

REVIEW PAPER

Doses of iron in prevention and treatment of anemia in pregnant women: an ongoing debate

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Abstract	Introduction	Methodology	Results	Conclusion	References	Citation	Tables / Figures
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Abstract

Iron supplementation during pregnancy, both as a preventive and therapeutic measure has been a matter of debate. The guiding principles behind supplementation include availability of adequate iron stores before pregnancy, diet during pregnancy and concomitant infections. No country performs routine screening of iron stores by measuring ferritin and the decision to supplement iron is largely based on haemoglobin (Hb) levels. Evidence suggests that Hb content of the mother's blood between 95 and 105 g/l in the third trimester correlates with the best clinical outcome. Effectiveness of routine iron supplementation during pregnancy for improving maternal hematological indices exists, but the clinical significance for both pregnant women and infants remains unclear. In the absence of conclusive evidence, several developed nations follow an individual based approach by evaluating the iron stores and then deciding on the course of treatment. On the other hand, in developing countries, where the baseline prevalence of anemia is high, existing data supports routine iron supplementation as a safe strategy to prevent maternal anemia. Controversies exist around the most appropriate dosage and frequency (daily v/s weekly) of iron supplementation for both preventive and therapeutic purposes because increased doses does not necessary yield better haematological and clinical outcomes. On the contrary, excess doses may be associated with more side effects and also may produce oxidative stress, release of free radicals, may interfere with the absorption of divalent cations, may block iron absorption by upregulating hepcidin and may result in hemoconcentration further leading to adverse outcomes. This document gives a snapshot of the existing evidence and provides a case for further deliberations on the most appropriate dosage for iron supplementation during pregnancy giving due weightage to epidemiological, physiological and clinical requirements.

Introduction

Iron is an element that is essential for both pregnant woman and the growing fetus. Majority of pregnant women who become iron depleted are those who do not take adequate iron. A substantial proportion among them develops iron deficiency anemia if the state of iron depletion continues for long. Pregnancy poses demands on iron supplies. Its requirements in the second and third trimesters cannot be fulfilled by dietary iron alone, notwithstanding its

bioavailability, unless stores of about 500 mg are believed to exist before pregnancy. (1)

Health authorities in the European community and other Western countries advocate the use of iron supplements in women whose body iron stores prior to pregnancy are less than 500 mg. Because no European country performs routine screening of iron status (analysis of serum ferritin) prior to or during early pregnancy, national health authorities advocate general iron prophylaxis in pregnant

women. (2) Arguments in support of prophylaxis and treatment include calculation of extra iron needed for the growth of the fetus and placenta. This is supported by surveys that indicate correlations between mother's anaemia and/or low serum iron and birth weight and mortality of the infant. However, iron supplementation programs have limited efficacy in reducing anemia especially in low income countries. It is unclear whether it is due to ineffective elimination of iron deficiency or because of other determinants like infections. Infections and infection induced inflammation are known to block iron absorption by upregulating hepcidin. (3)

Evidence suggests that haemoglobin (Hb) content of the mother's blood between 95 and 105 g/l in the third trimester correlates with the best clinical outcome. (4) There is no conclusive evidence that improvement of the iron status during the first and second trimester would improve the outcome of pregnancy; also the Hb values in the third trimester are not considered to influence the outcome significantly. (5) It is sometimes advisable to initiate treatment when Hb drops below 110 g/l. In most cases even serum ferritin content or MCV values are not essential in decision-making. However, because a high maternal Hb level is sometimes mistakenly equated with good iron status, its effect on pregnancy outcome has not received the same attention as anaemia. (2) The effectiveness of routine iron supplementation during pregnancy for improving maternal hematological indices exists, but the clinical significance for both pregnant women and infants remains unclear. More research is needed to understand the clinical outcomes of routine screening for iron deficiency anemia and its treatment during pregnancy. (6,7,8,9)

The necessity of iron supplementation during pregnancy has been a matter of debate in industrialized world and hence routine supplementation is not practiced universally in such countries. Existing data supports routine iron supplementation as a safe strategy to prevent maternal anemia in developing countries, where diets provide inadequate iron and presence of malaria and other endemic infections aggravate iron loss. (10) However, the debate concerning prophylactic iron supplementation to pregnant women is still controversial. Although World Health Organization (WHO) has made its recommendations, there is no worldwide consensus concerning iron prophylaxis and therapy during pregnancy. There

does exist a contradiction between scientific results and common practice.

More than 40 years of iron supplementation programs in nations such as India, aimed at controlling gestational anemia have been ineffective. Therefore, the opportunity is ripe for exploring new possibilities for iron supplementation. Policies ought to be guided by scientific justification and rationale that considers the physiological aspects related to iron supplementation and its clinical implications thereof. This approach considers the capacity of fresh intestinal cells to absorb iron and deliver it to transferrin in response to internal signals reflecting total body iron status and homeostatic need. Questions are on the logic of daily v/s intermittent oral administration of iron doses, and capacity of an individual to assimilate (absorb, utilize, and metabolize) iron safely and its translation to pregnancy outcome.

This document gives a snapshot of the existing evidence and opens doors for identifying knowledge gaps that would guide further deliberations.

Benefits of iron supplementation in pregnant women

Universal prenatal supplementation with iron alone or in combination with folic acid, provided either daily or weekly is effective in preventing anaemia and iron deficiency at term. No differences are evident between daily and weekly supplementation with regards to gestational anaemia. (8) There is however, inconclusive evidence on reduction in maternal and neonatal adverse clinical outcomes (low birthweight, delayed development, preterm birth, infection, postpartum haemorrhage). Compared with controls, women taking iron supplements have better fetal outcomes; low birthweight newborns (8.4% versus 10.3%, average RR 0.84; 95% CI 0.69 to 1.03), and preterm babies (RR 0.93; 95% CI 0.84 to 1.03) but this finding is not consistent across studies. (11) This suggests that implementation of iron supplementation recommendations may produce heterogeneous results depending on the populations' background risk for low birthweight and anemia, as well as the level of adherence to the intervention. (12) Other beneficial effects of routine iron supplement, such as lower frequency of caesarean section and of blood transfusions and a longer length of gestation in routinely supplemented compared with selectively supplemented women has also been reported.

Postpartum haemoglobin is also reported to be higher in routinely supplemented women. (13)

Newborns to iron supplemented women have higher serum ferritin compared to newborns to placebo-treated women. (3) Results from Danish population suggest that iron supplements in a dose of 20 mg/day is adequate to cover the iron needs of the newborn, because further increases to supplement dose does not influence the iron status. Apgar score, body weight, body length, or Body Mass Index (BMI) were however, not significantly different in the four iron supplement groups (20, 40, 60, and 80 mg) among newborns. (13) Effects of oral iron on cognitive development in young children are small or non-existent; further heterogeneity between trials and the low quality of many studies make assessment of effect difficult. (14)

A recent evidence suggests that the benefits of antenatal iron supplementation on maternal and neonatal health vary by maternal iron status, with substantial benefits in iron-deficient women. The benefits of universal supplementation are most likely to vary with the population prevalence of iron deficiency. As a consequence, the balance between benefits and risks is probably more favourable in low-income countries than in high-income countries despite the higher exposure to infectious pathogens. (3)

What is the most appropriate dose of iron supplementation in pregnant women?

Previously, there was a tradition to recommend high doses of iron supplements of 100–200 mg of ferrous iron daily in pregnancy in several countries. (13) A daily dose of 100 mg of ferrous iron induces a maximum rise in the Hb concentration and a dose of 200 mg of ferrous iron increases serum ferritin and Hb at term to the same or even higher level as in nonpregnant women. (13) Previous studies have demonstrated that a supplement of 66mg ferrous iron daily from 20 weeks of gestation prevents iron deficiency in 90% of women. (15,16) Even a smaller daily dose of 27 mg iron has a demonstrable positive effect on iron status. (17)

A placebo-controlled Danish dose–response study assessed the effect of various doses of iron supplements ranging from 20, 40, 60, to 80 mg of ferrous iron daily from 18 weeks of gestation to 8 weeks postpartum. (11) There were no significant differences in the serum ferritin concentrations in women taking 40, 60, or 80 mg of ferrous iron daily.

(13) A daily dose of 40 mg of ferrous iron appeared to be adequate to prevent iron deficiency anemia in more than 95% of the women. (11) The study could not demonstrate any significant difference in gastrointestinal symptoms in women taking 20, 40, 60, or 80 mg of ferrous iron daily in pregnancy. (13) Thus, the lowest recommended dose of ferrous iron supplement protecting against iron deficiency anemia is 40 mg daily. At individual level, it is advised that serum ferritin be measured before conception or in early pregnancy as a biomarker for iron status. If serum ferritin is 30–70 µg/l, supplement of 40 mg of ferrous iron daily is considered adequate and if it is <30 µg/l, supplement of 80–100 mg of ferrous iron daily should be considered. (13)

However, for populations in whom the prevalence of gestational iron deficiency anemia is above 40%, high daily doses of iron (60, 120, 240, and even 300 mg) are proposed. Estimates of the level of iron assimilated when supplemental iron doses above requirements are ingested for several days or weeks vary widely, from 2 to 3 mg/d to as high as 20 mg/d or even higher, depending on the dose and the total body iron status. In general, a sustained percentage of assimilated iron is less than 10% and bone marrow activity rarely increases more than three times the normal turnover. (4) Current evidence also shows that women receiving any intermittent iron regimen (with or without other vitamins and minerals) compared with a daily regimen did not show any difference in clinical outcomes (birth weight, premature birth or neonatal death). (7) In the last decade, many studies in different populations have confirmed that a weekly dose of iron could be effectively used for the prevention of iron deficiency in populations at risk, including during gestation. Even in short-term studies, this approach improves iron reserves and corrects mild to moderate anemia. (4) Moreover, intermittent regimens are 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 would increase. (7) Studies to assess the efficacy of single versus double daily iron dose on prevention of iron deficiency anemia with twin gestations shows that both are comparable. Doubling the dose is however associated with more side effects (18). Rationale behind having more dosages of iron could be because dietary components such as calcium, polyphenols, and phytate may inhibit the absorption of iron supplements, especially at low iron doses. For

example, the absorption of 30–90 mg of ferrous iron is, on the average, 40% lower when the iron is taken with a meal instead of between meals. (13). During pregnancy and otherwise also, iron deficiency may lead to an increased absorption of toxic divalent cations, including lead and cadmium. (11)

A low daily dose of iron (30 mg elemental iron) during pregnancy improves women's iron status and seems to protect their infants from iron-deficiency anemia. Several studies have also shown that a low daily dose of iron may improve birth weight even in non-anemic pregnant women. However, higher dosages are not recommended because of the potential negative effects on mineral absorption, oxidative pathways, and adverse gastrointestinal symptoms. (19) Evidence shows that fractional absorption in iron-depleted women is highest at low iron doses (40-80 mg) and that acute, consecutive day dosing results in decreased iron bioavailability. For total iron absorption, twice daily iron supplementation seems to have limited additional effect compared to daily administration. (20)

Potential harms and adverse effects with iron supplementation

From a physiologic and nutritional point of view, individual iron prophylaxis should be preferred. Iron has a negative influence on the absorption of other essential divalent metals and causes an increase in the oxidative stress. It is possible to avoid unnecessary iron loading of women with adequate iron status, i.e., iron reserves of ≥ 500 mg. (13)

Gastrointestinal symptoms during iron supplementation are dose related and most frequently observed when using large doses of iron, in the range of 180–400 mg/day. On the contrary, it is reported that there is a higher frequency of gestational complications, i.e. a higher frequency estimate of poor health status, a higher number of sick days, a higher number of in-patients days, a higher number of blood transfusions, and a higher frequency of caesarean sections in selectively iron-treated women compared with routinely treated women. (11) Associated adverse effects and hemoconcentration during pregnancy in particular, calls for a need to revise iron doses and guidelines of supplementation during pregnancy. (9)

Iron antagonizes the intestinal absorption of other essential divalent cations (zinc, copper, chromium, molybdenum, manganese, and magnesium) and increases the risk of damage to the intestinal

epithelium due to the formation of free radicals in the intestinal mucosa; therefore, iron doses should be kept as low as possible. (11) Women receiving iron are at increased risk of haemoconcentration (Hb concentrations greater than 130 g/L) during pregnancy. (12) This is more pronounced among women following daily regimens as compared to those following intermittent regimens. (8,11)

A few studies indicate undesirable perinatal and infant developmental outcomes from iron supplementation. Studies among healthy pregnant women have hypothesized that excessive iron supplementation can be dangerous. This is because it increases total Hb concentration above desirable levels and inhibits the normal decline of Hb concentration that reaches a nadir by 34 weeks of gestation. According to studies addressing different supplementation regimens it seems that the risk of developing hemoconcentration is significantly higher among anemic and non-anemic pregnant women (some iron deficient) consuming daily iron supplementation at recommended levels as opposed to women ingesting weekly iron. Hemoconcentration may be associated with increased perinatal risks although this has not been confirmed in existing studies. (4)

Probable shortcomings of iron supplementation include increased blood viscosity with impaired placental circulation, possibility of adverse effect caused by oxidative damage, and a negative influence on the absorption of other minerals. Also, special interest is on the following diseases of infants hypothesized to be caused or facilitated by iron: convulsions, malformations, cancer, and infectious diseases. (2) Expansion of the plasma volume during pregnancy reduces blood viscosity that favours blood flow in the maternal intervillous space thereby enhancing fetal growth. High Hb values could be associated with placental infarction, and pregnancy haemodilution, by preventing thrombosis in the uteroplacental circulation, may promote fetal nourishment and growth. (2)

Administration of iron causes local oxidative stress (OS). Based on animal models questions have been raised if previously iron-deficit pregnant women are more susceptible to therapeutic-iron-induced OS than iron-replete subjects. This further discourages routine supplementation with ferrous iron and emphasizes on the necessary cautions against iron therapy. High-grade OS (and iron) is widely considered to have a role in the pathogenesis of

neurodegenerative diseases, atherosclerosis, diabetes complications, and arthritis. (5)

The iron withholding process is regulated by hepcidin, a small peptide hormone that was discovered in 2000 and that is now known to be the key regulator of body iron homeostasis in many vertebrates. Plasma hepcidin negatively correlates with iron bioavailability. (20) Hepcidin is mostly produced by hepatocytes and acts by binding to ferroportin, the transmembrane iron exporter protein and by inducing its intracellular degradation, thus inhibiting cellular iron efflux. Hepcidin synthesis is significantly reduced by iron deficiency, causing increased absorption of ingested iron in enterocytes. In contrast, hepcidin is greatly increased by inflammation, which causes reduced iron absorption and a blockage of macrophage recycling of iron that would otherwise be available for erythropoiesis and other metabolic processes. (3) It is also known that iron supplementation acutely increases the circulating plasma hepcidin level thus reducing the bioavailability of iron. (20) Besides, high iron doses can potentially adversely affect the composition of the gut microbiome and increase inflammation. (21) A latest report found that Hemoglobin (Hb), total protein (TP), iron (Fe), albumin and alkaline phosphatase (ALP) levels were increased ($P < 0.001$; $P < 0.01$; $P < 0.05$) after treatment in mild, moderate, and severe anemia respectively. Data obtained from the study provided new insights into the mandatory application of liver function tests and monitor them at regular intervals during the course of pregnancy. (22) However, this area remains unexplored and needs further investigation.

To conclude, existing evidence suggests that for prevention of anemia, daily supplementation with 30–60 mg iron throughout pregnancy should be given, starting as early in pregnancy as possible. In settings where anaemia in pregnant women is a serious public health problem (with population prevalence of 40% or higher), a daily dose of 60 mg of elemental iron is preferred over a lower dose. Alternately, non-anaemic pregnant women may receive weekly supplementation with 120 mg iron throughout pregnancy, starting as early in pregnancy as possible. (3,23) Women with anaemia should be supplemented daily with 120 mg iron until haemoglobin concentration become normal, followed by the standard antenatal dose to prevent recurrence of anaemia.

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