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Review Article

Management of iron deficiency anemia in pregnancy in India: A review of current practices and challenges

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ABSTRACT

Background: Iron deficiency anaemia (IDA) is a major global health concern that can lead to difficulties for both the mother and the foetus, especially in pregnant women. The physiological demand of iron during pregnancy increases threefold to support fetoplacental development and maternal adaptation to pregnancy. This study aimed to identify gaps in current IDA management, limitations of conventional oral iron therapy, and the need for effective and well-tolerated treatments.

Objective: The objective of this study was to understand the gap of current treatment options in IDA management, its limitations, and possible effective strategies for better management.

Materials and Methods: A questionnaire-based opinion survey involving top gynecologists across India was conducted. The survey aimed to gather data on the challenges faced with conventional oral iron therapy, the desire for a change in oral iron salts, and the preference for novel oral iron prescriptions for their patients.

Results: Data obtained from the survey showed that 82% of gynecologists and obstetricians noticed challenges with conventional oral iron therapy. 86% wanted to change the oral iron salts, and 70% would like to prescribe novel oral iron for their patients. Ferric maltol, a novel form of chelated oral iron, was introduced as a potential solution for IDA management. It has been studied in various clinical indications, such as IDA associated with inflammatory bowel disease, chronic kidney disease, and pulmonary hypertension, showing significant improvements in hemoglobin and iron indices with good tolerability throughout treatment duration.

Conclusions: The study results demonstrate that ferric maltol is a suitable and convenient treatment option for individuals seeking long-term, convenient, and well-tolerated management of IDA.

1. Introduction

Iron deficiency anemia (IDA) occurs when the body lacks sufficient iron to generate an adequate number of healthy red blood cells, crucial for storing and transporting oxygen in the bloodstream. This results in symptoms like extreme fatigue, weakness, and paleness, as organs and tissues receive insufficient oxygen. IDA, the most prevalent form of anemia, can stem from factors such as blood loss, inadequate iron absorption, or insufficient iron intake.

The World Health Organization (WHO) has identified iron deficiency anemia as the most widespread nutritional deficiency globally, impacting 30% of the population.[1] In India, anemia during pregnancy poses a significant public health challenge, affecting 45.7% of urban and 52.1% of rural pregnant women with hemoglobin levels below 11 g/dL.[2] India ranks 170th out of 180 countries for women's anemia rates.[3] Causes of iron deficiency include insufficient intake, reduced absorption, and bleeding from sources

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such as gastrointestinal (GI) issues and menstruation. Inflammatory conditions like inflammatory bowel disease (IBD) and chronic kidney disease (CKD) can also lead to functional iron deficiency.[4]

During pregnancy, IDA is defined as hemoglobin levels below 11 g/dL in the first and third trimesters, and below 10.5 g/dL in the second trimester.[5] Increased iron requirements during pregnancy, necessary for maternal blood volume expansion and fetal growth, make diagnosing IDA challenging. Complications of IDA during pregnancy include premature birth, intrauterine developmental retardation, and diminished newborn iron storage. Managing IDA during pregnancy is crucial due to associations with conditions like autism, abnormal brain structure, and schizophrenia in offspring.[6]

Signs and symptoms of IDA during pregnancy encompass fatigue, reduced physical and mental capacity, headaches, vertigo, leg cramps, pagophagia, cold intolerance, koilonychias, mucosal paleness, and angular stomatitis.[7] Timely monitoring, accurate diagnosis, and effective treatment are essential. Screening for anemia during pregnancy is recommended in the first trimester, at 24–28 weeks, and at 36 weeks of gestation.[8]

During pregnancy, the demand for iron triples to support fetoplacental development and maternal adaptation. Dietary modifications focusing on increased intake of iron-rich foods and interventions improving iron absorption are crucial. Daily iron requirements rise from 4 to 6 mg/day in the second trimester to 10 mg/day in the last half of the third trimester. Thus, daily or intermittent oral supplementation is necessary to prevent IDA. WHO recommends weekly intermittent iron and folic acid supplementation for non-anemic pregnant women, while the Ministry of Health and Family Welfare suggests similar supplementations for all females aged 15-45 years.[5]

2. Current Treatment and Limitations

Oral iron replacement therapy using ferrous salts is the preferred method for treating iron deficiency anemia during pregnancy due to its affordability and convenience. However, its effectiveness may be hindered by limited bioavailability, with only a small percentage of iron (10-20%) being absorbed from oral ferrous formulations. Unabsorbed free iron can generate reactive hydroxyl radicals in the gastrointestinal tract, potentially causing GI irritation, damage, and other side effects. Conventional oral iron formulations also face challenges in patient compliance due to poor tolerability and side effects, exacerbating pregnancy-related GI disturbances.[5]

For individual's intolerant, non-compliant, or requiring rapid correction of iron stores, parenteral iron could be an alternative, especially for pregnant women with iron deficiency from the second trimester and during the postpartum period. Intravenous (IV) iron therapy provides complete bioavailability with fewer GI side effects and faster hemoglobin recovery compared to oral iron. However, its widespread use is limited by increased risks such as oxidant damage, higher costs, and a small but real risk of hypersensitivity reactions, anaphylaxis, hypophosphatemia, and iron overload. Physicians must carefully weigh the benefits and risks when considering IV iron therapy.[9]

Recognizing the unmet need for effective and well-tolerated treatments for iron deficiency anemia during pregnancy, there is a push for alternative oral iron therapies that match the efficacy of IV iron therapy while offering the convenience of oral administration. New formulations, including ferric maltol, ferric citrate, polysaccharide–ferric iron complexes, sodium feredate, and sucrosomial iron, aim to address this need by potentially improving bioavailability and reducing the risk of gastrointestinal side effects.[10]

One such alternative is ferric maltol (FM), a novel oral iron formulation designed to enhance the gastrointestinal absorption and tolerability of oral iron. FM, composed of iron in the stable ferric (Fe3+) state complexed with trimaltol, a naturally occurring sugar derivative, is a promising option for effective and convenient treatment of iron deficiency and iron-deficiency anemia. The ferric and trimaltol complex remains strongly chelated in the intestinal lumen until absorption, minimizing the risk of gastrointestinal toxicity. FM is available in Europe, the United States, and India for treating iron deficiency in adults, with or without anemia, across diverse populations, including those with conditions like inflammatory bowel disease (IBD), chronic kidney disease (CKD), and pulmonary hypertension.[10]

2.1. Ferric maltol in iron deficiency anaemia

In cases of mild-to-moderate anemia, ferric maltol may serve as a viable oral treatment option when individuals either cannot tolerate ferrous preparations or experience suboptimal efficacy after four weeks of treatment. For moderate anemia, especially in patients with gastrointestinal intolerance to oral ferrous iron, intravenous iron stands out as the preferred treatment. In the maintenance therapy of iron deficiency anemia (IDA), ferric maltol could play a significant role in sustaining the benefits achieved through intravenous therapy. This form of treatment ensures an adequate supply of iron to meet the body's erythropoietic needs, thereby reducing the reliance on blood transfusions or erythropoiesis-stimulating agents. Additionally, ferric maltol helps minimize the amount of free iron in the intestinal tract, reducing the risk of damage to the gut microbiome and preventing the exacerbation of underlying gastrointestinal diseases.[10]

Ferric maltol (FM) has demonstrated the ability to elevate serum iron parameters, including ferritin and transferrin saturation (TSAT), effectively addressing anemia associated with iron deficiency, especially during

Table 1: Properties of ferric Maltol vs other iron supplements

Property	Ideal characteristics	Ferric maltol	Ferrous fumarate	Ferrous Sulphate	Ferric Pyrophosphate	Ferric carboxymaltose
GI Irritation	Should be negligible or absent	Negligible	Present	Present	Negligible	NA
Labile Iron Release/NTBI Formation	Should be Absent	Relatively Absent	Present	Present	Relatively absent	Present
Oxidative stress	Should be Absent	Absent	Present	Present	Absent	Present
Single dose (mg)	Should be Optimum	29 mg	100 mg	100 mg	30 mg	15 mg/kg max 1000 mg
USFDA/EU Approval	Should be approved	Approved	Approved	Approved	Not Approved	Conditional approval
Can deviate Hepcidin – ferroprotein pathway	Should be yes	Yes	No	No	Yes	NA
Head on comparison with IV iron	Should be yes	Yes (With FCM)	No	No	No	Yes (With other IV iron)
HB rise	Should be at least 1% after 12 weeks	Almost 2%	0.5-1.4%	0.3-1.2%	More than 1%	Almost 2%

pregnancy. Its potential advantages encompass improved iron absorption, minimized gastrointestinal side effects, and a decreased dosage necessity. Furthermore, FM facilitates the absorption of iron through the intestinal wall and its subsequent transfer to transferrin and ferritin. This makes it a relatively safe and efficient oral iron therapy, potentially more tolerable than alternative oral iron formulations [11] (Table 1).

2.2. *Posology*

Ferric maltol is supplied in oral capsules, each containing 29 mg of elemental iron. The recommended dosage of ferric maltol ranges from once to twice a day, contingent on the severity of the individual's iron deficiency. For maximum absorption, it is recommended to take ferric maltol on an empty stomach, either one hour before or two hours after a meal. The absorption of iron is notably higher when ferric maltol is consumed on an empty stomach compared to when taken with food. To ensure the optimal effectiveness of ferric maltol capsules, it is important not to open, break, or chew them. The treatment duration is a minimum of 12 weeks or as determined by the severity of the patient's iron deficiency. Ferric maltol should be continued until blood tests confirm the replenishment of the body's iron stores.

Assessment of ferric maltol for the management of iron-deficiency Anemia: A questionnaire-based opinion survey among gynecologists and obstetricians in India.

To address the current treatment gaps in the management of IDA and explore potential strategies for its better management, a questionnaire-based opinion survey was conducted involving 50 top gynecologists and obstetricians across India. The survey aimed to gather insights into the limitations of current IDA therapies and assess the opinions of key opinion leaders (KOLs) regarding Ferric maltol, a novel oral iron formulation, for the management of IDA in pregnancy (Figure 1).

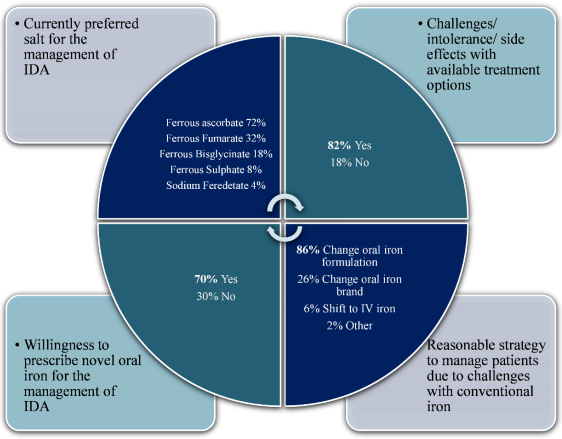

Figure 1: Opinion of top Gynaecologist and Obstetricians on Ferric maltol use for IDA management in pregnancy from questionnaire-based opinion survey

The survey results highlighted that 82% of gynecologists encountered challenges, intolerance, or side effects when using conventional oral iron replacement therapy, with Ferrous Ascorbate being their preferred standard treatment for iron deficiency anemia (IDA). Moreover, 86% of gynecologists and obstetricians expressed a willingness to change the oral iron formulation they currently prescribe. The reasons for resistance or intolerance to oral iron in patients include disruptions in iron homeostasis, underlying

inflammatory conditions, patient noncompliance, and undetected infection (Figure 2).

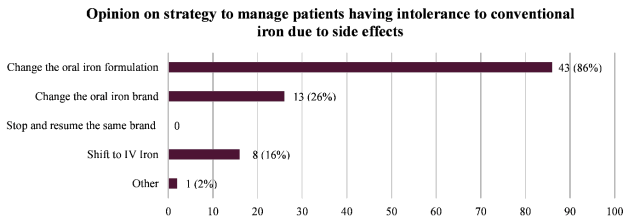

Figure 2: Opinion of top gynaecologists on the strategy to manage patients having intolerance to conventional iron due to side effects.

Moreover, 28% of surveyed gynecologists and obstetricians were familiar with contemporary oral iron supplements recognized for their superior efficacy and minimal side effects. Among them, 24% acknowledged Ferric Maltol—an iron formulation approved by both the USFDA and the European Union for treating iron deficiency anemia (IDA). The survey findings also revealed that 70% of these medical professionals expressed a preference for prescribing cutting-edge oral iron formulations, encompassing polysaccharide–ferric iron complexes, ferric maltol, sodium feredate, sucrosomial iron, and ferric citrate, for their patients. Nonetheless, 30% of respondents cited hurdles such as cost considerations, the need for additional scientific data, and a preference for tablets over capsules as reasons impeding the prescription of Ferric maltol.

These findings offer valuable insights into the current challenges and the potential of advanced oral iron formulations in addressing IDA management, particularly during pregnancy. The survey underscores the demand for more effective and well-tolerated IDA treatments, highlighting the potential of novel oral iron formulations to fulfil these unmet need.

3. Discussion

Iron-deficiency anemia (IDA) is a common issue in individuals with inflammatory bowel disease (IBD), chronic kidney disease (CKD), and pulmonary hypertension. This condition often results in fatigue, diminished quality of life, and an elevated risk of mortality. Ferric maltol, an innovative oral iron replacement therapy, has proven to be effective in addressing IDA in these patient groups. It is well-tolerated, providing sustained enhancements in both hemoglobin and iron levels.[12]

In a study conducted by Howaldt et al. in 2022, the effectiveness of oral ferric maltol was compared to intravenous ferric carboxymaltose for treating iron deficiency anemia (IDA) in patients with non-severely active inflammatory bowel disease (IBD). While ferric maltol resulted in a clinically relevant rise in hemoglobin levels, it did not establish non-inferiority to ferric carboxymaltose by week 12. Nevertheless, both treatments were well tolerated, and their long-term efficacy for hemoglobin and ferritin levels showed comparable outcomes over 52 weeks.[13]

Another study conducted by Schmidt et al. in 2016 reported that continuous ferric maltol treatment led to a significant increase in hemoglobin levels. At week 64, 89% of patients achieved normal hemoglobin levels, and this normalization was sustained in over 80% of patients from weeks 20 to 64 with prolonged ferric maltol treatment.[14]

Furthermore, the results from a phase 3, double-blind, randomized, placebo-controlled trial (AEGIS-CKD) indicated that ferric maltol led to statistically significant and lasting improvements in hemoglobin and iron indices among patients with chronic kidney disease (CKD). The treatment was well tolerated throughout the 52-week duration of the trial.[15]

Pergola and Kopyt's study in 2021 assessed the efficacy, preliminary safety, and tolerability of ferric maltol in patients with pulmonary hypertension, showing that the treatment significantly improved hemoglobin and iron status, with signs of improved right ventricular function and exercise capacity, supporting the importance of treating IDA in these patients.[16]

Clinical studies have consistently demonstrated the effectiveness and efficacy of ferric maltol as an oral treatment for iron deficiency and anemia in patients with various conditions, including IBD, CKD, and pulmonary hypertension. Ferric maltol has shown significant and sustained improvements in hemoglobin levels and iron status, with good tolerance throughout the treatment duration. These studies suggest that ferric maltol is an effective and convenient treatment option for individuals who seek long-term, well-tolerated management of iron deficiency anemia, irrespective of the underlying condition.

4. Conclusion

The research highlights the importance of a healthy diet and iron supplementation before or at the beginning of pregnancy. Ferric maltol offers a convenient alternative to oral treatment, potentially reducing the need for intravenous iron therapy for iron deficiency anemia during pregnancy. Clinical trials have consistently demonstrated the effectiveness of ferric maltol in diverse settings, including IBD, CKD, and pulmonary hypertension, making it a suitable option for long-term, well-tolerated management of iron deficiency anemia, especially for patient's intolerant to other oral treatments or non-compliant with intravenous therapy.

5. Source of Funding

Funding information is not applicable / No funding was received.

6. Conflicts of Interest

None.

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