EXPERT REVIEWS

Iron deficiency anemia in pregnancy

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Anemia is a common problem in obstetrics and perinatal care. Any hemoglobin (Hb) below 10.5 g/dl can be regarded as true anemia regardless of gestational age. Main cause of anemia in obstetrics is iron deficiency, which has a worldwide prevalence between estimated 20 and 80% of especially female population. Stages of iron deficiency are depletion of iron stores, iron-deficient erythropoiesis without anemia and iron-deficiency anemia, the most pronounced form of iron deficiency. Pregnancy anemia can be aggravated by various conditions such as uterine or placental bleedings, gastrointestinal bleedings and peripartum blood loss. Beside the general consequences of anemia, there are specific risks during pregnancy for the mother and the fetus such as intrauterine growth retardation, prematurity, feto-placental miss-ratio and higher risk for peripartum blood transfusion. Beside the importance of prophylaxis of iron deficiency, main therapy options for the treatment of pregnancy anemia are oral iron and intravenous iron preparations.

Keywords: anemia • intravenous iron • iron deficiency • iron therapy • pregnancy

The review focuses on the clinical, diagnostic and therapeutic aspects of gestational disorder in mothers, with its far-reaching consequences for the intrauterine development of the fetus and neonate. Because of its high prevalence, maternal iron-deficiency anemia will be at the center of the discussion.

Definition of anemia

The WHO (WHO 1972) defines anemia – regardless of its cause – as the presence of a Hb level of less than 11.0 g/dl during pregnancy and less than 10.0 g/dl during the postpartum period. The US Centers of Disease Control recommendations (CDC 1989) take into account the observation that there is a trough in the physiological course of Hb during pregnancy [1]. According to this definition, anemia is present if the Hb level is less than 11 g/dl during weeks 1–12 (first trimester) and 29–40 (third trimester) of gestation, and less than 10.5 g/dl during weeks 13–28 (second trimester). These Hb levels correspond to hematocrit values of 33.0, 32.0 and 33.0%, respectively [1,2].

Iron deficiency

Iron deficiency is the most common deficiency in women of childbearing age throughout the world, and is even more common in pregnancy, as might be expected from the increasing iron requirement during that period [3,4]. If we extrapolate from the high prevalence rates of anemia of pregnancy in developing countries and from the observed relationship between iron deficiency alone and iron-deficiency anemia in the developed world, we can assume that the percentage of cases of iron deficiency *per se* (i.e., before erythropoiesis is affected) is also higher in developing countries than actual anemia [5]. As expected, there are few studies in developing countries that have been able to document iron deficiency without anemia. It should be noted that there are several different stages of iron deficiency, which occur in the following sequence:

a. Depletion of the iron stores

b. Iron-deficiency erythropoiesis in which the indices have not fallen below the defined limit values for anemia

c. Iron-deficiency anemia, the most pronounced form of iron deficiency

Figures for the prevalence of iron deficiency alone, as a precursor of anemia, are available for Europe [4,6]. According to a recent CHERG iron report, the range of prevalence of anemia due to iron deficiency was 20–78% with a global average of 42.8%. In the authors' hospital, 50% of pregnant women showed a serum ferritin <15 µg/l at term, that is, they have depleted iron stores [7]. Risk factors to develop iron deficiency and anemia are listed in Table 1.

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Table 1. Risk factors to develop ID/ IDA in adults.

High menstrual blood loss
Vegetarians or adults with special diets
Athletes
Chronic blood loss, e.g., intestinal disease
Acute blood loss, e.g., surgery
Chronic diseases
Parasitic diseases

ID: Iron deficiency; IDA: Iron-deficiency anemia.

Anemia in general & iron-deficiency anemia in particular

Published rates of the prevalence of anemia during pregnancy in developing countries range from 53 to 61% for Africa, from 44 to 53% for South-East Asia and from 17 to 31% for Europe and North America [8]. It is *assumed* that iron and folate deficiency are the most common etiological factors responsible for this situation [5,9]. Anemia of pregnancy is not merely common in these countries, it is also frequently severe. It is estimated that 20% of pregnant women have Hb of less than 8 g/dl, and that between 2 and 7% have a value of less than 7 g/dl. The situation is aggravated during the postpartum period because of blood loss during labor and in the puerperium. Even in modern obstetrics, peripartum blood losses of more than 500 ml are not uncommon. A variety of the interventions used in obstetrics today, the technique by which labor is induced, the use of regional analgesia and factors such as assuming an upright position while giving birth, can all lead to heavier bleeding during labor and delivery.

The American College of Obstetricians and Gynecologists has estimated that 5% of women who give birth lose 1000 ml of blood or more during delivery. Bearing in mind that the limit value defining puerperal anemia is 1 g/dl lower, the prevalence of anemia during this period remains comparable with that observed during pregnancy.

Table 2. Risk groups to develop ID and IDA in pregnancy.

Pregnant women	Postpartum
After first trimester	ID and IDA during pregnancy
ID prior pregnancy	
Multiple pregnancies	Poor socio-economic status
Short recovery between pregnancies	Poor nutritional status
Multipara	
Poor socio-economic status	

ID: Iron deficiency; IDA: Iron-deficiency anemia.

Iron needs in pregnancy

During pregnancy, the average total iron requirement has been estimated to be approximately 1200 mg for an average weight of 55 kg in a pregnant woman. The iron is used mainly for the increase in maternal erythrocyte mass (450 mg), placenta (90–100 mg), fetus (250–300 mg) general losses (200–250 mg) and a blood loss at delivery corresponding to 150 mg iron (300–500 ml blood loss). Around 40% of women begin their pregnancy with low or absent iron stores (serum ferritin <30 μg/l) and up to 90% have iron stores of <500 mg (serum ferritin <70 μg/l), which is insufficient to meet the increased iron needs during pregnancy and postpartum. Iron absorption requirements in the first trimester are around 0.8 mg/day, rising to 7.5 mg/day at third trimester. Risk groups associated with iron deficiency and iron-deficiency anemia in pregnancy and postpartum are listed in Table 2.

General consequences of anemia

Any disorder that leads to anemia represents an increased risk of an abnormal course of pregnancy and greater maternal and infant morbidity and mortality. According to WHO data, anemia is associated with 40% of maternal deaths worldwide [2].

The clinical consequences of anemia of pregnancy are closely associated with the cause of the anemia. In this respect, it is difficult to determine whether the maternal and infant risks result from the anemia alone, or whether they are attributable to the cause of the anemia. Thus, the complications that occur in association with anemia secondary to iron deficiency differ from those associated with anemia secondary to hemoglobinopathy in the mother.

The following maternal consequences of anemia in pregnancy are observed regardless of the cause of the anemia.

- Fatigue, exhaustion, weakness, 'less energy'
- Cardiovascular symptoms (e.g., palpitations)
- Pallor, pale mucous membranes and conjunctivae
- Tachycardia, hypotension
- Cardiac hypertrophy in chronic cases

Iron-deficiency anemia

Maternal risks

It is known that iron deficiency influences a whole series of body functions, such as physical and mental performance, enzymatic functions (e.g., those of the respiratory chain), thermoregulation, muscular functions, the immune response and neurological functions (Table 3) [10,11]. Only a few of these potential effects have been specifically investigated in iron-deficiency anemia. In general, iron-deficiency anemia leads to numerous symptoms such as fatigue, a reduction in physical performance and fitness for work, increased cardiovascular stress (tachycardia, fall in blood pressure), reduced thermoregulation and an increased predisposition to infections [11]. Maternal thyroid function and synthesis of thyroxin is closely linked to maternal iron status [12].

In the gravida, the tolerance for peripartum blood loss is greatly reduced. Maternal mortality increases depending on the

severity of the iron-deficiency anemia. Causes include an increased rate of cardiovascular failure, a high risk of hemorrhagic shock and higher rates of infection during the puerperium and impaired wound healing [2]. Maternal morbidity may also be associated with additional factors such as socioeconomic status, the level of medical care, nutritional status, etc. A general problem in interpreting the available studies is that maternal and fetal outcome have been investigated in relation to the severity of the anemia, but not in relation to the duration or initial onset of the anemia, or indeed the severity, duration or onset of the iron deficiency.

Taking these limitations into account, several authors have postulated an association between maternal mortality and the degree of anemia; however, there are no prospective studies investigating this and it is not clear what level of Hb is critical with respect to maternal mortality. According to the CHERG report on iron deficiency, anemia is linked to maternal mortality, that is, the risk of maternal mortality decreases significantly for every Hb increase of 1 g/dl [13]. It appears at levels of less than 8–9 g/dl, but the association between moderate anemia and maternal morbidity is not clear. To date, there have been no studies investigating the association between iron-deficiency anemia before pregnancy and the course of pregnancy, and there are also no prospective studies on large populations demonstrating the effect of early intervention and treatment of anemia on maternal, fetal and neonatal outcome.

Fetal risks

Maternal Hb levels below 9.0 g/dl increase the risk of premature births (PMB), intrauterine growth retardation (IUGR) and intrauterine fetal death (IUFD) (Table 4) [3,13–19].

The association between maternal Hb and birth weight follows a U-shaped curve. Hb levels of more than 11.0 g/dl and less than 9.0 g/dl are associated with a two- to three-times greater risk of a light-for-dates neonate. Hb levels of more than 12.0 g/dl at the end of the second trimester are associated with an increased risk of preeclampsia and IUGR, probably due to a lack of plasma volume expansion.

The 'ideal' Hb range with respect to the prevention of prematurity and IUGR babies appears to lie between 9.5 and 11.5 g/dl.

There is increasing evidence of an association between the timing and duration of iron deficiency and anemia, and of pathological feto-placental changes. The risk of a premature birth is increased if there is iron deficiency during early pregnancy. However, it is not clear whether this is primarily the result of a lack of oxygen supply, or more the consequence of iron not being released or utilized. Various studies have investigated the effect of the iron stores themselves on infant outcome.

It was shown that serum ferritin levels correlate more closely with IUGR than do Hb levels, and that even high serum ferritin levels, possibly as a result of infections, correlate with a high rate of IUGR [20]. In other terms, high ferritin levels might reflect an inflammatory state in the pregnant woman which goes in parallel with elevated C-reactive protein (CRP) levels which finally result in iron restricted erythropoiesis and decreased erythropoietin levels. It is not known, if these changes might be then responsible for growth retardation in the fetus.

Table 3. Maternal consequences of anemia.

Maternal mortality with high blood loss
Maternal cardiovascular strain
Reduced physical and mental performance
Reduced peripartal blood reserves
Increased risk for peripartal blood transfusion

Serum ferritin levels that are too low, indicating depleted iron stores, appear to have a close association with growth retardation, while the correlation with high serum ferritin levels is less evident. Even with adequate or balanced diet, iron supplementation, especially during the third trimester reduces the risk for a small for gestational age (SGA) baby [20]. Recently, unknown effects of iron deficiency on the fetus and neonate have been described such as an impact on the rate of cleft palate frequency in the off spring and the pathogenesis of psychiatric disorders such as schizophrenia [21].

Newborn & breast milk iron

Little is known about iron entry into breast milk but it is probably enabled by the transferrin receptors on mammary plasma membrane. Other iron transporters that might be involved are divalent metal transporter 1 and ferroportin 1. There is no evidence that iron is stored in the mammary gland during lactation. Breast milk iron concentrations show individual and diurnal variation and, in some studies, a decline during the course of lactation, while other studies report them as stable. Iron absorption from breast milk and bioavailability are high in neonates and infants, due in part to enhanced expression of iron absorption proteins and transporters, as in adults, but the precise mechanism remains unclear. Although diet and nutritional status influence the nutrient composition of breast milk in general, they do not significantly affect total energy or energy nutrient ratios. However, poor nutritional status in terms of iron intake impacts breast milk iron content. Iron status in the neonate and infant depends mainly on prenatal iron availability, that is, on the ability of the fetus to accumulate iron during pregnancy.

Table 4. Fetal risks linked with maternal anemia.

Intra uterine growth retardation
Prematurity
Death *in utero*
Infection
Fetal programing (feto-placental miss-ratio)

If fetal stores are adequate, breast milk normally supplies enough iron for infants up to 6 months, after which supplementation is recommended in exclusively breast-fed infants. In neonates born to iron-deficient mothers, on the other hand, postnatal iron stores are probably insufficient to meet iron needs and will usually fail to normalize on breast milk alone [22].

Overall, the fetus' and newborn infant's iron status depend on the iron status of the pregnant woman and therefore, iron deficiency in the mother-to-be means that the growing fetus probably will be iron-deficient as well. Due to their high growth rate, newborns, infants and children have a high iron demand relative to caloric intake, and they therefore constitute a risk group for iron deficiency and iron-deficiency anemia. In fetuses and neonates, iron is prioritized to erythrocytes. If the iron supply does not meet the demand this can lead to iron deficiency in tissues including skeletal muscle, heart and brain [16]. Studies have shown that infants and children born to iron-deficient mothers have a poorer cognitive development of the brain functions and a lower intelligence quotient than infants and children born to iron-replete mothers [23,24]. Since iron deficiency is considered the world's most common single-nutrient disorder, infants and preschool-aged children are particularly vulnerable. The prevalence of iron deficiency in infants in developed countries is estimated to be between 4 and 45%.

Diagnosis

The pathogenesis of anemia is highly variable, as discussed earlier. As a result, a diagnosis based on Hb levels alone is generally insufficient. In all cases, therefore, it is necessary to determine the underlying reason for the reduced Hb production, whether by taking a targeted medical history, carrying out a clinical assessment or by means of further investigations done in addition to the basic diagnostic tests.

Basic diagnostic tests

Hemoglobin & erythrocyte indices

The first test for the investigation of anemia generally comprises the hematological profile with the following 'classic' parameters:

- Hb concentration
- Hematocrit (not needed if Hb levels are properly tested)
- MCV (if below 70 fl and ferritin is normal, indicator for thalassemia)
- MCH (no additional information, if MCV is tested)
- Erythrocyte count
- Occasionally, reticulocyte count

Although the Hb concentration is generally the first indicator of iron deficiency in everyday clinical practice, it should be noted that both the Hb level and erythrocyte indices such as MCV and MCH show very low sensitivity and specificity for the stratification of severity of iron-deficiency states; in most cases, these parameters show significant changes only in persistent, manifest iron deficiency. Many women may still show normal Hb values despite early or progressing iron deficiency. More specific and more sensitive tests should be used when assessing suspected cases, particularly when the aim is early detection of iron-deficiency states, and thus the prevention of iron-deficiency anemia [25–27].

Differential diagnosis & further investigations

Iron-deficiency anemia & specific parameters of iron metabolism

If the Hb level has fallen below the physiological limit value for pregnancy, the initial step is to investigate the patient for iron-deficiency anemia.

Serum ferritin

In the otherwise well patient, the determination of serum ferritin levels, which correlate well with iron stores, is the current 'gold standard' for the detection of iron-deficiency anemia by means of laboratory investigation [25–27]. Serum ferritin levels of less than 15 μg/l confirm the presence of iron deficiency, regardless of the Hb level. If an infection is also suspected, iron deficiency may be present even though the serum ferritin levels are normal [5]. During an infection, serum ferritin levels can show false normal values or be elevated, since apoferritin is an acute phase protein like CRP, and increases both during infections and inflammatory reactions (e.g., postoperatively). If this is the case, the presence of infection or inflammation should be ruled out. Serum ferritin can only provide a clear indication of the iron status once this has been done. We investigated the influence of delivery and the concomitant inflammatory reaction on iron status and the markers of the cellular immune response. These investigations showed that serum ferritin levels in particular are influenced by delivery, that is, serum ferritin, in its role as an acute phase protein, exhibits a postpartum rise similar to that of CRP or IL-6, and thus no longer reflects the iron stores [28].

Serum iron, transferrin, transferrin saturation

In general, whether during pregnancy or at any other time, assay of the serum iron and transferrin levels confers no additional benefits in determining whether there is iron deficiency. This is because serum iron levels, in particular, are subject to a variety of influencing factors, such as diurnal, intra-individual and inter-individual fluctuations. Firm conclusions regarding pre-latent iron-deficiency states can be made only in conjunction with transferrin values, that is, by determining transferrin saturation.

Serum ferritin levels within the normal range but transferrin saturation of less than 15% is a sign of latent iron deficiency, since more iron is now being released from the circulating transferrin in order to maintain erythropoiesis [27].

However, it should be noted that fluctuations in iron levels also affect the calculation of the transferrin saturation, and can thus lead to false interpretations.

Transferrin receptors

Various studies have shown that serum transferrin receptors increase in iron-deficiency states or under conditions of increased cellular iron requirements, and thus provide a

sensitive and specific indication of changes in iron kinetics. Transferrin receptors are probably not influenced by infections, effectively complementing serum ferritin level assays. The first studies during pregnancy have already been carried out. Low soluble transferrin receptor (sTfR) levels in early pregnancy appear to be associated with inhibited erythropoiesis during the first trimester. The rise in sTfR as pregnancy progresses is attributable first to increasing stimulation of erythropoiesis, and second to an increasing iron requirement due to iron-dependent cell proliferation. It is not known whether inhibition of erythropoiesis in early pregnancy has a negative influence on the detection of concomitant iron deficiency through sTfR determination. There is nothing to indicate that the sTfR concentration is influenced by inflammatory reactions. This parameter would thus also be suitable for the investigation of unclear conditions (normal serum ferritin with elevated CRP) during pregnancy and in the early puerperal phase. In our own studies, we were able to show that, in contrast to serum ferritin levels, postpartum sTfR levels are not influenced by the inflammatory reaction at the time of delivery [14,29,30]. Overview about main diagnostic tests is shown in Table 5.

Table 5. Laboratory parameters in iron deficiency and anemia.

	Hb	MCV	S-Ferritin	TSAT	sTfR
ID	N	N	↓	N	N
IDA	↓	N-↓	↓	↓	↑
ACD	↓	N-↓	N-↑	N-↓	N-↑

↓: Low.
↑: High.
IACD: Anemia of chronic disease or inflammatory states; ID: Iron deficiency; IDA: Iron deficiency anemia. N: Normal.

Prevention of iron deficiency

Most guidelines recommend an increase in iron consumption by about 15 mg/day (to about 30 mg/day), an amount readily met by most prenatal vitamin formulations. This is adequate supplementation for non-anemic and non-iron-deficient women. In a 2012 systematic review, daily iron supplementation reduced the risk of maternal anemia at term by 70% and iron deficiency at term by 57%. According to WHO guidelines, daily oral iron and folic acid supplementation is recommended as part of the antenatal care to reduce the risk of low birth weight, maternal anemia and iron deficiency [31]. Intermittent iron supplementation (one- to three-times per week) appears to be as effective as daily supplementation for preventing anemia at term and is better tolerated.

Women with iron-deficiency anemia (first or third trimester Hb <11 g/dl or second trimester Hb $\leq$10.4 g/dl and low serum ferritin) should receive an additional iron supplement of 30–120 mg/day until the anemia is corrected.

Treatment of iron-deficiency anemia in pregnancy

For most clinicians it seems clear that iron-deficiency states and anemia should be treated. Even in milder forms of anemia, it is often impossible to predict the course of the condition, or whether the situation is likely to worsen, and maternal and fetal risks increase as anemia becomes more severe. However, it should be pointed out that according to the recent Cochrane Collaboration Review by Reveiz *et al.*, due to poor study data, there is no clear evidence that iron deficiency anemia should be treated during pregnancy. This summary is in contrast to the CHERG report that shows a decline in maternal, neonatal and fetal mortality with an increase in maternal Hb [13,32].

Factors to be taken into account when deciding on the treatment approach to use include the time remaining until delivery, the severity of the anemia, additional risks (e.g., premature labor), maternal comorbidity and the patient's own wishes (e.g., refusal to receive donor blood to treat severe anemia). Thus, for example, a Jehovah's Witness with severe anemia 2 weeks before term needs more urgent treatment than a woman with moderate anemia and no additional risk factors during the second trimester. However in both cases, the treatment will be the same and best avoiding blood transfusion. At present, the main treatment options for anemia include oral iron, parenteral iron, the stimulation of hemopoiesis with growth factors (e.g., recombinant human erythropoietin [rhEPO]) and the administration of heterologous blood [33–38]. The review will focus on iron therapy only.

Oral iron

Oral iron is the gold standard for the treatment of mild to moderate iron-deficiency anemia. It is not clear whether weekly or intermittent administration of oral iron is equivalent to, or even better than, daily oral administration of iron. Studies investigating this question are currently underway. The ideal dosage for intermittent or weekly administration is also unclear. The absorption rate is inversely proportional to the administered dose. Doses of 100–200 mg iron per day are a compromise between the optimum Hb increase and the tolerability of the iron.

Dose-limiting gastrointestinal side effects such as constipation, heartburn and nausea, occurring in up to 50% of patients, are a significant disadvantage of oral iron preparations [39]. If these adverse effects occur, the dose must either be reduced or a different product tried [6,25,40,41,101].

Even then, lack of compliance is a common problem. It has been shown that only 36% of pregnant women regularly took oral iron, even if they had been specifically informed about the problems of iron deficiency. Studies from countries such as Tanzania and Indonesia also show a compliance rate of only 36–42%. This may be one reason for the disappointing results of WHO studies aimed at reducing the prevalence of iron-deficiency anemia with oral iron. Other possible reasons for the failure of oral iron therapy are as follows (see also Table 6):

- Gastrointestinal diseases (Crohn's disease, ulcerative colitis)
- The presence of an infection which suppresses erythropoiesis
- Malabsorption of iron (e.g., celiac disease)

Table 6. Conditions with low or limited response to oral iron preparations.

Non-compliance
Severe side effects (e.g., gastrointestinal)
Limited absorption (e.g., in inflammatory bowel disease)
Postoperative phase (first days to weeks)
Abnormal hepcidin regulation
Limited time
Chronic inflammatory stages (e.g., rheumathoid arthritis)
Use of red cell stimulating hormones (e.g., rhEPO, NESP)
Pre-existing moderate to severe iron deficiency anemia
Iron preparation with low pharmacological properties

NESP: Novel erythropoiesis-stimulating protein; rhEPO: Recombinant human erythropoietin.

- Additional complicating disorders (kidney failure)
- Additional hemorrhage (e.g., gastrointestinal, of parasitic origin)
- Drugs that inhibit erythropoiesis (e.g., cytotoxic agents, immunosuppressants)
- Incorrect diagnosis of iron deficiency

Oral iron preparations

Iron (II) salts

Iron (II) salts are the most frequently used oral iron preparations for the treatment of anemia. They are administered either in tablet form or as solutions. The most commonly used iron (II) compound is iron (II) sulfate; others include iron (II) fumarates, succinates and gluconates. They are comparable with regard to pharmacodynamics and pharmacokinetics, and also with regard to side-effect rate. Iron (III) compounds in the form of salts have very low bioavailability and are therefore not indicated for oral administration. The reason for this is that they form insoluble and virtually non-absorbable iron (III) hydroxide complexes in the acid environment of the intestine [42].

Iron (III) polymaltose complex

The iron (III) polymaltose complex dextriferron (Maltofer®, Ferrum Hausmann®) is one of the few available oral iron (III) compounds and belongs to the class of so-called slow-release iron preparations. Polymaltose acts like a casing around the trivalent iron, ensuring slower release of the iron from the complex [42]. The advantages of this iron preparation are, first, its favorable side-effect profile compared with iron (II) salts as a result of the slow release, and, second, that it can be taken with meals. Various authors have postulated that iron polymaltose complexes have lower toxicity compared with iron sulfate salts, due to reduced formation of oxygen radicals and thus decreased plasma lipid peroxidation. In studies carried out to date, their bioavailability is comparable with that of iron (II) sulfates and fumarates [43].

Parenteral iron preparations

Parenteral iron is the most important alternative to oral iron preparations.

The indications for the parenteral administration of iron include [6,34,40,42,44–46]:

- Insufficient or no response to oral iron
- Severe anemia
- Insufficient absorption of oral iron due to intestinal disease
- The need for rapid efficacy
- Intolerance of oral iron
- Poor compliance
- Combination with rhEPO (for the prevention of functional iron deficiency)

The parenteral administration of iron bypasses the natural mechanism of intestinal iron uptake and the associated protein binding. This allows free, non-protein-bound iron to circulate. Free iron is toxic, as it favors the formation of hydroxide radicals and oxygen radicals which, in turn, lead to cell and tissue damage as a result of peroxidation.

Therefore, parenteral iron should only be administered if the patient's iron status is known, to prevent potential iron overload. In principle, we can distinguish between three groups of preparations.

They differ with regard to pharmacokinetics, complex stability, molecular mass, toxicity and side effects [42,47,48].

Use of parenteral iron preparations in pregnancy

Table 7 summarizes the parenteral iron preparations which were used in pregnancy up to date according to Medline search on intravenous (i.v.) iron preparations in pregnancy.

All studies that compared parenteral iron with oral iron for the treatment of pregnancy anemia showed, independently from the preparation, a favorable outcome in the i.v. iron groups concerning mainly Hb and serum ferritin levels after treatment. The studies describing the use of *iron sucrose, iron carboxymaltose and iron polymaltose* did not report about major adverse events of anaphylactic reactions in pregnant mothers.

However, it must be pointed out that the numbers of treated patients were low in all studies [14,33,40,43–46,49–53].

Interestingly, one study showed a positive impact of i.v. *iron polymaltose* in pregnancy on quality of life parameters also in the postpartum period and an ongoing positive effect on maternal iron stores [54].

It must be pointed out that the newer LMWD preparations have a considerably improved safety profile compared with the HMWD complexes. According to the literature, a small number of pregnant patients with total dose infusions were reported recently. Here, 4/43 women showed adverse events, from these three-fourth were treated with anti-allergic therapy (methylprednisolone) [55]. *LMWD preparations* can also be infused as total dose infusions up to 1000 mg in a time period over 1 h. Another study from 2008 reports about 100 pregnant anemic women who were treated with total dose infusions of LMWD over 6 h. Here, minor side effects were seen in 4% of patients [56].

Table 7. Parenteral iron preparations used in pregnancy.

Substance	Iron carboxymaltose	Iron sucrose	Iron sorbitol	Iron gluconate (sodium feric gluconate)	Iron dextran (HMW)	Iron dextran (LMW)	Iron polymaltose (iron dextrin)
Trade name	*Ferinject®(EU)/Injectafer®(US)*	*Venofer®*	*Jectofer®*	*Ferrlicit®*	*Dexferrum®*	*INFeD®*	*Ferrosig®, Ferrum Hausmann®*
Pregnancy data (Ref.)	[58]	[33,37, 38, 45, 46, 47,48,50,51,52,53]	[53]	[55]	Historical data	[56,57]	[38]
					Off market in Europe		
Dosage/time	1000 mg/15 min i.v.	200 mg (5–15 min) i.v.	75 mg/dose i.m.	125 mg (10–60 min) i.v.	Total dose (1–4 h)	Total dose (1–4 h) i.v.	Total dose (2 h) i.v.
Major adverse events	Rare	Rare	Yes	Rare	High	Rare	Rare
Compare oral iron	Yes	Yes	No, to iron sucrose	No	Yes	Yes	Yes
Therapy response	Favors iron carboxymaltose	Favors iron sucrose	Favors iron sucrose	Favors iron gluconate	Favors HMWD	Favors LMWD	Favors iron polymaltose
Neonatal data	Yes	Yes	No	No	No	No	Yes

High-molecular-weight dextran iron preparations (HMW ID) are off market in most European countries.

Compared with iron polymaltose and iron gluconates, the major advantages of iron sucrose and iron carboxymaltose preparations are higher single dose administrations in short application times, namely 5–15 min, which makes the practical handling easy [57]. It should be pointed out, that both iron polymaltose and carboxymaltose are not available in the USA yet, therefore LMW iron dextran is regarded to be the safest high dose iron preparation in the USA at present.

New i.v. iron preparations such as *ferumoxytol* and *iron isomaltoside*, which show good safety data and can be applied in higher dosages in a short time are under registration, however no pregnancy data are published yet [40,58,59]. Table 8 summarizes conditions that would favor the use of intravenous iron as a first option in anemia therapy during pregnancy.

Summary

Iron-deficiency anemia is the most frequent form of anemia in pregnancy and can have serious consequences for both the mother and fetus. The majority of women do not have adequate iron stores to meet the dramatic increase in requirements during the second and third trimester of pregnancy. Currently, the main interventions are oral iron and blood transfusions. However, there is increasing evidence that intravenous iron is more effective, provides more rapid Hb correction, corrects iron stores and is better tolerated than oral iron in treating iron-deficiency anemia during pregnancy. Furthermore, recent studies have demonstrated the efficacy and safety of i.v. iron in the second and third trimester of pregnancy.

Expert commentary

Iron deficiency and anemia are among the most important risk factors for feto-maternal morbidity and mortality worldwide. Interestingly, despite this well-known problem and topic, morbidity and mortality numbers and prevalence have not significantly dropped in the last decades. The positive perspective is the fact that we face increasing clinical and scientific interest in anemia research, iron deficiency diagnostics and new therapeutic approaches. Concerning diagnostics, major progress has been made, including new parameters such as red cell flow cytometry, serum transferrin receptor essays and hopefully soon reliable serum hepcidin measurements. Concerning therapeutics, the main progress has been made, introducing safe and effective intravenous iron preparations that can be even used during pregnancy and postpartum for the sake of the mother and the child or fetus. The new parenteral iron preparations also play a key role in the new concept of 'bloodless medicine', namely the most important concepts how to reduce blood transfusion in obstetrics to a minimum. Personally, I am surprised that important official sites and

Table 8. Conditions favoring the use of i.v. iron for anemia therapy in pregnancy.

Pre-existing anaemia (moderate to severe)
No effect of oral iron (missing compliance, low resorption)
Side effects of oral iron
Refuse of blood transfusion
Limited time until delivery or planned operation
Coexisting risks (e.g., placenta praevia, Jehovah's whitness, etc.)
Pre-, postoperative phase

communities such as the FIGO committee and WHO have not yet included guidelines for the use of parenteral iron in our field.

Five-year view

Concerning anemia and iron diagnostics, serum hepcidin and other iron regulators will play a key role in understanding iron metabolism and resorption and mechanisms of deficiency and overload. In the developing world, ways and options for prevention of iron deficiency using iron fortified food and optimized iron preparations (improved resorption with low side effects) will hopefully be studied. Parenteral iron preparations will gain more importance for the therapy of chronic and advanced stages of anemia and the issue of reducing g blood transfusion. Using heterologous blood will be a kind of 'old fashioned' or abandoned medicine. Research wise, the influence of iron deficiency with and without anemia during pregnancy, on mother, fetal programming and placental development and postpartum, on maternal physical and mental morbidity will be better investigated and described.

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Key issues

- Anemia is a common problem in obstetrics and perinatal care.
- Hemoglobin (Hb) level below 10.5 g/dl can be regarded as true anemia regardless of gestational age.
- Main cause of anemia in obstetrics is iron deficiency, which has a worldwide prevalence between estimated 20 and 80% of especially female population.
- Stages of iron deficiency are depletion of iron stores, iron deficient erythropoiesis without anemia and iron-deficiency anemia, the most pronounced form of iron deficiency.
- It is estimated that in developing countries, up to 20% of pregnant women have hemoglobin less than 8 g/dl and up to 7% less than 7 g/dl, namely severe anemia. For industrialized countries, the WHO indicates a mean prevalence of anemia around 18%.
- Pregnancy anemia can be aggravated by various conditions such as uterine or placental bleedings, gastrointestinal bleedings and peripartum blood loss. Beside the general consequences of anemia, there are specific risks during pregnancy for the mother and the fetus such as intrauterine growth retardation (IUGR), prematurity, feto-placental miss-ratio and higher risk for peripartum blood transfusion.
- Gold standard for the diagnosis of iron-deficiency anemia is evaluation of hemoglobin levels in combination with serum ferritin for the assessment of iron stores. Red cell indices can be useful in selected cases such as thalassemia patients. Advanced diagnostics for differential diagnosis include serum transferrin receptor levels, percentage of hypochromic red cells and probably in the future hepcidin levels.
- Treatment of iron deficiency and iron-deficiency anemia is based on the use of oral and intravenous iron preparations. Oral iron preparations such as iron II salts and iron III complexes can be effective in cases of mild or moderate iron deficiency but are limited by their side effects and limited resorption. Intravenous iron preparations show high effectiveness even in chronic or severe stages of iron deficiency and anemia, a high compliance and are safe in the recommended dosages and administration rules.

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