Intravenous iron treatment for iron deficiency anemia in pregnancy

Gebelikte demir eksikliği anemisi için intravenöz demir tedavisi

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Abstract

Iron deficiency anemia in pregnancy can have serious deleterious effects for both mother and fetus. Estimates of prevalence vary widely, but those based on hemoglobin determinations are always considerably higher than those based on ferritin, emphasizing the need for a full hematological work-up in diagnosis. Intravenous therapy usually results in a more rapid increase in hemoglobin and iron stores, but unresolved concerns of possible teratogenicity mean that it should not be used in the first trimester, while cost considerations make it a second choice to oral treatment in the second trimester where this is feasible and effective, except in severe anemia where a more rapid response is desirable. On the other hand, intravenous administration is the first choice treatment in the third trimester and postpartum. All the available intravenous iron preparations are similar in molecular composition, but the exact nature of the complex determines the molecular weight and particle size, which to a large extent determine the properties of the preparation. All are effective and relatively safe, but the higher molecular weight iron dextrans are associated with a greater number of adverse events, and there are concerns about iron toxicity with ferric gluconate. It seems that a degree of expertise and experience and rigorous adherence to protocols and precautions may be required for their safe and effective use.

(J Turkish-German Gynecol Assoc 2009; 10: 109-15)

Key words: Anemia, iron deficiency anemia, pregnancy, intravenous, treatment

Received: 05 March, 2009 **Accepted:** 18 March, 2009

Özet

Demir eksikliği anemisi hem bebek hem de anne üzerinde olumsuz etkilere neden olur. Prevalansı geniş bir dağılım gösterse de, sadece hemoglobin üzerinden değerlendirme yapıldığında ferritin de değerlendirildiği zamanlardakinden daha sık gözlenir. İntravenöz demir tedavisi, her ne kadar teratojeniteden dolayı ilk trimesterde kullanılmasa da, derin anemide veya hızlı artışın arzulandığı zamanlarda serum demir ve hemoglobin seviyesini hızlı bir şekilde yükseltir. diğer yandan intravenöz demir tedavisi üçüncü trimesterde veya postpartum dönemde ilk seçenek olarak karşımıza çıkar. Piyasadaki tüm demir preparatları birbirine benzer, sadece moleküler ağırlıkları ve kompleksiteleri hazırlanış şekillerinden dolayı farklıdır. Tümü etkindir ve göreceli olarak güvenilirdir, ancak yüksek moleküler ağırlıklı demir dekstran daha sık yan etkilere yol açar. bu nedenle ferrik glukonat kullanımı ile ilgili şüpheler mevcuttur. Oyle görülmektedir ki, deneyim, uzmanlık ve uygun protokollere bağlı kalmak, demir preparatlarının etkin ve güvenli bir şekilde kullanılmasına olanak sağlar.

(J Turkish-German Gynecol Assoc 2009; 10: 109-15)

Anahtar kelimeler: Anemi, Demir eksikliği anemisi, gebelik, intravenöz, tedavi

Geliş Tarihi: 05 Mart 2009 **Kabul Tarihi:** 18 Mart 2009

Introduction

The World Health Organization defines iron deficiency anemia as anemia accompanied by depleted iron stores and signs of a compromised supply of iron to the tissues (1).

Because blood volume expands by a mean of 50% during pregnancy, with plasma volume increasing disproportionately compared with red cell mass (2), normal definitions of anemia are not quite appropriate in pregnancy. The World Health Organization cut-off point for the diagnosis of anemia in pregnancy is hemoglobin < 11 g/dL (3), while the Centers for Disease Control and Prevention criterion is < 11 g/dL in the first and third trimesters and < 10.5 g/dL in the second (since the hemodilution effect is greatest in the second trimester) (4).

For a diagnosis of iron deficiency anemia, it must also be shown that the patient is iron deficient. Serum ferritin has been regarded as the gold standard in establishing iron deficiency (4), with the most useful laboratory measure of iron status which generally accepted cut-off level for serum ferritin, below which iron stores are considered to be depleted is, < 15 ng/mL and ferritin level < 12 ng/mL is associated with iron deficiency anemia (5).

Iron deficiency anemia is usually quoted as the most common form of anemia in pregnancy (6). However, Alper et al found that only about half of their anemic pregnant women were iron deficient (6). Again, Milman's review of several trials found that, while 14-52% of participants were anemic according to the hemoglobin criterion, only 12-17% were iron deficient as indicated by serum ferritin (7). Similarly, in a national survey of pregnant women in Switzerland, Hess et al found a prevalence of anemia of 6% and of iron deficiency anemia of 3% (8).

It should needs to be remembered that hemoglobin, serum ferritin and transferrin saturation are all reduced during preg-

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nancy whether the woman is iron deficient or not (9). On the other hand, circulating transferrin receptor levels are normal in the iron replete and raised in the iron deficient, and may be the definitive test for iron deficiency in pregnancy (10, 11).

Causes of iron deficiency anemia in pregnancy

There is a high demand for iron during pregnancy, with some 800-1000 mg being required throughout the pregnancy and a net cost of some 600 mg (9). Some 7.5 mg/d is required in the third trimester (7). Since, at most, 30% of dietary iron can be absorbed (7), this means a necessary daily intake of 25 mg if this amount is to be obtained from the diet.

This amount is difficult to obtain from the average diet, even in the non-pregnant person. Several effects of pregnancy-nausea, vomiting, motility disorder with reflux esophagitis, indigestion, tendency to hemorrhoids (12), and achlorhydria (13)-make this even more problematic.

If a woman cannot consume the requisite amount of iron, she must rely on her stores, which are rarely sufficient. Cultural and nutritional habits or physiological reasons also affect the higher prevalence of anemia (14). Since >90% of Danish women have a dietary iron intake below the recommended amount, it is no surprise that only 14-20% of pregnant Danish women have the 500 mg or so of iron reserves needed to balance the loss through pregnancy (15, 16). It is unlikely that the situation is very different in other countries.

On top of the demands of pregnancy is the inevitable loss associated with delivery. A blood loss of ≥1 L occurs in 7% of vaginal deliveries. Furthermore, 23% of cesarean deliveries were associated with a blood loss of between 1000 and 1500 mL (17).

Effects of iron deficiency anemia in pregnancy

Iron is critical for the growth of all cells. It is therefore not surprising that iron-deficiency anemia independently increases morbidity and mortality (18).

Due to the ability of the fetus to extract its iron requirements even from an iron deficient mother (12), the effects of iron deficiency anemia are especially severe on the pregnant woman. These may include fatigue, lack of concentration, decreased mental, physical and cognitive performance (12), cardiovascular strain, reduced immune function, infection, negative thermoregulation, increased risk of blood transfusion (19), reduced exercise tolerance, stomatitis, gastritis, structural and chemical changes in the hair, nails and skin and impairment of thyroid metabolism and catecholamine turnover (20). Postpartum, the patient may have cardiovascular symptoms (palpitations), fatigue, dizziness, breathlessness, depression, infections, lactation failure and prolonged hospital stay (21).

The fetus may suffer intrauterine growth restriction, premature delivery, increased perinatal morbidity and mortality (22), fetal programming (23), low birth weight and sometimes irreversible damage to the central nervous system, with impairment of psychomotor development (24).

Prevention

Attempts at prevention of iron deficiency anemia in pregnancy by diet modification do not appear to have met with much success, while the promising strategy of iron fortification has never really got off the ground (25). Most countries have settled on an oral supplementation program.

Iron-treated pregnant women have greater iron reserves, higher hemoglobin levels and lower prevalence of iron deficiency anemia (0-25% on hemoglobin, 0-3% on ferritin) than placebo-treated women in pregnancy and postpartum, and children born to iron-treated mothers have higher serum ferritin levels than those born to placebo-treated mothers (9).

A Cochrane review found that antenatal supplementation with iron or with iron and folic acid results in a substantial reduction in the prevalence of hemoglobin levels below 100 or 105 g/L at or near term, but there was not enough data to determine whether such supplementation had any substantial benefits or adverse effects on maternal and fetal health and pregnancy outcomes (26).

Treatment

Despite a paucity of definite evidence for substantial benefit to either mother or child, the overwhelming consensus appears to be that iron deficiency anemia in pregnancy should be treated quite vigorously.

One cautionary finding has been that the ideal maternal hemoglobin for fetal birth weight is in the range of 95-135 g/L (27-30). However, in healthy pregnant women, there is no relationship between hemoglobin and birth weight of the newborn (31, 32), and the effect is probably due to inappropriate hemodilution (7).

If the decision to treat is made, the choice is largely between oral and intravenous treatments. Because of the attendant serious risks (allergic reaction, anaphylactoid reaction, circulatory overload, febrile reaction, hemolysis, immune modulation, infection, metabolic complications, purpura, graft-versus-host disease, acute lung injury) (33), transfusion is now regarded as a last resort. Also, an increasing number of patients refuse transfusions for religious reasons or through fear of infection.

Intramuscular preparations are available which give a better hematological response compared with oral (34). However, because of the adverse effects of pain, staining of the skin, abscess formation at the injection site, myalgia, and arthralgia (22) and a possibility that they may initiate sarcomas (35, 36) they are rarely used.

The decision between oral and intravenous usually attempts to balance effectiveness, safety and cost considerations. Breyman et al, (37) produced a fairly typical protocol:

If the hemoglobin is 90-105 g/L, give oral iron 160-200 mg/d.

If hemoglobin does not increase by 10 g/L or more in 2 weeks, consider intravenous iron (not in the first trimester).

If the hemoglobin is < 90 g/L, give intravenous iron in separate doses of 200 mg until the hemoglobin is > 105 g/L, and then consider maintenance therapy with oral iron.

The protocol put forward by Beris and Maniatis (38) is fairly similar:

Use oral iron initially in the first and second trimesters.

If a hemoglobin increase of 5 g/L or more is not obtained in 2 weeks and the duration of gestation > 14 weeks , consider intravenous iron.

Perewusnyk et al (20) are inclined more towards intravenous treatment:

If the hemoglobin is 100 - < 110 g/L, give oral iron; if < 100 g/L, give intravenous iron.

If no response after 2 weeks, add recombinant erythropoietin.

Oral iron treatments

Oral iron is effective, safe, low cost, and subject to natural regulatory mechanisms.For this reason, both Breymann et al (37) and Beris and Maniatis (38) see oral iron as the first therapeutic option in the first and second trimesters.

The effectiveness of oral iron is increased during pregnancy because of the increased iron absorption during gestation (39-41). Nonetheless, Govan and Scott recorded a 14.3% failure rate (13), and the position has not changed greatly in the intervening years. Failure may be due to non-compliance, achlorhydria, inflammatory bowel disease, or unrecognized bleeding.

Non-compliance is largely related to side-effects. Between 10% and 40% of patients suffer adverse gastrointestinal effects-constipation, diarrhea, epigastric discomfort, nausea, severe abdominal pain and vomiting (42). General malaise is also reported (20). These effects are dose-related (43). They can be decreased by food, but food decreases absorption by up to 40% (44, 45). Especially offending substances are phytates in wheat and other cereals, oxalates in rice, spinach and beetroot, polyphenols in tea and coffee (45, 46), calcium in dairy products (45), and fat (20). On the other hand, absorption is enhanced by meat (beef, poultry), and fish (47).

Oral iron (III) polymaltose has been reported to have maximum absorption and minimum side-effects and not to interact with food or drugs (20).

Oral iron is not sufficient and does not act sufficiently rapidly for treatment of postpartum iron deficiency anemia (48).

Intravenous iron treatments

General

Intravenous iron treatments produce a better hematological response than oral iron (34), including a faster increase in hemoglobin and faster replenishment of body iron stores (12, 48, 49), and can provide an alternative to transfusion in profound iron deficiency anemia (50).

They are generally well tolerated but may cause a variety of adverse events, including venous thrombosis (34). Intravenous iron therapy has effects on endothelial cells, polymorphonuclear leucocytes and cytokines, probably related to non-transferrin bound labile iron, which may suggest a role in infection and atherosclerosis (51). 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 jurisdictions 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.

Their place in therapy has been variously defined:

1. Non-response to oral iron and severe anemia during pregnancy and puerperium (13, 52).
2. Alternative to oral in pregnant women with severe iron deficiency in the third trimester (48).
3. Inability to tolerate side effects of oral iron, inflammatory bowel disease, peptic ulcer, non-compliance, documented iron malabsorption, pregnancies near term (34).
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 (7).
5. Requirement for emergency supplementation, contraindication to blood transfusion, chronic blood loss, combination with recombinant human erythropoietin (20).

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 (53).

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 (53).

Chondroitin sulfate iron colloid

Chondroitin sulfate iron colloid is marketed in Japan and other Asian countries (53). There is a dearth of information on its use in pregnancy.

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 (53). Life-threatening anaphylactic reactions (sudden cardiovascular collapse, respiratory failure) occurred in 0.1-2% of patients treated with this product (54), 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 (55), the experience is that most institutions using one of these products can be expected to experience adverse reactions (mainly dose dependent) (56), and studies in single institutions have found them as safe as ferric gluconate (57) or iron sucrose (58). Acute, severe anaphylactoid reactions occur in 0.6-0.7% (55). These usually occur within the first few minutes of administration 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 (59, 60). 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 (55).

Ferric gluconate

Ferric gluconate, marketed as Ferrlecit® in Europe and the United 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 (53). Although claimed to have a greater bioavailability than dextrans and to have a significantly lower reported mortality rate than dextrans (61), 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 (62). Anaphylactoid reactions are apparently rare, with the first case in a pregnant patient not reported until 2005 (63). However, Van Wyck (64), Danielson et al (65) and Hoigné et al (66) claim that, because of the lability of the complex and the pattern of iron distribution, toxic reactions can be expected even at low doses and that its intravenous use cannot be recommended.

Iron carboxymaltose

Iron carboxymaltose is marketed as Ferinject®. Its molecular weight is in the same range as the 'low molecular weight' dextrans 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 (67-69). It has been stated not to cause anaphylactic reactions (64). The most commonly reported adverse effect is changes in liver functions tests in 3.5%, followed by nasopharyngitis in 3.1% (67).

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 (70, 71). 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 (72).

Iron sucrose (iron saccharate, saccharated iron oxide)

More than 100 years have passed since parenteral iron was first given to humans (73). 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, by Nissim in 1947 (73). However, Davidson et al. reported severe reactions following the use of a similar solution (74). Govan and Scott found it to be effective in pregnancy, raising hemoglobin by 8% in the first week and relieving symptoms (incidentally, this was one of the very few studies to report on this facet). Minor side effects were observed in 20% and severe adverse events in 1-2% (13, 52).

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 (53), 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 (20). In line with its lower molecular weight, average particle size is only about 23% of that of Dexferrum® (53). 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 (75-77). However, Al et al, who compared iron sucrose with oral iron polymaltose, found a significantly greater increase in both hemoglobin and ferritin (48).

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 (49). Figures of 0.002% serious anaphylaxis hypersensitivity and 36% total adverse events have been cited (55), However, Breymann reports a <0.5% rate of minor side effects and no cases of serious anaphylaxis in 14 years usage at his institution (78) Several authors (12, 65, 79, 80) 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.

Breymann (19) and Perewusnyk et al (20) regard iron sucrose as a valid first option. Millman 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 (7)

Erythropoietin

Perewusnyk et al suggest adding erythropoietin if the hemoglobin is <90 g/L or if there is no response to parenteral iron after 2 weeks (20).

Postpartum, erythropoietin may improve iron levels in the blood but rare adverse effects occur (81). However, Wågström et al found that the addition of erythropoietin to intravenous iron sucrose did not further increase hemoglobin concentrations (80).

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 (19).

Conclusions

Since the dawn of life, all living forms have been obliged to include iron in their metabolism and homeostasis in one way or another. Iron is essential to man and an adequate body iron balance is crucial (82). Treatment with intravenous iron is superior to oral iron with respect to hematological response (83) which seems to be safe, as very few severe side-effects were observed, and may result in hastened recovery from anemia and lower transfusion requirements (84). Iron sucrose complex therapy is a valid first-line option for the safe and rapid iron-deficiency anemia (85).

1. Iron deficiency anemia is a significant problem in pregnancy and is likely to continue to be so, though there is considerable doubt about the validity of some estimates of prevalence based on hemoglobin values and the absence of other causes.
2. Patients should receive a full hematological work-up, including hemoglobin, iron, ferritin, transferrin saturation, and transferrin receptor values, before treatment.
3. Given the unknown risks of teratogenicity, oral supplementation is the only choice in the first trimester. Oral iron polymaltose may be better tolerated than ferrous sulfate but may not be as effective.
4. In the second trimester, the choice between oral and intravenous treatment will be governed by considerations of prior response to oral if known, degree of anemia, compliance issues, and cost.
5. In the third trimester, the most reasonable choice is intravenous.
6. Postpartum, the only choice is intravenous.
7. If total dose infusion is necessary because of remoteness or other factors, the choice is between Cosmofer® (and its equivalents) and iron polymaltose (where available), with iron polymaltose possibly having a better safety profile.
8. In other cases, the choice will be governed by effectiveness, safety, cost, availability, and experience. Because of concerns about iron toxicity, ferric gluconate cannot be recommended. The other preparations appear to be similar in effectiveness and to have acceptable safety, though adverse events seem to be many times more frequent with Dexferrum®/Dexiron® than with the others. Iron sucrose is the most thoroughly studied, most widely available, most widely used, has the longest history, and possibly has a better safety profile than the iron dextrans. However, it is expensive compared with the other products. There have been very few reports of serious safety concerns with iron carboxymaltose and iron polymaltose, but this may be because of their lower usage due to more restricted availability.
9. The wide discrepancy between reported adverse events and experience in individual institutions may reflect the fact that a certain familiarity with the use of these agents is essential for their optimal performance. It is suggested that all personnel who will be involved in administering these products should, wherever possible, be thoroughly trained in their use by someone with such familiarity, preferably in an institution with a long history of usage.
10. In any case, protocols and precautions given in the manufacturer's documentation should be thoroughly studied, understood, and rigorously followed.

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