Guide to iron supplementation in pregnancy

This publication can be used by GPs, Midwives, Health Visitors and Pharmacists

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Iron deficiency is common in pregnancy, with risks to mum and baby

The demand for iron increases threefold during pregnancy to meet the demands of the growing fetus and placenta, as well as maternal adaptations to pregnancy.[1] It is estimated that 30-40% of pregnant women in industrialised countries are iron deficient[1] and almost one in four women in the UK have iron deficiency anaemia.[2]

Iron deficiency during pregnancy is associated with several complications including increased risk of preterm birth, lower birth weight and perinatal mortality.[3,4] It is also linked to maternal postpartum fatigue and depressive symptoms, and infant iron deficiency in the first three months of life.[2,3] Treating iron deficiency therefore offers considerable benefits to both mother and baby.

Iron is recycled between functional and storage 'pools'

Around a quarter of the body's iron is stored as ferritin, mainly in the liver, ready to be mobilised if the body requires additional iron. The remaining iron is mostly 'functional' iron, found predominantly in haemoglobin (Hb) in circulating red blood cells but also in myoglobin in skeletal muscle. A small fraction (< 1%) circulates in the blood bound to transferrin; this is known as 'transport' iron.[3-5]

Iron stores are depleted before anaemia develops

Iron deficiency can be viewed as a spectrum from iron depletion through to iron deficiency anaemia dependent on the status of stored iron in the body (Figure 1).

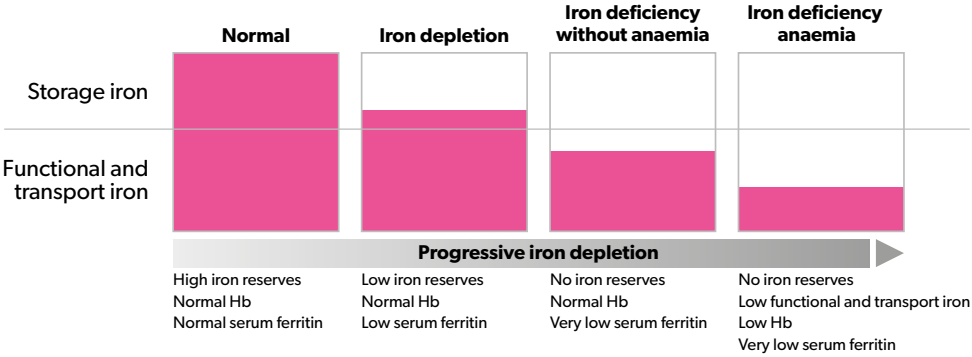

Figure 1: The spectrum of iron deficiency

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In iron depletion, levels of stored iron are reduced, while levels of circulating iron in Hb may not be affected.[3] In iron-deficiency anaemia, red blood cell production is diminished due to a shortage of both stored and circulating iron.[3]

Stored iron is therefore depleted before Hb decreases. Since iron is essential to all cells, symptoms of iron deficiency – such as fatigue, irritability, poor concentration and hair loss – may occur even in the absence of anaemia.[4]

Many women, especially those who experience heavy menstrual bleeding, already have low iron reserves at the time of conception, putting them at even greater risk of iron deficiency during pregnancy. Indeed, it is estimated that 10-20% of menstruating women are iron deficient.[4]

Current UK guidance on iron deficiency in pregnancy

The British Committee for Standards in Haematology (BCSH) published guidelines on the management of iron deficiency in pregnancy in 2012.[3] These are reflected in the latest NICE guidance on iron deficiency anaemia.[2]

The BCSH guidelines recommend a full blood count at booking and at 28 weeks. Normal Hb levels vary during pregnancy, therefore anaemia is defined as:[3]

- Hb <110g/L in the first trimester
- Hb <105g/L in the second and third trimesters
- Hb <100g/L in the post-partum period.

Women who are not anaemic but thought to be at increased risk of iron deficiency (see Box 1) should have their serum ferritin levels checked early in pregnancy. Serum ferritin levels progressively fall by 32 weeks to around 50% of pre-pregnancy levels due to haemodilution as plasma volume increases as well as mobilisation of iron.[2-4]

Even with this gradual decline in serum ferritin, levels <15ug/L indicate iron deficiency in all stages of pregnancy. Levels <30ug/L indicate early iron depletion, which will continue to fall during pregnancy unless treated.[2,3]

Dietary changes alone are insufficient to correct iron deficiency in pregnancy

Once a woman becomes iron deficient during pregnancy, dietary sources of iron will be insufficient to replenish levels and oral iron supplementation is recommended.[2,3,7]

NICE guidelines recommend that pregnant women with iron deficiency anaemia should be prescribed 200mg oral ferrous sulphate tablets two or three times a day. Treatment should continue for three months after the deficiency has been corrected to ensure iron stores are replenished.[2]

Hb levels (full blood count) should be rechecked after two to four weeks to assess response to treatment.[2]

Women with serum ferritin levels below 30ug/L should be offered iron supplements, as this indicates early iron depletion, which will continue to fall unless treated.[2]

Box 1: Women at higher risk of iron deficiency during pregnancy[2,8]

- Low iron stores before pregnancy
- Previous history of anaemia
- Pre-existing blood condition (e.g. sickle cell disease, thalassaemia)
- Age < 20 years
- Dietary deficiency: gut disorders affecting iron absorption (e.g. coeliac disease, inflammatory bowel disease, previous gut surgery); eating disorders; vegetarian/vegan
- Short spaces between pregnancies (< 18 months)
- Multiple pregnancy

Treating iron deficiency can be challenging

There are many non-haem iron supplements available over the counter. Ferrous sulphate is considered the 'gold standard' and is the most commonly prescribed form in the UK.[4] Oral iron supplements, however, can have limitations: only a small percentage of the iron is absorbed (around 10-15%)[10] and side effects are common, which may in turn lead to poor compliance.

Bioavailability among supplements varies, and it is important to distinguish between the amount of iron compound and the equivalent in terms of elemental iron. For example, hydrated ferrous sulphate contains 20% iron by weight, therefore a 300mg tablet contains 60mg of elemental iron.[4]

Iron is absorbed via a carrier mechanism, DMT-1

Although some nutrients can enter the body by passing between the gut mucosal cells, iron uptake and transfer depends on specific cellular carrier mechanisms. One of these, called the divalent metal transporter 1 (DMT-1), plays an important role in the uptake of non-haem iron.[4]

The absorption of most dietary iron occurs in the duodenum and upper jejunum, where DMT-1 is found on the surface of the absorptive cells (enterocytes) that line the small intestine (Figure 2).[11] The acidic pH in the duodenum is critical to the absorption of iron.[11]

Various factors can affect the absorption of iron supplements (see Box 2).

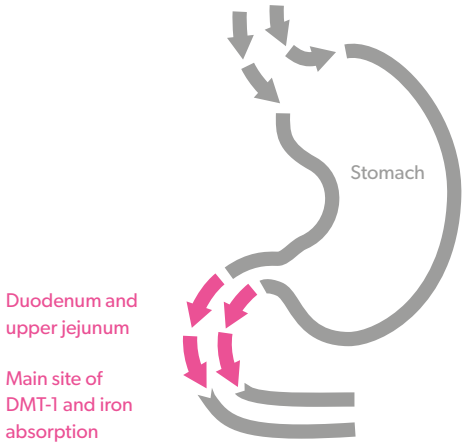

Figure 2: Absorption of iron

Box 2. Factors affecting the absorption of iron supplements

- **Solubility of the iron:** ferrous iron is more easily absorbed than ferric iron.[9,12]
- **Timing of the dose:** taking iron supplements with or after food may decrease absorption by 40-66%.[2,11]
- **Dietary factors:** iron absorption is inhibited by polyphenols (found in various plant-based food and beverages such as tea, coffee and chocolate), phytates (also found in plant-based diets), calcium, legumes, cereals and some animal and plant proteins;[5,11] conversely, iron absorption is increased is the presence of vitamin C.[5,11]
- **Other medication:** drugs that alter gastric acid production (e.g. proton pump inhibitors) can also substantially reduce iron absorption.[4,11]

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Side effects are common and affect compliance

Iron has a highly reactive chemical nature, which allows it to fulfil its essential functions within the body. However, this also gives it the ability to cause oxidative stress and cell damage within the gastrointestinal tract.[13]

Although iron absorption occurs mainly in the small intestine, traditional iron supplements tend to dissolve in the stomach or, in the case of delayed release products, the lower intestine where they can cause damage not only to the gut lining but also to the gut microbiome.[9,14] This can lead to inflammation and the potential for side effects including constipation, diarrhoea, heartburn, epigastric pain, faecal impaction, gastrointestinal irritation and nausea.[2,13]

Estimates of the incidence of gastrointestinal side effects with iron supplementation range from 30-47%.[15]

In pregnancy, the side effects of iron supplementation may be compounded by those of the growing fetus, such as nausea, heartburn and constipation.[9,15] Indeed, one study confirmed that pregnant women were more likely to report side effects when taking daily iron supplements than controls (25.3% versus 9.9%), particularly at doses of 60mg or more of elemental iron.[16]

Adverse effects are a common cause of non-compliance with treatment: up to 50% of patients are thought to discontinue iron supplements because of adverse effects.[9]

Active Iron offers a unique formula to increase absorption and reduce side effects

Active Iron is a new, ground-breaking iron supplement that delivers microspheres of iron sulphate in a whey protein formulation to the duodenum, the site of absorption. This not only increases the amount of iron absorbed, it also helps protect the gut lining from iron-related oxidative stress and damage resulting in fewer side effects.[14]

Active Iron Pregnancy is formulated for women during all stages of pregnancy, including those who are breastfeeding.

Better iron absorption than ferrous sulphate

Clinical evaluation of Active Iron showed significantly greater absorption of iron when compared with the gold standard of ferrous sulphate alone.[14] In this controlled, pharmacokinetic study of 21 healthy participants who were mostly women, iron absorption with Active Iron was double that of ferrous sulphate alone (Figure 3).[14]

Because iron absorption is dependent on a person's degree of iron depletion, further analysis was carried out. Multi-variable analysis showed that the greater absorption of Active Iron was independent of baseline serum iron, ferritin, transferrin and haemoglobin levels.[14]

The whey protein formulation means that iron is targeted to the site of absorption – the duodenum – rather than irritating in the stomach and bowel.[14] This targeting of the body's iron uptake mechanism, DMT-1, means greater absorption of iron.

Kinder on the digestive tract

In vitro studies with gut epithelial cells showed lower toxicity with Active Iron than with an equivalent dose of ferrous sulphate alone or a mixture of ferrous sulphate, vitamin C and whey protein.[14]

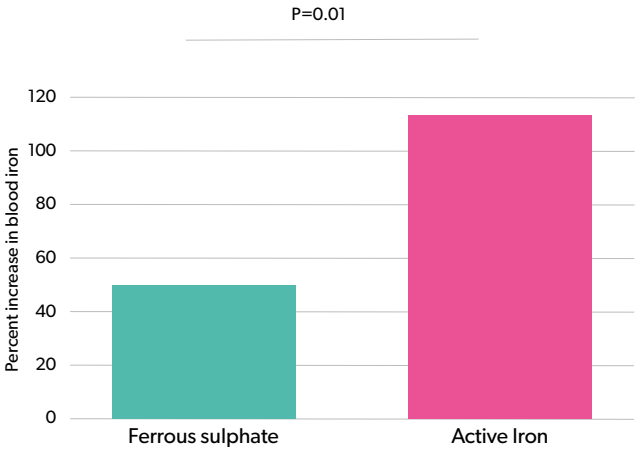

Figure 3: Active Iron achieves twice the absorption of ferrous sulphate alone[14]

The whey protein formulation around the ferrous sulphate helps protect the gut epithelial cells from oxidative stress and damage, resulting in fewer side effects.

Active Iron Pregnancy supports iron levels throughout pregnancy

Available over-the-counter, each capsule of Active Iron Pregnancy contains 17mg of elemental iron, which is 121% of the nutritional reference value of this mineral.

Clinically proven to have double the absorption rate of standard ferrous sulphate, Active Iron's formula is designed to reduce gut irritation and so is gentle enough to take on an empty stomach.[14]

Women should take one capsule per day (this can be increased to two capsules per day if recommended by a midwife).

Food supplements are not a substitute for a varied diet and healthy lifestyle.

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* Clinically proven twice the absorption compared to iron sulfate. Wang et al, Acta Haematologica 2017; 138: 223-232. Your doctor or midwife will advise you if you need to take iron supplements.