Section: Obstetrics and Gynaecology

Systemic Review

COMPARISON OF DIFFERENT IRON FORMULATIONS FOR TREATING IRON DEFICIENCY ANEMIA IN PREGNANCY – A SYSTEMIC REVIEW

H.Sharanya[1], K.S.Shivaranjani[2], S.Divya, R.Aishwarya[3]

[1]Assistant Professor, Department of Obstetrics and Gynaecology, Sri Lalithambigai Medical College and Hospital, Faculty of Medicine, Dr M.G.R Educational and Research Institute, Chennai, Tamilnadu, India.
[2]Assistant Professor, Department of Obstetrics and Gynaecology, Sri Lalithambigai Medical College and Hospital, Faculty of Medicine, Dr M.G.R Educational and Research Institute, Chennai, Tamilnadu, India.
[3]Assistant Professor, Department of Obstetrics and Gynaecology, Sri Lalithambigai Medical College and Hospital, Faculty of Medicine, Dr M.G.R Educational and Research Institute, Chennai, Tamilnadu, India.
[4]Assistant Professor, Department of Obstetrics and Gynaecology, Sri Lalithambigai Medical College and Hospital, Faculty of Medicine, Dr M.G.R Educational and Research Institute, Chennai, Tamilnadu, India.

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Corresponding Author:
Dr. R.Aishwarya,
Email: draishukrishi@gmail.com

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Abstract

Background: Iron deficiency anaemia (IDA) in pregnancy affects both mother and fetus. Appropriate iron supplement choice is essential. This review analyzes the safety and effectiveness of various iron formulations used for IDA during pregnancy. Oral iron supplements like ferrous sulfate and ferrous fumarate are commonly used for mild anaemia but may have issues with tolerance, compliance, and absorption rates. Gastrointestinal side effects are common and can cause adherence problems. Intravenous iron formulations such as iron sucrose and ferric carboxymaltose are recommended for moderate to severe IDA or poor oral iron tolerance. These offer higher bioavailability, rapid correction of iron levels, and effectiveness. Parenteral iron therapy is appropriate when oral iron is inadequate or not tolerated. It can be particularly useful for severe cases of IDA that need rapid iron level correction. Intravenous iron therapy is generally safe during pregnancy but requires monitoring due to the possibility of hypersensitivity reactions and iron overload risks. The review addresses factors that affect iron absorption, and individualized treatment selection based on anaemia severity, patient preferences, tolerability, and compliance is essential. The study provides insights for evidence-based clinical guidelines and resource allocation decisions. By implementing patient-centred care and considering the diverse iron formulations available, healthcare providers can effectively manage IDA during pregnancy and improve maternal and fetal health outcomes.

INTRODUCTION

Iron deficiency anaemia (IDA) occurs when there is inadequate production of haemoglobin, the oxygen-carrying protein in red blood cells, leading to reduced oxygen transportation throughout the body. This condition is prevalent and characterized by insufficient iron levels. Due to the expansion of the mother's blood volume and the requirements of the growing fetus, there is a significant increase in the need for iron during pregnancy. Pregnant women are more likely to have IDA because they need more iron to support both their health and the health of their developing unborn child.[1] Several negative effects on the mother's health during pregnancy can result from IDA. These effects include

- Fatigue and weakness: are common in anaemic women, making it difficult for them to carry out daily tasks and may impact their general quality of life.[2]
- Increased susceptibility to Infections: Pregnant women with iron deficiencies have weakened immune systems, which increases their susceptibility to infections.[3]
- Preterm birth and low birth weight: Severe anaemia has been linked to an increased risk of preterm birth and giving birth to an underweight baby, which can cause the newborn to experience several health problems.[4]

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- Postpartum complications: Women who are anaemic may experience difficulties giving birth and are more likely to experience postpartum haemorrhage.[5]

Pregnancy-related iron deficiency anaemia can significantly affect a fetus's health because it may limit its capacity to grow and develop to its full potential due to insufficient oxygen supply.[3] Fetal iron deficiency has been linked to delayed neurodevelopment, which may cause cognitive and behavioural issues in later life.[6] The right iron supplement formulation must be chosen to treat IDA effectively. Selecting an iron formulation is essential to attaining optimal treatment results, increasing patient compliance, and reducing side effects. The bioavailability, side effect profiles, and absorption rates of various iron formulations vary, which can have a big impact on how well they work to treat IDA. These are the significance of selecting suitable iron formulations for efficient management

- Bioavailability: The body's ability to absorb and use iron is called bioavailability. Choose formulations with higher bioavailability for improved management of iron deficiency and more effective iron absorption.
- Gastrointestinal (GI) side effects: are typical with oral iron supplements and can reduce compliance. To increase patient tolerance and adherence, pick formulations with softer side effects.
- Absorption Rate: The absorption rates of various formulations vary. While slow-release options reduce GI side effects but might need higher doses, quick-release options deliver results quickly. Comorbidities and Interactions: Consider any existing ailments and prescription drugs, as some formulations might not be appropriate for all patients.
- Considerations for Pregnant Women and Children: Special care must be taken to ensure the safety and effectiveness of pregnant women and children to support maternal and child health.[7] Diagnosis: Clinical assessment and laboratory tests diagnose IDA in pregnant women. Significant factors for diagnosis include.[8]
- Clinical evaluation: determining the severity of symptoms like weakness, paleness, breathlessness, and dizziness.
- Measuring the blood's haemoglobin (Hb) levels. Hb concentrations below 11.0 g/dL in the first and third trimesters and below 10.5 g/dL in the second trimester are considered anaemia.
- Measurement of the mean corpuscular volume (MCV) of red blood cells. Smaller red blood cells are indicated by decreased MCV in IDA.
- Serum ferritin level: measuring the body's iron reserves. Serum ferritin levels are frequently low in IDA, indicating insufficient iron stores.

Categorization of IDA in Pregnant Women.[9]

- Mild iron deficiency anaemia: Slightly decreased MCV and serum ferritin levels, mild symptoms, and slightly lower Hb levels.
- Moderate iron deficiency anaemia: Significantly lower Hb levels, obvious signs like fatigue and breathlessness, and even lower MCV and serum ferritin levels.
- Severe iron deficiency anaemia: Significantly low serum ferritin and MCV levels and severe symptoms like paleness and weakness. Choosing the most suitable iron formulation is important to achieve the best results for treating IDA.

MATERIALS AND METHODS

This article evaluates iron formulations' efficacy, safety, and implications for managing iron deficiency anaemia during pregnancy. A thorough literature search is conducted, and relevant studies are selected based on specific criteria. Different iron formulations regarding effectiveness, safety, tolerability, and impact on maternal and fetal outcomes are compared. Results are presented, and recommendations for clinical practice and future research are discussed. This review aims to provide evidence-based recommendations for effective IDA management in pregnant women.

Oral Iron Supplements

Effective management of IDA during pregnancy is crucial for better maternal and fetal outcomes. Proper selection of iron formulations can greatly impact treatment efficacy and patient compliance. Various oral iron supplements, such as ferrous sulfate, ferrous fumarate, ferrous gluconate, Iron polysaccharide complex, and Delayed-release/Slow-release iron, are available.[10]

Table 1: Comparison of the effectiveness and bioavailability of various oral iron formulations

Iron Preparation	Bioavailability	Efficacy	Side Effects
Ferrous Sulfate	Moderate to High	Effective	Typical gastrointestinal side effects include nausea, upset stomach, and constipation. [11]
Ferrous Fumarate	High	Effective	Typical GI side effects include nausea, upset stomach, and constipation. [11]
Ferrous Gluconate	Low to Moderate	Less Effective	GI side effects are less severe than ferrous sulfate and fumarate, but higher doses may be needed for the same effectiveness. [11]
Iron Polysaccharide Complex	Low	Less Effective	Low elemental iron content may necessitate higher doses despite minimal GI side effects and good tolerability. [10]
Delayed-Release/Slow-Release Iron	Variable	Variable	Slow-release results in fewer GI side effects but may contain less elemental iron, requiring higher doses to be effective. [10]

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They may have adverse effects and be a challenge to tolerate. Some frequent adverse effects include gastrointestinal discomfort, nausea, diarrhoea, constipation, a metallic taste, and teeth discolouration. Although rare, iron supplements can also mix with other drugs and cause adverse responses. The unpleasant side effects may harm compliance and cause some people to stop taking supplements.[12] To improve tolerance and reduce side effects:

- G.I. discomfort can be decreased by taking iron supplements with food.[13]
- Tolerability can be enhanced by increasing the dosage gradually.[10]
- Iron compositions with a delayed or slow-release limit gastrointestinal adverse effects.[10]
- It may be helpful to try alternative iron formulations if one develops intolerable adverse effects.[10]
- Taking iron supplements and vitamin C can improve absorption and decrease side effects.[14]

It is essential to follow the advice of medical professionals and share any concerns or adverse reactions when receiving therapy.

Intravenous Iron Therapy

Intravenous iron therapy can be considered if oral iron supplementation is insufficient or not tolerated well during pregnancy. In the following circumstances, the administration of intravenous iron may be advised.[15]

- Severe IDA: In cases of severe IDA during pregnancy, prompt correction of iron levels is essential to prevent complications for both mother and fetus.
- Intolerance to Oral Iron Supplements: Some pregnant individuals may experience gastrointestinal side effects or difficulty absorbing oral iron, making intravenous delivery a better option.
- Inability to Take Oral Iron: Intravenous iron therapy may be required for women who cannot safely consume oral iron supplements due to specific medical conditions or complications during pregnancy.
- Rapid Correction of Iron Deficiency: In situations where rapid correction is necessary, intravenous iron therapy is advantageous because it can cause haemoglobin levels to rise more quickly than oral supplements.There are different intravenous iron formulations approved for use during pregnancy. Some common types include.[16]

1. Iron Sucrose: Iron sucrose is a ferric hydroxide and sucrose compound. Typically, it is introduced intravenously in the form of short infusions. Research has demonstrated that its application during pregnancy is both safe and productive.
2. Ferric Carboxymaltose: A more recent formulation with a stable iron-carbohydrate complex is ferric carboxymaltose. It permits higher single-dose administration, which lowers the number of infusions required.
3. Iron Dextran: One of the earliest forms of intravenous iron was iron dextran, but due to potential risks and the availability of newer, safer formulations, its use has decreased. Safety Considerations and Potential Risks Associated with Intravenous Iron Therapy During Pregnancy: Intravenous iron therapy is safe and effective during pregnancy when used carefully under medical supervision. Nevertheless, safety issues and risks should be taken into account. These include.[15]

1. Anaphylactic Reactions: Severe allergic reactions, including anaphylaxis, may occur after intravenous iron administration. Healthcare providers must be prepared to manage such reactions quickly.
2. Hypersensitivity: A thorough medical history and risk assessment should be done before treatment because some people may experience hypersensitivity reactions to particular intravenous iron formulations.
3. Iron Overload: Excessive iron intake may cause hemochromatosis. Pregnant women require close observation to prevent iron overload.
4. Timing of Administration: In order to reduce potential risks during the early stages of fetal development, intravenous iron therapy is typically only used during the second and third trimesters of pregnancy.
5. Potential Impact on Preterm Birth: Intravenous iron therapy should be used cautiously in cases of preterm labor or other risk factors, even though the most recent research does not indicate an increased risk of preterm birth.

IV iron therapy for pregnant women must be given and supervised by qualified healthcare experts proficient in managing anaemia. They can evaluate individual needs and customize treatment to ensure the safety of both mother and baby.[15]

Parenteral Iron Therapy

Parenteral iron therapy introduces iron directly into the bloodstream instead of the digestive system. This method is used when oral iron supplementation is ineffective, poorly tolerated, or contraindicated. It is particularly advantageous for pregnant women with IDA who require rapid iron level correction. Various parenteral iron formulations have unique properties and safety profiles, including short intravenous infusions of iron sucrose. These are well tolerated and effective in raising haemoglobin levels and replenishing iron stores. Ferric carboxymaltose is a newer formulation that allows for higher single-dose administration, reducing infusions while maintaining effectiveness and a generally positive safety profile. Both iron sucrose and ferric carboxymaltose offer quick correction of iron levels and are safe when administered by qualified healthcare professionals. Individualized treatment plans considering medical histories and risk factors,

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are crucial for pregnant women receiving parenteral iron therapy.[17]

Absorption and Bioavailability

The absorption of iron from the gastrointestinal tract into the bloodstream makes it available for use by the body. Bioavailability represents the amount of ingested iron absorbed and available for physiological functions. Multiple factors influence iron absorption, and it is a complex process. Bioavailability refers to the percentage of ingested iron absorbed for physiological processes. Various variables can affect the complex process of iron absorption.[18]

Iron Absorption from Various Formulations is Affected by the Following Factors:

- Heme vs. Non-heme Iron: There are two types of iron in the diet: heme iron in animal-based foods and non-heme iron in plant-based foods and supplements. Heme iron is more easily absorbed due to its unique structure and resistance to gastrointestinal inhibitors.[19]
- Enhancers and Inhibitors: Dietary selections can affect iron absorption. Vitamin C and meat/fish improve iron absorption, while polyphenols and phytates hinder non-heme iron absorption.[11]
- Iron Status: The level of iron in the body impacts iron absorption. Absorption increases when iron stores are low and decreases when stores are high to prevent overload.[18]
- Formulation and Dosage: Various iron formulations exhibit different bioavailability due to their chemical structures, influencing their absorption in the body.[20]

Table 2: Comparison of bioavailability of different iron formulations

Iron Preparations	Bioavailability	Efficacy
Oral Iron Supplements	Lower bioavailability	Widely used, but may have gastrointestinal side effects and poor compliance.[21]
Intravenous Iron	Higher bioavailability	Bypasses GI tract, rapid correction of iron deficiency, effective when oral iron is not tolerated.[21]
Parenteral Iron Therapy	Superior bioavailability	Allows higher doses in single infusion, preferred for severe cases of iron deficiency anaemia.[22]

Treatment Response and Hemoglobin Improvement

The response time and haemoglobin improvement can vary depending on the degree of anaemia and the iron formulation used. Heme iron, present in animal-based foods, is typically better absorbed and causes haemoglobin to improve more quickly than non-heme iron, which is present in plant-based foods and supplements. However, the response rate may vary between various parenteral and oral iron formulations.[19]

Table 3: Time to respond and haemoglobin improvement with different iron formulations

Iron Preparations	Response Time	Mechanism
Oral Iron Supplements	Several weeks to months	Improvement in haemoglobin levels may take 4 to 8 weeks.[23]
Intravenous Iron	Rapid - Within a few days to a week	Direct infusion into the bloodstream leads to quicker response time.[24]
Parenteral Iron Preparations	Rapid - Within a few days	Both intravenous and intramuscular parenteral preparations offer rapid improvement due to direct iron infusion.[25]

Depending on the severity of anaemia, there are factors to consider when selecting a suitable formulation. The choice of iron formulation should be tailored to the severity of anaemia and the individual's ability to tolerate and absorb oral iron. Considerations include.

Table 4: Recommended Iron Preparations based on the severity of anaemia

The severity of Anaemia (Hb levels)	Recommended Iron Supplementation [26]
Mild (Hb: 10.0 - 10.9 g/dL)	Oral iron supplements
Moderate (Hb: 7.0 - 9.9 g/dL)	Oral and IV iron supplements
Severe (Hb: <7.0 g/dL)	IV or IM iron supplements

Maternal and Fetal Outcomes

Table 5: impact of iron formulations on Maternal Health Outcomes During Pregnancy

Iron Formulations	Impact on Maternal Health Outcomes During Pregnancy
Oral Iron Supplements	Adequate iron supplementation can enhance maternal haemoglobin levels and alleviate anaemia symptoms. However, effectiveness depends on compliance, absorption, and tolerability. Gastrointestinal side effects may lower compliance and outcomes for certain pregnant women. Oral iron is recommended for those who can tolerate and absorb it.[21]
Parenteral Iron Formulations	Compared to oral iron, parenteral iron provides better absorption and faster results. It can substantially enhance maternal health and decrease anaemia symptoms. It is effective when oral iron is not well received, has no effect, or when anaemia is severe. The adverse effects of iron deficiency in pregnancy can be reduced by quickly replenishing iron stores.[27]

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Iron deficiency anaemia during pregnancy is linked to a higher risk of low-birth-weight infants. Adequate iron therapy may improve birth weight outcomes. Iron deficiency is also associated with increased preterm birth risk, leading to health challenges for newborns. Intravenous iron therapy can reduce preterm birth and improve pregnancy outcomes.[28]

Compliance and Adherence

Compliance and adherence are crucial in managing IDA in pregnancy. Factors affecting compliance include gastrointestinal side effects, taste and smell, frequency and dosage, forgetfulness, lack of symptom relief, and fear of side effects on the baby. Strategies to improve adherence and reduce discontinuation rates include educating and informing, choosing a better-tolerated iron formulation, combining with vitamin C, simplifying the regimen, taking a personalized approach, monitoring and providing support, and using a combination of oral and parenteral iron if needed.[8,29]

Cost-Effectiveness and Healthcare Considerations

Cost analysis is important for understanding the economic implications of managing IDA in pregnancy. Healthcare systems must allocate resources effectively for optimal outcomes. Oral iron supplements are generally more cost-effective than parenteral iron formulations, but their effectiveness can be influenced by compliance, tolerability, and absorption rates. Parenteral iron formulations have higher upfront costs but offer higher bioavailability and faster response. Investing in early detection and management of IDA can lead to cost savings in the long run. Tailoring iron therapy to individual patient needs can improve cost-effectiveness. Regular follow-up and support for pregnant women on iron therapy can improve compliance and treatment outcomes. Healthcare systems must balance the cost and potential benefits of different iron formulations. Allocating resources for screening, early detection, and appropriate iron formulations for high-risk pregnant women can maximize treatment impact. Cost analysis of various iron formulations is crucial for making informed healthcare decisions for pregnant women with IDA.[30]

Recommendations and Clinical Guidelines

Mild anaemia during pregnancy can be treated with oral iron supplements such as ferrous sulfate, ferrous fumarate, or ferrous gluconate. Vitamin C can enhance absorption.[14] For moderate to severe cases or when oral iron is not tolerated, intravenous iron preparations like iron sucrose or ferric carboxymaltose are recommended.[8,26] Treatment selection should be individualized based on anaemia severity, patient preferences, tolerability, and compliance. Regular monitoring and follow-up are essential to assess treatment response and improve compliance and outcomes.

Key Considerations and Future Research Directions.[8]

- Patient-Centered Care: Tailoring treatment to pregnant women's preferences and characteristics improves adherence and outcomes.
- Comparative Studies: More research is needed comparing iron formulations in diverse populations.
- Long-Term Outcomes: Explore maternal and neonatal outcomes associated with various iron formulations, including birth weight and preterm birth rates.
- Optimal Dosage and Duration: Determine the ideal iron therapy dosage and duration for effective repletion with minimal side effects.
- Safety and Tolerability: Further assess the safety and tolerability of iron preparations, especially parenteral iron, on maternal and fetal health.
- Health Economic Studies: Evaluate cost-effectiveness to guide resource allocation decisions and clinical guidelines.[8,29]

CONCLUSION

The study of iron formulations for treating IDA during pregnancy provides important insights into their effectiveness, safety, and bioavailability. Oral iron supplements like ferrous sulfate, ferrous fumarate, ferrous gluconate, Iron polysaccharide complex, and Delayed-release/Slow-release iron are commonly used for mild anaemia. Still, their effectiveness can be influenced by tolerability, compliance, and absorption rates. Intravenous iron formulations like iron sucrose and ferric carboxymaltose are recommended for moderate to severe IDA or poor oral iron tolerance. Parenteral iron therapy is suitable when oral iron is inadequate or not tolerated, especially for severe cases of IDA. Treatment selection should be individualized based on the severity of anaemia, patient preferences, tolerability, and compliance. The findings have significant implications for clinical practice and public health interventions, including the need for healthcare providers to know the diverse iron formulations available and their respective efficacy and safety profiles. Clinical practice guidelines should incorporate evidence-based recommendations for iron supplementation in pregnancy, and public health interventions should focus on raising awareness, improving access to different iron formulations, and educating pregnant women about the benefits of iron therapy. Efforts to improve access to different iron formulations can contribute to better management of IDA during pregnancy. Personalized treatment approaches and patient-centred care can effectively manage IDA and improve maternal and fetal outcomes.

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