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TOG Functional Protocols on
ROLE OF LOW-DOSE ORAL IRON IN PREGNANCY

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TOG Functional Protocols on Low-Dose Iron

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FUNCTIONAL PROTOCOL ON THE ROLE OF LOW-DOSE ORAL IRON IN PREGNANCY

Introduction

Anemia during pregnancy is a significant global health issue, contributing to high rates of maternal morbidity and mortality.[1] Globally, iron deficiency (ID)/iron deficiency anemia (IDA) is the most common cause, responsible for around 50% of anemia cases.[2,3]

India reports the largest number of anemic pregnant women globally, with over 7.5 million affected. Despite early programs of the Indian Government prioritizing iron and folic acid supplementation for prevention and treatment of anemia, such as the National Nutritional Anaemia Prophylaxis Programme (1972) and the Anaemia Mukt Bharat initiative (2018), there has been limited reduction in the prevalence of anemia in pregnant women in the country.[3]

Inadequate intake of iron and folic acid during pregnancy can have negative effects on maternal health, pregnancy outcomes, and fetal development. Anemia in pregnancy is linked to serious complications such as low birth weight, fetal growth restriction (FGR), preterm birth, complications during pregnancy, postpartum hemorrhage, and neonatal anemia. Preventing anemia is therefore crucial to reduce maternal and infant morbidity and mortality.[4]

Oral iron supplements are generally the first-line treatment for ID/IDA due to their low cost, safety, and proven effectiveness. Iron salts have traditionally been the most commonly used form,[5] but the available preparations vary widely in dosage, compounds, cost, and bioavailability. Commonly used iron salts such as ferrous fumarate, ferrous sulfate, ferrous ascorbate and ferrous gluconate vary in their content of elemental iron from 60–200 mg per day for the treatment of ID/IDA. These iron salts are associated with common adverse effects such as epigastric pain, nausea, and constipation, which reduce compliance with therapy in 30%–70% of cases. Reports have shown that lower doses (≤50 mg/day of elemental iron) are better tolerated due to improved fractional absorption and lesser unabsorbed iron in the gut, which otherwise contributes to inflammation, dysbiosis, and growth of harmful bacteria.[6]

The poor absorption of iron salts often demands higher doses than the recommended dietary allowance, further increasing the risk of side effects and reducing treatment adherence.[5,6] Therefore, selecting the right iron compound and dose is essential for maximizing efficacy and minimizing side effects.[7] Amino acids are considered to be good chelators, and reports have shown that iron amino acid chelates (IAAC) are readily absorbed and less likely to cause intestinal side effects.[8] Further, the potential benefits of low-dose oral iron supplementation in enhancing gastrointestinal tolerability without compromising efficacy have been highlighted.[9]

This document outlines clinical practice points to assist healthcare providers in optimizing ID/IDA management during pregnancy with the use of a suitable, safe, and effective oral iron supplementation that improves adherence during pregnancy and enhances outcomes for both mother and child.

Scope

This guideline provides evidence-based recommendations on the use of low-dose oral iron amino acid chelates for managing IDA in pregnancy, which aims to support clinicians in optimizing maternal outcomes through safe and effective supplementation.

Methodology

Based on a comprehensive review of current evidence and clinical guidelines addressing iron supplementation in pregnant women with anemia, practice points were developed. A multidisciplinary task force comprising experts in obstetrics and gynecology, Hematology, and Gastroenterology reviewed the available literature and evaluated the role of low-dose iron supplementation in improving gastrointestinal tolerance and enhancing bioavailability.

Recommendations were formulated through iterative discussions until a consensus was reached. The task force prepared the initial draft in collaboration with a medical writer, and the document was reviewed and endorsed by the expert panel. The task force members employed a well-defined grading system (Table 1) for the critical appraisal of evidence and grading the strength of recommendations.

Table 1. Level of evidence and grading strength of recommendations

Level of evidence	Description
Level A	Data derived from multiple randomized trials or meta-analyses, or evidence-based clinical practice guidelines
Level B	Data derived from a single randomized trial or a large non-randomized trial
Level C	Consensus of experts or small studies, retrospective studies or registries, or narrative/literature reviews
Level D	Data derived from Clinical experience
Class of recommendations	
Class I	Evidence and or general agreement that a given treatment or procedure is beneficial, useful or effective. It is recommended
Class IIa	Evidence is in favor of efficacy/usefulness and should be considered
Class IIb	Efficacy/usefulness is less well established, and recommendations may be considered
Class III	Evidence and or general agreement that a given treatment or procedure is not beneficial, useful or effective, and in some cases may cause harm. Not recommended

PRE-PREGNANCY

Preventive strategy during the pre-pregnancy period

PRACTICE POINTS

- *A preventive weekly iron–folic acid supplementation strategy should be recommended during the pre-pregnancy period to maintain adequate iron status particularly before conception and during the first trimester of pregnancy. (Level A/ Class I).*

Discussion

As per the WHO, anemia was reported in an average of 18% of pregnant women in industrialized countries, with most of these women being anemic before conception. The iron requirements of the growing fetus and placenta are increased during pregnancy. Furthermore, despite the mobilization of iron deposits and increased iron absorption during pregnancy, it is difficult to fulfill iron requirements with only diet, especially when the woman is at risk of iron deficiency (serum ferritin < 20 µg/l) while conceiving or when iron supplementation is delayed. Therefore, gestation must be commenced with good iron status. This can also avoid the risks of high antenatal doses of iron.[10]

The WHO recommends a preventive weekly iron–folic acid supplementation strategy in regions where anemia prevalence among women of reproductive age exceeds 20% and where large-scale food fortification with iron and folic acid is unlikely to be implemented within the next 1–2 years. This approach helps maintain adequate iron status, particularly before conception and during the first trimester of pregnancy. It is aimed at preventing iron deficiency, building pre-pregnancy iron reserves, and improving folate status in women.[11]

PREGNANCY

1. Prophylaxis with 30 mg elemental oral iron supplementation during pregnancy

PRACTICE POINTS

- *Routine iron supplementation should be provided during pregnancy, as dietary intake alone is insufficient to meet increased physiological iron demands. (Level A/ Class I).*
- *As per the panel, prophylactic iron supplementation should be promoted as it reduces the risk of maternal anemia and iron deficiency/IDA at term. (Level A/ Class I).*
- *Low-dose iron supplementation is recommended starting in the first trimester to decrease the prevalence of maternal anemia at delivery. (Level A/ Class I).*
- *Daily prophylactic iron supplementation with 30 mg of elemental iron should be initiated after about 12 weeks of gestation to prevent maternal anemia and iron deficiency. (Level B/Class I).*
- *Following the normalization of hemoglobin levels during pregnancy, iron supplementation should be continued at a maintenance dose for at least three to six months during pregnancy and the postpartum period to ensure complete replenishment of iron stores and prevent recurrence of anemia. (Level A/Class I).*

Discussion

A well-balanced diet and proper nutritional guidance play a vital role in preventing anemia during pregnancy. However, due to the increased physiological demand for iron during this period, dietary intake alone is often insufficient to meet maternal and fetal needs. As a result, routine iron supplementation becomes essential.[12] Evidence shows that prophylactic iron supplementation can reduce the risk of maternal anemia by up to 70% and significantly lower the incidence of ID and IDA by 57% at term. Moreover, women who receive iron supplements typically achieve higher hemoglobin concentrations both at term and in the postpartum period, supporting better overall maternal health outcomes.[13]

The ACOG recommends a daily dietary allowance of 27 mg of iron during pregnancy. Low-dose iron supplementation has been shown to improve maternal hematologic parameters, lower the risk of ID at term, and is not associated with adverse effects.[14] As a prophylactic measure, the Centers for Disease Control (CDC) advises initiating 30 mg of elemental iron per day at the first prenatal visit.[12, 15] Similarly, the WHO recommends a daily intake of 30–60 mg of elemental iron for all pregnant women to prevent ID and support maternal health.[12, 16] Once hemoglobin or hematocrit levels return to normal for the gestational stage, the iron dose should be reduced to a maintenance level of 30 mg/day, as recommended by the CDC.[15]

To ensure complete replenishment of iron stores, UK guidelines advise continuing iron supplementation for at least three months after hemoglobin normalization and until six weeks postpartum.[7] **FOGSI GCPR** recommends that, following hemoglobin normalization, daily prophylactic iron supplementation be maintained for at least six months during pregnancy and extended for an additional six months into the postpartum period to sustain iron stores and prevent recurrence of anemia.[13]

2. Recommendations for screening of anemia during pregnancy

PRACTICE POINTS

- *Routine CBC assessment at first antenatal visit early during the 1st trimester, and during each trimester should be recommended for early detection and management of anemia in pregnancy. (Level A/Class I).*
- *Cut off levels to be considered: Hb<11 g/dL in first trimester and <10.5 g/dL in second and third trimesters and <10 g/dL postpartum indicates anemia. (Level A/Class I).*
- *A complete blood count, including hemoglobin, MCV, MCH, MCHC, and RDW, should be suggested as the initial and essential tests for detecting IDA in pregnancy, which should be repeated between 24 to 28 weeks of gestation. (Level A/Class I).*
- *Serum ferritin should be utilized as a diagnostic tool for detecting IDA in pregnancy; a level of <30 µg/l is indicative of iron deficiency. Normal ferritin levels do not exclude IDA. (Level A/Class I).*
- *HPLC should be routinely used as a universal screening tool for hemoglobinopathies, with molecular techniques like PCR and ARMS to confirm specific genetic mutations. (Level B/Class I).*

Discussion

Routine screening, especially for IDA, is essential for timely diagnosis, effective management, and prevention of complications due to the high prevalence of anemia in pregnancy and its impact on maternal and fetal outcomes.[17,18] The diagnostic process involves a combination of clinical assessment, review of medical history and risk factors, and laboratory investigations. Among these, laboratory testing serves as the cornerstone for diagnosing anemia in pregnancy.[18]

Table 1. Indian council of medical research (ICMR) classification of anemia in pregnancy

Severity	Hemoglobin (Hb) Level
Mild anemia	8.0 – 10.9 g/dL
Moderate anemia	5.0 – 7.9 g/dL
Severe anemia	<5.0 g/dL

The primary screening includes evaluating hemoglobin concentration and hematocrit levels.[19] The World Health Organization (WHO) classifies anemia in pregnancy based on trimester-specific hemoglobin thresholds and severity levels, providing a framework for appropriate diagnosis and management. The detailed values are presented in Table 1.[13,18,20] While specific screening protocols may vary across countries, most guidelines recommend routine hemoglobin assessment during each trimester.[17]

The initial assessment for IDA includes a complete blood count (CBC), evaluating parameters such as hemoglobin, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW).[13] According to the American College of Obstetricians and Gynecologists (ACOG), and the Centers for Disease Control and Prevention (CDC), all pregnant women should undergo a CBC at their initial antenatal visit.[17] The International Federation of Gynecology and Obstetrics (FIGO) further recommends a full blood count at booking and again at 28 weeks of gestation.[21] ACOG advises that all pregnant women undergo a complete blood count again to screen for anemia between 24 and 28 weeks of gestation. Anemia is diagnosed when hematocrit levels are below 33% in the first and third trimesters and below 32% in the second trimester. In such cases, further evaluation is necessary to identify the underlying cause. If ID is excluded, alternative causes should be investigated.[14]

In addition to hemoglobin measurement, a range of laboratory tests can be performed to determine the type and severity of anemia.[18]

Serum ferritin is a sensitive marker of iron status under normal conditions; however, as an acute-phase reactant, it may be elevated in the presence of inflammation, complicating its interpretation. Patients with inflammation may have restricted iron availability for erythropoiesis despite normal or elevated ferritin levels. Therefore, the standard threshold of serum ferritin for ID (<30 µg/L) does not apply in such cases. Instead, a ferritin level <100 µg/L or transferrin saturation (TSAT) <20% is considered diagnostic of ID, as TSAT more accurately reflects iron bioavailability under inflammatory conditions.[22]

The WHO also recommends its use for monitoring the effectiveness of iron supplementation programs.[19] Diagnostic thresholds for serum ferritin vary among guidelines: the ACOG defines ID as ferritin levels below 30 µg/L, while the WHO suggests a cutoff of less than 15 µg/L.[23] The UK guideline states that serum ferritin should be measured in women with a known hemoglobinopathy to identify concomitant ID and exclude iron loading states. Serum ferritin level with normal hemoglobin is indicative of ID.[7] In a study, researchers analyzed over 27,000 pregnant women and found that anemia was more common among young women with less education and those in the poorest wealth quintile. It was also significantly higher among women with short birth intervals. The findings highlight the urgent need for targeted nutritional and educational interventions to reduce maternal anemia in vulnerable groups.[24] Regular antenatal visits should be encouraged to follow an early diagnosis and treatment strategy for a safe pregnancy and delivery.

If IDA is ruled out, clinicians should consider other potential causes of anemia by reviewing clinical history and performing a comprehensive laboratory evaluation, including red blood cell (RBC) indices. Among these, MCV serves as a key indicator, typically decreased in microcytic anemias such as IDA and thalassemia, and elevated in macrocytic anemias due to folate or vitamin B12 deficiency.[19]

For suspected hemoglobinopathies, high-performance liquid chromatography (HPLC) serves as a reliable first-line screening tool, followed by molecular techniques such as polymerase chain reaction (PCR) and amplification refractory mutation system (ARMS) to confirm specific genetic mutations.[25]

PREVENTION OF ANEMIA DURING PREGNANCY AND POSTPARTUM PERIOD WITH LOW-DOSE ORAL IRON

1. Prevention of anemia during pregnancy

PRACTICE POINTS

- *Daily oral iron supplementation is recommended for all pregnant women to reduce the risk of IDA, and to improve maternal hemoglobin levels and overall hematologic status. (Level A/Class I).*
- *Begin routine iron supplementation early in pregnancy and continue through the postpartum period to replenish iron stores and reduce the risk of maternal anemia and low birth weight. (Level A/Class I).*
- *Low-dose daily oral iron supplementation (in the range of 27–30 mg elemental iron/day), initiated after about 12 weeks of gestation, is sufficient to meet pregnancy-related demands and prevent ID and IDA during pregnancy. (Level A/Class I).*

Discussion

Effective management of anemia during pregnancy is crucial for optimizing both maternal and fetal health outcomes. Treatment strategies should be individualized based on the underlying etiology, severity of anemia, and the patient's overall clinical profile. Key management approaches include nutritional support, (oral or parenteral) iron supplementation, erythropoietin) and in severe cases, blood transfusions.[17]

Iron supplementation remains the cornerstone in the management of IDA during pregnancy.[17] Evidence from multiple studies demonstrates that routine iron intake significantly improves hemoglobin levels and decreases the prevalence of anemia in pregnant women. Continued supplementation through the postpartum period is essential, not only to restore maternal iron stores but also to reduce the risk of adverse outcomes such as Anemia in newborns.[26] Nutritional support plays a vital role, particularly in addressing dietary iron insufficiency. In addition to iron, adequate intake of folate and vitamin B12 is essential to prevent megaloblastic anemia and support healthy hematopoiesis throughout pregnancy.[17]

Preventive strategies are equally important and include a combination of nutritional education, iron supplementation, regular screening, and efforts to address socio-economic barriers. Educating pregnant women on a diet rich in iron (lean meats, legumes, fortified cereals), folate (leafy greens, citrus fruits, grains), and vitamin B12 (animal products, dairy) is essential. Emphasis should also be placed on cooking techniques that preserve the nutrient content of food.[17]

According to WHO guidelines, routine daily supplementation with 30 mg to 60 mg of elemental iron should be initiated as early as possible during pregnancy and continued throughout the antenatal period to reduce the risk of maternal anemia, ID, and low birth weight.[16] Regular hemoglobin screening at the first prenatal visit and again during every trimester the is recommended to enable early identification and timely intervention.[17]

Moreover, assessing risk factors such as a personal history of anemia, multiple pregnancies, and inadequate dietary intake can guide individualized care. Addressing socio-economic determinants through community-based programs, nutrition counseling, and improving access to prenatal care services is critical to reducing the overall burden of anemia in pregnancy.[17]

A systematic review of 57 randomized or quasi-randomized trials involving 48,971 pregnant women evaluated the effects of iron supplementation during pregnancy. Among these, 40 trials compared daily oral iron supplements to a placebo or no supplementation. The findings indicate that iron supplementation may reduce the risk of maternal anemia at term (relative risk (RR): 0.30; 95% confidence interval (CI): 0.20–0.47) and ID (RR: 0.51; 95% CI: 0.38–0.68). It also reduces IDA at term (RR: 0.41; 95% CI: 0.26–0.63). Additionally, women receiving iron supplements were probably less likely to have infants with low birth weight (RR: 0.84; 95% CI: 0.72–0.99). Therefore, daily oral iron supplementation during pregnancy significantly lowers the risk of maternal anemia, ID, and low birth weight in infants.[27]

A systematic review and meta-analysis, including 48 randomized trials (17,793 women) and 44 cohort studies (1,851,682 women), evaluated the effects of iron supplementation during pregnancy. Iron supplementation significantly increased maternal mean hemoglobin concentration by 4.59 g/L (95% CI: 3.72 to 5.46) compared to placebo intervention and was associated with a reduced risk of anemia (RR: 0.50, 95% CI: 0.42 to 0.59), ID (RR: 0.59, 95% CI: 0.46 to 0.79), IDA (RR: 0.40, 95% CI: 0.26 to 0.60), and low birth weight (RR: 0.81, 95% CI: 0.71 to 0.93). Thus, iron supplementation in pregnancy is beneficial for improving maternal hematologic status and neonatal birth weight.[28]

2. Prevention of anemia during postpartum

PRACTICE POINTS

- *Oral iron supplementation should be recommended for hemodynamically stable postpartum women who are asymptomatic with mild anemia (Level A/Class I).*
- *Timely identification and treatment of IDA during pregnancy significantly improves hematologic parameters and maternal well-being in the post-partum period. (Level A/Class I).*

Discussion

ID and IDA are associated with a range of maternal complications, including preterm labor, postpartum hemorrhage (PPH), and even maternal mortality.[23] Postpartum anemia (PPA) is most commonly linked to pre-existing antepartum IDA and significant blood loss during childbirth. Although maternal iron stores are expected to replenish following delivery, the prevalence of postpartum anemia remains high, affecting 22%–50% women in developed countries and 50–80% in developing regions. PPH, occurring in approximately 3%–8% of all deliveries, is a major contributing factor to this burden.[29]

In a large observational study involving 70,939 women who underwent cesarean section, the strongest predictors of severe postpartum anemia were a predelivery hemoglobin level <10 g/dL (adjusted odds ratio (aOR): 30.6; 95% CI: 27.2–34.6) and the occurrence of PPH (aOR: 8.45; 95% CI: 7.8–9.2).[30]

Postpartum anemia is linked to increased maternal morbidity; therefore, effective management of anemia during the postpartum period is essential for optimizing maternal health outcomes. Substantial evidence supports that iron supplementation in the postpartum period significantly improves hematological recovery and restores iron stores, thereby facilitating overall maternal recovery.[29] In a meta-analysis of 18 randomized controlled trials involving 1,633 pregnant and postpartum women with IDA, iron supplementation was observed to significantly improve hemoglobin, ferritin, and hematocrit levels, supporting its effectiveness in managing IDA during pregnancy and postpartum.[31]

3. Low-dose oral iron supplementation to prevent PPH

Pregnant women with ID are at an increased risk for PPH due to reduced hemoglobin reserves, increased blood flow from bleeding vessels, and uterine atony from impaired uterine oxygenation.[32] Therefore, maintaining iron stores through regular supplementation is critical. WHO suggests that the supplement should contain 30-60 mg of iron as part of antenatal care. Daily supplementation throughout pregnancy, beginning as early as possible after conception, is recommended in all settings.[33]

Research has shown that low-dose daily oral iron supplementation (an average of 30 mg elemental iron once daily) prevents IDA during pregnancy. It was found that supplementation with 40 mg iron/day from 18 weeks of gestation prevented ID in 90% and IDA in at least 95% of the women during pregnancy. Another study showed that supplementation with 20 mg iron/day from week 20 of gestation is an effective strategy for preventing IDA and ID. Further, the authors strongly suggested that supplementation with 20–40 mg iron/day (corresponding to a total iron intake of 34–49 mg/day) from 12 weeks and beyond of gestation would be effective in preventing ID and IDA during pregnancy.[34]

GUIDELINE RECOMMENDATIONS

- *ICMR recommends that females with iron deficiency anemia in pregnancy should be treated with supplemental iron 60 mg and 500 micrograms folic acid, in addition to prenatal vitamins.*[35]
- *According to the Federation of Obstetric and Gynaecological Societies of India Good Clinical Practice Recommendations (FOGSI GCPR, 2022), pregnant women receiving oral iron supplements should be advised to take the tablets on an empty stomach either before meals or at least one hour after meals and to co-administer them with vitamin C to enhance iron absorption.*[13]

Oral iron for the management of IDA during pregnancy: Conventional Iron salts vs. 30 mg Elemental Iron Amino Acid Chelates (IAAC)

PRACTICE POINTS

- *The expert panel opined that IAAC formulations are suitable for pregnant women who require long-term oral iron supplementation due to their potential to improve tolerability and adherence to therapy. (Level B/ Class I).*
- *IAAC can be considered a preferred oral iron therapy for pregnant women with IDA, due to its non-inferior efficacy in improving hemoglobin levels and iron stores compared to conventional iron salts. (Level A/ Class I).*
- *The panel suggested that since IAAC in comparison to conventional iron salts, demonstrated better gastrointestinal tolerability as it bypasses commonly encountered absorption limitations, improving patient adherence, which is critical for effective and sustained treatment of IDA in pregnancy. This, combined with its enhanced bioavailability, supports its clinical utility in antenatal care. (Level A/Class I).*
- *The panel opined that since low-dose oral iron formulations (30 mg elemental iron) of IAAC are proven to be non-inferior to higher-dose iron salts, with improved safety and tolerability profiles, their use in clinical practice should be preferred. (Level B/ Class I).*

Discussion

Oral iron is considered the only safe and recommended option for iron repletion during the first trimester of pregnancy, due to the lack of sufficient safety data for parenteral iron use during the critical period of fetal

organogenesis.[17] **ACOG recommends Low-dose iron supplementation starting in the first trimester to decrease the prevalence of maternal anemia at delivery**.[14]

Various oral iron preparations are available, including iron salts (ferrous sulfate, ferrous fumarate, ferrous gluconate), iron chelates (iron amino acid chelates), Ferrous ascorbate and ferric hydroxide complexes. However, all iron formulations are not equivalent in terms of absorption and tolerability.

Ferrous iron formulations are generally better absorbed than ferric forms. Ferrous sulfate and ferrous ascorbate are the most widely used preparations, but is often associated with gastrointestinal side effects such as constipation, nausea, and abdominal bloating.[36] A meta-analysis of 20 trials demonstrated an increased incidence of gastrointestinal side effects with oral ferrous sulfate compared to placebo (odds ratio [OR]=2.32, 95% CI 1.74–3.08, p<0.001) and as a result, reduced compliance with therapy in 30%–70% of symptomatic cases.[37]

Effective iron repletion through oral supplementation necessitates relatively high doses of elemental iron ranging from 50 to 200 mg/day administered for 3 to 12 weeks. However, only about 10%–20% of the ingested iron is absorbed, with the remainder accumulating in the gastrointestinal tract, which leads to adverse gastrointestinal side effects. Further, excess iron can also disrupt the diversity and composition of the gut microbiota, favoring the growth of pathogenic bacteria. This imbalance is closely associated with a higher risk of infections, intestinal inflammation, and the development of metabolic syndrome-related conditions.[38]

Modified formulations, such as enteric-coated ferrous sulfate, are suggested to reduce gastrointestinal irritation, but may compromise iron absorption due to delayed release in the gastrointestinal tract.[36]

Alternative ferrous salts like IAAC, offer good bioavailability with improved gastrointestinal tolerability and are therefore preferred in patients who experience side effects with conventional iron preparations. IAAC has been investigated as a means to reduce treatment-related adverse effects, improve patient adherence with non-inferior efficacy, particularly in pregnant women requiring long-term oral iron therapy.[8, 36]

Benefits of iron amino acid chelates:

1. Amino acids are ideal and good chelators, from both chemical and nutritional points of view.8
2. IAAC is neutral chelate. The high absorbability of IAAC is primarily attributed to the unique structure of amino acid chelates, which are highly effective natural chelators. In these complexes, the iron is stabilized in a ring-like (bicyclic) configuration formed by the carboxyl oxygen and α-amino group of the amino acid, with no free electrochemical charges. This stable structure facilitates efficient absorption.[8]
3. Additionally, intestinal villi exhibit a high affinity for amino acids and can absorb up to 95% of them. Well-formulated amino acid chelates can pass through the mucosal cells intact, encountering minimal resistance during absorption.[8]
4. Its enhanced bioavailability enables efficient repletion of iron stores at lower daily doses, thereby minimizing the gastrointestinal side effects observed with conventional iron therapy.[36]
5. IAAC can lead to faster elevation of hemoglobin levels, the mechanism of which can be attributed to the increased assimilation by the chelation process.[36]
6. IAAC effectively overcomes the absorption limitations commonly associated with inorganic iron salts.[36]
7. The improved gastrointestinal tolerability and lower required doses of IAAC contribute to better patient compliance and improved adherence, with non-inferior efficacy, thus making it a more acceptable and sustainable option for IDA.[36]

A clinical study evaluated the efficacy and tolerability of iron amino acid chelate (IAAC; 15 mg elemental iron once daily) versus ferrous fumarate (FF; 350 mg capsule containing 115 mg elemental iron once daily)

in the management of IDA during pregnancy. A total of 150 pregnant women diagnosed with IDA were enrolled and randomized to either IAAC or FF for 12 weeks. The results demonstrated a significantly greater and more rapid increase in hemoglobin levels at 4, 8, and 12 weeks in the IAAC group compared to the FF group ($p \leq 0.001$). In terms of tolerability, gastrointestinal side effects were observed to be higher in the FF group. Constipation was reported in a significantly higher proportion of women, 60% in the FF group, compared to 41.3% in the IAAC group ($p=0.022$), while abdominal colicky pain occurred in 49.3% of the FF group versus 32% of the IAAC group ($p = 0.031$).[8]

These findings suggest that IAAC offers superior efficacy in improving hemoglobin levels and better gastrointestinal tolerability than FF. IAAC may therefore be considered a preferred oral iron formulation, particularly in pregnant women diagnosed with IDA later in gestation, where immediate correction of anemia is necessary.[8]

In another clinical study involving 150 pregnant women with IDA, IAAC demonstrated a faster cure rate and superior hematological outcomes compared to FF. Patients were divided into 2 equal groups- one group was administered IAAC containing 15 mg elemental iron once daily, and the other group FF (350 mg with elemental iron, 115 mg with double dose in severe cases) once daily. Both treatment groups showed significant hematological improvement, including an increase in hemoglobin, red blood cell indices, serum iron, and ferritin at 4, 8, and 12 weeks of therapy. However, the mean hemoglobin level was significantly higher in the IAAC group compared to the FF group by week 12 (11.6 ± 0.8 g/dL vs. 11.3 ± 0.9 g/dL). Additionally, the IAAC group demonstrated significantly greater improvements in serum ferritin, packed cell volume (PCV), MCV, MCH, MCHC, and serum iron levels at the end of 12 weeks.[39]

These findings indicate that IAAC may offer enhanced efficacy over FF in improving both hemoglobin levels and iron stores during pregnancy, supporting its use as a preferred oral iron formulation for rapid correction of IDA in pregnant women.[39]

A retrospective study was conducted in pregnant women with IDA having hemoglobin levels ranging from 8–11 g/dL, serum ferritin <15 µg/L. All participants (n=63) were prescribed IAAC, providing 30 mg of elemental iron daily. The results demonstrated a statistically significant improvement in hemoglobin levels, with a mean increase of 1.51 ± 1.13 g/dL from baseline to the end of the 12-week treatment period. Further, the mean difference in the serum ferritin levels was found to be 14.66 ± 13.64 µg/l from the baseline to the end of the 12th week, which was statistically significant. The authors concluded that IAAC may be particularly beneficial for women diagnosed with ID late during gestation period, where timely correction of anemia is clinically important.[40]

In a study, researchers compared the efficacy and safety of iron chelated amino acid therapy (15mg daily) vs. traditional oral iron therapy (iron sulfate and iron gluconate) in the treatment of IDA during pregnancy (n=450). The patients in the iron chelated amino acid therapy group showed significantly lower incidence of nausea ($p<0.001$), vomiting ($p<0.001$), constipation ($p<0.001$), abdominal cramping ($p<0.001$), and diarrhoea ($p<0.001$) vs. the other oral therapy. In the iron chelated amino acid therapy group, the rates of increase of reticulocytes, hemoglobin%, and corpuscular hemoglobin concentration were faster ($p<0.001$ for all).[41]

PRACTICE POINTS

- *Low-dose iron supplementation should be the preferred strategy for the prevention of ID and IDA in pregnancy, as it reduces side effects, improves treatment compliance and enhances iron absorption. (Level A/ Class I).*
- *In pregnant women, routine supplementation with low-dose 30 mg/day elemental iron is effective and sufficient to meet the increased physiological demands, as well as avoid iron overload and associated side effects. (Level A/ Class I).*
- *The panel suggested that iron supplementation at a dose of 30 mg/day elemental iron should begin after about week 12 of gestation, when the iron requirements for pregnancy begin to increase. (Level A/ Class I).*

Discussion

From a physiological and nutritional point of view, it is crucial to use the lowest dose of supplementary iron. Iron antagonizes the intestinal absorption of other essential divalent cations (zinc, copper, chromium, molybdenum, manganese, and magnesium) and increases the risk of damage to the intestinal epithelium due to the formation of free radicals in the intestinal mucosa; therefore, iron doses should be kept as low as possible. **A study has shown that a low dose of iron appears adequate to prevent ID in 90% and IDA in 95% of healthy pregnant women and has no recognizable side effects.**[42]

Additionally, pregnancy-dependent suppression of maternal hepcidin would promote the rapid absorption of commonly prescribed iron supplements, potentially **exposing normal pregnancies to iron excess. High iron levels can cause tissue damage by the generation of reactive oxygen species. Therefore, abnormal maternal iron status at either extreme, either deficient or excess iron, has negative consequences for both the mother and the baby.**[43]

Pregnant women with adequate iron do not significantly raise hemoglobin levels with extra iron beyond physiological regulation mechanisms. Daily supplementation with 30 mg of elemental iron is sufficient to meet the increased physiological demands in most healthy pregnant women.[44] **Single low doses of iron supplements (30 mg/day elemental) are associated with fewer gastrointestinal side effects and lower hepcidin secretion, resulting in better treatment compliance and enhanced fractional absorption.**[40]

A study in iron-depleted young women found that oral iron doses of 60, 180, 160, and 240 mg given in the morning acutely increased plasma hepcidin levels the same day and 24 hours later. This increase was strongly associated with decreased absorption from the second iron dose, given 24 hours after the first. Providing 60 mg of iron twice daily amplified the plasma hepcidin increase and decreased the fractional absorption of both the afternoon dose and the next morning dose, so that total iron absorbed from the 3 doses (2 mornings and afternoon) was not different from that of the 2 morning doses. **The study concluded that fractional absorption was highest at lower doses. Thus, low-dose iron supplementation may improve absorption efficiency, minimize gastrointestinal exposure to unabsorbed iron, and enhance overall tolerance and adherence to therapy.**[45]

Meta-analysis of seven case-control studies found significantly higher levels of circulatory hepcidin in GDM patients than in healthy pregnant women. In such cases, low-dose 30 mg elemental oral iron supplementation may be considered as a better option for the prevention and management of Anemia during pregnancy.[46]

A study was conducted to evaluate the safety, tolerability, and efficacy of low-dose iron (LDI; IAAC: 30 mg elemental

iron) chelate as an alternative to high-dose iron salt (HDI; ferrous ascorbate: 100 mg elemental iron) in mild anemic females. The White blood cells scintigraphy performed indicated gastrointestinal inflammation in 33.3% of the patients in the HDI group, but no inflammation was observed in the LDI group. The Hb rise in the LDI group was 15.6% higher than in the HDI group. the symptoms of nausea/vomiting, metallic taste, and abdominal pain were observed to be mild in the group treated with LDI compared to moderate in the group treated with HDI. Therefore, the LDI (30 mg) was safer, tolerable, and equivalent effective compared to high-dose iron salt.[47]

Do's and Don'ts for IDA during pregnancy

Do's	Don'ts
Include iron-rich foods (Lean red meat, poultry, fish, Green leafy vegetables (spinach), legumes (lentils, beans), nuts, seeds).	Avoid tea, coffee, and cola around meals/supplement intake as the tannins and caffeine inhibit absorption.
It is beneficial to consume iron-rich foods with vitamin C–rich foods.	Avoid consuming high-calcium foods/supplements together as calcium reduces the absorption of iron.
It is necessary to take iron supplements on an empty stomach.	Avoid consuming iron with antacids as they interfere with absorption.

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