Original Article

Oral Iron And Parenteral Iron In Correction Of Iron Deficiency Anemia During 3rd Trimester

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Abstract

Anemia in pregnancy is associated with increased maternal and neonatal morbidity. There is increasing awareness amongst obstetricians about the need to screen for iron deficiency anemia (IDA), as well as growing literature on diagnosis and treatment. This review aims to summarize treatment, and evaluation of IDA in pregnancy.

Introduction:

Iron deficiency anemia is the most common nutritional disorder worldwide and it is the most common form of anemia. Approximately 40% of all pregnancies are complicated by anemia, which causes increased perinatal morbidity and mortality, as well as low birth weight and preterm labor. Ferrous salts are preferred to ferric salts due to the poorer absorption and bioavailability of the latter. Available ferrous salts include ferrous fumarate, ferrous sulphate and ferrous gluconate. It is the amount of elemental iron that is important and this varies by preparation. Multivitamins and 'off the shelf' preparations usually have insufficient iron to correct anaemia and, furthermore, often contain other minerals that interfere with iron absorption. Combined iron and folic acid preparations are available but their efficacy compared to oral iron alone is unknown **(1).**

Table 3. Recommended daily dose and elemental iron content of oral iron preparations (2)

Iron salt	Preparation	Elemental iron content
Ferrous fumarate	210 mg	65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous sulphate (dried)	200 mg	65 mg
Ferrous feredetate	190 mg/5 ml elixir	27·5 mg/5 ml elixir

The recommended dose of elemental iron for treatment of iron deficiency has been 100–200 mg daily. However, more recent studies suggest that lower doses or intermittent supplementation may be advantageous **(3).**

Moretti et al., (4) reported that fractional absorption of iron in iron-depleted young non-pregnant women is maximised by taking elemental iron doses of 40–80 mg once per day or alternate days, avoiding twice daily dosing. Higher doses potentially increase side effects due to the excess unabsorbed iron remaining in the gastrointestinal tract.

Shinar et al., (5) reported that 68 mg daily, started at 17 weeks' gestation, did not result in a higher Hb by 35 weeks than 34 mg daily.

Oral iron supplementation should be taken on an empty stomach, as absorption is reduced or promoted by the same factors that affect absorption of dietary non-haem iron. It may be taken with water or a source of vitamin C to enhance absorption **(3).**

Response to oral iron

The degree of increase in Hb that can be achieved with iron supplements will depend on the Hb and iron status at the start of supplementation, ongoing losses, iron absorption and other factors contributing to anaemia, such as other micronutrient deficiencies, infections and renal impairment. However, compliance and intolerance of oral iron preparations are the usual factors limiting efficacy. Iron salts may cause gastric irritation and up to a third of patients may develop dose-limiting side effects, including nausea and epigastric discomfort. This is minimised by correct administration, which optimises absorption. It may be necessary to titrate the dose down to a level where side effects are acceptable or try an alternative preparation **(6).**

A repeat Hb at 2–3 weeks is required to assess response to treatment. The timing of further checks will depend upon the degree of anaemia and period of gestation. Once the Hb is in the normal range, treatment should be continued for a further 3 months and until at least until 6 weeks postpartum to replenish iron stores **(7).**

Parenteral iron treatment

Intravenous iron treatments produce a better hematological response than oral iron, including a faster increase in hemoglobin and faster replenishment of body iron stores, and can provide an alternative to transfusion in profound iron deficiency anemia. They are generally well tolerated but may cause a variety of adverse events, including venous thrombosis **(8).**

Intravenous iron therapy has effects on endothelial cells, polymorphonu-clear leucocytes and cytokines, probably related to non-transferrin bound labile iron, which may suggest a role in infection and atherosclerosis **(8).**

However, this possibility remains largely theoretical. Cost is also several times greater than for oral treatments, and the fact that the procedure is somewhat invasive and must take place in a hospital or outpatient setting is another disadvantage, Because manufacturers have not submitted appropriate data to the regulatory authorities, especially as regards possible teratogenicity, the treatment of iron deficiency anemia in pregnancy with these products is not an approved indication in many juris-dictions or is confined to use in the third trimester. This means that much usage is off-label and is likely to remain so, since it is probably unlikely that teratogenicity studies will be forthcoming. Despite this, there is a considerable history of their safe and effective use, though this is usually confined to the second and third trimesters **(8).**

Their place in therapy has been variously defined:

1. Non-response to oral iron and severe anemia during pregnancy and puerperium.

2. Alternative to oral in pregnant women with severe iron deficiency in the third trimester.

3. Inability to tolerate side effects of oral iron, inflammatory bowel disease, peptic ulcer, non-compliance, document-ed iron malabsorption, pregnancies near term.

4. Second option if oral iron fails to increase hemoglobin in 2 weeks; first option if hemoglobin <90 g/L beyond 14 weeks gestation; first option in third trimester.

5. Requirement for emergency supplementation, contraindication to blood transfusion, chronic blood loss, combination with recombinant human erythropoietin **(9)**.

All intravenous iron agents consist of spheroidal nanoparticles in which a core of iron-oxyhydroxide gel is surrounded by a shell of carbohydrate that stabilizes the iron-oxyhydroxide, slows the release of bioactive iron, and maintains the particles in colloidal suspension. After injection, the particles mix with plasma, enter the reticuloendothelial system and are taken up by phagocytes in the liver, spleen and bone marrow. There, the iron is released into an iron pool, from which it is either incorporated by ferritin into intracellular iron stores or released from the cell and taken up by transferrin for delivery to erythroid precursors **(10).**

Dosage is usually calculated by an equation of the form: Deficit iron (mg)=0.24 x body weight (kg) x hemoglobin deficit (g/L)+deposit iron (mg), where hemoglobin deficit=target hemoglobin-actual hemoglobin, and deposit iron=15 mg/kg body weight to 35 kg. While several such agents have been produced over the past 50 years, most are not currently marketed. Currently available agents are chondroitin sulfate iron, ferric gluconate, iron dextran, iron carboxymaltose, iron polymaltose, and iron sucrose, though many of these are available only in selected countries **(11).**

Chondroitin sulfate iron colloid

Chondroitin sulfate iron colloid is marketed in Japan and other Asian countries. There is a dearth of information on its use in pregnancy **(12).**

Iron dextran

Iron dextran compounds are stable, strong complexes of relatively high molecular weight and consequent relatively long half-life and relatively slow release. Imferon had a molecular weight of 103 kD and a half-life of about 30 hours **(13).**

Life-threatening anaphylactic reactions (sudden cardiovascular collapse, respiratory failure) occurred in 0.1-2% of patients treated with this product, and it was withdrawn because of Current Good Manufacturing Practice issues. Its place was largely taken by a very similar product marketed as Cosmofer in most of Europe, Ferrisat in France, and INFeD in the United States. This has a molecular weight of 96 kD and a half-life of about 30 hours. It is suitable for total dose infusion. Although adverse reactions of up to 50% have been reported, the experience is that most institutions using one of these products can be expected to experience adverse reactions (mainly dose dependent), and studies in single institutions have found them as safe as ferric gluconate or iron sucrose. Acute, severe anaphylactoid reactions occur in 0.6-0.7% **(14).**

These usually occur within the first few minutes of adminstration and are generally characterized by the sudden onset of respiratory difficulty and/or cardiovascular collapse and fatalities have been reported. Anaphylactoid reactions (urticaria, rashes, itching, nausea and shivering) are uncommon. Possible severe delayed reactions characterized by arthralgia, myalgia and sometimes fever may occur from several hours to four days after administration and last two to four days. A much higher molecular weight (265 kD) product is marketed as Dexferrum in the United States and DexIron in Canada. In line with its high molecular weight, it has a long half-life of 60 hours. In most respects, it is similar to Cosmofer/INFeD, but appears to have a rate of adverse events somewhere between twice and eight times that of the lower molecular weight products. The iron dextran products are considerably cheaper than ferric gluconate or iron sucrose, the cost per gram of iron being not much more than half **(11).**

Ferric gluconate

Ferric gluconate, marketed as Ferrlecit in Europe and the Unit-ed States, is a labile, weak complex with a molecular weight of 38kD. In line with this low molecular weight, it has a very short half-life of about 1 hour. Although claimed to have a greater bioavailability than dextrans and to have a significantly lower reported mortality rate than dextrans, it delivers complexed iron to all types of proteins, not just to the specialized iron binding proteins. Thus, the main part of the iron is deposited in the parenchyma and not in the reticuloendothelial system, resulting in severe and extended liver necrosis. Anaphylactoid reactions are apparently rare, with the first case in a pregnant patient not reported until 2005 **(15).**

Iron carboxymaltose

Iron carboxymaltose is marketed as Ferinject. Its molecular weight is in the same range as the 'low molecular weight' dextran and it has a similar half-life of about 24 hours. Reported trials have been mainly concerned with its use in postpartum iron deficiency anemia, in which it was found to bring a rapid response in improving hematological values, while producing fewer adverse reactions than oral ferrous sulfate. It has been stated not to cause anaphylactic reactions. The most commonly reported adverse effect is changes in liver functions tests in 3.5%, followed by nasopharyngitis in 3.1% **(16).**

Iron polymaltose (iron dextrin)

Iron polymaltose is similar in molecular weight and half-life to iron carboxymaltose. It is marketed under a number of different trade names in different countries, and is usually given as a single total dose infusion. Studies of its use in pregnant women have found it to be more effective, better tolerated, and cost effective compared with oral ferrous sulfate **(11).**

In one safety audit, there were no cases of anaphylaxis or other cardiorespiratory compromise, although the infusion was terminated prematurely because of adverse events in 1.6% of patients **(16).**

Iron sucrose (iron saccharate, saccharated iron oxide)

More than 100 years have passed since parenteral iron was first given to humans. Carbohydrate was first coupled to iron oxide, reducing the fierce toxicity of ferric iron and saccharated iron oxide was the first such complex to be used clinically **(17).**

Iron sucrose is marketed as Venofer® in at least 68 countries and as Fesin® in Japan. It has a low molecular weight (43 kD), more or less on a par with ferric gluconate, though the complex is much less labile, and deposition of iron in the parenchyma does not occur to any noticeable extent, iron release being to endogenous iron-binding proteins, with a half-life of about 6 hours. In line with its lower molecular weight, average par-ticle size is only about 23% of that of Dexferrum® **(11).**

This can be expected to result in a more rapid release of iron. This has been borne out in trials versus oral iron supplementation, which have generally found that iron sucrose restored iron stores faster and more effectively than oral iron. Studies which used ferrous sulfate have generally found no significant difference in hemoglobin between the two treatments, but a significantly higher ferritin value at each sampling time **(18).**

However, **Al et al., (19)**, who compared iron sucrose with oral iron polymaltose, found a significantly greater increase in both hemoglobin and ferritin. The most commonly reported side effects are temporary changes in taste, fever, shivering, injection site reactions and nausea. Hypotension occurs in <1%. Anaphylactoid reactions triggered by antigen-antibody interaction with mast cell receptor, with release of histamine and characterized by hypotension, facial swelling and difficulty in breathing rarely occur.

Figures of 0.002% serious anaphylaxis hypersensitivity and 36% total adverse events have been cited, However, **Breymann, (20)** reports a <0.5% rate of minor side effects and no cases of serious ana-phylaxis in 14 years usage at his institution Several authors conclude that iron sucrose is not only effective but carries a minimal risk of allergic accident and iron overload, especially after a comprehensive pretreatment work-up.

Perewusnyk et al., (21); Breymann, (22) regard iron sucrose as a valid first option.

Milman, (23) sees it as a first option if the hemoglobin is <90 g/L in a patient beyond 14 weeks gestation, and as a second option if oral iron fails to increase hemoglobin within 2 weeks.

Erythropoietin

Perewusnyk et al., (21) suggest adding erythropoietin if the hemoglobin is <9 g/dl or if there is no response to parenteral iron after 2 weeks.

Postpartum, erythropoietin may improve iron levels in the blood but rare adverse effects occur. However, **Wågström et al., (24)** found that the addition of erythropoietin to intravenous iron sucrose did not further increase hemoglobin concentrations. If erythropoietin is used in the treatment of anemia, the addition of parenteral iron is mandatory to prevent iatrogenic iron depletion and functional iron deficiency during treatment.

Intravenous iron sucrose versus oral ferrous fumarate for correction of anemia during 3rd trimester of pregnancy

Anemia interferes with the normal intrauterine growth leading to fetal loss and perinatal deaths. It is associated with increased preterm labor (28%), preeclampsia (31%) and maternal sepsis **(25).**

Over the past years, various oral, intramuscular and intravenous preparations of iron have been used for correction of IDA (Iron Deficiency Anemia) in pregnant patients. The first choice in the treatment of iron deficiency anemia for almost all patients is oral iron replacement because of its effectiveness, safety, and lower cost **(16).**

The major problem with oral iron therapy in its classic ferrous form is poor tolerability and up to 40% adverse reaction rate. The most common complaints are nausea, abdominal pain, diarrhea and constipation **(26).**

Severe systemic adverse effects associated with iron dextran and iron gluconate limited the use of intravenous iron. Iron sucrose complex (ISC) is a relatively new drug, which is used intravenously for the correction of IDA. Iron sucrose complex is a widely used and safe molecule, which has become major interest to prevent iron deficiency anemia **(27).**

Oral iron is effective, safe, low cost, but there may be failure in the effectiveness due to non-compliance, achlorhydria, inflammatory bowel diseases, or unrecognized bleeding. Noncompliance is largely related to side effects. 10 to 40% of patients suffer adverse gastrointestinal effects - constipation, diarrhea, epigastric discomfort, nausea, severe abdominal pain and vomiting. They can be decreased by food, but food decreases absorption by 10 to 40% **(28).**

Iron dextran compounds are stable, strong complexes of relatively high molecular weight, long half-life and relatively slow release. Life threatening anaphylactic reactions (sudden cardiovascular collapse, respiratory failure) occurred in 0.1 to 2% of patients treated with this product. 30% of patients suffered from adverse effects which include fever, arthritis, urticaria. It is associated with arthritis flare up hence contraindicated in rheumatoid arthritis. Iron sucrose complex seems to be safe with fewer and milder side effects even in patients with rheumatoid arthritis **(29).**

Intramuscular iron, iron-sorbitol citric acid complex causes metallic taste on tongue, nausea, vomiting and pain at the injection site. Other parenteral iron preparations available are ferric gluconate, ferric citrate but are found to cause severe and extended liver necrosis **(30).**

Iron sucrose belongs to the iron complexes of medium strong type (molecular mass between 30,000 and 100,000 Da). In the regulation of marrow proliferation iron delivery rate to the marrow is a major factor. The pharmacokinetic properties of iron dextran and iron sucrose are different. Iron dextran has a half-life of 3 to 4 days whereas iron sucrose has a terminal half-life of approximately 5 to 6 h and is quickly cleared from serum and thus rapidly available for erythropoiesis **(31).**

ISC has small molecular weight hence anaphylaxis is very rare. Until now, only one case of possible anaphylactic reaction has been described. ISC is taken up mainly by the reticuloendothelial system and it is unlikely that it would be taken up by the parenchymal cells of liver, kidney, adrenal gland or other organs, hence, organic toxicity like pancreatic, myocardial or hepatic hemosiderosis is less likely even with iron sucrose complex overload **(32).**

In a random, prospective, open study done by **Bayoumeu et al., (33)**, 24 women were given intravenous iron sucrose in 6 slow I.V injections on days 1, 4, 8, 12, 15 and 21 with a maximum of 200 mg of iron each time and 23 women were given 240 mg oral ferrous sulfate. An increase in hemoglobin was observed on day 30 in both oral and I.V group (Not significant) but serum ferritin was higher in the IV group.

Al Momen et al. (34) reported similar findings. They compared 52 women treated with intravenous iron sucrose 200 mg in 100 ml Normal saline daily till total dose was met and 59 women treated with 300 mg of oral iron sulfate and found that intravenous treatment resulted in higher hemoglobin levels in shorter periods compared with the oral treatment group (mean 6.9 versus 14.9 weeks). However, in their study 30% of the patients had poor compliance with oral treatment**.**

I.V iron sucrose was well tolerated and not associated with any serious adverse effects and was only associated with burning, pain and swelling at the injection site in 6 patients. It was reduced by thrombophobe ointment, ice pack and by injecting 5 cc of normal saline or distilled water at the end of I.V sucrose infusion. Previous larger studies that have investigated the safety profile of intravenous iron sucrose both during pregnancy and in the postpartum period support this finding **(31).**

Perewusnyk et al., (21) studied 500 women who received iron sucrose. Minor general adverse effect including a metallic taste, flushing of the face and burning at the injection site occurred in 0.5%, with doses up to 200 mg. The high tolerance of the drug has been partly attributed to slow release of iron from the complex and also due to low allergenicity of sucrose.

The compliance with oral treatment was surprisingly good and was reinforced by verbal contact which is in contrast with compliance findings described in other studies. Gastrointestinal adverse effects are thought to be dose related and occur more frequently at higher doses and are also related to type of iron formulation used **(31).**

In a study by **Dede et al. (35)**, 50 patients were included in the I.V iron sucrose group (200 mg in 100 ml normal saline daily till total dose was met) and 25 patients were included in oral ferrous sulfate group (300 mg tablet containing 60 mg elemental iron thrice daily). Blood samples were taken to evaluate levels of Hb, serum ferritin, serum iron, CRP (C-Reactive Protein), MCV (Mean corpuscular volume), TIBC (Total iron binding capacity) before the start of therapy and at days 7 and 28. It was shown in the study that intravenous iron therapy with an iron sucrose complex significantly increased serum ferritin levels within a short time with fewer adverse effects than oral iron therapy in women with post partum iron deficiency anemia.

The total dose of iron sucrose can be administered over a short period. This treatment will certainly help in reducing the risk of homologous blood transfusion during the peripartum period if used in time. Overall iron sucrose appears to be a treatment of choice with no serious side effects indicated in the rapid correction of anemia in pregnancy or restoring maternal iron stores **(36).**

Intravenous iron Sucrose Complex (ISC) is safe and effective in the treatment of iron deficiency anemia during pregnancy. Intravenous iron sucrose is a most promising iron preparation for use in obstetrics because it is safe, effective and easy to administer **(31).**

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