demonstrating any added benefit versus any potential risks of iron supplementation.

The majority of this literature defines iron status by measuring maternal hemoglobin concentration. However, precisely defining iron status in the context of what is termed the physiologic anemia of pregnancy is problematic. The physiologic anemia of pregnancy occurs because of a disproportionately greater expansion of the plasma volume (+50%) than of the red cell mass (+25%), leading to a dilutional reduction in hemoglobin concentration. Maternal hemoglobin concentrations between 95 and 110 g/dL have been associated with the best pregnancy outcomes and, thus, would be considered normal. Hemoglobin concentrations higher than this range have been associated with higher rates of preeclampsia, prematurity, and fetal growth restriction. A smaller number of trials have assessed the effect of iron supplementation on women with high hemoglobin concentrations (i.e., >132 g/L) and found an increased rate of maternal preeclampsia and fetal growth restriction.

A nonanemic hemoglobin concentration would typically be considered a biomarker of iron sufficiency in nonpregnant women, whereas excessively high hemoglobin would be consistent with total-body iron overload, given that iron is predominantly found in red cells. Alternatively, elevated hemoglobin concentrations during pregnancy may not indicate iron overload but



instead reflect low plasma volume expansion, that is, cases in which the 2:1 ratio of plasma volume to red cell mass expansion is not achieved. In that circumstance, serum ferritin may be normal or even low. Thus, an elevated hemoglobin concentration may be misinterpreted as iron overload. Studies that associate high hemoglobin concentrations during pregnancy with poorer outcomes should be interpreted cautiously as to whether the mechanistic causes of the poorer outcomes are a fundamental gestational pathology that leads to low plasma volume expansion, true iron overload, or both. The possibility that iron plays a primary role in plasma volume dysregulation must be considered because such information would have a direct impact on the decision to offer iron supplementation to women with normal or high hemoglobin concentrations. The lack of adequate studies hinders the ability to provide guidelines regarding universal iron supplementation in nonanemic pregnant women.

Future studies could avoid dividing pregnant women into the two traditional hemoglobin categories, anemic or nonanemic, and instead consider a three-group model: anemic, normal, and polycythemic. Data support this approach since a U-shaped risk curve of pregnancy complications as a function of hemoglobin concentration has been described. Moreover, women with normal hemoglobin concentrations may have preanemic iron deficiency. Women with high hemoglobin concentrations may be iron-sufficient, but not iron overloaded, if the high hemoglobin concentration is due solely to the failure of plasma volume expansion.

Assessing pregnancy outcomes as a function of iron-specific biomarkers could potentially provide more direct insight than measuring hemoglobin alone. In turn, these markers could be used to identify candidates for supplementation during pregnancy. Among these markers, serum ferritin has been most often utilized in outcome studies. WHO recently assessed its usefulness as a screening tool. Clinical interpretation of ferritin concentrations relies on the understanding that if iron stores are replete, sufficient iron is present to support iron-dependent cellular processes at the tissue level. Serum ferritin is an excellent specific metric for low-iron states because no condition other than iron deficiency results in low serum ferritin concentrations. Interpreting high serum ferritin concentrations is more problematic with respect to understanding serum ferritin's relationship to tissue iron status. High ferritin concentrations could indicate iron overload or, alternatively, a shift of iron into reticuloendothelial cell storage as part of a response to inflammation. Mathematical correction of ferritin concentrations for the degree of inflammation as indexed by an inflammatory biomarker has been proposed, but has not been widely implemented.

The majority of published studies on pregnancy outcomes as a function of maternal iron status utilized serum ferritin as the biomarker. They reported that higher ferritin concentrations early in pregnancy were associated with more positive pregnancy outcomes, whereas higher ferritin concentrations in the third trimester were associated with poorer outcomes, including premature delivery and low birth weight. Interpreting these studies is difficult because it is unclear whether the high ferritin concentrations during the third trimester indexed increased total-body iron or a shift of iron into the storage pool due to inflammation. There is a great need for a sensitive and specific biomarker that indexes tissue iron status and is not influenced by inflammation.

Assessing iron status by quantifying iron intake has yielded mixed results with respect to pregnancy and offspring outcomes. On one hand, iron intake in non-iron-deficient mothers early in pregnancy appears to protect against autism in the offspring, and iron intake during the third trimester induces a more mature gray matter pattern on diffusion tensor imaging in term infants. Conversely, iron supplementation in women with high hemoglobin concentrations (i.e., >132 g/L) during the second trimester leads to even higher hemoglobin concentrations in the mother, but a greater risk of fetal growth restriction, most likely due to maternal hypertension. Iron supplementation in pregnant women has also been linked in observational studies to a greater risk of gestational diabetes mellitus.

### **Approach to Iron Administration in Pregnancy<sup>1</sup>**

At present, neither the US Preventive Services Task Force nor the American College of Obstetricians and Gynecologists (ACOG) take a position on routine iron supplementation in pregnancy, and society guidelines in the UK recommend against it. Both the ACOG and the UK guidelines recommend screening for anemia as a surrogate for detecting ID. The recommended standards at which anemia should be investigated from both societies are generally consistent with the earlier discussion in this review of the expected degree of anemia from the physiologic anemia of pregnancy: 11.0 g/dL in the first and third trimesters, and 10.5 g/dL in the second trimester (ACOG), or 11.0 g/dL in the first trimester and 10.5 g/dL in subsequent trimesters (UK). Both guidelines suggest a trial of iron as the initial step, with subsequent investigation for other causes if there is an insufficient response. This approach poses a risk of missing individuals who are iron deficient but not anemic as well as the early stages of ID. It has been suggested, based upon cross-sectional studies of reproductive age

women who are not pregnant, that a hemoglobin threshold of 12.8 g/dL (higher than the World Health Organization standard of 12.0 g/dL) is a more appropriate cut off for identifying women at risk for ID. Neither the ACOG nor UK guidelines recommend routine screening with iron studies, but the UK guidelines recommend measuring serum ferritin in women perceived to be at high risk for ID, even if they are not anemic. The most effective approach to anticipating and managing ID risk in pregnancy is a critical topic for future research.

There are two general approaches to iron supplementation in pregnant women who are not anemic. These are selective supplementation, typically guided by laboratory values or by patient demographics in high-risk areas; and routine or universal supplementation. One well-described approach to selective supplementation is based on estimation of iron stores by serum ferritin. When the serum ferritin is greater than 70 µg/L, iron stores are considered adequate to support pregnancy and no supplementation is given. When serum ferritin is less than 30 µg/L, iron stores are considered absent or nearly absent, and the patient is treated with 80–100 mg elemental iron/day orally. Women whose ferritin values are between these points receive low-dose supplementation of 30–40 mg/day. A recent systematic review supports the concept that intermittent iron supplementation in pregnancy (2–3 times weekly, as opposed to daily) is as effective as daily supplementation, and associated with fewer side effects and presumably, higher compliance.

By those criteria, more than 75% of the women participating in the Third NHANES study overall would require supplementation at some level, and more than 90% of Latina women would require supplementation. For this reason, many physicians utilize routine or universal iron supplementation in all pregnant women.

An alternate approach to selective supplementation has been proposed using hepcidin as the indicator of early ID and a need for therapy. A recent report comparing a hepcidin-guided supplementation approach to a universal prophylaxis approach showed similar patient outcomes in both groups. This study was performed in a high-risk population in Gambia, and this approach may have different outcomes in other venues.

One reason to avoid routine supplementation in the less developed world is concern that iron supplementation will increase risk of infection with iron dependent microorganisms and parasites, including malaria. A study in Papua New Guinea found that the benefits of iron supplementation on maternal anemia and birthweight exceeded potential risk, although the benefits were most pronounced in patients who had some degree of ID. In general, iron

supplementation is considered low risk, and an iron supplement of 65 mg elemental iron mg/day beginning at or before 20 weeks' gestation generally is adequate to prevent ID during pregnancy. However, one of the arguments against routine iron supplementation, particularly in the less-developed world, is that benefits on infant neurocognitive development (as distinct from benefits on maternal anemia and iron stores) have not been demonstrated clearly, as was discussed earlier.

In keeping with the UK and ACOG guidelines, investigation for an etiology of anemia would occur if Hb were below the levels described. At this point, the focus moves beyond supplementation (which could be regarded as providing the additional iron required for gestation to a person with adequate iron stores) to the treatment of IDA. The objective in the treatment of IDA is correction of anemia and also repletion of absent iron stores. If initiated early in pregnancy, therapy will need to accommodate the 500–800 mg of iron that will be transferred to the newborn as well as maintaining the maternal Hb/Hct and repleting iron stores. A reasonable approach to therapy is to provide 60–100 mg of elemental iron per day. A variety of oral iron preparations are available and patient preference and, in some cases, considerations of the financial cost to the patient, can govern choices. Traditionally, ID was treated with oral iron three times daily. Subsequent studies investigating the interaction of oral iron therapy with the hepcidin axis led to the recognition that the hepcidin increment caused by therapeutic doses of iron salts or saccharates decreases absorption for approximately 24 h, implying that once daily oral iron therapy is as effective or more effective than the traditional twice or three times daily dosing. Failure to respond to oral iron should lead to a re-assessment of iron status. This would be to address problems with iron absorption leading to a poor response or (more commonly) lack of compliance with iron therapy, but also to consider other potential etiologies of anemia in pregnancy. Oral iron therapy for IDA in pregnancy should continue until the Hb/Hct and MCV are in the normal range, and until the serum ferritin has also returned to a solidly normal value (certainly higher than 30 µg/L and probably higher than 50 µg/L) indicating adequate iron stores.

Most pregnant patients are able to tolerate oral iron, particularly when given once daily or on an intermittent schedule. However, if the patient is unresponsive to oral iron, or unable/unwilling to take iron orally, intravenous iron therapy is safe and effective. An advantage of intravenous iron therapy is that it corrects Hb/Hct and iron stores concurrently and rapidly. Recent systematic reviews indicate that intravenous iron therapy in pregnancy allows more complete achievement of desired Hb concentrations. A number of intravenous

iron preparations are available, with different dosing schedules, and a detailed discussion of these is outside the scope of the current review. In most cases, the total dose to be administered intravenously is 1000–1500 mg elemental iron.

In the absence of gastrointestinal signs or symptoms, endoscopic evaluation of the gastrointestinal tract is unlikely to identify a lesion accounting for blood loss in premenopausal women with ID, and can be deferred safely in favor of a trial of iron replacement. As noted earlier, failure to respond to iron therapy should prompt evaluation for either ongoing sources of blood loss if there is persisting evidence of ID, or consideration of other etiologies of anemia.

### **Ferric carboxymaltose<sup>3</sup>**

Ferric carboxymaltose (FCM) is a new iv iron formulation. It is a polynuclear iron(III)–hydroxide carbohydrate complex designed to mimic physiologic ferritin. FCM is a water-soluble, brown, amorphous powder with a relative molecular weight of 150,000 Da, containing approximately 1,000 iron atoms, which corresponds to an iron content of 24%–32%, together with 25%–50% dextran, ≤10% water, and <6% NaCl. It is pH neutral (5–7) and has physiologic osmolality. FCM does not contain dextran or modified dextran and does not react with dextran antibodies.

After iv FCM administration, the carbohydrate shell is incompletely broken down in the blood by  $\alpha$ -amylase.

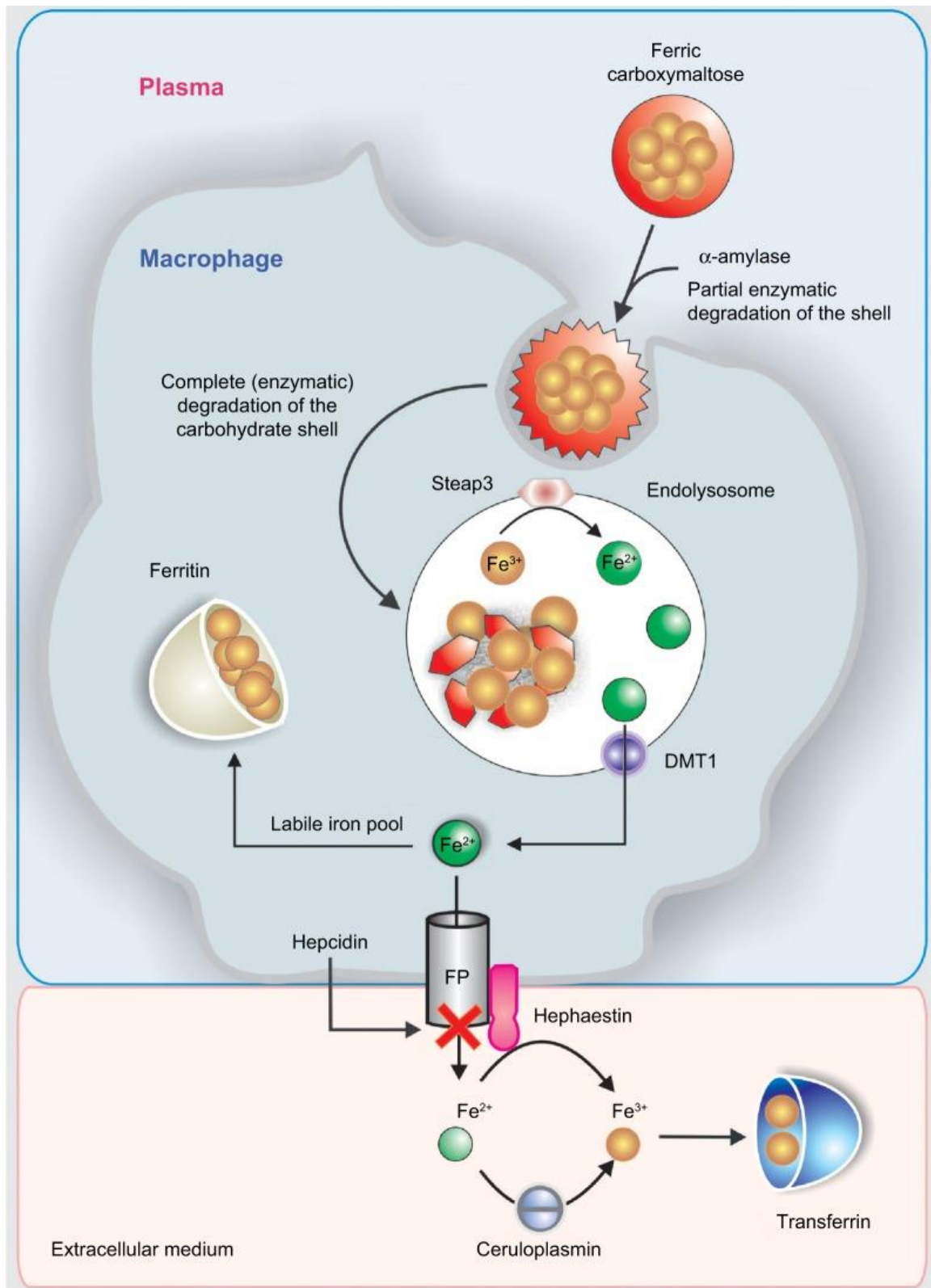


Figure 3. Schematic sequence illustrating the metabolic pathway of ferric carboxymaltose in the macrophage.

**Abbreviations:** DMT1, divalent metal transporter 1; FP, ferroportin.

Then, macrophages take the FCM by an endocytic mechanism by which the carbohydrate shell and the polynuclear iron core may be completely broken down in the endolysosomes to release  $\text{Fe}^{3+}$ . Then, six-transmembrane epithelial antigen of the prostate 3 (Steap3) is likely to reduce the released  $\text{Fe}^{3+}$  into  $\text{Fe}^{2+}$

$\text{Fe}^{2+}$  is extruded from the endolysosomes to the cytosolic labile iron pool by the activity of DMT1 and from the cytosol to the plasma by FPN. Finally, it is transported by TF to the liver, bone marrow, and other tissues.

Four ascending doses were investigated in a total of 24 patients with mild IDA: 100 mg iron as FCM given as an iv bolus injection, and 500 mg, 800 mg, and 1,000 mg iron as FCM given as an iv infusion over 15 minutes. Assessments were made of pharmacokinetic iron status parameters up to 168 hours post dose. In comparison with placebo, a rapid, dose-dependent rise in total serum iron was observed across all dose groups. Peak serum iron levels occurred within 0.3–1.2 hours. Mean maximum total serum iron levels were 36.9  $\mu\text{g/mL}$  following a 100-mg iv dose, 154.1  $\mu\text{g/mL}$  following a 500-mg iv dose, and 306.4–317.9  $\mu\text{g/mL}$  following a 1,000-mg iv dose.

Iron supplied as FCM is quickly provided to different tissues, mainly to the bone marrow, liver, and spleen, the volume of distribution being approximately 3 L. Following the administration of an i.v. dose of FCM, the level of total serum iron presents a reduction between 24 hours and 72 hours. After 60–96 hours post FCM infusion, most patients show total serum iron levels under the limit of quantification. Concerning serum ferritin, a dose-dependent, but not dose-linear, increase maybe observed within 48–120 hours post FCM dose, with maximum levels of a 23–210-fold increase above baseline level.

In an uncontrolled multidose study in patients with moderate IDA secondary to gastrointestinal disorders, a 15-min infusion of either FCM (500 mg iron) weekly for up to 4 weeks or FCM (1,000 mg iron) weekly for up to 2 weeks resulted in maximum serum iron levels of 154  $\mu\text{g/mL}$  and 306  $\mu\text{g/mL}$  at 1 hour post dose, respectively, and returned to baseline values at 4–7 days. Before the following dose, serum iron levels stayed within the normal level, and no change was observed with repeated infusions. Following a single infusion of FCM 100 mg labeled with  $^{52}\text{Fe}/^{59}\text{Fe}$  as a tracer in patients with IDA or anemia related to chronic kidney disease (CKD), a rapid increase of radiolabeled iron incorporation from FCM into red blood cells was observed by the first 6–9 days. Additionally, after 24 days, iron incorporation was greater (91%–99%) in IDA patients than in those with renal anemia (61%–84%). iron was quickly



removed from plasma and mostly delivered to the liver, spleen, and bone marrow, but bone marrow showed a much higher iron uptake.

Most iron administered as FCM is utilized or eliminated within 24 hours (100-mg dose) or 72 hours (500–1,000-mg dose). The clearance for FCM appears to be essentially mono-exponential, suggesting that iron as FCM is not deposited in a body store from where it could diffuse back to the serum. FCM has a terminal elimination half-life of 7.4–12.1 hours. Less than 0.01% of the administered dose is excreted in urine. Concerning breastfed infants, there were no adverse effects reported.

### **Clinical studies evaluating the efficacy of FCM<sup>3</sup>**

Studies with FCM in patients with anemia related to gynecological and obstetrics disorders

Van Wyck et al conducted a randomized, controlled trial to assess the efficacy of iv FCM versus oral FS in the management of anemia in more than 400 women with anemia, ID, and heavy uterine bleeding (HUB). The patients received either iv FCM ( $\leq 1,000$  mg over 15 minutes, repeated weekly to obtain a full calculated supplement dose) or 325 mg of FS (65 mg elemental iron) orally thrice daily for 6 weeks. Compared to those assigned to FS, more patients in the FCM group presented an increase in Hb of 2.0 g/dL or more (82% vs 62%,  $P < 0.001$ ), obtained an increase in Hb of 3.0 g/dL or more (53% vs 36%,  $P < 0.001$ ), and achieved anemia correction (73% vs 50%,  $P < 0.001$ ). More vitality and less fatigue ( $P < 0.05$ ) were reported by patients treated with FCM in comparison with those receiving FS. No severe AEs were reported, and it was concluded that FCM was more effective than FS in resolving anemia, refilled iron deposits, and enhancing QoL in patients with IDA due to HUB.

Recently, Herfs et al performed a multicenter, prospective, noninterventional study on the efficacy and tolerance of FCM use in ordinary gynecological practice. The data from ~300 patients with iron deficiency or IDA were evaluated.

The etiologies of iron deficiency/IDA were hypermenorrhea, postpartum condition, or other causes. FCM was most frequently (92 %) administered by infusion (average 21 minutes), and in 7% of the patients by bolus injections.

The average total iron dosage was 788.7 mg (range: 50–3,000 mg)/patient and the median individual dosage was 500 mg (range: 50–1,000 mg)/patient. In most cases, the total dosage



was given as single application. The increase in Hb value was 2.5 g/dL in the whole group. However, in the IDA group, the value increase was 3.4 g/dL, with 80 % of women reaching normal Hb values. TSAT values and serum ferritin were also increased (16.3 %–22.8 % and 17.2–88.8 µg/L, respectively). No severe AEs were reported.

The role of FCM in pregnancy has been evaluated in some studies. There is general consensus in considering IS as a safe ICC to be used in the treatment of pregnant women with IDA. However, since the total iron dose usually requires numerous applications, the Hb target for an individual patient is not always achieved. Hence, in a retrospective analysis of 206 pregnant women who received either FCM or IS for IDA due to intolerance to oral iron substitution or insufficient Hb increase after oral iron treatment, Christoph et al evaluated comparatively the side effects and tolerance of these two ICCs. Mild AEs were reported in 7.8% for FCM and 10.7% for IS. The mean rise of Hb value was 1.5 g/dL for FCM and 1.1 g/dL for IS. FCM had a similar safety profile to IS, with the advantage of a higher iron dosage at a time, this diminishing the requirement of multiple administrations.

On this background, a recent prospective observational study was performed to test the safety and effectiveness of FCM in treating pregnant women with mild, moderate, and severe IDA in the second and third trimester. A total of 65 anemic pregnant women were treated with FCM between 24 weeks and 40 weeks of pregnancy. The FCM efficacy was tested by changes in Hb and by a report of the patients' well-being in the postpartum period. The fetal heart rate and occurrence of AEs were recorded during the infusion as a safety evaluation. A significant ( $P<0.01$ ) rise in Hb was observed after FCM administration in all women. This positive Hb change was found at 3 weeks and 6 weeks post FCM application and in some cases up to 8 weeks. Moreover, serum ferritin also increased after FCM administration. No negative impact of the drug on the fetus was observed. Two-thirds of the interviewed women reported an improvement in their well-being, and one-third did not perceive any substantial modifications following FCM application. The rate of mild AEs was 20%.

There are some studies with FCM in postpartum anemia. In three of them, FCM was compared to oral iron— and in one versus IS. In a randomized, open label, controlled trial, Van Wyck et al estimated the efficacy of FCM ( $\leq 1,000$  mg over 15 minutes, repeated weekly to achieve a total calculated replacement dose) compared with oral iron therapy (FS, 325 mg orally tid for 6 weeks) in anemic women ( $\text{Hb} \leq 10.0$  g/dL) within 10 days postpartum. One-hundred and seventy-four patients received 350 iv doses of FCM (mean total dose 1,403.1 mg) in three, two,

or one injection (10.9%, 79.3%, or 9.8% of patients, respectively); 178 received FS. Although an equivalent proportion of patients in both groups obtained an increase in Hb  $\geq 2.0$  g/dL, the therapeutic response was earlier with FCM (7.0 days vs 14.0 days,  $P < 0.001$ ). Additionally, the FCM group was more likely to normalize Hb (90.5% vs 68.6%,  $P < 0.001$ ). There were no serious AEs. In conclusion, FCM was an effective therapy for postpartum anemia. Moreover, in comparison with FS, FCM showed a quicker response and was better tolerated.

Another study was a multicenter, randomized, controlled one, including 291 women with  $< 10$  days after delivery with Hb  $\leq 10$  g/dL. The patients received FCM ( $n = 143$ )  $\leq 1,000$  mg over 15 minutes or less, repeated weekly to a calculated replacement dose (maximum 2,500 mg) or FS ( $n = 148$ ) 325 mg orally tid for 6 weeks. FCM-treated subjects were significantly more likely to achieve an Hb  $> 12$  g/dL in a shorter time period with a sustained Hb  $> 12$  g/dL at day 42. Additionally, these patients achieved an Hb rise of 3 g/dL faster than those with FS, together with higher TSAT and ferritin levels. Drug-related AEs occurred less frequently with FCM.

Breyman et al conducted a multicenter (20 centers in three countries), open-label, randomized, and controlled Phase III study in women with postpartum IDA (Hb  $\leq 10.5$  g/dL). The patients were randomized to receive FCM (up to three weekly doses of 1,000 mg maximum, applied in 15 minutes;  $n = 227$ ) or FS (100 mg bid, 12 weeks;  $n = 117$ ). Both therapeutic regimens were equally effective in changing the Hb value. However, in the case of FCM, there was a shorter treatment period (2 weeks vs 12 weeks) and the ferritin levels were significantly higher. Except for the burning at the injection site, FCM was better tolerated than FS, mostly regarding gastrointestinal AEs. There were no safety concerns identified in breastfed infants.

A retrospective comparative study between FCM and IS in postpartum anemia was carried out in a cohort of 210 anemic inpatient women who received FCM (15 mg/kg; maximum, 1,000 mg) or IS (2 times 200 mg), respectively, in the postpartum period.

Both treatments were tolerated with overall AEs of 5% (FCM) versus 6% (IS); the most common complaint was burning and pain at the injection site. FCM was as effective as IS in changing Hb levels from the baseline. There was no difference in the mean daily Hb increase between the groups. Both drugs were effective and offered a rapid normalization of Hb after delivery. However, women with severe anemia showed the most effective responsiveness with FCM.

### **Clinical and experimental information on the safety profile of FCM<sup>3</sup>**

Since iv iron may cause a variable degree of toxicity, a number of experimental studies in basic science have been performed in order to evaluate the safety profile of FCM.— In this sense, a comparative study of FCM versus other iv iron preparations (FG, IS, HMWID, and LMWID) demonstrated that after a similar dose of iv iron (weekly administration for 4 weeks) to nonanemic rats, FCM presents a better profile with respect to FG, HMWID, and LMWID on oxidative stress and inflammatory markers in tissue (liver, heart and kidney). Furthermore, in another study in rodents, FCM administration did not result in detectable levels of nitrotyrosine (marker of nitrosative stress) or significant levels of caspase 3 (apoptosis) in liver, heart, or kidney, versus control.

In clinical investigation, a direct comparison study on the safety of FCM versus iron dextran in patients with IDA was conducted by Hussain et al. Most of the patients were women, whose principal cause of anemia was HUB, IBD, or other gastrointestinal pathologies. FCM increased Hb levels, replenished iron stores, and had a low incidence of AEs. In this study, there was also a lower rate of allergic reactions in the FCM group with respect to the iron dextran group. The trial confirmed the safety profile of FCM in comparison with another frequently administered iv iron, iron dextran. Moreover, Onken et al have recently evaluated the efficacy and safety of FCM versus oral iron and versus standard care iv therapy in IDA patients who had presented inadequate response to oral iron after a 2-week treatment. Safety endpoints occurred in 3.4% in the FCM group versus 3.2% in the comparator groups. In conclusion, two 750 mg FCM infusions were safe and superior to oral iron in improving Hb in this cohort of patients.

Although the mechanism remains unknown, potential negative consequences on bone metabolism (hypophosphatemia and alterations in fibroblast growth factor 23 (FGF23) plasma level) have been attributed to iv iron therapies, including FCM. Some recent clinical and experimental data have contributed to clarify this controversial topic. In a post hoc analysis of a prospective study carried out in 47 NDD-CKD patients with IDA who had received a single 1,000-mg injection of FCM, Prats et al examined the effect of FCM on phosphate metabolism and FGF23 levels in patients with CKD using markers of mineral metabolism. They concluded that in NDD-CKD patients, FCM induced a reduction in serum phosphate levels that persisted for 3 months. Moreover, FCM produced a substantial reduction in FGF23 levels without modifications in other bone metabolism markers. Furthermore, in non-iron-depleted normal

and uremic rats, a single high dose of FCM had no effect on the plasma levels of FGF23 and phosphate for up to 7 days.

It has been suggested for years that iv iron may impair host defense and promote bacterial growth, although the risk of infection associated with iron supplementation is controversial. Fell et al assessed the “in vitro” effect of different concentrations of ICCs including FCM on stimulated mature monocytes and hematopoietic CD34<sup>+</sup> stem cells during their differentiation into monocytes and phagocytosis and antigen presentation capacity. The authors reported no substantial specific immunologic effects after FMC stimulation, with no significant alterations in the differentiation of monocytes from hematopoietic CD34<sup>+</sup> stem cells. Moreover, FCM did not affect the expression of CD14, CD16, or CD86 in human monocyte subsets collected from control subjects without overt CKD.

Notably, using a standard experimental model of malarial anemia, Maretty et al studied the effect of FCM treatment on erythropoiesis, parasitemia, and weight as a marker of disease severity. They reported that FCM did not have a negative effect on parasitemia and disease progression. FCM resulted in significantly higher animal weights, enhanced reticulocytosis, and faster recovery in comparison with controls.

Concerning the safety of FCM administration during pregnancy, the transplacental passage of FCM (radio-labeled with <sup>59</sup>Fe) was evaluated in an “in vitro” perfusion model of human placenta. FCM was added to the maternal circuit in order to obtain a final iron concentration of 11 mM, which represents a 10 times higher iron concentration than the maximum predicted level in blood after an administration of 200 mg iron as FCM. No transferred iron radioactivity was detected in the fetal circuit. Importantly, there were no effects of FCM on placental permeability and other placental functions. In conclusion, FCM did not cross the placenta.

### **Quality of life in patients treated with FCM<sup>3</sup>**

Various studies with FCM have included diverse evaluations on the changes in QoL. All of them have reported an improvement in QoL. Just to mention some of them, in the field of cardiovascular medicine, Comin-Colet et al performed a subanalysis of the previously published FAIR-HF study. They assessed baseline QoL in iron deficiency patients with CHF and the outcome of FCM on QoL. FCM remarkably improved QoL after 4 weeks and during the remaining study period. The favorable effects of FCM were independent of the anemia

status. In line with this, another subanalysis on the FAIR-HF study was conducted by Gutzwiller et al in which a multivariate analysis was carried out with various clinical variables as independent variables and QoL measures as dependent variables. They concluded that the treatment with FCM positively influenced the measures of QoL in patients with HF and ID.

Chronic fatigue is a regrettable condition affecting QoL. A randomized, placebo-controlled, single-blinded study tested the effectiveness and tolerability of a single dose of iv FCM in iron-deficient premenopausal women with symptomatic unexplained fatigue. Fatigued women with iron deficiency (ferritin <50 µg/L and TSAT <20%, or ferritin <15 µg/L) and normal or borderline Hb ( $\geq 11.5$  g/dL) were enrolled in 21 sites in Europe, blinded to the study drug and randomized (computer-generated randomization sequence) to a single FCM (1,000 mg iron) or saline (placebo) infusion. FCM enhanced fatigue, mental QoL, cognitive function, and erythropoiesis in iron-deficient women with normal or borderline Hb.

## References:

1. Means RT. Iron Deficiency and Iron Deficiency Anemia: Implications and Impact in Pregnancy, Fetal Development, and Early Childhood Parameters. *Nutrients*. 2020;12(2):447.
2. Georgieff MK, Krebs NF, Cusick SE. The Benefits and Risks of Iron Supplementation in Pregnancy and Childhood. *Annu Rev Nutr*. 2019;39:121-146.
3. Toblli JE, Angerosa M. Optimizing iron delivery in the management of anemia: patient considerations and the role of ferric carboxymaltose. *Drug Des Devel Ther*. 2014;8:2475-2491.

# Survey Form

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**1. How frequently do you prescribe Ferric Carboxymaltose (FCM) for treating iron deficiency anemia in pregnant patients?**

- a) Very frequently
- b) Frequently
- c) Occasionally
- d) Rarely

**2. What percentage of your pregnant patients with iron deficiency anemia are prescribed Ferric Carboxymaltose (FCM)?**

- a) 0-25%
- b) 26-50%
- c) 51-75%
- d) 76-100%

**3. In your experience, how effective is Ferric Carboxymaltose (FCM) in improving hemoglobin levels in pregnant patients with iron deficiency anemia?**

- a) Very effective
- b) Effective
- c) Moderately effective
- d) Not very effective

**4. What percentage of your pregnant patients with iron deficiency anemia experience resolution of anemia following Ferric Carboxymaltose (FCM) therapy?**

- a) 0-25%
- b) 26-50%
- c) 51-75%
- d) 76-100%

**5. What factors influence your decision to prescribe Ferric Carboxymaltose (FCM) over other iron supplementation methods for pregnant patients?**

- a) Efficacy in correcting anemia
- b) Tolerability profile
- c) Convenience of dosing regimen
- d) Safety profile for mother and fetus

**6. What considerations guide your choice between Ferric Carboxymaltose (FCM) and oral iron supplements for pregnant patients with iron deficiency anemia?**

- a) Severity of anemia
- b) Patient's ability to tolerate oral supplementation
- c) Compliance with oral dosing regimen
- d) Other medical conditions or medications affecting iron absorption

**7. How do you monitor the response to Ferric Carboxymaltose (FCM) therapy in pregnant patients with iron deficiency anemia?**

- a) Regular hemoglobin checks
- b) Clinical symptoms assessment
- c) Ferritin levels measurement
- d) None of the above

**8. In your opinion, what are the main advantages of using Ferric Carboxymaltose (FCM) over other iron supplementation methods in pregnant patients?**

- a) Rapid correction of anemia
- b) Lower gastrointestinal side effects
- c) Convenience of administration
- d) Improved compliance

**9. What percentage of your pregnant patients with iron deficiency anemia are candidates for Ferric Carboxymaltose (FCM) therapy based on current guidelines?**

- a) 0-25%
- b) 26-50%
- c) 51-75%
- d) 76-100%

**10. What percentage of your pregnant patients with iron deficiency anemia have comorbid conditions that may affect their response to Ferric Carboxymaltose (FCM) therapy?**

- a) 0-25%
- b) 26-50%
- c) 51-75%
- d) 76-100%

**11. How do you assess the risk-benefit ratio before initiating Ferric Carboxymaltose (FCM) therapy in pregnant patients?**

- a) Reviewing medical history and comorbidities
- b) Discussion with the patient about potential risks and benefits
- c) Consideration of current guidelines and recommendations
- d) Consultation with other specialists if necessary

**12. How frequently do you encounter pregnant patients with iron deficiency anemia in your clinical practice?**

- a) Rarely
- b) Occasionally
- c) Frequently
- d) Very frequently

**13. What percentage of your pregnant patients experience improvements in fatigue and overall well-being following Ferric Carboxymaltose (FCM) therapy?**

- a) 0-25%
- b) 26-50%
- c) 51-75%
- d) 76-100%



**14. How do you evaluate the need for repeat doses of Ferric Carboxymaltose (FCM) in pregnant patients with persistent iron deficiency anemia?**

- a) Monitoring hemoglobin levels over time
- b) Assessing response to initial therapy
- c) Considering other causes of anemia
- d) None of the above

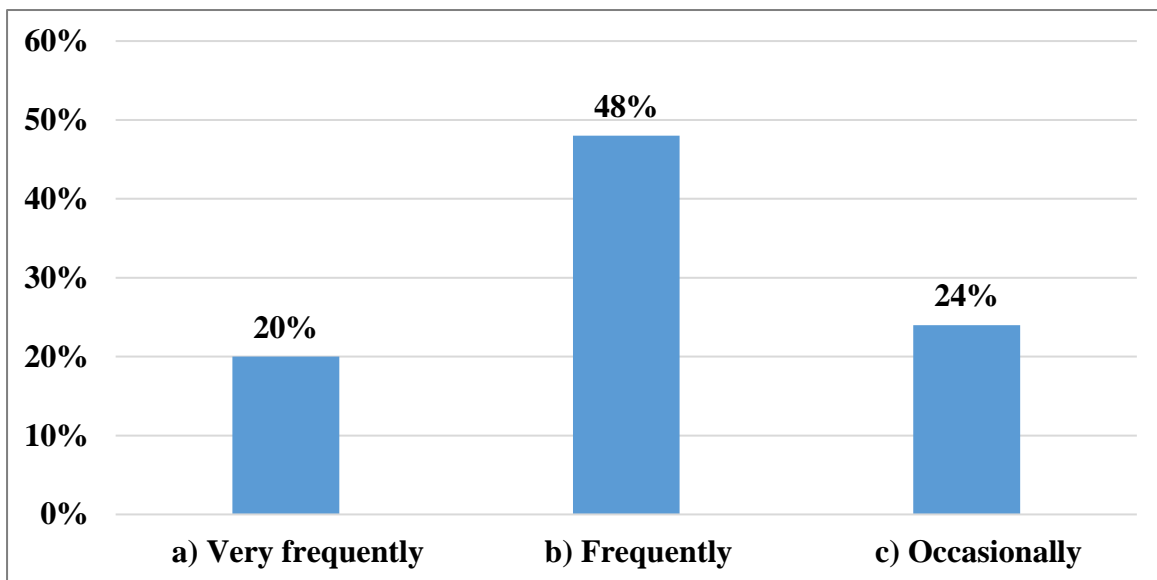
**15. What factors influence your decision to recommend Ferric Carboxymaltose (FCM) as the preferred iron supplementation method for pregnant patients?**

- a) Severity of anemia
- b) Patient's medical history
- c) Risk of adverse effects with other iron supplements
- d) All of the above

# Survey Findings

## 1. How frequently do you prescribe Ferric Carboxymaltose (FCM) for treating iron deficiency anemia in pregnant patients?

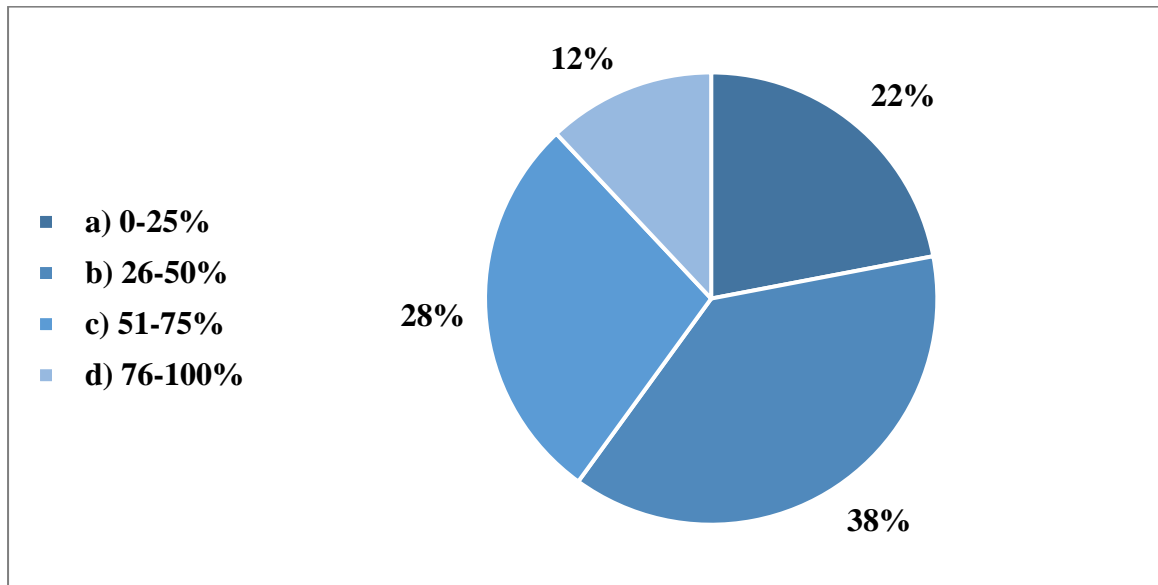
- a) Very frequently
- b) Frequently
- c) Occasionally
- d) Rarely



48% of doctors frequently prescribe Ferric Carboxymaltose (FCM) for treating iron deficiency anemia in pregnant patients.

**2. What percentage of your pregnant patients with iron deficiency anemia are prescribed Ferric Carboxymaltose (FCM)?**

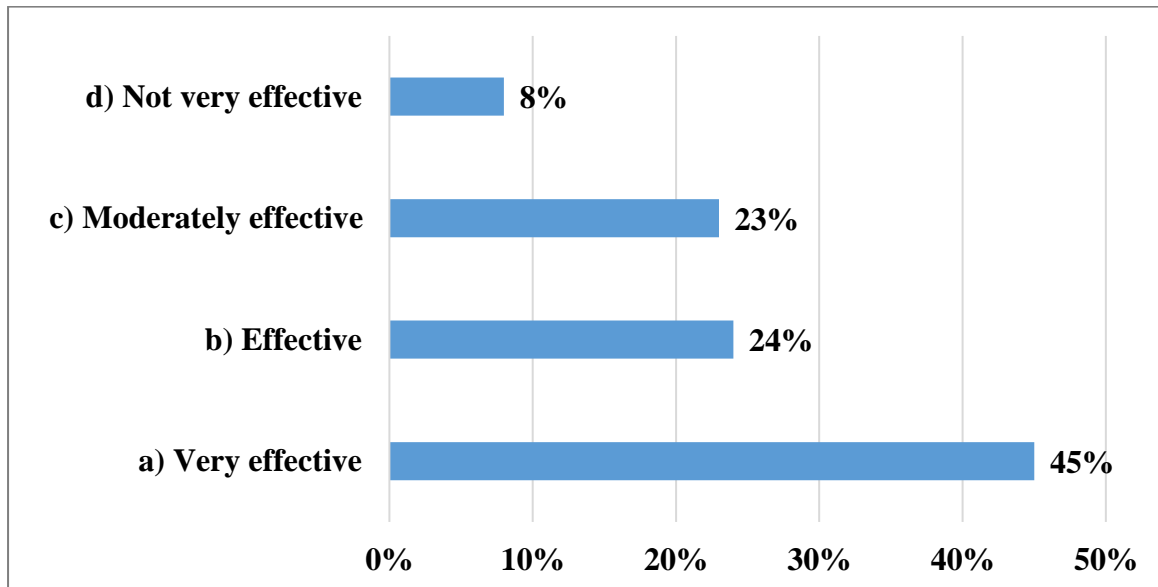
- a) 0-25%
- b) 26-50%
- c) 51-75%
- d) 76-100%



According to 38% of doctors, 26 – 50% of their pregnant patients with iron deficiency anemia are prescribed Ferric Carboxymaltose (FCM).

**3. In your experience, how effective is Ferric Carboxymaltose (FCM) in improving hemoglobin levels in pregnant patients with iron deficiency anemia?**

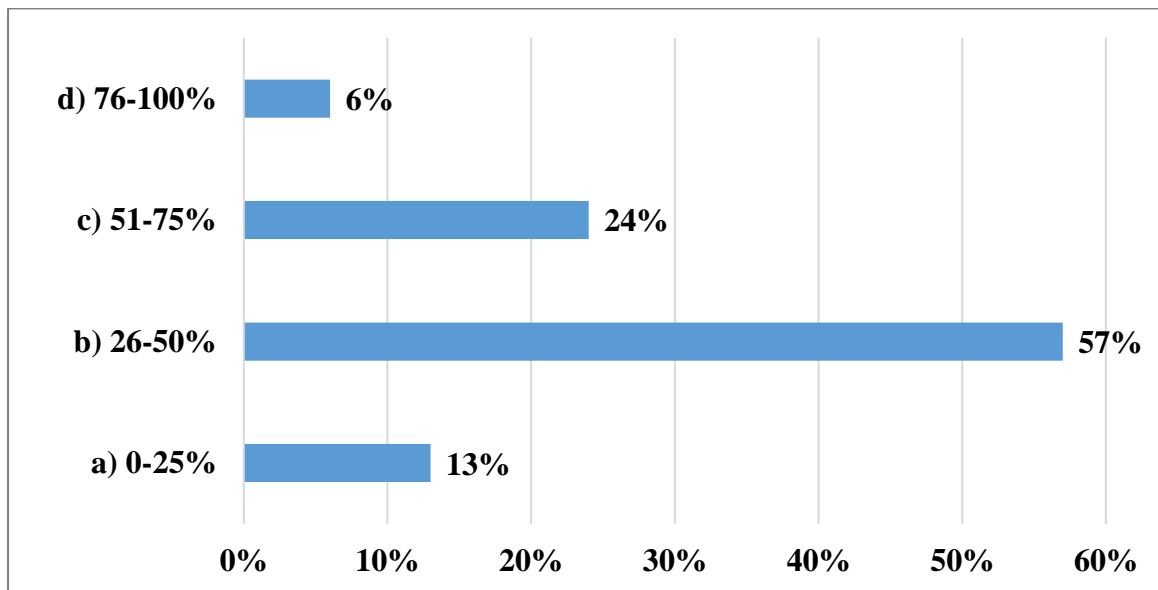
- a) Very effective
- b) Effective
- c) Moderately effective
- d) Not very effective



In the experience of 45% of doctors, Ferric Carboxymaltose (FCM) is very effective in improving hemoglobin levels in pregnant patients with iron deficiency anemia.

**4. What percentage of your pregnant patients with iron deficiency anemia experience resolution of anemia following Ferric Carboxymaltose (FCM) therapy?**

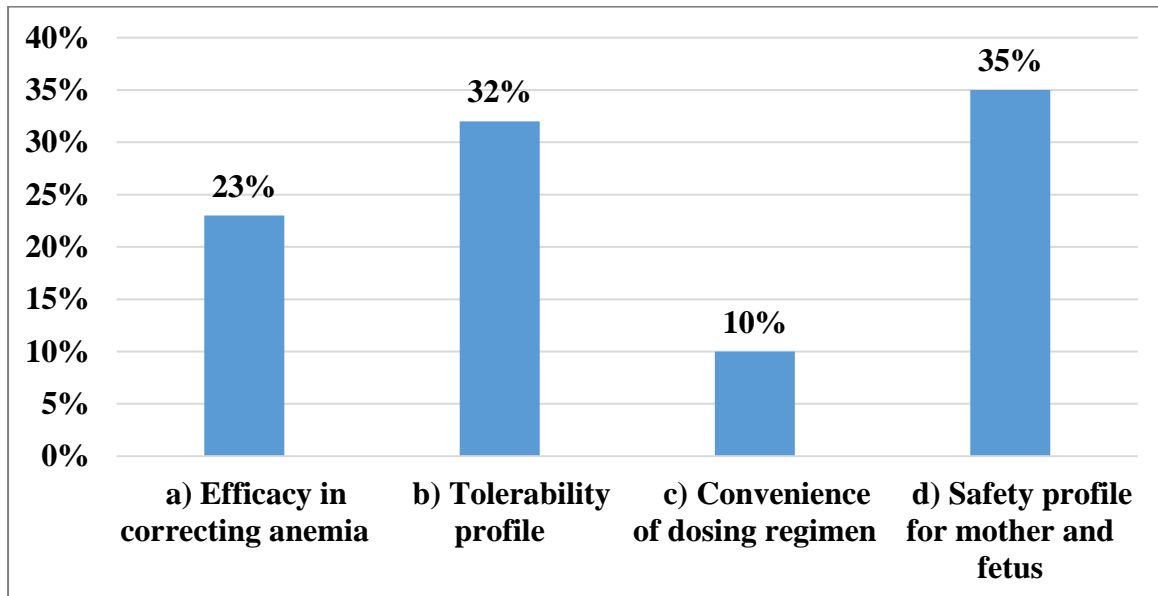
- a) 0-25%
- b) 26-50%
- c) 51-75%
- d) 76-100%



According to 57% of doctors, 26 – 50% of their pregnant patients with iron deficiency anemia experience resolution of anemia following Ferric Carboxymaltose (FCM) therapy.

**5. What factors influence your decision to prescribe Ferric Carboxymaltose (FCM) over other iron supplementation methods for pregnant patients?**

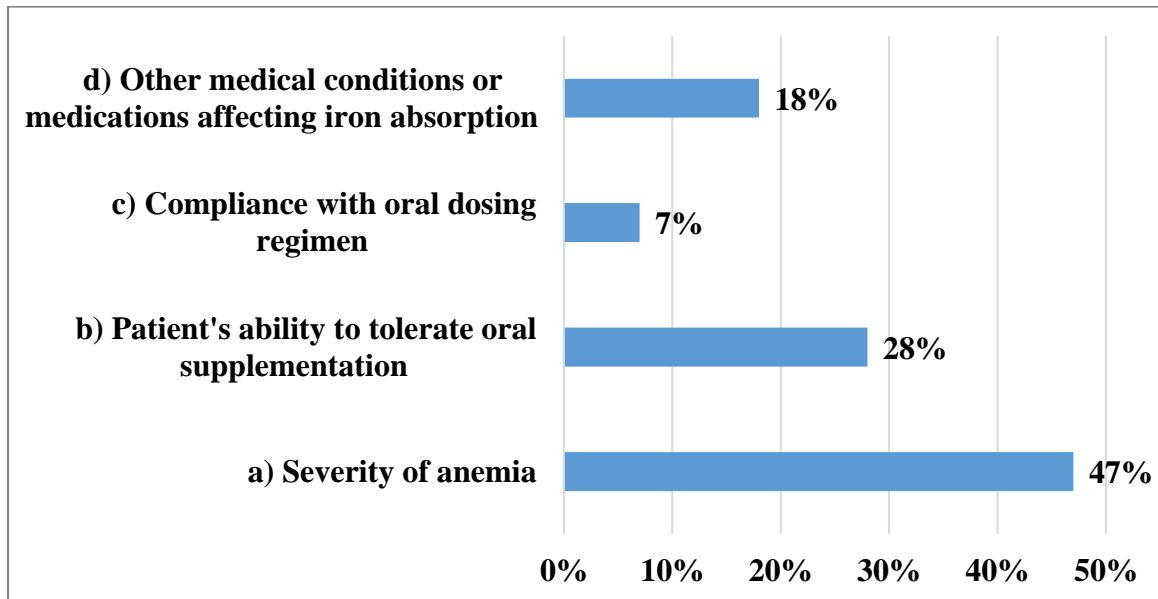
- a) Efficacy in correcting anemia
- b) Tolerability profile
- c) Convenience of dosing regimen
- d) Safety profile for mother and fetus



For 35% of doctors, safety profile for mother and fetus influences their decision to prescribe Ferric Carboxymaltose (FCM) over other iron supplementation methods for pregnant patients.

**6. What considerations guide your choice between Ferric Carboxymaltose (FCM) and oral iron supplements for pregnant patients with iron deficiency anemia?**

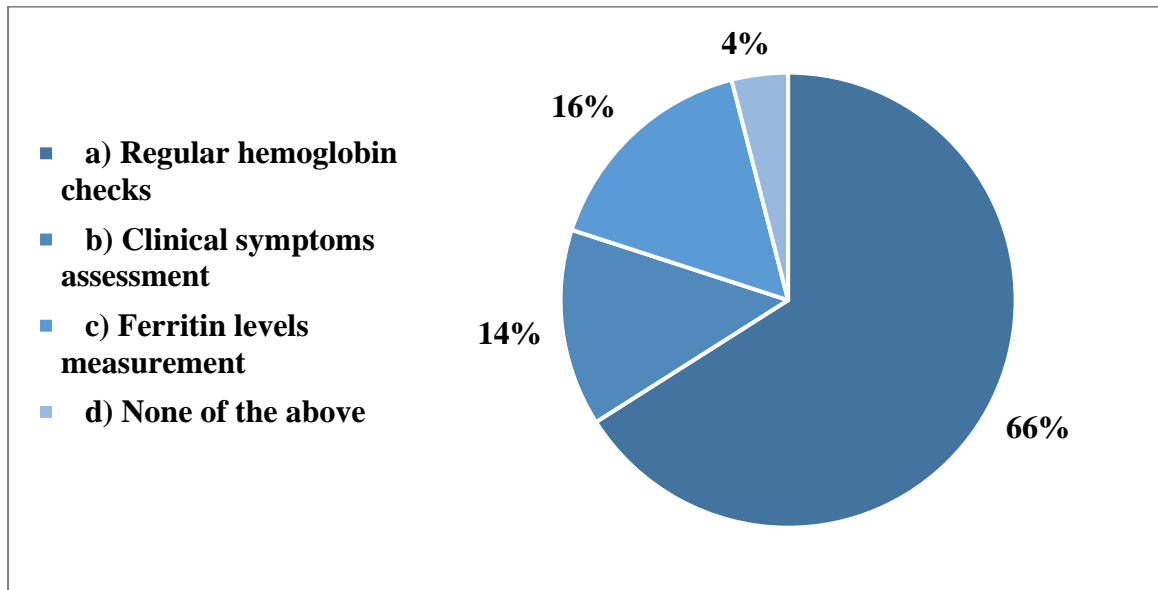
- a) Severity of anemia
- b) Patient's ability to tolerate oral supplementation
- c) Compliance with oral dosing regimen
- d) Other medical conditions or medications affecting iron absorption



According to 47% of doctors, severity of anemia guide their choice between Ferric Carboxymaltose (FCM) and oral iron supplements for pregnant patients with iron deficiency anemia.

**7. How do you monitor the response to Ferric Carboxymaltose (FCM) therapy in pregnant patients with iron deficiency anemia?**

- a) Regular hemoglobin checks
- b) Clinical symptoms assessment
- c) Ferritin levels measurement
- d) None of the above

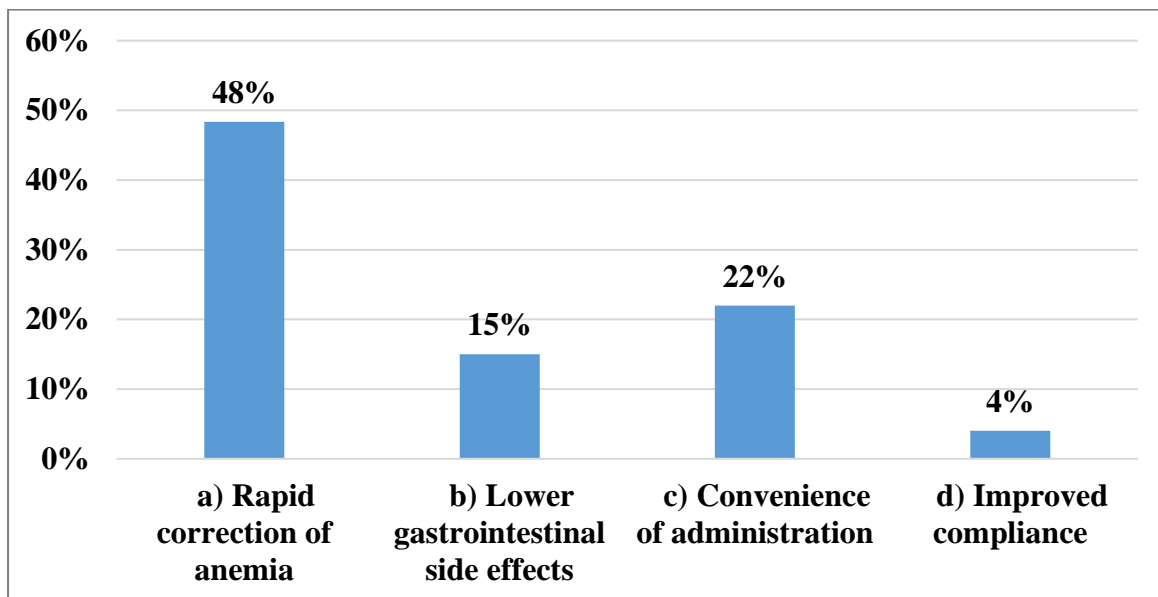


Majority of doctors, 66%, monitor the response to Ferric Carboxymaltose (FCM) therapy in pregnant patients with iron deficiency anemia by regular hemoglobin checks.



**8. In your opinion, what are the main advantages of using Ferric Carboxymaltose (FCM) over other iron supplementation methods in pregnant patients?**

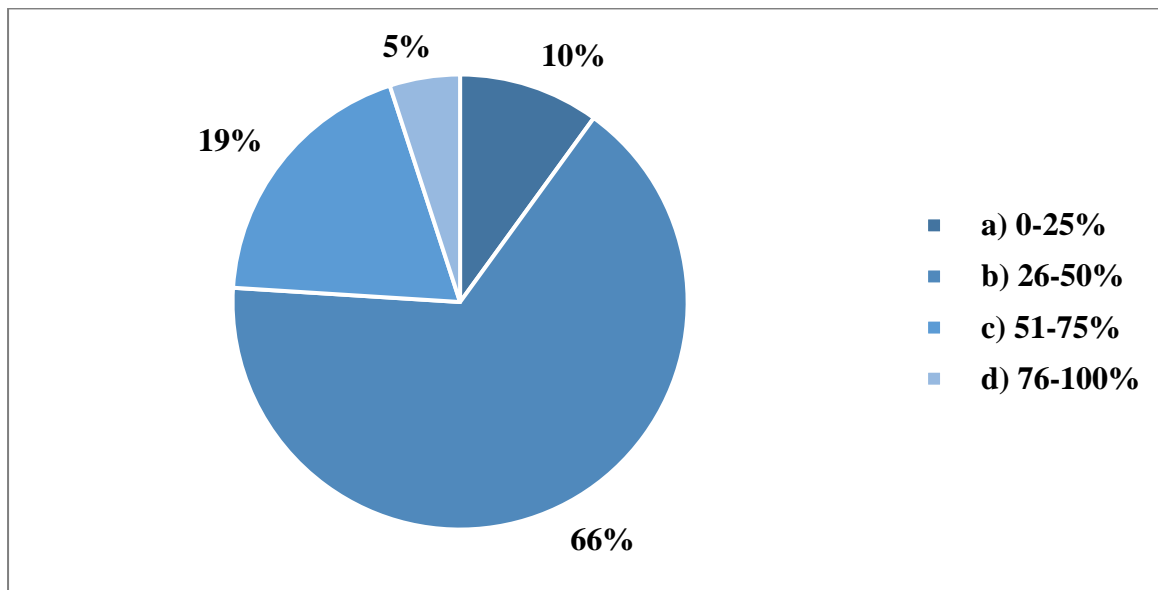
- a) Rapid correction of anemia
- b) Lower gastrointestinal side effects
- c) Convenience of administration
- d) Improved compliance



In the opinion of 48% of doctors, the main advantages of using Ferric Carboxymaltose (FCM) over other iron supplementation methods in pregnant patients is rapid correction of anemia.

**9. What percentage of your pregnant patients with iron deficiency anemia are candidates for Ferric Carboxymaltose (FCM) therapy based on current guidelines?**

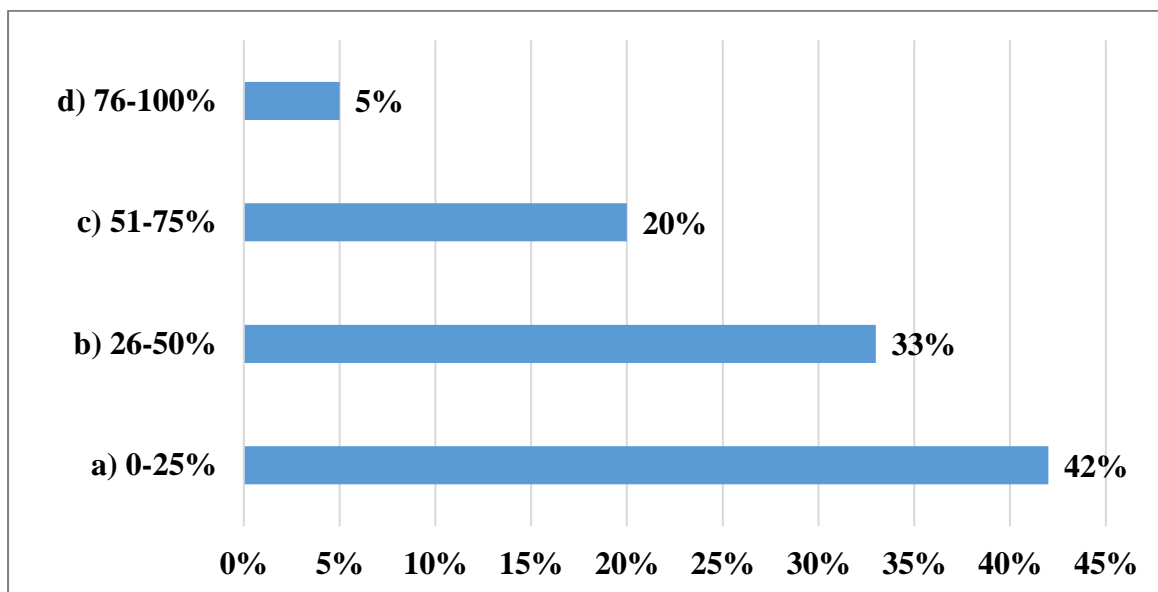
- a) 0-25%
- b) 26-50%
- c) 51-75%
- d) 76-100%



According to majority (66%) of doctors, 26 – 50% of their pregnant patients with iron deficiency anemia are candidates for Ferric Carboxymaltose (FCM) therapy based on current guidelines.

**10. What percentage of your pregnant patients with iron deficiency anemia have comorbid conditions that may affect their response to Ferric Carboxymaltose (FCM) therapy?**

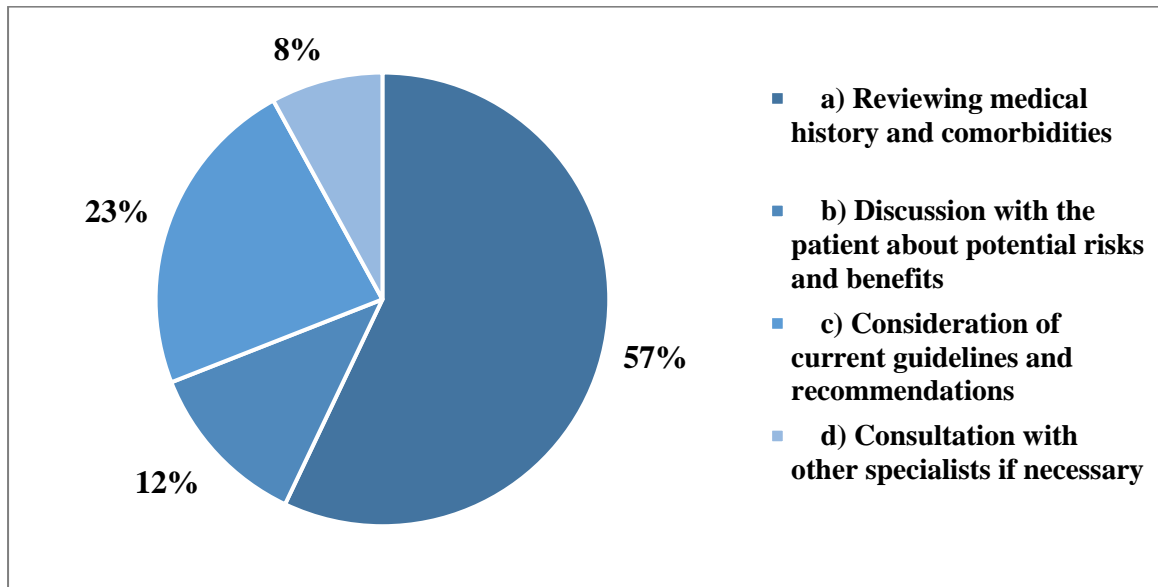
- a) 0-25%
- b) 26-50%
- c) 51-75%
- d) 76-100%



According to 42% of doctors, 0 – 25% of their pregnant patients with iron deficiency anemia have comorbid conditions that may affect their response to Ferric Carboxymaltose (FCM) therapy.

**11. How do you assess the risk-benefit ratio before initiating Ferric Carboxymaltose (FCM) therapy in pregnant patients?**

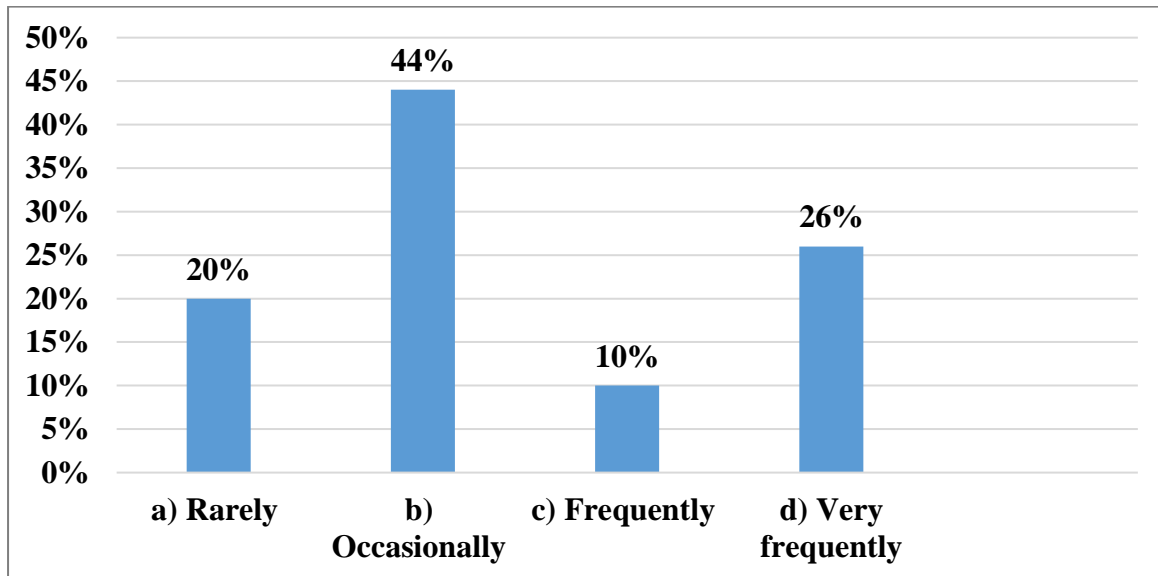
- a) Reviewing medical history and comorbidities
- b) Discussion with the patient about potential risks and benefits
- c) Consideration of current guidelines and recommendations
- d) Consultation with other specialists if necessary



57% of doctors assess the risk-benefit ratio before initiating Ferric Carboxymaltose (FCM) therapy in pregnant patients by reviewing medical history and comorbidities.

**12. How frequently do you encounter pregnant patients with iron deficiency anemia in your clinical practice?**

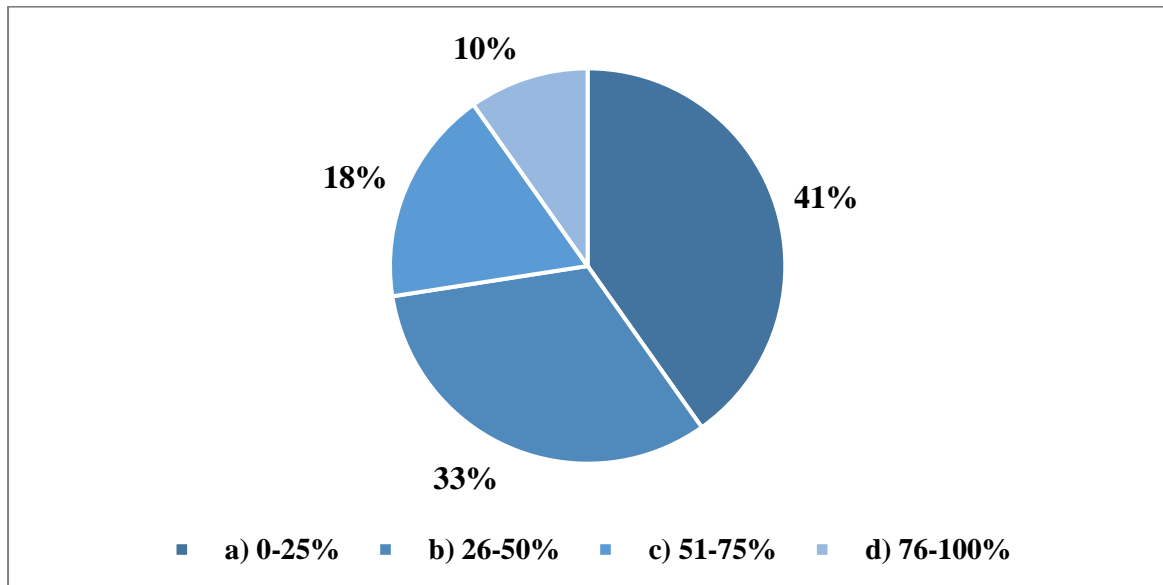
- a) Rarely
- b) Occasionally
- c) Frequently
- d) Very frequently



44% of doctors occasionally encounter pregnant patients with iron deficiency anemia in their clinical practice.

**13. What percentage of your pregnant patients experience improvements in fatigue and overall well-being following Ferric Carboxymaltose (FCM) therapy?**

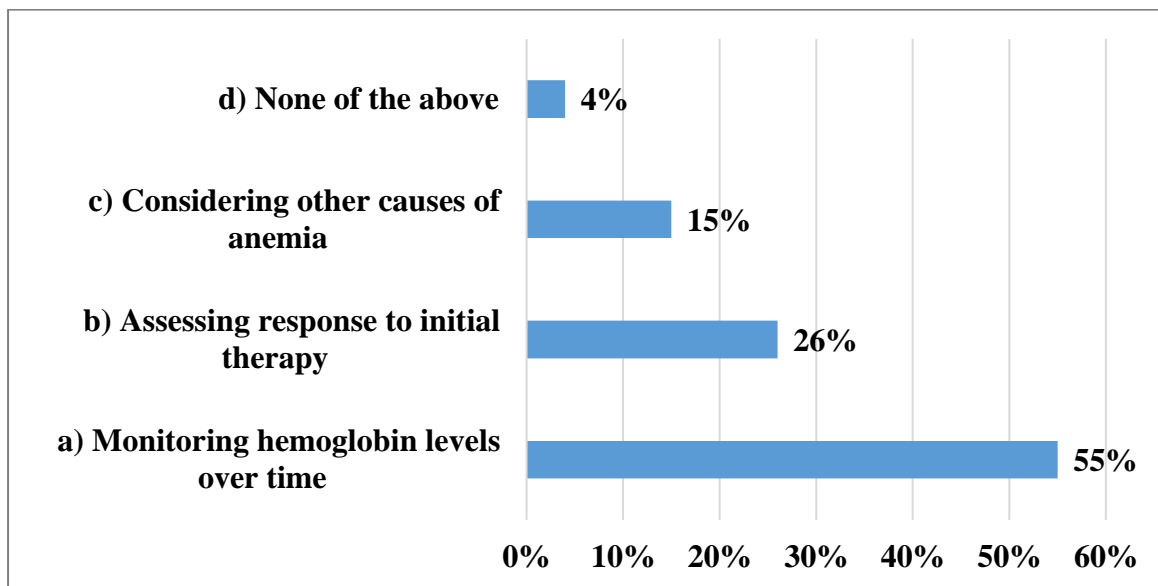
- a) 0-25%
- b) 26-50%
- c) 51-75%
- d) 76-100%



As per 41% of doctors, 0 -25% of their pregnant patients experience improvements in fatigue and overall well-being following Ferric Carboxymaltose (FCM) therapy.

**14. How do you evaluate the need for repeat doses of Ferric Carboxymaltose (FCM) in pregnant patients with persistent iron deficiency anemia?**

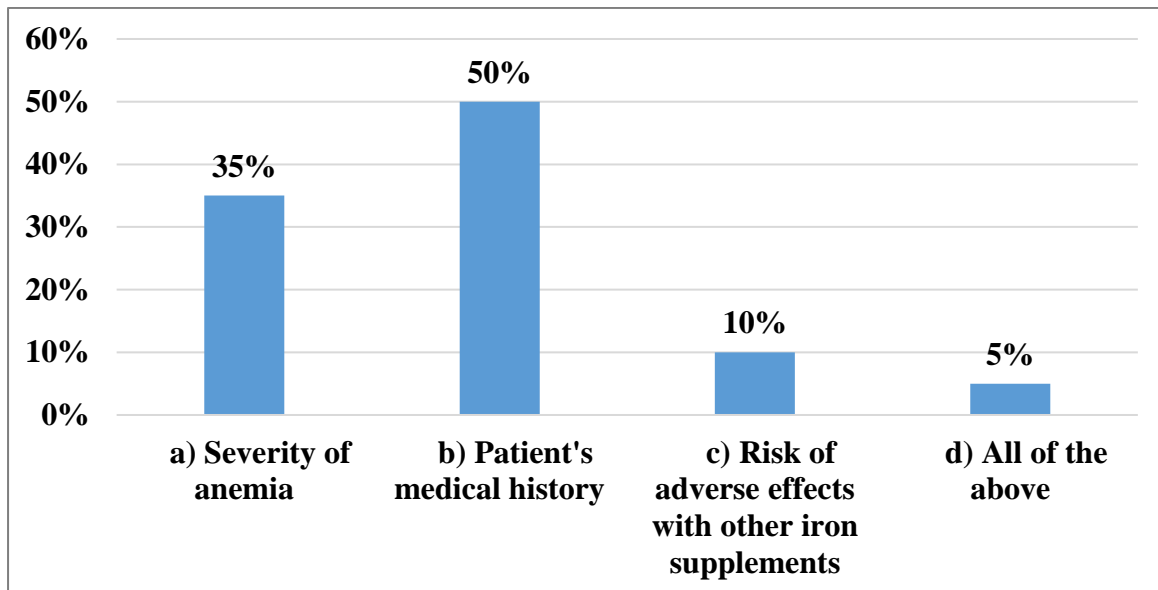
- a) Monitoring hemoglobin levels over time
- b) Assessing response to initial therapy
- c) Considering other causes of anemia
- d) None of the above



55% of doctors evaluate the need for repeat doses of Ferric Carboxymaltose (FCM) in pregnant patients with persistent iron deficiency anemia by monitoring hemoglobin levels over time.

**15. What factors influence your decision to recommend Ferric Carboxymaltose (FCM) as the preferred iron supplementation method for pregnant patients?**

- a) Severity of anemia
- b) Patient's medical history
- c) Risk of adverse effects with other iron supplements
- d) All of the above



As per half the doctors, 50%, patient's medical history influence their decision to recommend Ferric Carboxymaltose (FCM) as the preferred iron supplementation method for pregnant patients.



# Summary

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- 48% of doctors frequently prescribe Ferric Carboxymaltose (FCM) for treating iron deficiency anemia in pregnant patients.
- According to 38% of doctors, 26 – 50% of their pregnant patients with iron deficiency anemia are prescribed Ferric Carboxymaltose (FCM).
- In the experience of 45% of doctors, Ferric Carboxymaltose (FCM) is very effective in improving hemoglobin levels in pregnant patients with iron deficiency anemia.
- According to 57% of doctors, 26 – 50% of their pregnant patients with iron deficiency anemia experience resolution of anemia following Ferric Carboxymaltose (FCM) therapy.
- For 35% of doctors, safety profile for mother and fetus influences their decision to prescribe Ferric Carboxymaltose (FCM) over other iron supplementation methods for pregnant patients.
- According to 47% of doctors, severity of anemia guide their choice between Ferric Carboxymaltose (FCM) and oral iron supplements for pregnant patients with iron deficiency anemia.
- Majority of doctors, 66%, monitor the response to Ferric Carboxymaltose (FCM) therapy in pregnant patients with iron deficiency anemia by regular hemoglobin checks.
- In the opinion of 48% of doctors, the main advantages of using Ferric Carboxymaltose (FCM) over other iron supplementation methods in pregnant patients is rapid correction of anemia.
- According to majority (66%) of doctors, 26 – 50% of their pregnant patients with iron deficiency anemia are candidates for Ferric Carboxymaltose (FCM) therapy based on current guidelines.
- According to 42% of doctors, 0 – 25% of their pregnant patients with iron deficiency anemia have comorbid conditions that may affect their response to Ferric Carboxymaltose (FCM) therapy.
- 57% of doctors assess the risk-benefit ratio before initiating Ferric Carboxymaltose (FCM) therapy in pregnant patients by reviewing medical history and comorbidities.

- 44% of doctors occasionally encounter pregnant patients with iron deficiency anemia in their clinical practice.
- As per 41% of doctors, 0 -25% of their pregnant patients experience improvements in fatigue and overall well-being following Ferric Carboxymaltose (FCM) therapy.
- 55% of doctors evaluate the need for repeat doses of Ferric Carboxymaltose (FCM) in pregnant patients with persistent iron deficiency anemia by monitoring hemoglobin levels over time.
- As per half the doctors, 50%, patient's medical history influence their decision to recommend Ferric Carboxymaltose (FCM) as the preferred iron supplementation method for pregnant patients.

# Consultant Opinion

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## Market Opportunities:

The frequency of prescription (48%) indicates a significant market opportunity for pharmaceutical companies manufacturing Ferric Carboxymaltose (FCM) formulations. Companies could focus on developing innovative formulations or delivery methods to enhance the efficacy and safety of FCM for pregnant patients.

## Value for Healthcare Professionals:

Healthcare professionals should receive education and training on the appropriate use of Ferric Carboxymaltose (FCM) for treating iron deficiency anemia in pregnant patients. Continuing medical education programs can help ensure that healthcare professionals stay updated on the latest evidence-based practices and guidelines.

## Adverse Effect Management:

Healthcare professionals should be vigilant in monitoring pregnant patients for potential adverse reactions to Ferric Carboxymaltose (FCM), both for the mother and fetus. Regular follow-up visits and assessments can help detect and manage adverse effects promptly, ensuring the safety of both the mother and baby.

## Withdrawal Management:

Clear guidelines should be established for the duration and frequency of Ferric Carboxymaltose (FCM) therapy in pregnant patients to prevent overuse and minimize the risk of adverse effects. Healthcare professionals should assess the need for repeat doses based on the patient's response and ongoing monitoring of hemoglobin levels.

## Market Positioning:

Pharmaceutical companies can capitalize on the rapid correction of anemia provided by Ferric Carboxymaltose (FCM) by emphasizing this benefit in their marketing strategies. Highlighting

the safety profile and efficacy of FCM compared to other iron supplementation methods can help position it as a preferred option for pregnant patients with iron deficiency anemia.

#### Personalized Treatment Decisions:

Healthcare professionals should consider individual patient factors, such as the severity of anemia, comorbid conditions, and medical history, when deciding whether to prescribe Ferric Carboxymaltose (FCM) for pregnant patients. Personalized treatment decisions can optimize outcomes and minimize the risk of adverse effects.

#### Improving Patient Outcomes:

Patient education is essential to ensure optimal outcomes with Ferric Carboxymaltose (FCM) therapy. Pregnant patients should be informed about the potential benefits and risks of treatment, as well as the importance of adherence to prescribed regimens. Additionally, healthcare professionals should regularly assess patient response and adjust treatment plans as needed to achieve optimal correction of anemia and overall well-being.

## NOTES

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## NOTES

This image shows a full page of white paper with evenly spaced, light blue horizontal ruling lines. The lines run across the entire width of the page, leaving small gaps between them. There are no margins, text, or other markings on the paper.



Developed by:



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