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SHORT COMMUNICATION

# Diagnosis and treatment of iron-deficiency anaemia during pregnancy and postpartum

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**Abstract**
*Introduction* Iron-deficiency anaemia during pregnancy and postpartum occurs frequently and may lead to severe maternal and foetal complications. New treatment regimens include intravenous iron administration in particular clinical situations. The aim of the study was to determine optimal diagnostic and therapeutic approaches to iron-deficiency anaemia during pregnancy and postpartum.
*Methods* The evidence from data available from published studies and recommendations regarding diagnosis and treatment were reviewed. As conclusions, recommendations are given by an expert panel.
*Results* During pregnancy, oral iron therapy is given as first-line treatment. In cases with lack of efficacy, unwarranted side effects or very low haemoglobin values, intravenous iron treatment with iron carboxymaltose is a preferable alternative, although data regarding safety are limited. In the postpartum period, haemoglobin values less than 95 g/L are treated ideally by intravenous carboxymaltose, leading to more rapid haemoglobin recovery.
*Conclusion* New intravenous iron preparations such as iron carboxymaltose have an excellent efficacy, side effect profile and advantages as compared to oral iron preparations for particular clinical indications.

**Keywords** Anemia · Pregnancy · Postpartum · Iron deficiency

Expert Panel Recommendation, Quality Assurance Commission of the Swiss Society of Obstetrics and Gynecology.

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## Introduction

Anaemia is one of the most common problems in obstetrics. It is well known that, depending on its severity, anaemia constitutes an important risk factor in both maternal and foetal morbidity. If the mother suffers from iron-deficiency anaemia, the risks to the foetus include a higher rate of premature birth, intrauterine growth retardation, unfavourable impact on placental development, and reduced neonatal iron stores. Maternal risks include depleted blood reserves during delivery and thus an increased risk of an allogeneic blood transfusion in case of significant blood loss, cardiovascular stress, anaemia symptoms (fatigue, reduced physical and mental capacities, headaches, orthostatic dizziness, exhaustion, prolonged hospitalizations, decreased milk production in the puerperium, depleted maternal iron stores postpartum and subsequently. For these reasons, the efficient treatment of anaemia following its diagnosis has a positive impact on maternal as well as foetal outcomes. One main focus is on reducing or at best avoiding the need for an allogeneic blood transfusion, as a result of an adequate anaemia treatment prior to delivery. In the following, the primary focus is on the treatment and not on the prophylaxis of iron-deficiency anaemia.

## Anaemia in pregnancy

### Diagnosis

The lower threshold value for haemoglobin in pregnant women is defined as Hb <110 g/L in the first and last trimester and <105 g/L in the second trimester (CDC 1998). An Hb level, <105 g/L thus, indicates anaemia at any stage during pregnancy, requiring diagnostic clarification and

treatment because of its association with an increased risk of intrauterine growth retardation and premature birth. For diagnostic clarification, the first tests to be performed should be a red blood count and a serum ferritin assay. As a rule, determining the serum ferritin level is sufficient for the diagnosis of iron-deficiency anaemia: a value of <15 μg/L provides clear evidence for iron-deficiency anaemia. For normal and/or elevated serum ferritin levels, other causes have to be investigated (e.g. haemoglobinopathies, such as $\beta$-thalassaemia, sickle cell anaemia, anaemia of infection, haemorrhagic anaemia, vitamin $B_{12}$ or folic deficiency, etc.). Determining the serum ferritin level in addition to the haemoglobin level at the beginning of pregnancy may be a good strategy. If ferritin is <30 μg/L, there is a 90% certainty that iron stores are depleted, even if there is no indication as yet of anaemia. In these cases, iron substitution during pregnancy is indicated. Caution: as part of an inflammatory response, serum ferritin can be "false normal" or "false high", as it reacts in the same way as an acute phase protein. For that reason, the recommendation is to determine the CRP level at the same time as ferritin levels. In the following cases, the advice is to perform a haemoglobin electrophoresis or a haemoglobin chromatography (HPLC high-performance liquid chromatography) to identify $\beta$-thalassaemia or another haemoglobinopathy as the cause of the anaemia: (1) positive family case history of the pregnant woman or her partner, (2) anaemia without iron deficiency (ferritin level normal), (3) MCV (erythrocyte mean corpuscular volume) level of <70 fL and an MCH (mean corpuscular haemoglobin) level of <27 pg (caution: Hb electrophoresis can be normal for α-thalassaemia) and (4) depending on ethnicity (caution: blood count for sickle cell anaemia without pathological findings). In case of a proven—usually heterozygous—haemoglobinopathy, the partner also has to be examined and the option of invasive prenatal diagnostics offered, if a relevant risk to the foetus exists.

## Treatment

The choice of treatment depends on the cause of the anaemia, i.e. generally iron deficiency. The primary treatment for mild cases of iron-deficiency anaemia (Hb 90–105 g/L) is a peroral iron therapy (iron II salts or iron III polymaltose) in doses of 160–200 mg/day (ideally on an empty stomach (iron II salts), fractionated). The same also applies to depleted iron stores at the beginning of pregnancy (ferritin <30 μg/L) without anaemia, because of the additional requirement for iron in the course of the pregnancy.

A switch to an intravenous iron preparation is advantageous in a number of cases, including: a lack of response to oral iron (Hb levels rising by less than 10 g/L within 14 days), lack of compliance, intolerance of oral iron preparations (gastrointestinal side effect), severe, advanced or progressive anaemia (Hb < 90 g/L), desire for rapid anaemia treatment (advanced gestational age, Jehovah's witness and many more). Several studies have shown that intravenous iron therapy is superior to oral iron treatment with respective indications. In addition, the gastrointestinal side effects of the oral iron therapy can be avoided.

### *Iron III saccharate (Venofer®)*

The iron III saccharate complex has been proven worldwide as a safe and very well-tolerated iron preparation. It is approved for administration in pregnancy from the second trimester onwards, with a general rate of side effects below 0.5%. Venofer® should only be infused in institutions equipped for cardiopulmonary resuscitation. The maximum dose of parenteral iron III saccharate is 200 mg per application, preferably diluted in 100 mL 0.9% NaCl solution administered as infusion. The solution is infused over a period of approximately 30 min through an intravenous access (caution: rapid infusion bears the risk of a hypotensive reaction). Depending on the baseline Hb level, these intravenous applications are to be repeated 1–3 times a week, until an Hb level of >105 g/L has been achieved. The patient can then be switched to oral iron substitution for maintenance. Iron overloading is not expected.

### *Iron carboxymaltose (Ferinject®)*

Iron carboxymaltose (Ferinject®) is a new non-dextran iron complex with the advantage that it can be administered in high doses of up to 1,000 mg/administration over a short period of time (15–30 min per infusion). This makes it possible to avoid costly repeat infusions of small intravenous iron quantities at a good level of tolerance, probably matching that of iron III saccharate. In line with iron III saccharate, the preparation is also approved for administration during pregnancy from the second trimester onwards. To date (as for iron III saccharate), there are no large-scale randomized studies on foetal safety during pregnancy; for that reason, prior to giving any intravenous iron preparation, it is necessary to evaluate the risk/benefit ratio carefully even in the second and third trimester. In a placental perfusion model, iron carboxymaltose has been shown not to cross the placental barrier to the foetal side (Malek 2009). Iron carboxymaltose is administered as a rapid infusion over 15–30 min or as a bolus injection over 1–2 min (not SC or IM!). As a rapid infusion, iron carboxymaltose can be administered as a single dose of up to 1,000 mg iron or, respectively, 15 mg/iron/kg body weight (up to the level of the desired total dose); the maximum dose for intravenous bolus administration is 200 mg. Higher doses if required (>1,000 mg) need to be fractionated and administered at 7-day intervals.

[According to a recent update of the Cochrane database (Reveiz, Gyte and Cuervo, 2007, CD 003094), there is no clear recommendation as to the choice of treatment of iron-deficiency anaemia during pregnancy. The administration of parenteral iron results in a faster increase in haemoglobin levels than the oral administration, countered, though, by a lack of data regarding the safety of parenteral iron in respect of thromboses and severe allergic reactions. In addition, the data from 17 studies are insufficient to assess the benefit in respect of maternal and foetal treatment outcomes. However, this updated does not include recent studies on the efficacy and safety of iron saccharate in pregnancy.]

There are no large-scale studies for either preparation (iron carboxymaltose and iron III saccharate) with respect to foetal safety.

## Postpartum anaemia

### Diagnosis

An Hb level <100 g/L is seen as a clinically significant postpartum anaemia. This is usually a combination of haemorrhagic anaemia and in some instances pre-existing iron-deficiency anaemia. The decision on Hb control during the puerperium is to be taken into consideration of the blood loss and the clinical state of the puerpera (symptoms of anaemia). In addition of relevance is the prepartum Hb level. The nadir of the postpartum Hb level is reached approximately 48 h after the primary plasma volume distribution. The additional determination of the ferritin level in the puerperium does not make sense, because for the first 6 weeks after delivery, both a "false normal" and a "false high" reading may be present (see above: ferritin = acute phase protein). The iron stores of puerperia can be assessed before delivery or from about 6 weeks after. There is no point in determining ferritin levels in cases of combined pre- and postpartum anaemia, because depleted iron stores can safely be assumed. Parenteral iron treatment without prior ferritin assessment can be dangerous, although, in cases of haemochromatosis (heterozygote frequency 1:10).

### Treatment

The treatment depends on the severity of the anaemia and the puerperia's state of health. As a rule, the recommended treatment for mild anaemia with an Hb of 95–120 g/L is the peroral administration of iron of approximately 80–200 mg (iron II salts or iron III polymaltose). In case of bad (gastrointestinal) tolerance of the peroral iron therapy, the intravenous administration of iron is a good alternative. For moderately severe (Hb < 95 g/L) to severe anaemia (Hb < 85 g/L), the parenteral administration of iron is an important alternative to the oral one. Several studies showed an advantage of the parenteral administration of iron III saccharate when compared with orally administered iron. One study even showed that the introduction of parenteral iron III saccharate to treat anaemia led to a reduction in allogeneic blood transfusion within the study collective. The maximum dose of parenteral iron III saccharate is 200 mg per application, preferably diluted in 100 mL 0.9% NaCl solution as an infusion. The solution is infused over a period of approximately 30 min through an intravenous access (caution: infusing too rapidly bears the risk of a hypotensive reaction). Depending on the baseline Hb level, these intravenous applications are to be repeated 2–3 times a week, until an Hb level of >100 g/L has been achieved. The patient can then be switched to oral iron substitution for maintenance. Iron overloading is not expected. Within 14 days, levels are expected to increase by 30 g/L. At the end of the observation period, puerperia treated with parenteral iron III saccharate have higher ferritin levels than women who received oral treatment, and thus probably also persistently higher iron stores. This is particularly beneficial in a quick succession of pregnancies.

The new preparation Iron carboxymaltose (Ferinject®) has already been tested in several randomized multicentre studies in comparison with oral iron substitution for the treatment of postpartum anaemia and demonstrated an outstanding safety profile comparable to that of iron III saccharate, combined with great effectiveness. In three of the four studies, the intravenous administration of iron carboxymaltose for the treatment of postpartum anaemia showed superiority in efficacy to oral iron therapy, while one study showed intravenous iron carboxymaltose to be equal to oral therapy over 12 weeks. The safety profile has to be rated as very high and comparable to that of iron saccharate. The dosage is the same as described above. Practical benefits, patient comfort and the reduction in cost associated with a single administration support the advantage of iron carboxymaltose over iron III saccharate.

In cases of severe anaemia (<80 g/L), the administration of recombinant erythropoietin (rhEPO) in addition to parenteral iron carboxymaltose may be considered. According to the Cochrane database, the administration of rhEPO can support the treatment of anaemia, but only in conjunction with parenteral iron, to avoid an ineffective erythropoiesis. Erythropoietin (rhEPO) should only be given in cases of severe anaemia combined with additional factors (pronounced clinical symptoms, rejection of donor blood, etc.). A sample dose is, e.g. 150 IE/kg bodyweight once a day SC, a total of four doses of epoietin alpha (Eprex®) in addition to the parenteral treatment with iron carboxymaltose. Consideration also has to be given to the fact that the administration of rhEPO is an off-label use with considerable associated costs.

The critical Hb value below which an allogeneic blood transfusion has to be considered is at approximately 60 g/L, but depends on the clinical symptoms. A decision on an allogeneic blood transfusion should always be made on an individual basis giving full consideration to the patient's wishes. There is no general threshold value (e.g. Hb 60 g/L = blood transfusion), but consideration has to be given to inapparent complications, e.g. indications of silent myocardial ischaemia.

References: With the authors

**Conflict of interest statement** None.