

REVIEW ARTICLE

Comparison of Various Treatment Modalities of Iron Deficiency Anemia in Pregnancy

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ABSTRACT

More than a quarter of the world's population is anemic, with about one half of the burden from iron deficiency. Iron deficiency anemia occurs when iron deficiency is severe enough to diminish erythropoiesis and cause the development of anemia. The prevention and treatment of iron deficiency is a major public health goal especially in women, children, and individuals from low-income countries.

Keywords: Chelated iron, Ferrous iron salts, Oral iron supplementation, Parenteral iron.

How to cite this article: Nanjundan P. Comparison of Various Treatment Modalities of Iron Deficiency Anemia in Pregnancy. *World J Anemia* 2017;1(1):23-26.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Anemia in pregnancy is a serious global health concern. Physiologic anemia is well recognized during pregnancy, attributed to a greater degree of maternal plasma volume expansion causing hemodilution. Pathologic anemia can develop or present during pregnancy because of essential hematinics, such as iron, vitamin B12, and folate, which can adversely affect fetal growth and development and also increases the risk of maternal morbidity and mortality. According to the World Health Organization (WHO) report, worldwide around 32.4 million pregnant women suffer from anemia of which 0.8 million women were diagnosed with severe anemia. Severe anemia is common in resource-poor countries with an estimated 75% of women having anemia. Nearly 50% cases of anemia are attributable to iron deficiency anemia (IDA). The WHO definition of anemia in pregnancy is hemoglobin of less than 11 gm/dL.^{1,2}

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IRON DEFICIENCY ANEMIA

Nutritional IDA is the common cause of anemia in pregnancy. The additional iron requirements for pregnancy are estimated to be around 1000 mg, of which 0.8 mg/day of elemental iron is during the first trimester, 4 to 6 mg/day is in the second trimester increasing to as high as 8 to 10 mg/day in the last 6 weeks of pregnancy.^{3,4} Since only 10% of oral dietary iron intake is absorbed, iron supplementation is justified to meet the increased demands of pregnancy.

NUTRITIONAL SUPPLEMENTATION

- Include heme iron-rich foods from animal sources like meat and liver which is better absorbed than the nonheme iron from cereals, vegetables, pulses which is poorly absorbed. Intake of green leafy vegetables, sprouts, and jaggery should be encouraged.⁵
- Overcooking should be avoided and cooking in iron vessels should be encouraged.
- Fortification of foods like salt, rice, maize, yam, wheat, etc., with iron compounds will improve the dietary supplementation of iron, a cost-effective strategy in developing countries.⁶

ORAL IRON SUPPLEMENTATION

Oral iron should be the preferred first-line treatment for iron deficiency. Table 1 shows the recommended iron supplement intake during pregnancy and postpartum.

Oral iron therapy is notorious for its side effects namely constipation, heartburn, diarrhea, nausea, and epigastric pain seen in around 20% of patients, which may limit the compliance of oral iron intake. Unfortunately, oral iron intake along with meals to minimize the gastrointestinal upset also impairs iron absorption by as much as 50%.⁷ As compared with the ferrous salts, ferric salts are much less well absorbed. All iron has to be reduced to ferrous form to enter the mucosal cells. Hence, bivalent iron salts are preferred over ferric salts. Ferrous iron passes through gastrointestinal mucosal cells directly into blood and is immediately bound to transferrin which transports iron to bone marrow where it is incorporated into hemoglobin. Of all the iron preparations, ferrous sulfate, ferrous fumarate, and ferrous ascorbate are the preferred formulations. The different classes of iron salts are indicated in Table 2.

Table 1: Recommended antenatal oral iron supplementation

Dosage	World health organization recommendation	Ministry of health (India) recommendation
Prophylaxis (pregnancy)	60 mg elemental iron + 400 µg folic acid till term or at least 6 months	100 mg elemental iron + 500 µg folic acid daily for at least 100 days
Treatment (pregnancy)	120–200 mg elemental iron + 400 µg folic acid till term for mild to moderate anemia	Mild anemia – 2 Iron folic acid tablets/day for 100 days; moderate anemia – intramuscular iron therapy + oral folic acid; severe anemia – parenteral iron
Postpartum	Daily 60 mg elemental iron and 400 µg folic acid for 3 months	100 mg elemental iron + 500 µg folic acid daily for 6 months

Table 2: Categories of iron salts

Category	Iron salts
Inorganic	Ferrous sulfate, ferrous fumarate, ferric ammonium citrate
Organic	Ferric polymaltose
Elemental	Carbonyl iron
Chelated iron	Ferrous bisglycinate
Technological	Ferrous ascorbate

Table 3: Various iron salt preparations containing 60 mg elemental iron

Iron salt preparations	Mg of iron salt equivalent to 60 mg elemental iron
Ferrous fumarate	180 mg
Ferrous gluconate	500 mg
Ferrous sulfate	300 mg

Iron Salts

The amount of iron salts used to deliver the same amount of elemental iron varies with preparations (Table 3). The more the content of elemental iron, the more is the gastric irritation and other gastrointestinal symptoms.

Ferrous Sulfate

Ferrous sulfate is the most commonly used oral iron supplement, available as 325 mg tablet (contains 65 mg elemental iron per tablet), 220 mg/5 mL oral elixir (contains 44 mg elemental iron per 5 mL), and 75 mg/mL oral solution (contains 15 mg elemental iron/mL).

Ferrous Ascorbate

Ascorbic acid facilitates iron absorption by preventing oxidation of ferrous iron and is the most widely used reducing agents for facilitating iron absorption in clinical practice. It also exerts protective antioxidant effect on the gastrointestinal mucosa and helps to mobilize the iron stores in ferritin. The chelate formed by ascorbic acid with ferrous ions at acidic pH remains soluble in the alkaline pH of small intestine.

Ferrous Fumarate

It is available as 325 mg tablet containing 106 mg elemental iron per tablet.

Ferrous Gluconate

It is available as 240 mg (contains 27 mg elemental iron per tablet) and 325 mg (contains 36 mg elemental iron per tablet).

Chelated Aminoacid Iron Complex

It is the bonding of iron to an aminoacid, making it easier for the body to absorb and utilize it. This chelated iron aminoacid complex is known as ferrous bisglycinate. Since it is a different form of iron molecule compared with a nonheme iron salt, the absorption characteristics of ferrous bisglycinate are also different. Its main advantage is its relatively high bioavailability in the presence of dietary inhibitors. Chelation gives protection to the iron by limiting its reactivity with dietary components or gastric acid. Absorption from chelated iron is four times higher than from ferrous sulfate.⁸

Sustained release preparations like iron polymaltose complex and iron hydroxide polysucrose complex are also available. The iron in this is a stable nonionic form, hence, absorption is not affected by food or milk and with lesser side effects. But the sustained release and enteric-coated capsules are poorly absorbed as iron is released too far distally in the intestinal tract.

Among these, there is no evidence that one is more effective or has fewer side effects than another. Preparations, such as polysaccharide-iron complex and heme iron are more expensive and lack prospective evidence of efficacy or toxicity advantages compared with ferrous sulfate.

There are various factors which enhance and inhibit the absorption of iron from supplements and diet (Table 4).

Table 4: Various factors affecting iron absorption⁹

Enhancers of iron absorption	Inhibitors of iron absorption
Best taken on empty stomach	Antacids, H ₂ receptor blockers, proton pump inhibitors, milk and dairy products, calcium supplements, and antibiotics like quinolones and tetracyclines
Orange/lemon juice/ vitamin C	Phosphates, phytates, and tannates

Adverse Effects of Oral Iron

Approximately more than 30% of women will have gastrointestinal symptoms like nausea, constipation, epigastric distress, and vomiting.

Response to Therapy

Reticulocyte count increases 7 to 10 days after the start of therapy. Hemoglobin levels increase by 0.3 to 1 g/dL per week with adequate replacement.

PARENTERAL IRON THERAPY

Parenteral iron is indicated when oral iron is not tolerated or absorbed or patient compliance is in doubt or if the woman is approaching term and there is insufficient for oral supplementation to be effective.

Parenteral Preparations¹⁰

- Intravenous (IV) formulations like iron sucrose (IS), ferric carboxymaltose, ferric gluconate (FG), and iron isomaltoside. Low-molecular weight iron dextran (LMW ID) complex can be given intramuscularly or IV.
- Iron sorbitol citrate (Jactofer) which can only be given intramuscularly.

All of these products are equally effective in treating iron deficiency. Major differences include cost, formulary/purchasing agreements, and number of visits/time required to administer the full dose.

Intramuscular Route

It was more popular for many years and it is important to test for hypersensitivity. The disadvantages are pain, sterile abscess formation, nausea, vomiting, headache, fever, lymphadenopathy, allergic reactions, and rarely anaphylaxis.

Intravenous Route

Iron Dextran

It is a stable least expensive parenteral iron with a molecular weight of 100 to 500 kDa that allows administration of high single dose. Low-molecular weight iron dextran can be given as single as well as multiple doses. Prior to

first dose, a test dose of 0.5 mL is to be given gradually over at least 30 seconds preferably over 5 minutes. If no symptoms occur during the first 5 to 10 minutes, administer 1000 mg dose in 250 mL of normal saline over 1 hour.

Iron Gluconate

Ferric gluconate also called FG complex can be given over multiple infusions. A test dose is recommended if the patient has a history of drug allergies. A typical dose of 10 to 15 mL (equivalent to 125 to 187.5 mg elemental iron, based on a concentration of 12.5 mg elemental iron per mL) is diluted in 100 mL normal saline and infused over 20 to 30 minutes or as a 2-minute bolus (e.g., in patients undergoing hemodialysis).

Iron Sucrose

Iron sucrose also called iron saccharate can be given only IV. It is the most common iron preparation used in India and available as 20 mg/mL, given over multiple infusions, with a maximum individual dose of 10 to 15 mL (equivalent to 200 to 300 mg elemental iron). A test dose of 1.25 mL by slow IV push is recommended only if the patient has a history of drug allergies. Usually, it is infused as 200 mg over 60 minutes.

Ferric Carboxymaltose

Ferric carboxymaltose is a colloidal iron hydroxide complex with tighter binding of elemental iron to the carbohydrate polymer than some other IV iron preparations. Ferric carboxymaltose can be given as a dose of up to 20 mL over 15 minutes (equivalent to 1,000 mg of elemental iron, based on a concentration of 50 mg of elemental iron per mL). As with all formulations, start slowly, observe for signs of allergy or infusion reaction, and if not seen, administer the balance over 15 minutes. A second dose can be repeated in the next week depending upon the iron deficit.

The comparison of IV formulations is mentioned in Table 5.

BLOOD TRANSFUSION

With improved tolerance and safety of parenteral iron preparations, blood transfusion is considered as a last resort. If the hemoglobin is less than 7 gm/dL in labor

Table 5: Comparison of different formulations of parenteral iron

Parenteral iron preparation	Elemental iron concentration (mg/mL)	Maximum approved dose/day – mg of elemental iron	Test dose
LMW ID	50	100	Required
FG	12.5	125	Only if drug allergies present
IS	20	200–300	Only if drug allergies present
Iron isomaltoside	100	20 mg/kg	No
Ferric carboxymaltose	50	20 mg/kg (max – 1000 mg)	No

or in the immediate postpartum period, the decision to transfuse should be made according to the individual's medical history and symptoms, earlier if indicated.¹¹

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