

UK guidelines on the management of iron deficiency in pregnancy

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Iron deficiency remains a significant problem for pregnant women in the UK. The objective of these guidelines is to provide healthcare professionals with recommendations for the prevention, diagnosis and treatment of iron deficiency in pregnancy and in the postpartum period. The guidelines update and replace the previous ones (Pavord *et al*, 2012). The prevalence of anaemia in pregnancy remains high. In order to minimise adverse outcomes, including use of blood transfusion, further research is required to define optimal management, as many current recommendations are not supported by high quality evidence.

Methods

This guideline was compiled according to the British Society for Haematology (BSH) process at b-s-h.org.uk. GRADE criteria were used to quote levels of recommendation and grades of evidence (<https://www.gradeworkinggroup.org>).

Searches were performed using the online search engine Medline (OVID), Embase (OVID) and CENTRAL (The Cochrane Library). Search terms were: ("pregnancy" OR "postpartum") AND; "anaemia" AND "transfusion"; "anaemia" AND "iron"; "ferritin"; "intravenous iron"; "prevention of iron deficiency"; "hepcidin"; "transfusion AND red cells"; "iron deficiency"; "iron deficient"; "iron depletion"; "positive predictive value"; "positive predictive value" AND ("true positive" OR "true negative"); "negative predictive value"; "negative predictive value" AND ("false positive" OR "false negative"); "pregnancy outcome for mother and baby"; "pregnancy outcome" AND; "birth weight"; AND

"gestational age"; AND "admission to intensive care unit"; AND "preterm delivery".

Filters were applied to include only publications written in English, studies carried out in humans, clinical trials, clinical studies, comparative studies and systematic reviews published between 1 February 2012 and 31 January 2018, inclusive. Searches of individual journals were not implemented because it was felt that publications not captured during the database search process would have had limited availability and would have had little impact on the scientific community.

Opinions were also sought from practice development midwives and obstetric anaesthetists.

Definition and prevalence of iron deficiency anaemia in pregnancy

Definition

Anaemia is defined as a low haemoglobin concentration (Hb); the lower limit of current reference ranges is two standard deviations below the mean in a healthy population [World Health Organization (WHO), 2011]. In pregnancy, there is a physiological expansion of plasma volume beginning in the first trimester and plateauing by the third (Costantine, 2014), which exceeds the increased production of red blood cells and haemoglobin. The resulting haemodilution contributes to the fall in Hb during pregnancy. Several factors may restrict or curtail this expansion, including pre-eclampsia and some medical comorbidities (Fisher & Nemeth, 1967). Anaemia in pregnancy can be caused by numerous other factors, including vitamin B12 and folate deficiency, the presence of a variant haemoglobin or thalassaemia, inflammatory disorders, haemolysis and blood loss, and, most commonly, by deficiency of iron. This guideline addresses iron deficiency, which is by far the most common cause of anaemia in pregnancy.

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Iron deficiency is a progressive process, in which iron stores fall, from being replete to deplete and finally absent, consequently resulting in iron deficiency anaemia. Progressive iron deficiency can be measured by a variety of biomarkers. In iron depletion, the body's stored iron is reduced and individuals are at greater risk of anaemia in situations of increased demand. Iron utilisation is increased during pregnancy, as iron is required for fetal growth and development (Scholl, 2005), as well as for increased maternal erythropoiesis (Bothwell, 2000; Fisher & Nemeth, 1567S).

The current Hb thresholds defining anaemia in pregnancy are based on historical normal values derived from non-pregnant populations, which are not clearly linked to clinical outcomes and there is ongoing debate as to the applicability of these values (Pasricha *et al*, 2018). The WHO is reviewing the evidence relating to the Hb below which anaemia should be defined (WHO, 2011; Pasricha *et al*, 2018). Until then, the guideline group agreed that the existing thresholds, being Hb <110 g/l in the first trimester, <105 g/l after 12 weeks and <100 g/l immediately postpartum (Pavord *et al*, 2012) were most practical, but that further work is needed to validate them.

Recommendation

Anaemia should be defined as haemoglobin concentration (Hb) <110 g/l in first trimester and <105 g/l in second and third trimesters and <100 g/l postpartum (2D).

Prevalence

Iron deficiency is the most common nutritional deficiency globally and is the leading cause of anaemia (Stevens *et al*, 2013; McLean *et al*, 2009; WHO, 2017). In pregnancy, iron deficiency is usually due to an imbalance of demand and supply, which worsens as pregnancy advances. The prevalence of maternal anaemia approaches 50% in low- and middle-income countries, largely due to a combination of nutritional deficiency, infectious diseases and the presence of a variant haemoglobin or a thalassaemic disorder (Balarajan *et al*, 2011). In the UK, the prevalence of anaemia was found to be 24% in a multicentre national study (Barroso *et al*, 2011) and a two-centre English study found 46% of women had anaemia at the booking or 28-week checks (Nair *et al*, 2017).

Clinical effects of iron deficiency anaemia in pregnancy

Iron is an essential requirement for erythropoiesis and iron-dependent enzymes are present in all cells, including placental and fetal tissue. Iron deficiency anaemia has been linked to poor health outcomes in the mother, fetus and infant.

Maternal morbidity and mortality

Iron deficiency with or without anaemia, is associated with maternal fatigue (Lee & Zaffke, 1999; Pratt & Khan, 2016) and, potentially, poorer quality of life and increased risk of postpartum depression (Corwin *et al*, 2003). A recent systematic review of non-anaemic iron deficiency found that fatigue improves with iron replacement (Pratt & Khan, 2016), although there was only one randomised control trial and one other relevant study. Altered thyroid metabolism can also occur in iron deficiency anaemia (lower thyroid-stimulating hormone and T3 hormone) and contribute to fatigue (Beard *et al*, 1989, 1990).

Maternal anaemia may also increase the risk of postpartum haemorrhage (PPH). A large prospective observational study at 2 maternity services in the UK found that 60% of women with Hb <85 g/l sustained PPH, with a quarter progressing to severe PPH (Briley *et al*, 2014). One explanation is impaired uterine contractility due to reduced availability of oxygen.

An increased risk of puerperal sepsis has been suggested by systematic reviews (Peña-Rosas *et al*, 2012); however, the number of studies that report on this outcome is small and further studies are needed to validate this finding.

Data from the WHO, derived mainly from low-income countries, show that the risk of maternal mortality increases with the severity of anaemia, although the multiple causes of anaemia make it difficult to determine the direct effects of anaemia per se (Brabin *et al*, 2001) and at what Hb threshold mortality is increased. A recent study adjusting for confounding factors, such as PPH, massive transfusion and admission to intensive care units, found that an Hb <70 g/l antenatally or postpartum was associated with a two-fold increase in mortality, in low- and middle-income countries (Daru *et al*, 2018).

Pregnancy outcome

Maternal anaemia has been associated with a significantly higher risk of perinatal and neonatal mortality, low birth weight and pre-term birth, in a systematic review and meta-analysis of studies from low- and middle-income countries (Rahman *et al*, 2016). Recent studies in a multi-ethnic population in England (Nair *et al*, 2017) and in northern India (Nair *et al*, 2016) support this, finding an association between severe antenatal anaemia and stillbirth and perinatal death, and with small for gestational age infants, low birth weight infants and maternal PPH. However, a meta-analysis of randomised controlled trials on the effect of iron supplementation showed only a modest effect on birth weight of 41–69 g, with a small reduction in low birth weight and uncertainty on the size of the effect on preterm birth, duration of gestation or small for gestational age infants (Haider *et al*, 2013).

The fetus and infant

Most fetal iron is acquired in the third trimester, in preparation for the high growth rate in the first 4–6 months after birth (Balesaria *et al*, 2012). Regulation of fetal iron levels is a complex process and, in maternal iron deficiency anaemia, there is an increase in placental iron receptors and iron absorption across the placenta to maximise fetal iron supply (Gambling *et al*, 2011).

Despite this, studies have found that maternal iron deficiency at delivery is associated with lower serum ferritin in cord blood of neonates (Shao *et al*, 2012; Mireku *et al*, 2016), suggesting that the prioritisation of fetal iron supply must be compromised at some point. Shao *et al* (2012) found that cord iron levels were reduced when mothers had serum ferritin levels below 13 µg/l.

The late fetal and early postnatal period are recognised as a critical period where there is rapid brain development, high neural plasticity and high nutritional requirement (Gluckman & Hanson, 2004; Georgieff *et al*, 2015). Animal studies show maternal iron deficiency late in pregnancy is associated with neurodevelopmental impairment. Observational studies in pregnant women have found that iron deficiency anaemia late in pregnancy is associated with premature birth and low Apgar score (<5 at 1 min) (Lone *et al*, 2004), and impaired motor, cognition and language development in the neonate. However, a systematic review found that the majority of studies are observational and there is no consistent evidence that maternal anaemia affects infant cognition (Veena *et al*, 2016).

Recommendations

Healthcare professionals should be aware that iron deficiency anaemia in pregnancy is common and associated with increased risk of maternal morbidity and mortality (1B).

Healthcare professionals should be aware that iron deficiency anaemia in pregnancy is associated with increased risk of perinatal morbidity and mortality, and has important potential implications for the future neuro-development of the infant (2B).

Diagnosis

Clinical symptoms and signs

The clinical symptoms of iron deficiency anaemia in pregnancy are non-specific and cannot be relied on for diagnostic purposes. Fatigue is the most common symptom but women may also present with pallor, weakness, headache, palpitations, dizziness, dyspnoea, irritability and restless legs. Pica, a craving for non-food items such as ice (pagophagia) and soil (geophagia), may develop (Lumish *et al*, 2014).

In early iron depletion, women may experience symptoms of fatigue, irritability, poor concentration and hair loss

(Holm *et al*, 2018; Lee & Zaffke, 1999). Information given to women about these symptoms may facilitate earlier presentation of iron depletion, before anaemia develops.

Laboratory testing

Whilst there is no evidence to determine the required frequency for checking Hb in pregnancy, current good practice guidelines advise testing at the booking appointment and at 28 weeks [Pavord *et al*, 2012; Royal College of Obstetricians & Gynaecologists, 2015; White *et al*, 2016; National Institute for Health and Care Excellence (NICE) 2016]. New near-patient test assays may allow more frequent testing in the future.

Red cell indices. A low Hb, mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC) are suggestive of iron deficiency, but need to be interpreted with caution in view of the physiological increase of MCV in pregnancy, of around 6 fl (Chanarin *et al*, 1977). Microcytic, hypochromic indices may also occur in haemoglobinopathies.

One study in Sri Lanka found the MCHC to have the best sensitivity for detection of iron deficiency, compared with Hb and the other red cell indices (Rabindrakumar, *et al*, 2018). This has not been supported by UK studies (Vora *et al*, 2019) but potential biomarkers need to be further investigated to find a practical, cost effective measure for the early detection of iron depletion.

Serum ferritin. A low serum ferritin is diagnostic of iron deficiency in pregnancy. However, a normal ferritin level does not exclude iron deficiency, as pregnancy is associated with a physiological rise in acute phase proteins (Kaestel *et al*, 2015) and changes in iron utilisation and metabolism (Costantine, 2014), both of which influence serum ferritin levels. A recent systematic review showed there is marked variation in the threshold of serum ferritin used to diagnose iron deficiency, both in research studies and in national and international guidelines (Daru *et al*, 2017). The two benchmark studies that compared serum ferritin with iron stores in the bone marrow, and that have guided currently used thresholds, have significant limitations (Hallberg *et al*, 1993; van den Broek *et al*, 1998). Research on pregnancy-specific cut-offs of serum ferritin are lacking (Roy & Pavord, 2018) and there is ongoing debate as to which serum ferritin level to use as threshold to diagnose iron deficiency (Garcia-Casal *et al*, 2014). In the UK, the majority of clinicians are familiar with using a serum ferritin level <30 µg/l (Daru *et al*, 2017; Pavord *et al*, 2012). It may be appropriate to use a higher cut-off, but as of yet there are no data to support this in pregnancy and the guideline group encourage continued use of a serum ferritin level <30 µg/l until good quality evidence suggesting another cut-off emerges.

Other biomarkers of iron deficiency. Transferrin saturation has not been widely used in pregnancy, outside the context of research but is useful in non-pregnancy settings and requires further evaluation in pregnancy. It is however derived from serum iron and total iron binding capacity, which are influenced by diurnal variation, infection and inflammation (McSorley *et al*, 2019).

Other biomarkers may be promising but have not yet been validated in pregnancy, such as soluble transferrin receptor levels (sTfR) (Choi *et al*, 2000) and reticulocyte haemoglobin content (a key test for diagnosis of iron deficiency in chronic kidney disease). Data are emerging on the use of serum hepcidin (Nemeth & Ganz, 2006), however, reference ranges and the correlation of hepcidin levels with clinical outcomes are unknown (Koenig *et al*, 2014) and there is insufficient evidence to support its use in pregnancy.

Trial of oral iron

Oral iron, if taken according to the recommendations indicated below (early morning, on an empty stomach), is effective at correcting iron deficiency anaemia (Haider *et al*, 2013). In anaemic women, a trial of iron therapy for simultaneous diagnostic and therapeutic purposes is helpful. A rise in Hb should be demonstrable by 2 weeks and supports the diagnosis of iron deficiency (Pavord *et al*, 2012). Women who are haemoglobinopathy carriers should have serum ferritin testing prior to iron administration, to confirm concomitant iron deficiency and exclude iron overload. If haemoglobinopathy status is not yet known, a trial of iron can be started at the same time as haemoglobinopathy testing.

An effective system for reviewing blood results is imperative. If there has been no improvement in Hb following 2 weeks of optimal therapy and compliance, more definitive testing and treatment is required.

Non-anaemic women at risk of iron deficiency anaemia

Many iron-depleted women are not yet anaemic when they first present in pregnancy, as erythropoiesis is usually preserved until the advanced stages of iron deficiency. An observational study of 102 non-anaemic women in the first trimester showed that 14% were iron depleted, defined by ferritin levels <30 µg/l, and 37% had a low transferrin saturation of <20% (Auerbach *et al*, 2019). Iron-deficient women are at high risk of anaemia and need to be identified by careful history at the booking clinic (Table I). There is no good evidence to inform the management of these women, however it is the opinion of the guideline group that they should either be started on prophylactic iron empirically or have their serum ferritin checked first. Routine screening with serum ferritin has been proposed (Crispin *et al*, 2018), but given the associated costs, delays and limitations of the test, a careful history to identify these patients may be preferred.

Further research is needed to inform the optimal management of non-anaemic women with iron deficiency.

Recommendations

Healthcare workers should be aware that iron deficiency is the most common cause of anaemia in pregnancy and the risk of iron deficiency should be considered in all pregnant women (1B).

Haemoglobin concentration should be routinely measured at booking and at around 28 weeks' gestation (1D).

Systems must be in place for timely review of blood test results, including monitoring the response to therapy (1B).

If anaemia without an obvious other cause is detected, a diagnostic trial of oral iron should be given without delay, with a repeat full blood count in 2–3 weeks (1D).

The optimal diagnostic strategy for anaemia in pregnancy is unknown but unselected routine screening with serum ferritin outside the context of research is not currently recommended (1D).

Serum ferritin should be measured in women with a known haemoglobinopathy to identify concomitant iron deficiency and exclude iron loading states (1D).

Non-anaemic women at risk of iron deficiency should be identified and either started on prophylactic iron empirically or have serum ferritin checked first (1D).

A serum ferritin level of <30 µg/l in pregnancy is indicative of iron deficiency. Levels higher than this do not rule out iron deficiency or depletion (2C).

Other biomarkers of iron status are not currently recommended for screening as there is insufficient validation in pregnancy (2B).

Management of iron deficiency

Dietary advice

The average daily iron intake from food for women in Great Britain is 10 mg, of which 10–15% is absorbed. The capacity for absorption is enhanced in pregnancy but physiological iron requirements increase from 1–2 mg to 6 mg per day (Bothwell, 2000), with increasing demand as pregnancy advances. The recommended daily intake (RDA) of iron for the latter half of pregnancy is 27 mg, twice that of a non-pregnant woman (<https://www.nhlbi.nih.gov/health-topics/iron-deficiency-anemia>).

The amount of iron absorption depends upon the amount of iron in the diet, its bioavailability and physiological requirements. Haem iron from meat, fish and poultry is absorbed 2- to 3-times more readily than non-haem iron. Meat also contains organic compounds that promote the absorption of iron from other less bioavailable non-haem iron sources (Skikne & Baynes, 1994). However, approximately 95% of dietary iron intake is from non-haem iron sources. Vitamin C (ascorbic acid) significantly enhances iron

Table I. Indications for empirical iron supplementation and/or serum ferritin.

Anaemic women where testing serum ferritin is necessary prior to iron supplementation:

- Known haemoglobinopathy
- Prior to parenteral iron replacement

Non-anaemic women with high risk of iron depletion for empirical iron treatment with/without serum ferritin testing:

- Previous anaemia
- Multiparity ≥ 3
- Twin or higher order multiple pregnancy
- Interpregnancy interval < 1 year
- Women who have poor dietary habits
- Those following a vegetarian/vegan diet

Pregnant teenagers

- Recent history of clinically significant bleeding

Non-anaemic women where serum ferritin may be necessary:

- High risk of bleeding during pregnancy or at birth
- Women declining blood products, such as Jehovah's Witnesses
- Women for whom providing compatible blood is challenging

absorption from non-haem foods (Lynch, 1997), the size of this effect increasing with the quantity of vitamin C in the meal. Germination and fermentation of cereals and legumes improve the bioavailability of non-haem iron by reducing the content of phytate, a food substance that inhibits iron absorption. Tannins in tea and coffee inhibit iron absorption when consumed with a meal or shortly after.

Recommendations

All pregnant women should receive dietary advice (2B).

Once women become iron-deficient in pregnancy it is not possible to ensure repletion through diet alone and oral supplementation is needed (2B).

Education and counselling regarding diet may improve iron intake and enhance absorption but the degree of change achievable remains in question (2B).

Oral iron preparations

Oral iron is an effective, cheap and safe way to replace iron. Ferrous salts are preferred to ferric salts due to the poorer absorption and bioavailability of the latter (Davidsson *et al*, 2000; Nagpal & Choudhury, 2004). Available ferrous salts include ferrous fumarate, ferrous sulphate and ferrous gluconate. It is the amount of elemental iron that is important and this varies by preparation, as detailed in Table II. Multivitamins and 'off the shelf' preparations usually have insufficient iron to correct anaemia and, furthermore, often contain other minerals that interfere with iron absorption. Combined iron and folic acid preparations are available but their efficacy compared to oral iron alone is unknown. Daily folic acid (400 μg) is required before 12 weeks' gestation to reduce the incidence of neural tube defects.

Until now, the recommended dose of elemental iron for treatment of iron deficiency has been 100–200 mg daily (Joint Formulary Committee, 2017; Pavord *et al*, 2012). However, more recent studies suggest that lower doses or intermittent supplementation may be advantageous (Pena-Rosas *et al*, 2015). Moretti *et al* (2015) showed that fractional absorption of iron in iron-depleted young non-pregnant women is maximised by taking elemental iron doses of 40–80 mg once per day or alternate days, avoiding twice daily dosing. Higher doses potentially increase side effects due to the excess unabsorbed iron remaining in the gastrointestinal tract. Iron is known to cause gastric irritation, nausea and disturbed bowel function, affecting compliance (Smith *et al*, 2014). Shinar *et al* (2017) showed that 68 mg daily, started at 17 weeks' gestation, did not result in a higher Hb by 35 weeks than 34 mg daily. Data reported by Stoffel *et al* (2017) suggest that optimal absorption occurs from alternate day dosing, due to higher hepcidin levels with consecutive day dosing. However, a balance between optimal absorption, ease of compliance and need for rapid response may lead to a daily regime being preferred. Hepcidin levels are lowest in the morning, suggesting that a morning dose is preferable (Schapp *et al*, 2013). Oral iron supplementation should be taken on an empty stomach, as absorption is reduced or promoted by the same factors that affect absorption of dietary non-haem iron. It may be taken with water or a source of vitamin C to enhance absorption.

Recommendations

Ferrous iron salts are the current preparation of choice for oral iron supplementation (1C).

Until further research determines the optimal dose of elemental oral iron, 40–80 mg every morning is suggested, checking Hb at 2–3 weeks to ensure an adequate response (2C).

Women should be counselled as to how to take oral iron supplements correctly. This should be on an empty stomach, with water or a source of vitamin C. Other medications, multivitamins and antacids should not be taken at the same time (1B).

Treatment for anaemia should be started promptly by the healthcare professional caring for the woman. Escalation to specialist medical care is required if anaemia is severe (Hb < 70 g/l) and/or associated with significant symptoms or advanced gestation (> 34 weeks) (2B), or if the Hb is failing to respond after 2–3 weeks of oral iron correctly taken.

In non-anaemic women at increased risk of iron depletion, 40–80 mg elemental iron once a day should be offered empirically, or serum ferritin should be checked and iron offered if the ferritin is < 30 $\mu\text{g/l}$ (1B).

Response to oral iron. The degree of increase in Hb that can be achieved with iron supplements will depend on the Hb

Table II. Recommended daily dose and elemental iron content of oral iron preparations.

Iron salt	Preparation	Elemental iron content
Ferrous fumarate	210 mg	65 mg
Ferrous gluconate	300 mg	35 mg
Ferrous sulphate (dried)	200 mg	65 mg
Ferrous ferredetate	190 mg/5 ml elixir	27.5 mg/5 ml elixir

and iron status at the start of supplementation, ongoing losses, iron absorption and other factors contributing to anaemia, such as other micronutrient deficiencies, infections and renal impairment. However, compliance and intolerance of oral iron preparations are the usual factors limiting efficacy. Iron salts may cause gastric irritation (Pereira *et al*, 2014) and up to a third of patients may develop dose-limiting side effects (Breyman, 2002), including nausea and epigastric discomfort. This is minimised by correct administration, which optimises absorption. It may be necessary to titrate the dose down to a level where side effects are acceptable or try an alternative preparation. Enteric-coated or sustained release preparations should be avoided, as the majority of the iron from such preparations is carried past the duodenum, limiting absorption (Tapiero *et al*, 2001). The relationship between dose and altered bowel habit (diarrhoea and constipation) is less clear (Tapiero *et al*, 2001), and other strategies, such as use of laxatives are helpful.

A repeat Hb at 2–3 weeks is required to assess response to treatment. The timing of further checks will depend upon the degree of anaemia and period of gestation. Once the Hb is in the normal range, treatment should be continued for a further 3 months and until at least until 6 weeks postpartum to replenish iron stores.

Recommendations

For nausea and epigastric discomfort, alternate day dosing or preparations with lower iron content should be tried. Slow release and enteric-coated forms should be avoided (1A).

Repeat Hb testing is required 2–3 weeks after commencing treatment for established anaemia, to assess compliance, correct administration and response to treatment (1B).

Once the Hb is in the normal range, replacement should continue for 3 months and until at least 6 weeks postpartum to replenish iron stores (1D).

If response to oral iron replacement is poor, compliance should be confirmed and concomitant causes that may be contributing to the anaemia considered, such as folate deficiency or malabsorption (1A).

Intravenous iron therapy

Systematic reviews and meta-analyses found that pregnant women receiving intravenous (IV) iron, compared with oral

iron, achieved the target Hb more often, had an increased Hb after 4 weeks and had fewer side effects (Govindappagari & Burwick, 2018; Govindappagari & Burwick, 2019; Qassim *et al*, 2018).

IV iron therapy is indicated when there is absolute non-compliance with, or intolerance of, oral iron therapy or proven malabsorption or when a rapid Hb response is required. Contraindications include a history of anaphylaxis or serious reactions to parenteral iron therapy, first trimester of pregnancy, active acute or chronic bacteraemia and decompensated liver disease.

The intravenous iron preparations currently available in the UK and their properties are summarized in Table III. Iron sucrose has a higher availability for erythropoiesis than iron dextran and experience suggests a good safety profile in pregnancy (Bayoumeu *et al*, 2005). Its use is limited by the total dose that can be administered in one infusion, requiring multiple infusions. Iron carboxymaltose and iron isomaltoside overcome this problem, allowing single dose administration (Lyseng-Williamson & Keating, 2009; Gozzard, 2011; Qassim *et al*, 2018).

Fast-acting intravenous iron preparations. Iron III carboxymaltose (Ferrinject) is a ferric hydroxide carbohydrate complex and Iron III isomaltoside (Monofer) has strongly bound iron in spheroid iron-carbohydrate particles. Both allow controlled delivery of iron within the cells of the reticuloendothelial system (primarily bone marrow) and subsequent release of bioavailable iron to the iron binding proteins, ferritin and transferrin. The rapid uptake by the reticuloendothelial system minimises the risk of release of free iron. Randomised controlled trials have shown non-inferiority (Breyman *et al*, 2016; Van Wyk & Martens, 2007) and superiority (Seid *et al*, 2008; Khalafallah *et al*, 2018) to oral ferrous sulphate in the treatment of iron deficiency anaemia in pregnancy and postpartum, with rapid and sustained increases in Hb. It should be noted that many studies on the effects of IV iron are powered on haematological outcomes, not clinical ones.

Dosing. Traditionally the Ganzoni formula (Ganzoni, 1970) has been used for estimation of iron dose. However this is cumbersome, prone to error and can underestimate iron requirements (Dignass *et al*, 2015); use of a simplified approach to dosing has been recommended (Dignass *et al*, 2015).

Table III. Summary of intravenous iron preparations available in the UK.

	Cosmofer Iron (III) hydroxide dextran complex	Venofer Iron (III) hydroxide sucrose complex	Ferinject Iron (III) carboxymaltose	Monofer Iron (III) isomaltoside
Dose of elemental iron	50 mg/ml	20 mg/ml	50 mg/ml	100 mg/ml
Test dose required as per manufacturer	Yes, before every IV dose, once before IM treatment	First dose new patients only	No	No
Routes of administration	Slow IV injection IV infusion of total dose IM injection total dose	Slow IV injection IV infusion	Slow IV injection IV infusion	Slow IV injection IV infusion
Able to administer total dose	Yes (up to 20mg/kg bw over 4–6 h)	No	Yes [up to 20 mg/kg bw (maximum of 1000 mg/week) over 15 min]	Yes (up to 20 mg/kg bw over 15–30 min)
Half-life	5 h	20 h	7–12 h	5h
Dosage	100–200 mg per IV injection up to 3 times a week Total dose infusion up to 20 mg/kg bw over 4–6 h (100 mg IM into alternate buttocks)	Total IV single dose no more than 200 mg, can be repeated up to 3 times in 1 week	Total dose infusion up to 20 mg/kg bw. Maximum weekly dose of 1000 mg, which can be administered over 15 min.	Total dose infusion up to 20 mg/kg bw. Doses up to 1000 mg can be administered over >15 min, doses >1000 mg should be administered over >30 min.
Use in pregnancy	No adequate data for use in pregnant women, contra-indicated in first trimester thereafter risk benefit based on clinical need	Not in first trimester	Avoid in first trimester	Avoid in first trimester
Lactation	Risk not known	Unlikely to pass to maternal milk; no clinical trials	<1% iron passed into milk; unlikely to be significant	Low transfer of iron into milk; unlikely to be significant
Adverse drug-related events	5% of patients may experience minimal adverse events (dose-related) Risk of severe anaphylaxis <1/10 000 Risk of anaphylactoid symptoms >1/1000 to <1/100	0.5–1.5% of patients may experience adverse events Risk of anaphylactoid reaction >1/10 000 to <1/1000	Risk of anaphylactoid reaction >1/10 000 to <1/1000	Risk of anaphylaxis/anaphylactoid reactions >1/10 000 to <1/1000

bw, body weight; IM, intramuscular; IV, intravenous.

Adverse effects and cost effectiveness. Genuine hypersensitivity is rare and no difference between the risk for hypersensitivity reactions has been identified among IV iron products available in the UK. In rare cases, fetal bradycardia has been observed in pregnant women with hypersensitivity reactions to parenteral iron (<https://www.medicines.org.uk/emc/product/5676/smpc>). The European Medicines Agency (EMA, 2013) concluded that the benefit-risk balance of intravenous iron-containing medicinal products is favourable, as the benefits continue to outweigh the risks in the treatment of iron deficiency when the oral route is insufficient or poorly tolerated. Facilities and staff trained in management of anaphylaxis should be available.

Hypophosphataemia can occur after administration of IV iron, particularly ferric carboxymaltose. Case reports in non-pregnant patients have shown associated clinical consequences (Zoller *et al*, 2017). The drop in phosphate may be greater in pregnant than non-pregnant women (Huang *et al*, 2018) but the significance of this is not known.

Haemosiderin skin staining can result from extravasation, particularly if the cannula is incorrectly placed. Women should be advised of this and should be requested to report any pain at the infusion site (Thompson *et al*, 2014).

IV iron is significantly more costly than oral iron, with costs covering not only the drug but also the support for administration.

Breastfeeding after IV iron. A study of 65 patients who received therapeutic dose IV iron isomaltoside, showed a transient increase in iron in breast milk, 3 days after treatment, compared with oral iron. However, the mean iron concentration remained within the normal range and the difference disappeared one week after treatment (Holm *et al*, 2017a).

Recommendations

IV iron should be considered from the second trimester onwards for women with confirmed iron deficiency anaemia who are intolerant of, or do not to respond to, oral iron (2B).

IV iron should be considered in women who present after 34 weeks' gestation with confirmed iron deficiency anaemia and an Hb of <100 g/l (1C).

Management of delivery in women with iron deficiency anaemia

Whilst best practice includes prevention of anaemia or early identification and antenatal treatment, some women enter labour with iron deficiency anaemia. As for all women, it is important that active measures to minimise blood loss at birth are planned.

There is no place for offering routine induction of labour based on isolated iron deficiency anaemia; efforts to

maximise pre-delivery Hb should be made and induction planned according to usual obstetric indications.

Iron deficiency anaemia should not influence the planned mode of birth, and decisions should be made according to obstetric indications.

The intended place of birth may be influenced by pre-labour Hb, as anaemic women may have both a higher likelihood of PPH and lower iron stores for coping with haemorrhage [National Institute for Health and Care Excellence (NICE) 2014]. Other risk factors that might influence the likelihood or impact of haemorrhage should also be taken into consideration, including previous PPH, grandmultiparity, fibroid uterus, multiple pregnancy, severity of anaemia and whether blood components will be accepted or not.

Women with Hb <100 g/l approaching birth should have an individualised plan, including the potential role of intravenous access, 'group and save' in labour, birth in an obstetrician-led unit and active management of third stage of labour (Rogers *et al*, 1998), discussed and documented clearly in the birth plan or maternity notes.

Recommendations

Iron deficiency anaemia should not influence the mode and timing of delivery (2D).

Women with iron deficiency anaemia with an Hb of <100 g/l should deliver in an obstetrician-led unit (1D).

Women with iron deficiency anaemia should have active management of the third stage of labour (1D).

Postpartum anaemia

Postnatal anaemia is defined as an Hb <100 g/l. The risk of postnatal anaemia is reduced by identification and management of iron deficiency in the antenatal period. Women with uncorrected anaemia antenatally should have a Hb check within 48 h of birth, as should those who have had blood loss >500 ml, or symptoms suggestive of postpartum anaemia. Blood loss at delivery is associated with fatigue (Güven *et al*, 2018) and clinical assessment is necessary to consider the best method of iron replacement. Where there is no active bleeding, or clinical requirement to increase Hb urgently, oral iron should be sufficient, provided it is supported with information about the correct administration. Severe symptoms of anaemia may require IV iron for faster benefit (Holm *et al*, 2017b). A large retrospective study of women with a postpartum Hb <80 g/l, confirmed the efficacy of IV iron, with a mean increase in Hb of 19 g/l in 7 days and 31 g/l in 14 days (Broche *et al*, 2005). This is supported by a small randomized controlled trial of IV iron versus blood transfusion for postpartum Hb between 56 and 81 g/l (Holm *et al*, 2017c).

Use of IV iron undoubtedly allows some red cell transfusions to be avoided. However transfusion may be needed if there is continued bleeding or risk of further bleeding,

imminent cardiac compromise or significant symptoms requiring urgent correction. If, after careful consideration, elective transfusion is required, a single unit should be given followed by clinical reassessment and repeat Hb. Women should be fully counselled about potential risks of transfusion and alternative treatments and offered information; consent should be obtained.

Recommendations

Prompt recognition of iron deficiency in the antenatal period followed by iron therapy may reduce the risk of postpartum anaemia (1A).

After delivery, women with blood loss >500 ml, those with uncorrected anaemia detected in the antenatal period or those with symptoms suggestive of anaemia postnatally should have their Hb checked within 48 h of delivery (2A).

Women with Hb <100 g/l within 48 h of delivery, who are haemodynamically stable, asymptomatic, or mildly symptomatic, should be offered oral elemental iron 40–80 mg daily for at least 3 months (2A).

Use of IV iron postpartum should be considered in women who are previously intolerant of, or do not respond to, oral iron and/or where the severity of symptoms of anaemia requires prompt management (2B).

Obstetric units should have guidelines for the criteria to be used for postnatal red cell transfusion in anaemic women who are not actively bleeding (2A).

The decision to transfuse women in the postpartum period should be based on careful evaluation, including whether or not there is risk of bleeding, cardiac compromise or symptoms requiring urgent attention, considering oral or parenteral iron therapy as alternatives (1A).

Women receiving red cell transfusion should be given full information regarding the indication for, and risks of, transfusion and alternative treatments. Consent should be sought and documented in the clinical records (1A).

Prevention of iron deficiency

Prevention offers an alternative strategy to reduce the impact and prevalence of anaemia developing during pregnancy, although there are no clear data to inform the role of universal iron supplementation. Although current guidelines are based on prompt identification and treatment of anaemia and recognition of women at risk, practice audits indicate limited effectiveness of this approach. For example, one study of 14 001 pregnant women from two maternity hospitals found that 46% had an Hb <110 g/l at booking and/or at 28 weeks' gestation and 64% of those with anaemia in the first trimester were still anaemic at 28 weeks (Nair *et al*,

2017). Additional benefits to prevention may relate to cost-effectiveness, including reducing the need for iron supplementation, transfusions, family and social care for preterm births and stillbirths and support for infant neurodevelopment. The US Preventive Services Task Force (2015) stated that the current evidence is insufficient to assess the full balance of benefits and harms of routine iron supplementation during pregnancy.

Regular antenatal iron supplementation will reduce the risk of maternal anaemia, but there is less clarity on the impact on maternal and infant clinical outcomes (Haider *et al*, 2013). In a Cochrane review on use of intermittent iron (21 trials involving many developing countries) the quality of evidence on maternal and infant outcomes was overall assessed as low or very low (Pena-Rosas *et al*, 2015). A structured literature search against UK National Screening Committee criteria also confirmed uncertainty in the magnitude of the adverse outcomes associated with maternal anaemia and the need for research on the role of preventative strategies (Parker *et al*, 2012; Rukini *et al*, 2015).

Recommendations

There is insufficient evidence to assess the benefits and potential hazards of, routine iron supplementation for all women in pregnancy (2C).

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Research recommendations

- 1 Screening and identification of at risk women who are not yet anaemic and determination of the optimal management of such individuals
- 2 Investigation of the sensitivity of biomarkers for detecting iron depletion in pregnant women in the UK
- 3 Determination of the optimal oral iron dose for treatment of iron deficiency anaemia
- 4 Investigation of the role of universal iron supplementation for primary prevention of iron deficiency anaemia during pregnancy

Author contributions

Dr Sue Pavord led and coordinated the guideline and all authors contributed.

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