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RESEARCH ARTICLE

IRON DEFICIENCY IN PREGNANCY

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ABSTRACT

World over, half of the anaemic burden is assumed to be due to iron deficiency. In pregnancy, it has been estimated that 38.2% (95% CI: 33.5-42.6) of pregnant women which corresponds to 32 million women have anaemia globally. Iron deficiency results when there is inadequate iron intake and absorption, increased iron requirement during growth, and excessive iron losses. Iron absorption is tightly regulated according to body iron reserves and the intensity of erythropoiesis. An important iron regulatory peptide hormone, hepcidin secreted by the liver, is detected to play significant role in iron homeostasis. Serum ferritin levels are the accurate indicator of total body iron stores and serum sTfR a sensitive marker of iron deficiency in pregnancy. Iron deficiency anaemia in pregnancy is known to be associated with increased risk of maternal and perinatal morbidity and mortality. Iron is important for early placental development, which maintains pregnancy and provides nutrients and oxygen to the developing fetus. Iron deficiency can adversely impact birth outcomes and result in preterm birth and low birth weight. Dietary iron which is the commonest source of iron is mostly in ferric form and it has to be reduced by the enzyme ferric reductase to the ferrous form before it can be absorbed by the enterocytes in the duodenum and jejunum. Iron absorption can vary from 1% to 40%, depending on the mix of enhancers and inhibitors in the meal. Oral iron therapy is standard care for the iron deficiency anaemia and parenteral iron is indicated when oral iron cannot be tolerated or absorbed or patient compliance is in doubt or if the woman is approaching term and there is insufficient time for oral supplementation to be effective (Level C recommendation). It is, however, more invasive and expensive to administer. Due to risk of allergic reactions, intravenous iron products should only be administered when staff trained to evaluate and manage anaphylactic or anaphylactoid reactions, as well as resuscitation facilities, are immediately available.

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INTRODUCTION

Worldover, half of the anaemic burden is assumed to be due to iron deficiency. In pregnancy, it has been estimated that 38.2% (95% CI: 33.5-42.6) of pregnant women which corresponds to 32 million women have anaemia globally. The WHO South-East Asia, Eastern Mediterranean and African regions have the lowest mean haemoglobin concentration and highest prevalence of anaemiain various groups of it's population. It's prevalence has been 38.9% (95% CI:32.7 to 46.3) to 48.7%(95% CI:36.1 to 58.9) for pregnant women in these regions (WHO 2015). Main requirement of iron is for the production of hemoglobin, an essential protein found in red blood cells which transports oxygen throughout the body from the respiratory organs and returns carbon dioxide. Other iron containing heme proteins include myoglobin, cytochromes, cytochrome oxidase, homogentisic oxidase, peroxidases, and catalase. Iron is stored in the body in the form of ferritin or haemosiderin (Blackwww.who.int/publications/cra/chapters/volume1/0163-0210.pdf). Iron deficiency results when there is inadequate iron intake and absorption, increased iron requirement during growth, and excessive iron losses. Iron deficiency anaemia in pregnancy may be associated with increased risk of maternal and perinatal morbidity and mortality. Death of women may occur inchildbirth as a result of heart failure occurring due to blood loss, which may be precipitated by iron deficiencyanaemia. Similarly, babies may die in the perinatal period fromcause such as preterm birth. A direct sequelae of iron deficiency in fetus have been found to

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be decreased work productivity and altered child development (or intelligence) (Sant-RaynPasricha *et al*., 2013).

Iron requirement

The requirement for absorbed iron during first trimester of pregnancy is 0.8 mg/day which increases gradually through gestation to7.5 mg/day in the third trimester. Throughout the pregnancy the average requirement is 4.4 mg/day (Svanberg, 1975; Both well, 2000; Hallberg, 1988).The iron that is absorbed is mainly required for: 1) expansion ofthe woman's erythrocyte mass. 2) fulfillment of the foetus's iron requirements and 3) compensation for iron losses (i.e. blood losses) at delivery. During a normal pregnancy the total iron requirement has been estimated to be about 1,240 mg. After the delivery, the postpartum erythrocyte mass of mother declines. However, 610mg of iron is saved due to increased erythrocyte mass during pregnancy (450mg) and amenorrhoea of pregnancy (160 mg). Hence, the net iron loss related to pregnancy is about 630 mg (Both well, 2000; Hallberg, 1988). A newborns' body iron content depends to a large extent on their birth weight (Saddi and Shapira, 1970).

Iron absorption and homeostasis

Iron in diet is mostly in ferric form and it has to be reduced by the enzyme ferric reductase to the ferrous form before it can be absorbed by the enterocytes in the duodenum and jejunum. Iron absorption is dependent on gastric acid because it maintains iron in its soluble ferrous (Fe2+) form rather than the insoluble ferric (Fe3+) form. Iron absorption across the cell membrane requires the action of divalent metal transporter 1 (DMT1). These two enzymes increasein iron deficiency, thereby improving iron absorption. Once inside the cell, the ferrous iron is oxidized by Fe-oxidase hephaestin back to the ferric form (Morgan and Oates, 2002). Iron absorption is tightly regulated according to body iron reserves and the intensity of erythropoiesis. Iron from both intestinal epithelial cells and macrophages, derived from old erythrocytes by erythrophagocytosis, is transported, via ferroportin channels, to the circulation. Then it binds to serum transferrin, which carries the bound iron to the target cells. Transferrin receptors on the surface of erythroblasts, lymphocytes, and other proliferating cells bind and internalize the transferrin-iron complex, releasing iron intracellularly through the transferrin cycle. Intracellularlly, ferritin, an intracellular protein binds and sequesters iron and it also leaks into the circulation in small levels. Serum ferritinlevels are an accurate indicator of total body iron stores (Alfred lan Lee *et al*., 2011). Transferrin receptors (TfR) are located on the surface of the young erythrocytes, and their number increases during iron deficiency. The detached receptors circulate in the blood and can be analysed in serum as "soluble" receptors (sTfR). The number of receptors on the young erythrocyte is related to the serum sTfR level and it rises in states of iron deficiency. Serum sTfR is an indicator of iron deficiency on the cellular level, whereas, serum ferritin level is informative about the capacity of body iron reserves. When serum iron levels in body are adequate, serum sTfR level is quite stable, because it is independent of the size of body iron reserves. Serum sTfR begin to rise when the supply of iron to the erythrocytes fall due to exhausted iron reserves. Therefore, serum sTfRidentify women with low serum ferritin, who also has significant iron deficiency. Serum sTfR is a sensitive marker of iron deficiency inpregnancy, and when combined with measurements of serumferritin, diagnosis of entire spectrum of iron deficiency is made possible (Baynes, 1994; Carriag *et al*., 1991; Akesson *et al*., 1998).

More than a decade back an important iron regulatory peptide hormone, hepcidin secreted by the liver, was detected to play significant role in iron homeostasis. Hepcidin blocks both non-heme iron absorption from the diet and iron mobilization from macrophages and hepatocytes. It binds ferroportin and induces its endocytosis and degradation in lysosomes. When the level ofhepcidinare high, as seen in anaemia of inflammation, it causes intracellular accumulation of iron and impairment of iron use and it's levels are suppressed by erythropoietic activity and hypoxia. Ferritin and hepcidinare acute phase reactants, and there levels may be elevated during infection, inflammation, or stress (Mary Dawn Koenig *et al*., 2014). All the iron required for fetal growth and development is transported from the mother to the fetus by the placenta, actively. A net transfer of roughly 270 mg of iron occurs across the placenta which is accumulated by the developing fetus, most of which occurs over the last 10 weeks of gestation (Allen, 2000). The iron delivered to the fetus is obtained from three primary sources, dietary iron, supplemental iron, or endogenous maternal iron.

The maternal iron is transported across the epithelium of the placental villi, syncytiotrophoblast. This interfaces with maternal blood contains Tf receptors (TfR) on the surface facing maternal circulation. The binding of iron transferring (Fe-Tf) to TfR depends on the pH levels, having a greater affinity at pH 7.4. The Fe-Tf/TfR complex is endocytosed into a vesicle and at a lower pH, dissociation of iron from the maternal Tf takes place. After release, iron is actively transported out of the cytosol, where it is used for cellular processes, stored in ferritin or exported into fetal circulation. The TfR and Tf then return back to the maternal surface of syncytiotrophoblast where Tf is released into the maternal circulation and the cycle repeats. Both maternal and fetal hepcidin may determine the degree of placental iron transfer. Also, it is believed that fetal-derived hepcidin may play a role in the regulation of Fpn expressed at the basolateral side of the syncytiotrophoblast and it may determine the rate of iron entry into fetal circulation (McArdle *et al*., 2011). In the presence of infection or inflammation, maternal iron bioavailability is significantly reduced, limiting the amount of iron present for both uptake by the placenta and for transfer to the fetus (Mary Dawn Koenig *et al*., 2014).

Diagnosis

The US Centers for Disease Control (CDC) defines anemia in a no pregnant woman as an Hb level of less than 12 g/dL. In pregnancy, an Hb level of less than 11 g/dL in the first and third trimester or 10.5 g/dL in the second trimester is considered anemia (Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States, 1998).The World Health

Organization defines iron deficiency anemia in pregnancy when a woman has a haemoglobin level of less than 11g/dL (or <110 g/L) and a hematocrit level of less than 33 percent. Evidence of test sensitivity and specificity for iron deficiency anemia in pregnant women is not available. Therefore, haemoglobin alone (haemoglobin level <11 g/dL) is not an ideal screening parameter for iron deficiency anemia. Classical laboratory tests, include measurement of haemoglobin, mean corpuscular haemoglobin concentration, meancorpuscular volume, total iron-binding capacity, transferrin saturation, and zinc-erythrocyte protoporphyrin (http://www.who.int/ nutrition/publications/micronutrients/anaemia_iron_deficiency/ WHO_NHD_01.3/en). Serum ferritin levels are the accurate indicator of total body iron stores and serum sTfRa sensitive marker of iron deficiency in pregnancy. According to WHO a serum ferritin value of less than 15 µg/L in pregnant women is accepted as a cutoff for depleted iron stores among pregnant women (http://www.who.int/vmnis/indicators/ferritin/en/ index.html2011).

The nadir of maternal serum ferritin is found to occur by 28 week and as the higher iron demands start after this gestation, there is a decrease which is partially explained by the normal plasma volume expansion that occurs during pregnancy. It has been found that maternal anemia diagnosed early in pregnancy is associated with an increased risk for preterm delivery but anemia diagnosed during the third trimester is not associated with this negative outcome (McDonagh *et al*., 2015). Third-trimester anemia, which may be due to hemodilution, makes it difficult to distinguish between iron-deficiency anemia and anemia due to an expanded plasma volume with no adverse outcome. The U.S. Preventive Services Task Force (USPSTF) recommends routine screening for iron deficiency anemia in asymptomatic, pregnant women (level B recommendation). This recommendation is based on evidence that the benefits of routine screening for iron deficiency anemia in asymptomatic, pregnant women outweigh the potential harms (McArdle *et al*., 2011). The American College of Obstetricians and Gynecologists also support routine screening of pregnant women at the first prenatal visit and again early in the third trimester (ACOG Practice Bulletin No 95 2008).

Effects on pregnancy

Other than the clinical symptoms of fatigue, weakness, pallor, tachycardia, and shortness of breath iron deficiency can also negatively impact the immune response and thus increase the risk of infection during pregnancy (Bhaskaram, 2001). Women can die of heart failure due to blood loss, which is made more precipitous by iron deficiency anaemia. Iron is important for early placental development, which maintains pregnancy and provides nutrients and oxygen to the developing fetus. Iron deficiency can adversely impact birth outcomes and result in preterm birth and low birth weight. The exact mechanisms by which iron deficiency may affect birth outcomes are unknown. The potential reasons could be hypoxia, oxidative stress, and increased risk of infection (Allen, 2000). Hypoxia, as a result of iron deficiency, could initiate a stress response, including the release of corticotropin-releasing hormone from the placenta and increased production of cortisol by the fetus, both of which are associated with increased risk of preterm birth (Gulmezoglu *et al*., 1996). Iron deficiency when associated with increased oxidative stress could damage the placenta during early development also. In the fetus decreased iron in utero may directly cause decreased oxygen delivery to muscles and the brain affecting developmental and metabolic programming and brain development. Low iron stores at birth have been reported to be associated with cognitive deficits, decreased fine motor skills, and impaired language ability(Tamura *et al*., 2002). There is evidence that maternal Hb levels below 9.5 gm/dl before or during the second trimester of gestation are associated with increased risk of giving birth to a low birth weight infant and premature delivery (Burke *et al*., 2014).When the Hb levels in pregnancy are below 9.0g/dl, indicative of moderate (between 7.0 and 9.0 g/dl) or severe (less than 7.0 g/dl) anaemia, it is associated with increased risk of maternal and childmortality and infectious diseases (International Nutritional Anemia Consultative Group (INACG) 2001). Favourable pregnancy outcomes occur 30% to 45% less often in anaemic mothers, and also it has been estimated that their infants have less than one-half of normal iron reserves (Bothwell and Charlton, 1981). During postpartum period iron deficiency anaemia can be associated with palpitations, tiredness, shortness of breath, and increased incidence of infection. Iron deficiency is also known to cause emotional and cognitive effects including emotional instability, decreased cognition, and increased risk of postpartum depression(Milman, 2011).

Sources of Iron

Prevention of iron deficiency anaemia comprises of adequate dietary iron intake and prophylactic iron supplementation. Dietary iron has two main forms: heme and nonheme. Plants and iron-fortified foods contain nonheme iron only, whereas meat, seafood, and poultry contain both heme and nonheme iron. Iron absorption can vary from 1% to 40%, depending on the mix of enhancers and inhibitors in the meal. Therefore, the bioavailability of iron in usual diets can be improved by addition of enhancers. Enhancers of iron absorption includehaem iron, ascorbic acid or vitamin C(present in fruits, juices, potatoes and some other tubers), and other vegetables such as green leaves, cauliflower, and cabbage, and some fermented or germinated food and condiments (http://www.who.int/nutrition/publications/micronutrients/ anaemia_iron_deficiency/WHO_NHD_01.3/en). Inhibitors of iron absorption are phytates (present in cereal bran, cereal grains, high-extraction flour, legumes, nuts, and seeds), food with high inositol content, iron-binding phenolic compounds like tannins (present in tea, coffee, cocoa, herbal infusions), certain spices (e.g. oregano), and calcium particularly from milk and milk products.

Iron therapy

Iron has been used to treat anemia for more than 300years. However, it was not until the 19th century that oral iron therapy became standard care for the iron deficiency anaemia. Oral iron therapy comprises of iron in ferric and ferrous forms. Ferrous iron is preferred because it is better absorbed from the intestinal tract. The 3 most common oral iron preparations are ferrous sulfate, ferrous gluconate, and ferrous fumarate. The current

recommendations for prophylactic iron supplementation in all pregnant women include the provision of a standard daily dose of 30 to 60 mg of elemental iron and 400 µg (0.4 mg) of folic acid starting as soon as possible after gestation begins and continuing for the rest of the pregnancy(http://apps.who.int/iris/bitstream/10665/77770/1/9789241501996˙eng.pdf, accessed 18 May 2015). Ameta-analyses has suggested that iron supplementation can increase the mean blood haemoglobin concentration by 10.2 g/L (95% CI: 6.1—14.2) in pregnant women and 8.6 g/L (95% CI: 3.9—13.4) in non-pregnant women (WHO, 2015). The recommended daily dose of oral iron for the treatment of IDA is 150 to180 mg/d of elemental iron in divided doses 2 to 3 times per day (Centers for Disease Control and Prevention, 1998). Because higher doses are less well absorbed from the duodenum, the total daily dose should be divided into 2 to 4 fractions, each taken on an empty stomach (1 hour before eating or 2 hours after).Maintenance of stomach acidity is important for absorption. A positive response is confirmed by reticulocytosis, generally seen within 1 week, and increased Hb levels approximately 2 to 3 weeks after iron supplementation is started (Johnson-Wimbly and Graham, 2011). Iron has the potential to cause directerosion and irritation of the gastrointestinal mucosa, to cause oxidative damage of lipid membranes, proteins or DNA, can stimulate inflammation or as an essential nutrient, fertilise the growth of pathogens. High-dose iron supplements are commonly associated with constipation and other gastrointestinal effects including nausea, vomiting and diarrhea, the frequency and severity of which vary according to the amount of elemental iron released in the stomach. The Institute of Medicine has established the tolerable upper limit for iron during pregnancy as 45 mg/day of iron, a daily dose much lower than international recommendations (Institute of Medicine, 2001). In addition to the problem of adverse effects, impaired iron absorption also can be an issue. The common practice of administering iron supplements with food in an attempt to alleviate gastrointestinal adverse effects can effectively decrease absorption by 40% to 66%. Oral iron agents need to rapidly dissolve in the stomach in order to be absorbed in the duodenum or upper jejunum. Long-acting or enteric-coated formulations designed to increase compliance and limit adverse effects may actually be ineffective, because they do not dissolve in the stomach (Little, 1999). Acochrane review on benefits and harms of intermittent iron supplementation (twice or thrice weekly) in pregnant women on haematological and pregnancy outcomes found that intermittent regimens produced similar maternal and infant outcomes as daily supplementation but were associated with fewer side effects and reduced the risk of high levels of Hb in mid and late pregnancy, although the risk of mild anaemia near term was increased. While the quality of the evidence was assessed as low or very low, intermittent may be a feasible alternative to daily iron supplementation among those pregnant women who are not anaemic and have adequate antenatal care (Peña-Rosas *et al*., 2015).

Another Cochrane review concluded that supplementation with iron to pregnant women may be used as a preventive strategy to improve maternal and infant outcomes in all settings, although the magnitude of the effect may vary depending on the background risk ofanaemia and low birthweight (Peña-Rosas *et al*., 2015). It compared Forty-four trials to assess the effects of daily oral supplements containing iron versus no iron or placebo. It found that women taking iron supplements were less likely to have low birth weight and preterm new borns and have heavier babies although these findings did not reach statistical significance. Results also suggested that babies born to mothers receiving iron were less likely to be born before 34weeks' gestation. For other infant outcomes there were no clear differences between groups. Regarding maternal outcomes, women who received iron were less likely to be anaemic at term (13.06% versus 35.71%) and were less likely to have iron deficiency (28.50% versus 51.33%) and iron-deficiency anaemia at term (4.37% versus 13.18%). Also they reported side effects (25.30% versus 9.91%), although this was not statistically significant. Women who received iron had high haemoglobin (Hb) concentrations at any time during second or third trimester and at term and in the postpartum period. Hence, there were clear positive effects on maternal haematological status while the effects on infant outcomes were uncertain.

IV iron

Although oral iron is the first-line therapy for IDA ,clinical studies have shown a greater rise in Hb concentration and iron stores over a shorter period using IV iron when compared with oral iron along with their safety (Arnold *et al*., ?). Reveiz *et al* conducted a systematic Cochrane database review of the medical literature on the treatment of IDA in pregnancy and concluded that the administration of IV iron was superior to the use of oral iron supplementation in improving Hb levels, although they could not find a proven benefit in clinical outcome. This supports the use of IV iron as the treatment of choice for specific situations in pregnancy but do not y*et al*low to recommend this treatment modality for all anemic pregnancies (Reveiz *et al*., 2011).

Simple iron salts such as ferrous sulphate when dissolved in water, form ferrous ions which can then react with oxygen to form reactive oxygen species that can induce tissue damage. On the other hand, ferric ions are stable only under very acidic conditions and form insoluble and polynuclear precipitates at the physiological pH of about 7.0. Hence ferric ion is unavailable to cells. Iron can be kept in solution as colloidal particles in the form of carbohydrate complexes such as sucrose, dextran and dextrin and they have all been used therapeutically. These iron-carbohydrate complexes aresimilar to ferritin. Such complexes do not release ionic iron at neutral pH, but theiron is therapeutically available. These complexes aremetabolized and the iron can either be delivered to the transport system, i. e. transferrin, or, depending on the physiological need, be stored in ferritin. These complexes vary in their size (indicated by their molecular weight, Mw) and the rate at which they release iron (indicated by their degradation kinetics parameter, k), and classified accordingly. Type I complexes, such as ferric carboxymaltose (FCM) or iron dextran, are robust and strong and they release only minimal amounts of ionic iron in the circulation. They are taken up from the plasma by the macrophages of the reticulo-endothelial system (RES) with a half-life of 16 h for FCM and 3–4 days for iron dextran. The RES route of uptake prevents the

formation of harmful reactive oxygen species. Such complexes therefore do not damage tissues such as the liver, kidney or spleen. Because of their stability, Type I complexes can be given at high doses. The large size of the high-molecular weight (HMW) iron dextran can produce allergic and occasionally dextran-induced anaphylactic reactions (DIAR) due to the presence of anti-dextran antibodies. These antibodies may be present as a result of earlier treatments with iron dextran or even in previously untreated patients. Type II complexes such as iron sucrose are semirobust and moderately strong and thus less stable than. Type I complexes. They release larger amounts of iron in the circulation. Iron is taken up largely by the RES, with plasma half-lives of hours rather than days. Type III complexes are the least stable and release relatively large amounts of ionic iron into the circulation. Consequently, transferr in becomes saturated at low doses, and excess iron will be bound to other proteins such as albumin. Type IV or the mixed complexes are the heterogenous mixtures that display a number of properties of the other types, including their side effects such as allergic responses and saturation of the iron transport system. An ideal form of iron for intravenous administration should be capable of delivering sufficient amounts of iron to correct iron deficiency rapidly, but without causing any side effects. It should be free from any compounds, such as dextran, that could lead to antibody production and/or react with anti-dextran antibodiesand induce DIAR. For ease and comfort of injection, intravenous preparations should have a neutral pH and be isotonic(Felix Funk *et al*., 2010).

The intramuscular route of iron administration is painful, cause permanent discoloration of the skin, and have been associated with gluteal sarcomas in addition to there ported adverse effects similar to intravenous administration. Hence this route of iron administration is not supported by evidence (Auerbach *et al*., 2007) The patient's iron dose for replacement of iron can be calculated using the Ganzoni formula(Ganzoni, 1970).

Cumulative iron deficit (mg) = body wt(kg) x [target Hb (g/dl) – actual Hb (g/dl)] x 2.4 + iron storage depot (mg)*

*Depot iron for body weight 35 kg and above = 500mg

Although the safety of IV iron has been demonstrated in studies comprising thousands of patients with numerous clinical entities associated with iron deficiency, safety concern is very significant. Alliron products can cause hypersensitivity or other reactions, some of which can be severe. RCOG recommends that parenteral iron is indicated when oral iron cannot be tolerated or absorbed or patient compliance is in doubt or if the woman is approaching term and there is insufficient time for oral supplementation to be effective (Level C recommendation). It is, however, more invasive and expensive to administer. Due to risk of allergic reactions, intravenous iron products should only be administered when staff trained to evaluate and manage anaphylactic or anaphylactoid reactions, as well as resuscitation facilities, are immediately available. Human erythropoietin as a treatment for iron deficiency anaemia is associated with lot of adverse effects. These include mild flu-like symptoms such as sore throat, cough, fever, muscle pains and weakness, headache and fatigue. Uncommon but more serious adverse effects include hypertension, thromboembolic complications, seizures, and pure red cell aplasia. Recent research has shown an association with certain haematological cancers (Kliger *et al*., 2012). The role of recombinant human erythropoietin (rHuEPO) for non-end-stage renal anaemia in pregnancy is not established (level B). There is no firm indication for initiating red cell transfusion in pregnancy. The decision to perform blood transfusion should be made on both clinical and haematological grounds. Blood transfusion is almost always required when the Hb is less than 6g/dl and it is rarely required when the Hb is greater than 10 g/dl. It should also be remembered that patients with acute haemorrhage can have normal Hb; hence the clinical evaluation of the patient in this situation is extremely important for red cell transfusion (https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg47/). Treatment options for postpartum iron deficiency includes oral or intravenous iron, erythropoietin which stimulates red blood cell production, and substitution by red blood cell transfusion. Parenteral therapy offers a shorter duration of treatment and a quicker response than oral therapy (Bhandal and Russell, 2006). The cocharane review did not find evidence to reach a clear conclusion regarding the efficacy of the interventions on postpartum iron deficiency anaemia. It remains unclear regarding which treatment modality is most effective in alleviating symptoms of postpartumanaemia (Markova *et al*., 2015).

The goal of this review was to focus the clinician's attention on the most important cause of nutritional deficiency, iron deficiency anaemia in pregnant women and provide a simple, evidence-based approach to its identification and treatment.

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