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Review

Burden of iron deficiency anemia in obstetrics

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Abstract

Worldwide, attention over iron deficiency anemia (IDA) in pregnancy has been recently shifted towards supplementation during pregnancy and ensuring that women, especially adolescents have adequate iron stores prior to conception. Many researchers claim that adolescent or adult women still need supplements during pregnancy in order to avoid IDA, even if iron stores are adequate. The possible relationship between IDA and increased risk of preterm delivery before the 37th week of gestation or low-birth weight infants and the impact on maternal and infant morbidity and mortality has been supported by several studies. Researchers have attempted to distinguish actual IDA from the normal influences of pregnancy, like associated hemodilution as gestation proceeds, from pathological causes, by studying pregnant women as early as possible in gestation. The following review focuses on studies, which aim to give new aspects regarding prevention of IDA and its complications before, during and after pregnancy.

Key Words: anemia; iron; dietary supplementations; pregnancy; maternal-fetal relations

Introduction

There have been many studies focusing on iron deficiency before, during and after pregnancy. Iron deficiency anemia (IDA) remains the most frequent and significant single-nutrient deficiency in both developing and developed countries. Worldwide 1.6 billion to 2 billion people are anemic. Although iron deficiency is responsible for at least half of the cases of anemia, there are also some other possible causes, like genetic, infectious, and other nutritional deficiencies. Iron is normally regulated by the control of absorption in humans. Deficiency and excess are both associated with significant morbidity and mortality. Almost half of preschool-aged children and pregnant women, and nearly one-third of non-pregnant women world wide, present anemic.

The following review focuses on studies, which aim to give new aspects regarding prevention of IDA and its complications before, during and after pregnancy.

The impact of improving iron status before delivery

When a woman is diagnosed with anemia before mid-pregnancy, it has been reported that there might be an increased risk of preterm delivery[1]. Third-trimester anemia is usually not connected with increased risk of preterm delivery[1,2,3]. But

high hemoglobin concentration, increased hematocrit and increased levels of serum ferritin late in pregnancy, have all been associated with increased preterm delivery[3].

This increased risk may be associated in part with the failure to expand maternal plasma volume adequately, thus diminishing appropriate placental perfusion[3,4,5]. Although controlled methods of iron supplementation during pregnancy have consistently demonstrated positive effects on maternal iron status at delivery, they have shown reductions in factors that are associated with anemia, for example increased risk of preterm delivery and infant low birth weight[1,3,4,6,7]. One reason for this conclusion may be the exclusion of many gravidas with iron deficiency, from these trials or data that concern gravidas such as preterm delivery from the analysis.

Recently there have been many concerns about the potential harmful effects of iron supplementation during pregnancy. On the other hand, no adverse effects of iron supplementation on pregnancy outcome have been demonstrated to date. There are still many questions about the efficacy of iron supplementation during pregnancy for reducing adverse outcomes, such as preterm delivery and side effects from iron supplementation, including the potential for oxidation of lipids and DNA, but it is certain that we need more studies and further researches to declare accurately the status in iron-deficient women[1, 3, 7, 8, 9, 10, 11].

Prevention of IDA during pregnancy

There is a continuous debate regarding prevention of IDA and the supplementations used during pregnancy. Meier P et al. in an interesting study tried to determine whether adolescent or adult women still need supplements during pregnancy to avoid IDA, and if it has a real impact to maternal and infant morbidity and mortality[12]. Thus, they studied adolescent women 18 years or less in their first pregnancy, and adult women 19 years or older, who were healthy with sufficient iron storage at their first prenatal visit. All these women were randomized to receive 60 mg/day iron supplementation or placebo[12]. When IDA was discovered at the second trimester, a therapeutic dose of 180 mg of elemental iron per day was initiated. 47% of all placebo-supplemented and 16% of all iron-supplemented patients exhibited IDA and 59% percent of adolescent placebo-supplemented and 20% of adolescent iron-supplemented patients exhibited IDA[12].

IDA is common in healthy, iron-replete adolescent pregnant women during the second trimester, and body stores of iron are reduced in both adolescent and adult pregnancies. The risk of anemia during adolescent and adult pregnancies is significantly reduced with 60 mg of elemental iron per day and IDA will affect less the pregnant women when they get the proper amount of iron daily. However, it is still not clear if maternal or neonatal health will benefit from correcting these deficits[12, 13].

IDA is found more frequently in women of low socioeconomic status, in pregnant women, and in ethnic minorities. The relationship between anemia early in pregnancy and the increased risk of preterm delivery has been demonstrated[1,12,14,15]. The adverse pregnancy outcomes due to high hemoglobin and increased iron stores have been also noticed, but the advantages and disadvantages of prophylactic iron supplementation in pregnant women, who are not iron deficient, remains a source of debate[12,13,15].

Providing iron supplements during pregnancy aims to meet the needs of both mother and fetus. Randomized clinical trials in the United States and in Nepal which involved early iron supplementation, showed some reduction in the risk of low birth weight or preterm low birth weight, but not in preterm delivery[1,3,12,14,15].

During the third trimester, maternal anemia is usually not associated with adverse pregnancy outcome. Researchers found that high levels of hemoglobin, hematocrit and ferritin are usually associated with an increased risk of fetal growth restriction, preterm delivery and preeclampsia[14, 15,16]. While iron supplementation increases maternal iron status and stores, factors that underlie adverse pregnancy outcome, are considered to result in this

association. Controversially iron supplements and increased iron stores have been connected to maternal complications like for example gestational diabetes and increased oxidative stress during pregnancy[9, 16, 17, 18, 19].

Postpartum iron supplementation in non-anaemic iron-deficient women

Krafft A, et al. investigated the effect of oral iron on postpartum red cell and iron parameters in non-anaemic women with iron deficiency. They administered oral iron sulphate 80 mg daily or placebo for 12 weeks[18]. The population studied, was fifty-two women with antenatal iron deficiency (serum ferritin <15 microg/L) and no antenatal or postnatal anaemia (haemoglobin >11 g/dL up to 48 hours before delivery, and >10 g/dL postpartum), divided into two groups comparable in antenatal iron status. The results of the study showed that haemoglobin levels and iron stores in women with term gestational iron deficiency profit from iron supplementation compared with placebo, even in an industrialized population[9, 18].

Iron deficiency and mental development

As mentioned before, there is a concern regarding possible association of IDA with poor neurocognitive development in infants and children. The adverse effects may be reversible and they are depending on the stage of development at the time of deficiency. Recent studies[6, 20, 21, 22, 23], used sensitive measurements and they have declared that the deposition of iron in the brain varies according to brain region and age.

Studies referred that anemia might weak the immune status and resistance to infections, to reduce work capacity, and it is possibly associated with repression of the child growth. Infants with anemia are presented with slower psychomotor and mental development, and many of these effects seem irreversible. Iron deficiency affects cognition and motor development in children and adolescents[7, 20, 21, 22, 23].

Iron deficiency was identified as one of the leading nutrition-related causes of impaired child developments. Correction of low iron helps the child to get better development, particularly in geographical regions in which iron deficiency is endemic[23, 24, 25]. It is estimated that the effect of iron deficiency on cognitive losses during childhood results in an estimated 2.5% loss of earnings during adulthood[23, 26, 27]. Given the high proportion of the population with iron deficiency or anemia in most developing countries, interventions to improve the iron status of young children should be given high priority.

A series of studies performed in South Africa concluded that iron-deficient mothers showed significant improvements in mental health (depression and stress), cognition, and interactions with their children after receiving iron supplementation[24, 25]. The infants of mothers with anemia had lower scores on standardized measures of development than infants of mothers who had a normal iron level. These studies suggest that the deficits in maternal mental health, cognition, and mother-child interaction associated with maternal iron deficiency may negatively affect infant development. The beneficial effects of maternal iron treatment have significant public health importance for the health and well being of mothers and their young children[23, 28].

Iron sucrose for the treatment of severe postpartum anemia

Postpartum anemia is a common major problem in obstetrics and very often blood transfusion is needed, which leads to increased risk for further complications. The aim of the study of Krafft A and Breymann C was to examine the effectiveness of recombinant human erythropoietin (rhEPO) combined with iron sucrose compared to iron sucrose alone in patients with severe postpartum anemia[29]. This study used two groups, the first group received 200 mg iron sucrose intravenously daily on days 1-4 and the second group received 200 mg iron sucrose plus 10,000E rhEPO in the same regimen. Twenty women were enrolled in each group. The follow-up period was two weeks. The baseline Hb was 7.1 g/dL and 7.5 g/dL, respectively, depending on the subgroup and it was increased close to nor-

mal values within two weeks in both groups treated with iron sucrose alone or in combination with rhEPO (10.5 g/dL, 10.7 g/dL, respectively). So, iron sucrose alone is a proper therapy agent for treating anemia. The advantage of the therapy lies in the avoidance of allogenic blood transfusions with their potential side effects. If there is severe anemia after operative delivery, additional rhEPO therapy can result in a faster Hb increase[29].

Iron dietary requirements in pregnancy and birth

As we know, the iron deficiency during pregnancy causes adverse birth outcomes, especially if it is already present during early gestation. Iron supplements are worldwide recommended during pregnancy, but until now the evidence of their benefit in relation to infant outcomes is not well established. A study that was done in the United Kingdom showed that until now iron supplements are not routinely recommended during pregnancy in this country and it gave a good opportunity to investigate the association between iron intake in pregnancy and size at birth[13, 30].

The method used a prospective cohort of 1,274 pregnant women between 18-45 years old, dietary intake was reported in a 24-h recall administered by a research midwife at 12-week gestation. Dietary supplement of iron intake was determined using dietary recall and three questionnaires in the first, second and third trimesters of pregnancy. So the results of all pregnant women who participated in the research, the 80% reported dietary iron intake, which was below the UK Reference Nutrient Intake of 14.8 mg/day. Vegetarians seemed more likely to have low dietary iron and they needed to take supplements during the first and second trimesters.

The conclusion of the study was that there was a positive association between total iron intake, both from food and supplements, in early pregnancy and the birth weight. Iron intake, both from food and supplements, was higher during the first trimester of pregnancy in vegetarians and significantly higher in women with a better socioeconomic profile[13, 30, 31, 32, 33].

Iron Deficiency Anemia and iron oral supplements in pregnancy

Iron deficiency is still the one of the most common nutritional deficiency and IDA is the most prevalent and frequent type of anemia. The prevalent groups, which are affected from iron deficiency, include women of childbearing age, pregnant women, and postpartum women who chose to lactate their children. To prognose the iron deficiency problems, different food iron fortification programs have been introduced in many countries, iron supplementation guidelines have been written worldwide, and iron therapy schemes and doses which involve both oral and intravenous administration, have been proposed (Figure 1).

But despite these efforts and the recommendations by the World Health Organization, the problem concerning iron deficiency and anemia still exists in most countries and the studies are still going on. On the other side, many industrialized countries have still the theme of iron deficiency and pregnancy unattended, and there is a lack of consensus concerning guidelines in different countries.

Up to present, the data for iron are quite significant, but they are often scarce if we look on other vitamins and micronutrients, except for folic acid. Periconceptional intake of folic acid has the potential to reduce the incidence of neural tube defects like spina bifida. There are articles concerning the treatment of IDA in and after pregnancy including papers from China, France and Denmark. The first results focus on the prevention of postpartum anemia through hemostatic sealing of the placental trauma at caesarean section, so they reduce the blood loss during operation. Some others show the relationship between periconceptional deficiency of folate and neural tube deficiencies and others address the supposed relationship between iron deficiency and postpartum depression. Together, these papers illustrate some of the many facets of the complexity of the prevention and treatment of

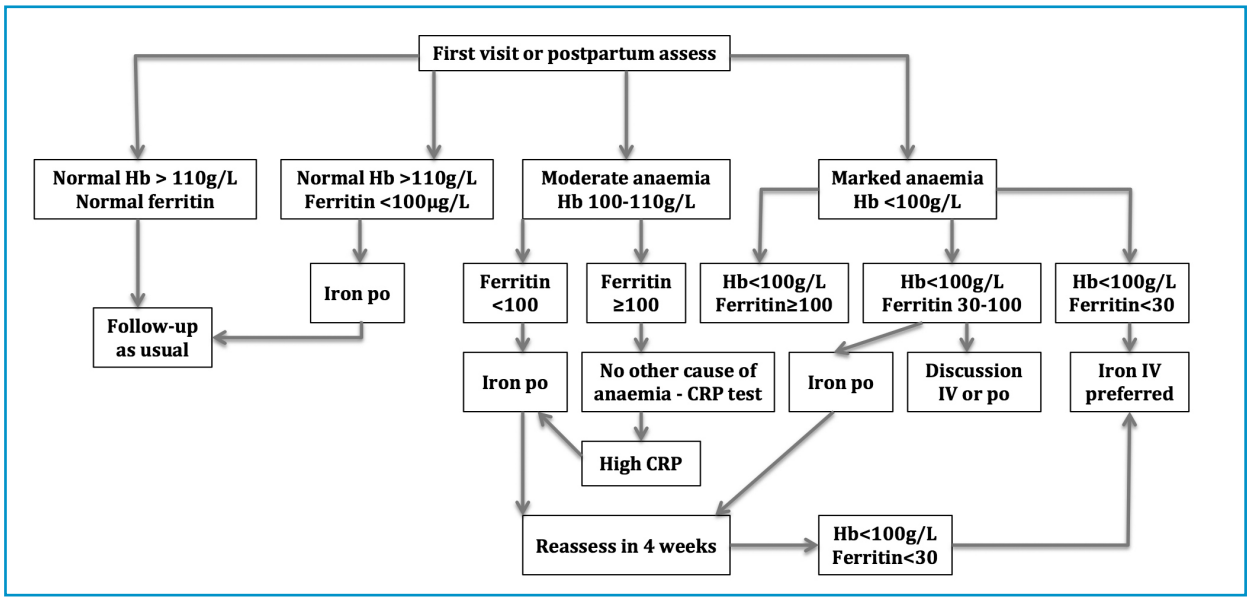

Figure 1

anemia in pregnant and post- partum women[13, 34].

As we already know, a large percentage of women of fertile age in developing countries have iron deficiency and IDA. But even in developed countries, this problem is also substantial[31]. So a low-dose oral iron supplementation is indicated in the majority of pregnant women for example 60 mg daily ferrous iron in developing and 30-40 mg per day in developed countries. Earlier recommendations introduced that the best time to start on prophylactic iron was at 20 weeks gestation. This limit was chosen according to the results of studies showing increasing iron absorption after 20 weeks gestation[35]. Considering the significance of iron for the fetal brain development, course of pregnancy and birth weight of the newborn, low-dose iron prophylaxis should probably start when pregnancy is planned or as early in pregnancy as possible. In most countries recommending iron prophylaxis, this is initiated at the first visit to the antenatal care clinic, which may vary from 10 to 20 weeks gestation according to the structure of antenatal care in various countries. The Danish National Board of Health has recently changed their recommendation for starting iron prophylaxis from 20 to 10 weeks gestation[36].

In developing countries, iron prophylaxis is most possible to reach it, while in developed countries, individual iron prophylaxis should be considered and proposed. Prophylactic programs should be structured, according to the iron status of women of fertile age in many countries where it is indicated[13, 17, 31, 37, 38].

In developed countries, even though exists substantial evidence of the positive effects of iron supplements on so-called "soft values", that is, iron status and hematological status, there is only a small effect on the "hard values", that is, maternal and fetal outcome of pregnancy and delivery[31, 33, 39].

So the beneficial effects of oral Iron supplements for pregnant women, are lower prevalence of iron deficiency and the finally improved physical and psychical well-being. In postpartum women, there is higher iron status at delivery and lower prevalence of postpartum iron deficiency, and IDA due to peripartum blood losses. In fetuses and newborns there are significant beneficial effects for the development of the brain and other organs, lower frequency of premature birth, and finally decreased prevalence of low birth weight at term and low for gestational age birth weight. The infants show larger body iron reserves at birth and lower prevalence of iron deficiency and IDA in the initial 2 years of life[17, 31, 33, 39].

The disadvantages for pregnant women are the increased oxidative stress locally in the small intestines, the increased oxidative stress in the body in general, the increase in plasma non transferrin bound iron, the gastrointestinal side effects at high iron doses, and finally the accelerated body iron overload in women with (non-diagnosed) genetic hemochromatosis[12, 31].

Conclusion

Iron deficiency is still the world's most common nutritional deficiency, and generally, IDA is the most potent form of anemia. As it has already been referred, the main population groups, which are mainly affected from iron deficiency, include women of childbearing age, pregnant women, and lactating postpartum women. Many studies tried to resolve this problem, and they propose different food iron fortification programs. Iron supplementation guidelines have been elaborated worldwide and iron therapy schemes involving both oral and intravenous administration have been introduced. But despite these efforts and the recommendations by the World Health Organization, the problem concerning iron deficiency before, during and after pregnancy is still unsolved in most parts of the world. Even in many industrialized countries, the relationship between iron and pregnancy often stays unattended and there is a lack of important guidelines in different countries. However, there is still no clear evidence whether maternal or neonatal health will crucially benefit from regardless correcting the iron deficits in pregnant or non-pregnant women, adolescent or adult ones.

Conflict of interest

The authors declare no conflicts of interest.

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