International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Chandra I et al. Int J Reprod Contracept Obstet Gynecol. 2015 Oct;4(5):1264-1271
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: http://dx.doi.org/10.18203/2320-1770.ijrcog20150695

Review Article

Iron status and choice of iron therapy during pregnancy: advantages and disadvantages

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Received: 09 July 2015
Revised: 22 August 2015
Accepted: 29 August 2015

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ABSTRACT

Iron deficiency anaemia (IDA) still becomes major health problem all over the world and pregnant women at particular risk. IDA is associated with negative outcomes for both mother and infant. Therefore, many laboratory assessments can be used as estimation of iron status during pregnancy, with haemoglobin (Hb) and serum ferritin (SF) as the most widely used tools. However, the uses of these two indicators remain controversies, because of physiological hemodilution that appears during pregnancy. Other methods are used to provide more accurate results of iron status, all with their advantages and drawback. Therapeutic options of IDA ranging from oral to intravenous therapy. Oral iron replacement became first choice for many years due to its safety and low cost. However, in some conditions such as severe anaemia and intolerance to oral iron, intravenous iron is preferable. Nowadays there are several preparations of intravenous iron in the market: Iron sucrose (IS), ferric gluconate, ferric carboxymaltose, iron dextran (high and low molecular weight dextran), iron isomaltoside and ferumoxytol. These preparations provide rapid replenishment of iron stores with good safety profiles. The present review summarizes methods to assess iron status during pregnancy, and choices of iron therapy, with their advantages and disadvantages.

Keywords: Iron deficiency anaemia, Iron status, Pregnancy, Oral iron therapy, Intravenous iron therapy

INTRODUCTION

According to World Health Organization (WHO), around 2 billion people, amounting to over 30% of the world's population are anaemic, although prevalence rates are variable because of differences in socioeconomic conditions, lifestyles, food habits, and rates of communicable and non-communicable diseases.[1] Iron deficiency is the most common cause of anaemia and is the most widespread nutritional disorder in the world, with pregnant women at particular risk.[2,3] It is not only prevalent in developing countries but also in developed countries. Other causes include parasitic diseases such as malaria, hookworm infections, and schistosomiasis; micronutrient deficiencies including folic acid, vitamin-A, and vitamin B_{12} and genetically inherited hemoglobinopathies such as thalassemia.[4]

IDA is associated with negative outcomes for both mother and infant. There are higher risk of infections and haemorrhage which lead to maternal mortality. There also increased risk of low birth weight of the new-born, premature birth, birth asphyxia, lower Apgar score, or less cognitive development of the child.[5-8] Small for gestational age (SGA) babies are those whose birth weight lies below the 10th percentile for a particular gestational age. Full term SGA infants may not have complications related to organ immaturity like those of pre-term infants of similar size, but are at an increased risk of stillbirth and perinatal/neonatal mortality due to perinatal asphyxia, meconium aspiration and

hypoglycaemia.[7] Several factors other than iron deficiency may play roles, such as age, race, altitude, smoking, inflammation and other micronutrient deficiencies.[8]

Definition

The hemoglobin concentration (Hb) has been considered as a proxy of iron deficiency and widely recommended as a criterion for the indication of iron-therapy in pregnant women, particularly in location with few resources.[9] According to current guidelines based on recommendations of the Center of Disease Control (CDC), anemia in pregnancy is defined by a hemoglobin value less than 11.0 g/dL in both the first and third trimesters and less than 10.5 g/dL in the second trimester.[9-14] Ferritin reflects iron stores and is the test to diagnose iron deficiency anemia, with cutoff point 15 ng/mL.[15] Assessment of the hematological profile during pregnancy is troublesome because the maternal blood volume expansion occurs at a larger proportion (45%) than the increase in red blood cell mass (30%), which results in physiologic anemia and hemodilution.[16] This phenomenon is responsible for the U-shaped curve that Hb and hematocrit levels display a steady fall from late first trimester, reaching a nadir at 25 weeks gestation, and rises during the remaining period of pregnancy to reach peak levels shortly before delivery.[9,17]

Iron metabolism

Iron is an essential element in the production of Hb for the transport of oxygen to tissues and in the synthesis of enzymes that are required to use oxygen for the production of cellular energy.[18] The total body iron amount (~3–4 g) is regulated by a subtle balance between body requirements, iron supply (absorption of dietary), and blood losses.[19] About 1 g of iron is stored mostly in the hepatocytes and macrophages in the liver and spleen. Hepatocyte and macrophage iron is stored in cytoplasmic ferritin and is readily mobilized during period of high iron demand.[20] Another pivotal component of systemic iron metabolism is hepcidin, a circulating peptide hormone synthesised by hepatocytes and secreted in plasma and urine.[21] It is secreted as a 25-amino acid peptide form and is evolutionarily conserved. Hepcidin regulates the entry of iron into plasma through ferroportin (a trans membrane iron exporter present on macrophages, enterocytes and hepatocytes).[22] The production of hepcidin is regulated by iron, so that more hepcidin is produced by hepatocytes when iron is abundant, limiting further iron absorption and release from stores, resulting in lowered serum iron, increased reticuloendothelial iron stores, and decreased intestinal iron absorption.[23] When iron is deficient, hepatocytes produce less or no hepcidin and ferroportin is displayed on basolateral membranes of enterocytes, allowing more iron to enter plasma.[20]

Iron metabolism in pregnancy

Iron transfer from mother to fetus involving iron uptake from the maternal circulation, its transport across the placenta and subsequent transfer into the fetal circulation. Transfer of iron to the fetal circulation occurs via ferroportin as this has been shown to localize to the basal membrane of syncytiotrophoblast cells.[24] Therefore, high levels of hepcidin could induce internalisation and degradation of placental ferroportin, thus decreasing iron transport to fetus.[21] The iron requirements during pregnancy increase to amount a total of 1.2 gm mainly due to increase in the mother's erythrocyte mass in the second trimester and to the growth of the placenta and fetus in the third trimester.[25,26] Half of it are obligatory losses because they occur even when the mother is iron deficient, additional 300 mg goes to the fetus and placenta, 500 mg are used in order to cover the necessities of the expanded blood volume, and 200 mg are lost through normal routes of excretion.[14] Even though mobilization of iron deposits and increased iron absorption occur during pregnancy, research has suggested that iron requirements during pregnancy cannot be covered by the diet alone, so more external iron is required to balance increased demand for iron. In a randomised, double-blind, placebo controlled study of 207 healthy women conducted by Milmann et al., 92% of placebo groups developed exhausted iron stores, 65% of latent iron deficiency, and 18% of iron deficiency anaemia.[27] Furthermore, pregnant women are subject to iron loss during and after delivery.[28-30]

Assessment of iron status

Importance of accurate assessment of iron status during pregnancy has been recognized in recent years in order to evaluate the adverse effects of iron deficiency and iron excess during pregnancy on pregnancy outcome. The most widely used methods for IDA are estimations of Hb and serum ferritin (SF), because of its low cost and efficiency. However, the use of these two indicators during pregnancy has been criticized. Levels of Hb are largely influenced by increased red cell mass and plasma volume expansion and have been shown to cause a decrease in Hb concentration up to 20 g/L by 26 to 28 week of gestation from the pre-pregnancy/ early pregnancy level.[31] Blood ferritin concentrations are reflection of the amount and the changes of intracellular ferritin, the main iron storage protein, as confirmed by robust data obtained in experimental studies.[32] SF concentrations have been shown to decrease substantially during the second and third trimesters due to hemodilution, and it's level increased as a result of non-specific responses to infection and inflammation, working as a positive acute phase reactant that can mask the diagnosis of iron deficiency.[31] A SF concentration of 60 mg/L corresponds to iron stores of around 500 mg, while iron deficiency is defined as empty iron stores with SF <12–15 mg/L. There are no strict criteria for defining latent iron deficiency, but SF in the range 15–30 mg/L

signal iron stores which are too small to cover the need for iron in pregnancy.[33] Other markers include serum iron, mean corpuscular volume (MCV), transferrin saturation, and total iron binding capacity (TIBC).[34] Serum iron exhibits diurnal variations, with higher concentrations late in the day, and may transiently reach reference values after the ingestion of meat or oral iron supplements.[33,35] Serum iron concentrations exhibit variability according to assay methodology and the presence of haemolysis. MCV increases approximately 4 femtolitres in healthy pregnant women also in the presence of iron deficiency, and it is therefore not a reliable marker for iron deficiency.[33]

In cases of severe anaemia, e.g. iron deficiency, or during functional iron deficiency, e.g. erythropoietic stress with insufficient iron supply, synthesis of Hb molecules is severely impaired which leads to the production of erythrocytes with low Hb concentration (hypochromic red blood cells/HRBC).[13,36] New automated blood cell analysers can provide information about individual cell characteristics, including the quantity of HRBC and the percentage of HRBC of total red cells. These data are helpful in the diagnosis of IDA, β-thalassemia (β-thal) carriers, and anaemia of chronic disease (ACD).[37] Normally, the percentage of HRBC is < 2.5%, and in iron deficiency a value of >5–10% is seen.[14]

The transferrin receptor (TfR) is a 760-amino-acid glycoprotein. The functional receptor is composed of two such monomers, linked by two disulphide bridges to form a molecule of 190,000 Da.[38] TfR mediates iron delivery to erythroblasts by the interaction of plasma transferrin with cell surface TfR Cell surface TfR concentration reflects iron requirements of the cell.[39] Receptor density on proliferating cells is related to the availability of iron. When there is diminished intracellular iron available for a cell's metabolic requirements, cell surface TfR is up regulated in an effort to acquire more iron, while cell surface TfR is down regulated when there is sufficient intracellular iron content.[40] Virtually all cells, except mature red cells, have TfR on their surface, but the largest numbers are in the erythron, placenta and liver. In a normal adult, about 80% of TfR are in the erythroid marrow.[41] TfR density in the placenta has been shown to correspond with increased placental iron uptake and iron availability and is believed to be a major determinant of placental iron transfer. Previous research has demonstrated that maternal iron deficiency leads to increased TfR mRNA.[42] A circulating form of TfR has been found in human as well as animal serum.[38] The soluble form of TfR (sTfR) in human serum was first described by Kohgo et al., and sTfR was subsequently identified as a truncated form of cellular TfR derived from proteolytic cleavage of the extracellular segment.[39,43] According to some studies, sTfR concentration is elevated in iron deficiency anemia.[41] sTfR is based on the fact that erythroblasts in the bone marrow will increase the presentation of membrane TfR in the setting of iron deficiency. It is not affected by inflammation, which would make sTfR a more reliable test than SF.[44] sTfR levels have been monitored in a wide range of anaemia's including those with more complex pathogenesis, e.g. anaemia's of chronic disease.[43] However, in most laboratories worldwide sTfR is not a test that can be reliably reproduced with high precision.

Because SF reflects storage iron and sTfR reflects functional iron, the sTfR/log ferritin index (sTfR-F index), based on these two values, can be calculated and has been shown to be a more sensitive indicator of estimation of body iron compared to sTfR or SF alone.[8,45] Quantitative estimates of body iron greatly enhance the evaluation of iron status. Body iron (mg/kg) is calculated as -[log (sTfr/SF) - 2.8229]/0.1207.[8] However, a recent meta-analysis demonstrated the greater clinical value of sTfR rather than the sTfR-F index.[32]

The examination of Prussian blue–stained bone marrow aspirate for the presence or absence of histiocytic iron granules has been considered the "gold standard" in evaluating iron-depleted states.[46] However, marrow examinations are expensive, uncomfortable, and has been largely superseded by non-invasive methods.[47]

Erythrocyte zinc protoporphyrin (ZnPP) is a sensitive test to diagnose iron deficiency anemia. Ferrous iron incorporates into protoporphyrin to form heme in in the heme biosynthetic pathway. In the absence of iron, ZnPP increases because zinc replaces the missing iron during formation of the protoporphyrin ring. It indicates iron deficient erythropoiesis.[35] Because ZnPP concentration in erythrocytes is not influenced by plasma volume; it could be a better test in diagnosing iron deficiency in pregnant women. However, the specificity of ZnPP may be limited because ZnPP also increased in other pathologic processes such as anaemia of chronic disease, chronic infections and inflammation, haemolytic anaemia's, or hemoglobinopathies in the absence of iron deficiency.[47-49]

Iron therapy

Iron supplementation during pregnancy has been recommended since usually no basic changes occur in the composition of the diet.[50] The first choice in the prophylaxis of iron deficiency anaemia for almost all women is oral iron replacement because of its effectiveness, safety, and low cost.[51] According to WHO, all pregnant women should be given a standard dose of 60 mg iron + 400 μg folic acid daily for 6 months or, if 6 months of treatment cannot be achieved during the pregnancy, either continue supplementation during the postpartum period or increase the dosage to 120 mg iron during pregnancy. Where the prevalence of anaemia in pregnancy is over 40%, advice the woman to continue the prophylaxis for three months in the postpartum period.[52] But the major obstacle to iron supplementation is compliance with treatment. This is often due to its side-effects and women's lack of awareness.[50] The most common adverse effects are constipation, diarrhoea,

epigastric discomfort, nausea, severe abdominal pain and vomiting.[12,53] Previous studies showed large differences in the proportion of pregnant women who did not comply with iron supplementation guidelines, ranging from 27% to 75%. Study conducted by Habib et al. showed that almost half of participants who didn't comply with iron supplementation were mainly caused by its side effects.[50]

Many oral iron preparations are available; the most frequently used being ferrous sulphate (FS) and ferric preparations with an iron polymaltose complex (IPC). Gastrointestinal tolerability has been shown to be superior with IPC compared to FS. However, IPC has extremely poor solubility in alkaline media and it needs to be transformed into ferrous iron before being absorbed, so bioavailability of IPC is 3 to 4 times less than that of conventional. FS remains the established and the standard treatment of iron deficiency given its acceptable tolerability, high effectiveness, and low cost.[54,55]

On the other hand, in recent years, evidence of the undesirable secondary effects caused by excessive Hb and high ferritin levels during pregnancy, has increased.[56] Pregnancy is characterized by dynamic changes in multiple body systems resulting in increased basal oxygen consumption and in changes in energy substrate use by different organs including the fetoplacental unit. The fetoplacental unit is very susceptible to oxidative damage induced by reactive oxygen species.[57] Therefore, pregnancy is a condition with increased propensity to produce free radicals compared to non-pregnant states.[56,57] Women with ferritin levels that are elevated for the 3rd trimester of pregnancy (41 ng/mL), possibly associated with excess iron and/or inflammation, have a greatly increased risk of preterm delivery. Another plausible mechanism for high ferritin levels is failure of the maternal plasma volume to expand.[58] In order to avoid the increased risk of hemoconcentration (defined in a recent Cochrane review as values of hemoglobin >130 g/L at the 2nd trimester of gestation) associated with daily iron supplementation, preventive weekly supplementation has been proposed. Research conducted by Casanueva et al. showed that among two groups of pregnant women assigned with different method of iron supplementation (one is daily supplementation and the other is twice in a week), none of them have Hb concentration below the cut-off point associated with perinatal risk.[23]

Intravenous (IV) iron formulations offer an alternative approach for patients with moderate or severe iron deficiency or deficiency that unresponsive to oral iron therapy. In the past, parenteral iron was used with extreme caution and as a last resort due to a poor safety profile, notably anaphylactic reactions. Parenteral iron therapy with iron dextran was implicated in 31 deaths between 1976 and 1996.[59] Acute adverse reactions after IV iron administration may vary with the iron preparation used and with the pre-existing morbidity of the recipient. They cannot be distinguished by their clinical presentation. The two main possibilities are immunological IgE-mediated responses, for example, to the dextran component of IV iron preparations containing this molecule, and complement activation-related pseudo-allergy (CARPA).[60] The currently available IV iron preparations are generally considered equally efficacious but vary in terms of molecular size, kinetics, bioavailability and toxicology.[61] Currently available iron carbohydrate preparations for IV iron treatment are based on six compounds: iron sucrose (IS), ferric gluconate, ferric carboxymaltose (FCM), iron dextran (high- and low-molecular-weight dextran), iron isomaltoside and ferumoxytol.[62]

Sodium ferric gluconate, IS, and FCM do not contain dextran or any dextran derivatives and thus do not cross-react with anti-dextran antibodies in vitro.[63] IS belongs to the iron complexes of the half robust and medium strong type (molecular mass between 30,000 and 100,000 Da), which after IV administration, deliver the complexed iron from the serum to endogenous iron-binding proteins with a half-life of 90 min.[14] IS complex 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 (such as pancreatic, myocardial or hepatic hemosiderosis) is less likely even with IS complex overload.[29] When compared to oral iron in pregnancy, iron stores is superior with respect to the rate of both haemoglobin increase and iron store replenishment, combined with a good safety profile.[56,64,65] Serious adverse effects are rare with IS, however minor side effects occur in patients which may associated with irritating and uncomfortable vasoactive reactions.(56) Recently there is increasing interest on alternative therapeutic options like intravenous IS and human recombinant erythropoietin (rhEPO).[66] Because parenterally administered iron stores is also safe and effective, the combination of the 2 substances increases the efficacy of anaemia therapy by stimulating erythropoiesis (rhEPO) at the same time that it delivers enough iron for haemoglobin synthesis and iron stores (IS).[53]

High molecular weight iron dextran has been linked to an increased risk of anaphylaxis and anaphylactoid reactions, and it is not available in Europe. Although this problem is very much reduced with low molecular weight iron dextran, there is still a test dose requirement and the infusion of larger doses is hampered by a 4–6 hours infusion time.[67]

After infusion, sodium ferric gluconate complex was taken up directly by the reticuloendothelial system before being delivered back to transferrin. The majority of iron (80%) was delivered back to transferrin and made available to the erythroid marrow within 24 hours of infusion.[68] Although Sodium ferric gluconate has a good safety profile, it is not without risks. In 2005 Cuciti et al. reported case of a severe anaphylactoid reaction to

intravenous Sodium gluconate which resulted in significant airway and cardiovascular compromise in the third trimester of pregnancy.[59]

FCM is a macromolecular ferric hydroxide carbohydrate complex, which allows for controlled delivery of iron within the cells of the reticuloendothelial system and subsequent delivery to the iron-binding proteins ferritin and transferrin, with minimal risk of release of large amounts of ionic iron in the serum.[69] Iron supplied as FCM is quickly provided to different tissues, mainly to the bone marrow, liver, and spleen, the volume of distribution being approximately 3 L.[19] Administered intravenously, it is effective in the treatment of iron-deficiency anemia, delivering a replenishment dose of up to 1000 mg of iron during a minimum administration time of ≤15 minutes.[69,70]

Ferumoxytol is a semisynthetic, polyglucose sorbitol carboxymethylether coated super-paramagnetic iron oxide nanoparticle developed as an IV iron replacement therapy.[71] A full course of ferumoxytol (1.02 g) requires only two IV injections of 510 mg delivered at a rate of up to 1 ml/s (30 mg/ml) between 3 and 8 days apart.[72] Ferumoxytol was generally well tolerated in randomized controlled clinical trials. Most adverse events were mild or moderate in intensity; serious hypersensitivity or hypotensive reactions were uncommon. Local injection-site reactions were the most common system/organ-class adverse events in a pooled analysis of clinical studies and post-marketing experience.[73]

Isomaltoside 1000 has a mean molecular weight of 1,000 Da and consists predominantly of three to five glucose units. The carbohydrate isomaltoside is linear and unbranched with a low immunogenic potential. Iron isomaltoside 1000 has strongly bound iron within the ironisomaltoside formulation, which enables a controlled slow release of bioavailable iron to the iron-binding proteins with minimal risk of free iron toxicity.[61,67,74] This enables iron isomaltoside 100 to be administered as a rapid high dose infusion in doses over 1000 mg.[67] Several studies of iron isomaltoside 1000 treatment of iron deficiency anaemia have been published, including the use of bolus injections and high single-dose infusions, without detected unexpected safety issues.[61]

CONCLUSION

IDA remains major disease affect people worldwide, with pregnant women at particular risk. Accurate method needed to diagnose IDA in pregnancy in order to avoid negative outcomes to both mother and baby. Although sTfR considered the most accurate predictor for IDA in pregnancy, however in most laboratories worldwide sTfR is not a test that can be reliably reproduced with high precision. In the end, Hb and SF still become the most widely used method to diagnose IDA, especially in the low-middle resources country. Oral iron replacement is the first choice in the prophylaxis of iron deficiency anaemia for almost all women because of its effectiveness, safety, and low cost. But the major obstacle to iron supplementation is due to its side effect, mostly from the gastrointestinal tract. IV iron therapy offers alternative approach to treat IDA, especially moderate or severe iron deficiency or deficiency that unresponsive to oral iron therapy. Nowadays IV formulations have good safety profile and can provide rapid replenishment to iron stores compared to oral iron.

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Cite this article as: Chandra I, Sun L. Iron status and choice of iron therapy during pregnancy: advantages and disadvantages. Int J Reprod Contracept Obstet Gynecol 2015;4:1264-71.