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Iron in Pregnancy – How Do We Secure an Appropriate Iron Status in the Mother and Child?

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Key Words
Anemia · Iron deficiency · Ferritin · Hemoglobin · Iron · Pregnancy · Postpartum period

Abstract
Iron deficiency and iron deficiency anemia (IDA) during pregnancy are risk factors for preterm delivery, prematurity, and small for gestational age birth weight. Iron deficiency has a negative effect on intelligence and behavioral development in the infant. It is essential to prevent iron deficiency in the fetus by preventing iron deficiency in the pregnant woman. The requirements for absorbed iron increase during pregnancy from ~1.0 mg/day in the first trimester to 7.5 mg/day in the third trimester. More than 90% of Scandinavian women of reproductive age have a dietary iron intake below the recommended 15 mg/day. Among nonpregnant women of reproductive age, ~40% have plasma ferritin ≤30 μg/l, i.e. an unfavorable iron status with respect to pregnancy. An adequate iron status during pregnancy implies body iron reserves ≥500 mg at conception, but only 15–20% of women have iron reserves of such a magnitude. Iron supplements during pregnancy reduce the prevalence of IDA. In Europe, IDA can be prevented by a general low-dose iron prophylaxis of 30–40 mg ferrous iron taken between meals from early pregnancy to delivery. In affluent societies, individual iron prophylaxis tailored by the ferritin concentration should be preferred to general prophylaxis. Suggested guidelines are: ferritin >70 μg/l, no iron supplements; ferritin 31–70 μg/l, 30–40 mg ferrous iron per day, and ferritin ≤30 μg/l, 60–80 mg ferrous iron per day. In women with ferritin <15 μg/l, i.e. depleted iron reserves and possible IDA, therapeutic doses of 100 mg ferrous iron per day should be advised.

Introduction

Iron is an essential mineral to man. It is necessary for the synthesis of hemoglobin and myoglobin as well as for the function of many vital iron-dependent enzymes. In women of reproductive age, iron deficiency even in the absence of iron deficiency anemia (IDA) reduces cognitive ability and physical performance [1, 2]. In pregnant women, an adequate iron status is important to ensure an uncomplicated pregnancy as well as the normal development of the fetus and maturity of the newborn child [3]. The aim of this paper is to describe the consequences of iron deficiency and IDA in pregnancy and to outline strategies for prevention.

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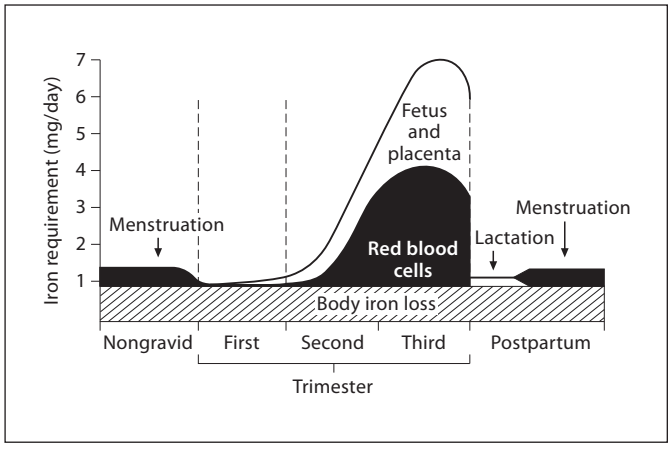

Fig. 1. Requirements for absorbed iron during pregnancy and lactation (reproduced with permission from Bothwell [7]).

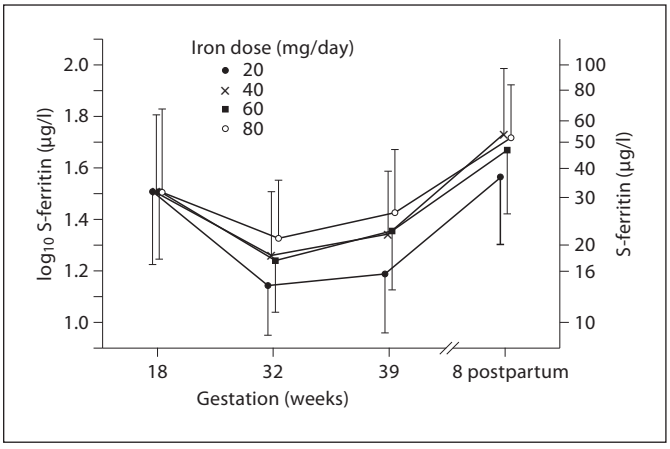

Fig. 2. Serum ferritin (geometric mean ± SD) in Danish women during pregnancy taking different doses of ferrous iron prophylaxis (reproduced with permission from Milman et al. [23]).

How Is the Iron Status of Women of Reproductive Age before Pregnancy?

In Europe, the majority of women of reproductive age have a low iron status with a median plasma ferritin of ~40 µg/l [4], corresponding to mobilizable body iron reserves of 200–300 mg. For comparison, a blood donation phlebotomy of 500 ml contains ~240 mg of iron. Approximately 45% of women have ferritin ≤30 µg/l, indicating small or absent iron reserves. Only 15–20% have ferritin >70 µg/l, i.e. iron reserves >500 mg, which nearly balances the net iron loss during pregnancy; this means that they can complete pregnancy and delivery without taking iron supplements and still avoid IDA.

In European societies, certain subgroups of women have a higher risk of iron deficiency, including multipara, multiple pregnancies, blood donors, vegetarians, women of low socioeconomic status, and immigrants from Africa and the Middle and Far East [5].

In developing countries, iron deficiency and IDA are far more prevalent than in Western societies and constitute a major health problem among women of reproductive age and pregnant women [6].

Demands for Iron Increase Markedly in Pregnancy

During pregnancy the physiologic need for iron is extraordinarily high. In women of reproductive age, the requirement for absorbed iron is on the average 0.8 mg/day. The average requirements for absorbed iron increase steadily during pregnancy from 0.8 mg/day in the early first trimester to 7.5 mg/day in the third trimester (fig. 1). The average requirement for absorbed iron in the entire gestation period is ~4.4 mg/day [7, 8].

The absorbed iron goes to: (a) expansion of the pregnant woman's red cell mass, (b) organ development and growth of the fetus, (c) the placenta and umbilical cord, and (d) compensation for blood (iron) loss at delivery [8]. The total iron content of a newborn child increases with the birth weight, being ~270 mg at a 'normal' birth weight of 3,500 g.

Estimated total requirements for absorbed iron in normal pregnancies are ~1,240 mg. After delivery, when the mother's red cell mass declines to the prepregnancy level, the hemoglobin iron is recycled to replenish body iron reserves. Therefore, the net iron requirements associated with pregnancy per se are ~630 mg [7, 8].

Dietary Iron Intake

Apparently, women do not make major changes in their dietary habits when they become pregnant [9]. Danish women have a mean dietary iron intake of 9 mg/day (90th percentile, 12 mg) indicating that ~90% have an intake below the recommended 15 mg/day [8, 10]. Women in the UK have a mean dietary iron intake of 10 mg/day [11].

The dietary iron intake in pregnant women is apparently higher than in the general population of women, probably due to selection bias. Pregnant Scandinavian

women have a mean dietary iron intake of 11 mg/day; 96% have an intake <18 mg/day [9]. Pregnant British women have a mean dietary iron intake of 11.5 mg/day; 80% have an intake below the UK Reference Nutrient Intake of 14.8 mg/day [11]. Pregnant Bavarian women have a mean dietary iron intake of 13.3 mg/day, which is far below the recommended intake [12].

Dietary iron consists of heme iron and nonheme iron; heme iron has the highest bioavailability. The major fraction of dietary iron, ~90%, is nonheme iron, which in the average European diet has a bioavailability of 10–15% depending on the amount of meat, fish, and poultry in the diet. This means that the dietary iron absorption in pregnant women is approximately 1.0–1.4 mg/day, which is far below the requirements during pregnancy (see above). In the USA and Germany a dietary iron intake of 27–30 mg/day during pregnancy is recommended. Such an intake would imply drastic and unrealistic dietary changes. Therefore, the Nordic Nutrition Recommendations have refrained from giving figures for the recommended dietary iron intake in pregnant women.

Monitoring Iron Status in Pregnant Women

The hemoglobin concentration is often used as a pseudomarker for iron deficiency. However, hemoglobin is not suitable to assess iron status – especially not in pregnancy due to hypervolemia and hemodilution. Hemoglobin yields information about the presence of anemia in general and IDA in particular when body iron reserves are depleted [3, 8].

Iron status can be assessed by biomarkers, including plasma ferritin, plasma transferrin saturation, and serum soluble transferrin receptor (sTfR). In nonpregnant women, a ferritin concentration of 1 μg/l corresponds to 7–8 mg of mobilizable iron [3]. Ferritin levels ≤30 μg/l indicate a low iron status, verified by the absence of bone marrow hemosiderin [13]. Ferritin levels <15 μg/l are consistent with depleted iron reserves and levels <12 μg/l are associated with IDA. A plasma transferrin saturation <15% and a serum sTfR >8.3 mg/l both indicate an inadequate supply of iron to the red cell precursors and other tissues.

Plasma ferritin provides information about the capacity of body iron reserves, and serum sTfR and plasma transferrin saturation yield information about iron deficiency on the cellular level, while hemoglobin gives information about iron deficiency on the functional level. For practical purposes, hemoglobin, i.e. a full blood count, and plasma ferritin are adequate to assess the iron status and diagnose IDA.

Iron Deficiency and IDA

Consequences for the Pregnant Woman

Iron deficiency even without IDA reduces cognitive abilities, physical performance, and working capacity [1, 2]. In pregnant women, IDA produces the same symptoms and has the same negative consequences on the quality of life as in nonpregnant women. The following factors contribute to the spectrum of IDA: general weakness; fatigue; dizziness; impaired thermogenesis; gastrointestinal symptoms; structural changes in hair, nails, and skin; restless legs, and impaired immune response predisposing to infections. Furthermore, IDA is associated with an adverse outcome of pregnancy and complications at delivery, including premature birth [14] and increased perinatal maternal mortality [6].

Consequences for the Fetus and Newborn Child

Iron is mandatory for the normal development of the fetus and is especially important for the development of the brain [15]. Iron deficiency in fetal life and infancy may have a negative effect on intelligence as well as on cognitive and behavioral development [16, 17]. It is therefore essential to prevent iron deficiency in the fetus/newborn child by preventing iron deficiency in the pregnant woman. Furthermore, IDA during pregnancy is a risk factor for preterm delivery, prematurity, and small for gestational age birth weight [11, 18] as well as for increased perinatal mortality of the newborn [14].

Consequences for the Postpartum Lactation Period

The development of postpartum IDA relies on two factors: (a) the presence of prepartum iron deficiency/anemia and (b) the magnitude of blood loss at delivery. This indicates that the prevention of postpartum anemia should start already during pregnancy. The prevalence of postpartum anemia in Europe varies from 25 to 50% in mothers who do not take iron supplements during pregnancy and is lower, i.e. ~14%, in iron-supplemented mothers [19].

Iron deficiency and IDA during the lactation period are associated with an impaired quality of life from both a physical and a mental point of view and is a significant health issue in both developing and developed countries [19]. It is associated with reduced physical performance,

increased frequency of infections [20], impaired cognitive performance, emotional instability, increased risk of postpartum depression, and impaired mother-child interaction, compromising the emotional bonds between the mother and baby [21].

Strategies to Ensure an Adequate Iron Supply for Pregnant Women

In pregnant European women not taking iron supplements, the prevalence of prepartum IDA is approximately 25% compared to 0–3% in women taking iron supplements [3]. According to the World Health Organization, the estimated number of women with prepartum anemia in Europe is ~2.5 million.

Dietary measures by themselves are ineffective in obtaining a good iron status in the majority of pregnant women (see above). A safe way to secure an adequate iron status in the mother and child is to give iron supplementation during pregnancy. It is highly evidence based that oral iron supplements in appropriate doses are very effective in the prevention of iron deficiency and IDA [3, 22, 23].

Guidelines for the Prevention of Prepartum Iron Deficiency

Many countries do not have guidelines on iron prophylaxis in pregnancy and guidelines vary considerably among European countries. There is a strong need for consensus on this important issue.

In the USA, women are recommended to take 30 mg ferrous iron supplements daily from early pregnancy and in Denmark the recommendation is 40 mg/day [23]. In the UK, iron supplements are not recommended and in Germany there are no common nationwide guidelines.

Which Dose of Iron Supplements Is Appropriate?

Due to the potential side effects of oral iron, we should aim at giving the smallest dose of iron, which is effective in the prevention of iron deficiency and IDA in more than 95% of pregnant women. A dose response study [23] has demonstrated that 40 mg ferrous iron per day taken at bedtime or between meals is effective in preventing IDA, while a dose of 20 mg iron per day appeared to be insufficient (fig. 2). Apparently, there was no benefit of giving higher doses of 60 or 80 mg of iron.

When Should Iron Supplements Start?

Ferrokinetic studies in pregnant women have shown that the red cell mass starts to increase already around 12 weeks of gestation [24]. In order to obtain the maximum effect of iron on the growing fetus and on the birth weight, low-dose iron supplements should be started as early in pregnancy as possible, e.g. when pregnancy is verified or at the first antenatal care visit, and should continue until delivery. Whether supplements should be continued during the lactation period is as yet unclear, but it should at least be recommended for women with significant blood loss at delivery.

Iron Prophylaxis – General or Individual?

There are two options in oral iron prophylaxis: a simple general prophylaxis where iron is recommended to all pregnant women and a more complex individual prophylaxis where iron supplements are adjusted to the woman's iron status [24, 25].

General Iron Prophylaxis

Existing evidence indicates that in European women a general iron prophylaxis should consist of 30–40 mg ferrous iron per day taken between meals starting as soon as pregnancy has been confirmed. In developing countries with a greater prevalence of IDA, the iron dose should be higher, i.e. in the range of 60–100 mg ferrous iron per day. In order to minimize gastrointestinal side effects and oxidative stress, iron should preferably be given in slow-release formulas.

Individual Iron Prophylaxis

In affluent European countries, individual iron prophylaxis should be preferred. Approximately 15–20% of women of reproductive age have adequate body iron reserves $\geq$500 mg, i.e., they can complete pregnancy without iron supplements. Furthermore, iron overload disorders, i.e. HFE-related hemochromatosis, are the most frequent inherited disorders in subjects of northern European descent [26], and non-HFE-related hemochromatosis [27] is frequent in the Mediterranean.

Plasma ferritin measured either when pregnancy is being planned or early in first trimester is a reliable biomarker of body iron reserves and can be used to tailor an individual iron prophylaxis regimen. Women with ferritin levels >70 μg/l have adequate iron reserves and do not need iron supplements. Women with ferritin levels of 31–70 μg/l should be recommended to take 30–40 mg ferrous iron per day at bedtime or between meals. Women with ferritin levels $\leq$30 μg/l have a poor iron status and should be recommended to take 60–80 mg ferrous iron per day. The fraction of women who have ferritin levels <15 μg/l, i.e. iron depletion and possibly IDA, should

have iron in therapeutic doses of 100 mg ferrous iron per day and should have a follow-up of the therapeutic response.

Multivitamin-Multimineral Tablets

Vitamin-mineral supplements have become quite popular and specific tablets are designed for pregnant women. They contain several essential divalent minerals among which iron constitutes the dominant part. These minerals compete with each other in the gastrointestinal absorption process and there is probably a low absorption of iron for these composite tablets [3]. In order to optimize iron absorption, iron should be withdrawn from multivitamin-mineral supplements designed for pregnant women and should be administered in separate slow-release formulas taken at bedtime or between meals.

Conclusion

During pregnancy, iron status can be monitored by plasma ferritin and a full blood count. The iron requirements during pregnancy are extraordinarily high and cannot be fulfilled by dietary interventions alone. Oral iron supplements are necessary in more than 80% of pregnant women in order to prevent iron deficiency and IDA. As a general iron prophylaxis, low-dose ferrous iron formulas of 30–40 mg/day from early pregnancy to delivery are effective. Ideally, individual iron prophylaxis tailored according to iron status should be preferred in countries with the available antenatal health care resources.

Disclosure Statement

The author declares that there are no conflicts of interest.

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