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# Iron deficiency anaemia in pregnancy: A contemporary review

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and Charlotte J Frise<sup>6,7</sup>

## Summary

Iron deficiency anaemia is a global health problem, which particularly affects pregnant women. Iron deficiency anaemia during pregnancy is associated with increased maternal and perinatal morbidity and mortality. Maternal iron deficiency may also be associated with neurocognitive deficits in infants. Iron requirements increase during pregnancy and are influenced by hepcidin, the master regulator of iron homeostasis. The enduring global burden of maternal anaemia suggests that currently employed iron supplementation strategies are suboptimal. Recent developments in our understanding of systemic and placental iron homeostasis may improve therapeutic effectiveness by altering the dose and frequency of oral iron. Intravenous iron appears to be a safe treatment to correct maternal anaemia rapidly but research on patient-centred outcomes and cost-effectiveness is needed. Future trials should be adequately powered to assess outcomes relevant to pregnant women.

## Keywords

Anaemia, pregnancy, iron deficiency, iron

Date received: 24 January 2020; accepted: 13 May 2020

## Introduction

Approximately 1.24 billion people worldwide are affected by iron deficiency anaemia (IDA).<sup>1</sup> It is one of the leading global causes of years lived with disability, particularly affecting women, low–middle social demographic groups and populations of Asia and sub-Saharan Africa.<sup>1</sup> Maternal anaemia is thought to affect 32 million women worldwide.<sup>2,3</sup> A large, UK cohort study reported that 46% of women were anaemic at some point during pregnancy.<sup>4</sup> Iron deficiency (ID) is by far the most common cause of maternal anaemia but other causes include haemoglobinopathies, such as sickle-cell anaemia and thalassaemia; deficiencies of folate, B12 or both; hookworm infection; schistosomiasis and HIV infection.

The association between anaemia and poor maternal, fetal and neonatal outcomes is now well established.<sup>5,6</sup> Anaemia is increasingly recognised as a potentially modifiable risk factor for postpartum haemorrhage – a leading cause of maternal morbidity and mortality.<sup>7–9</sup> Adverse fetal and neonatal outcomes include preterm labour, growth restriction and increased mortality.

This review discusses iron homeostasis and current definitions of IDA in pregnancy, adverse maternal and neonatal outcomes associated with anaemia, and the most recent treatment recommendations for IDA during pregnancy and the postpartum period. Management of other causes of anaemia is beyond the scope of this review and is reviewed elsewhere.<sup>10–14</sup>

## Methods

We searched MEDLINE, PubMed, Cochrane Central Register of Controlled Trials, EMBASE and Google Scholar. Titles and abstracts were screened and references of all identified systematic reviews, randomised controlled trials, observational studies, review

articles and current treatment guidelines were checked for further relevant literature. The search was restricted to literature from 1 January 2000, but older important publications were not excluded. The end date of the literature search was 12 January 2020. Topics beyond the scope of this review were referenced by relevant narrative reviews, systematic reviews or clinical guidelines where applicable. The literature searches included the following terms: iron; anaemia/anemia; haemoglobin/haemoglobin; outcomes; pregnancy; obstetric; neonatal; fetal/foetal; and parturient. The results are shown in Supplementary Figure 1.

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## Iron homeostasis during pregnancy

### Iron requirements during pregnancy

Iron is an essential element required by almost all organisms due to the indispensable roles it plays in processes such as DNA synthesis, cell growth and differentiation, immunity, mitochondrial function and responses to hypoxia.<sup>15–19</sup> Iron requirements increase approximately 10-fold during pregnancy from 0.8 mg/day in the first trimester to 7.5 mg/day in the third trimester in order to support the increase in maternal red cell mass, sustain placental and fetal growth, and accommodate blood loss during delivery.<sup>20,21</sup> The placenta requires around 90 mg of iron in its own right and transports approximately 270 mg of iron to the fetus over the course of a normal pregnancy.<sup>22</sup>

### The role of hepcidin

Systemic iron homeostasis is controlled by hepcidin – a peptide hormone predominantly produced in the liver and excreted by the kidneys.<sup>16</sup> Hepcidin works by regulating the activity of ferroportin – the sole mammalian iron transport protein.<sup>16</sup> Ferroportin delivers stored, dietary or recycled iron to blood plasma and is expressed at all sites involved in iron–plasma exchange, including the basolateral membrane of duodenal enterocytes, macrophages, hepatocytes and the basal surface of placental syncytiotrophoblasts facing the fetal

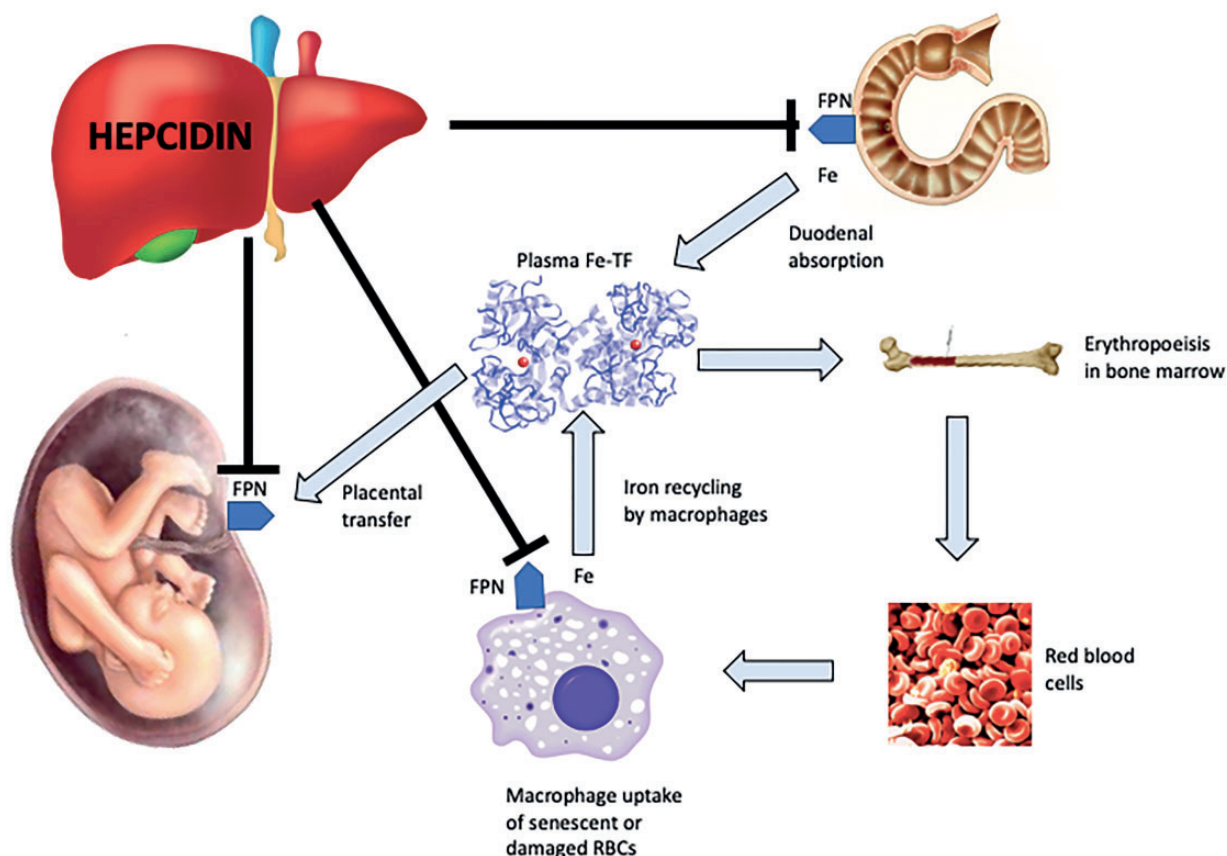
circulation.<sup>16,23</sup> At each of these sites hepcidin causes intracellular degradation of ferroportin, thereby preventing iron export to blood plasma (Figure 1). Changes in hepcidin levels can lead to rapid fluctuations in plasma iron concentrations.

Expression of hepcidin is increased in response to inflammation, infection, malignancy and iron overload.<sup>19</sup> Hepcidin-mediated degradation of ferroportin causes iron to remain trapped within macrophages and duodenal enterocytes and therefore unavailable for those tissues that require it. Inhibition of duodenal absorption of iron – known as the ‘hepcidin block’ – may explain why oral iron is ineffective in inflammatory states. Hepcidin expression is reduced in states of ID, anaemia, hypoxaemia and increased erythropoietic drive.<sup>19</sup>

In healthy pregnancy, hepcidin increases in the first trimester when compared with the non-pregnant state, but then decreases in the second and third trimesters (Figure 2).<sup>24,25</sup> It is presumed that this pattern facilitates increased absorption of dietary iron and release of iron from stores. However, the mechanism underlying maternal hepcidin suppression as pregnancy progresses is still unknown.<sup>22</sup> The development of ID may be the key driver, although low hepcidin concentrations are reported even in women who are iron replete at delivery.<sup>26</sup>

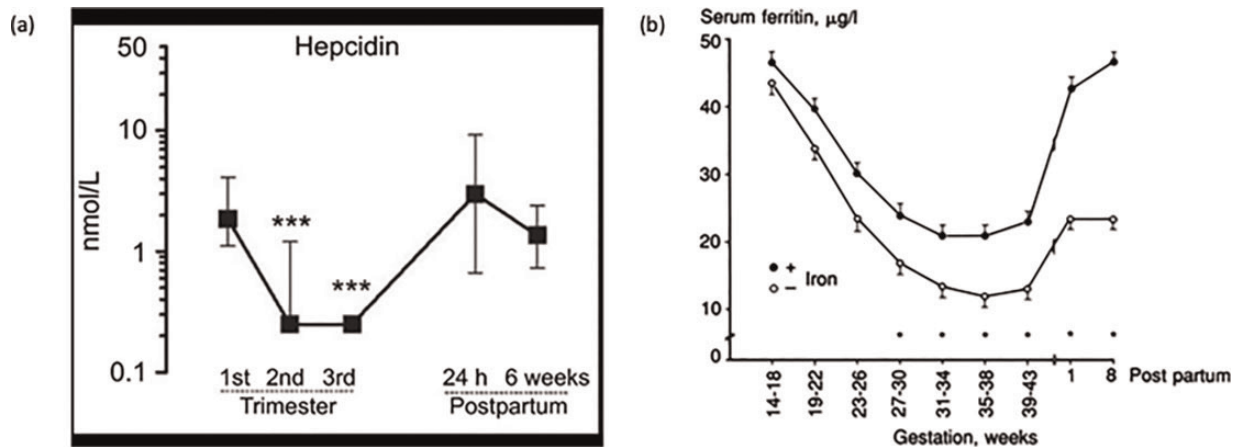
### Placental and fetal iron homeostasis

The majority of iron transfer to the fetus occurs during the third trimester, which coincides with the period of lowest hepcidin expression.<sup>22</sup> This transfer is unidirectional. Iron is bound to transferrin in



**Figure 1.** Hepcidin–ferroportin interaction and major systemic iron pathways. Hepcidin expression results in degradation of ferroportin which impairs release of iron from macrophages and duodenal enterocytes. Reduction in hepcidin during pregnancy increases the availability of iron for placental transfer.

Fe-TF: iron-transferrin; FPN: ferroportin; RBC: red blood cell.



**Figure 2.** Serial changes in serum hepcidin and ferritin concentrations during pregnancy and postpartum. (a) Median (IQR) serum hepcidin concentrations in 31 women during pregnancy and postpartum. \*\*\*Compared with first-trimester values,  $P < 0.0001$ . (b) Geometric mean  $\pm$  SEM serum ferritin concentrations during pregnancy in women given oral iron supplementation (filled circles;  $n = 63$ ) compared with controls (open circles;  $n = 57$ ). Source: Reproduced with permission from van Santen et al.<sup>25</sup>

the maternal circulation and is taken up by transferrin receptor 1 located on the apical membrane of the syncytiotrophoblast.<sup>22</sup> This complex is then endocytosed and eventually exported to the basal surface of the syncytiotrophoblasts where, through ferroportin, iron enters the fetal circulation.<sup>21,22</sup> Relatively little is known about fetal hepcidin and the responses of the maternal-placental-fetal unit to changes in maternal iron status. A recent study evaluating mechanisms in murine and in vitro trophoblastic models of severe ID observed an unexpected response that prioritised placental iron retention over fetal iron transfer.<sup>23</sup> This response may have an evolutionary benefit to protect iron-dependent placental processes, and may provide overall benefit for the fetus despite diminishing fetal iron availability. This work also suggests that the fetus may be unable to compensate for maternal ID by increasing placental iron transfer.<sup>23</sup> Further studies are required to clarify the significance of these findings.

### Changes in other markers of iron status during pregnancy

Concentrations of serum ferritin and iron, along with transferrin saturation, gradually fall to a nadir in the third trimester.<sup>22,24</sup> The decrease is less marked in pregnant women receiving iron supplementation.<sup>22</sup> However, since ferritin is an acute phase protein, and transferrin a negative acute phase protein, these parameters become unreliable as indices of iron status in pregnancies complicated by inflammatory pathologies.<sup>16</sup>

### Defining IDA in pregnant women

IDA is a composite diagnosis based on haemoglobin (Hb) and ferritin concentrations. The World Health Organisation (WHO) has defined anaemia in pregnancy as a Hb concentration less than 110 g/L irrespective of trimester, but recognises that Hb may fall physiologically by around 5 g/L during the second trimester.<sup>27</sup> This is due to a rise in plasma volume of  $\sim 50\%$ , disproportionate to the concomitant  $\sim 25\%$  rise seen in red cell mass.<sup>28,29</sup>

The WHO definition has been questioned as it is derived from studies conducted in the 1950s and 1960s that did not include pregnant women and used now superseded methods for measuring Hb. Recent evidence has also questioned the validity of the figure of 5 g/L

for the physiological fall in Hb during the second trimester. A large, multi-ethnic, observational study of 7054 pregnant women found that the fall in Hb was in the order of 14 g/L, or 11% of the first trimester value.<sup>27</sup> Such findings have significant implications for the diagnosis and management of maternal anaemia.<sup>30,31</sup> The use of a lower Hb threshold compared with men for the diagnosis of anaemia in non-pregnant women has been recently challenged,<sup>32</sup> and guidelines now recommend targeting an Hb  $> 130$  g/L in patients undergoing major surgery, irrespective of sex.<sup>33</sup>

The most recent British Committee for Standards in Haematology (BCSH) guidelines on the management of ID have defined anaemia as Hb  $< 110$  g/L in the first trimester,  $< 105$  g/L in the second and third trimesters, and  $< 100$  g/L in the immediate postpartum period.<sup>34</sup> It is recommended that Hb routinely be measured at the initial booking consultation with a healthcare professional in the first trimester and at around 28 weeks' gestation. Although not supported by high-quality evidence, these timepoints were felt to be practically feasible.

Most stored iron is located in the liver, bound to the iron storage protein ferritin. The most common test of iron status, serum ferritin, provides a convenient measure of storage iron. Current BCSH guidelines recommend using a ferritin of less than 30 µg/L to diagnose ID in pregnancy, but this is not unified globally.<sup>34,35</sup> The ferritin threshold of 30 µg/L is derived from two studies published in the 1990s that compared serum ferritin with histochemical assessments of bone marrow iron stores.<sup>36,37</sup> These studies had limitations including small sample sizes and inclusion of women with possible coexisting inflammatory conditions. As already mentioned, ferritin is an acute phase protein. Ferritin may even be elevated as a result of pregnancy itself, so while a low ferritin almost invariably indicates ID, a normal ferritin cannot reliably be used to exclude it. To date, no high-quality studies have been undertaken to investigate pregnancy-specific ferritin thresholds.

Most experience with other biomarkers of iron status such as transferrin saturation, soluble transferrin receptor, reticulocyte Hb content, mean cell Hb concentration and hepcidin comes from non-pregnant populations; experience in pregnancy is largely limited to research purposes.<sup>38-41</sup>

### Non-anaemic iron deficiency

Anaemia is the final manifestation of ID as erythropoiesis is often preserved until the advanced stages of ID.<sup>42</sup> Therefore, much of the



burden of ID in pregnant women will go unnoticed if the absence of anaemia is taken to imply adequate iron stores. Non-anaemic iron deficiency (NAID) is increasingly being recognised as a disease but the clinical relevance in pregnancy is unclear.<sup>42</sup> A recent study of 102 non-anaemic pregnant women found that 42% had evidence of ID as determined by a ferritin less than 30 µg/L or transferrin saturation less than 20%, but data on maternal and fetal outcomes were lacking.<sup>43</sup>

A recent systematic review of iron supplementation in healthy non-pregnant women suffering from NAID showed lower levels of subjective fatigue in participants who received iron.<sup>44</sup> However, there were no improvements in objective measures of physical capacity such as time trials, time to exhaustion tests or maximal oxygen consumption. Furthermore, the overall quality of evidence was judged to be low to moderate. Small exploratory studies in patients undergoing elective colorectal and cardiac surgery have suggested worse postoperative outcomes in patients with NAID when compared with iron-replete individuals.<sup>45,46</sup>

Relying on the presence of anaemia to prompt assessment of iron status may result in large numbers of pregnant women with ID being missed. Further research into the diagnosis of NAID and its impact on maternal and fetal outcomes is needed. Routine screening of pregnant women using serum ferritin has been suggested; however, cost implications and lack of well-designed prospective studies to support this approach mean that a more targeted approach of identifying and treating at-risk pregnant women is currently recommended.<sup>34</sup>

**[AQ1]**

## Outcomes associated with maternal anaemia

### Maternal outcomes

The clinical signs and symptoms of IDA include fatigue, pallor, angular cheilitis, weakness, palpitations, shortness of breath, restless legs, pica syndrome, irritability and poor concentration. These may also be present in NAID.

Observational studies<sup>47,48</sup> have demonstrated an association between maternal anaemia and mortality, with one study demonstrating a 29% linear increase in maternal mortality with each 10 g/L decrease in maternal Hb.<sup>48</sup> A recent study reported that severe anaemia, defined as Hb < 70 g/L during pregnancy or postpartum, doubled the risk of death.<sup>49</sup> Of particular concern, maternal anaemia – with or without ID – increases the risk of developing postpartum haemorrhage.<sup>7,50</sup> A large, two-centre, UK study, involving 10,213 women, found that 62% of women with Hb < 85 g/L developed postpartum haemorrhage, and 26% progressed to develop severe (greater than 1500 mL) postpartum haemorrhage.<sup>51</sup>

It is important to note that the majority of these data come from low- and middle-income countries.<sup>48,49</sup> The timing of Hb measurement is not always clear and therefore it is difficult to determine whether postpartum haemorrhage led to severe anaemia, or whether severe anaemia during pregnancy increased the risk of postpartum haemorrhage. In addition, despite attempts to control for multiple confounders such as haemorrhage, sepsis and critical care admission, it is possible that a weaker association between anaemia and poor maternal outcomes exists than is initially suggested by such data.

Postpartum anaemia has been linked to depression,<sup>52–54</sup> fatigue,<sup>55</sup> impaired cognition,<sup>56</sup> impaired lactation and early cessation of breast feeding.<sup>57,58</sup> Trials of postpartum iron therapy have demonstrated improvements in Hb and serum ferritin concentration but data on patient-centred outcomes are lacking.<sup>59</sup>

### Fetal and neonatal outcomes

Maternal IDA is a recognised risk factor for preterm labour, low birthweight and small-for-gestational age (SGA) babies.<sup>5,7,60,61</sup> The Baby's Vascular health and Iron in Pregnancy (BABY VIP) study showed that maternal ID in the first trimester was associated with a two-fold increase risk of having a fetus with SGA. Every 10 g/L decrease in maternal Hb before 20 weeks' gestation was associated with a 30% increase in the relative risk (RR) of SGA.<sup>61</sup> A systematic review of 48 randomised controlled trials (a total of 17,793 women) and 44 cohort studies (a total of 1,851,682 women) found that iron supplementation resulted in a modest increase in birthweight (weighted mean difference (WMD) 41–69 g) with a small reduction in the risk of delivering a low birthweight infant.<sup>60</sup> There was no evidence of an effect on gestation length, preterm birth or SGA infants.

Maternal anaemia is also associated with increased perinatal and neonatal mortality.<sup>4,7</sup> A large, multi-ethnic, UK observational cohort study which evaluated over 14,000 pregnant women, found that women with Hb < 100 g/L had a three-fold increased risk of perinatal death and a five-fold increased risk of stillbirth when compared with women who had Hb > 110 g/L.<sup>4</sup> The authors controlled for multiple confounders including advanced maternal age, ethnicity, body mass index, smoking status and a range of medical comorbidities.

There is increasing interest in the impact of maternal ID on the neonatal brain and cognitive development.<sup>62</sup> Fetal brain growth accelerates rapidly in the last trimester and continues for the first 2 years after birth,<sup>63</sup> by the end of which total brain volume reaches 80%–90% of adult volume.<sup>64</sup> The iron-dependent processes occurring during this period include monoamine neurotransmission, myelination and hippocampal development.<sup>65</sup> ID has been shown to alter expression of genes critical for hippocampal development and function.<sup>66</sup> Infants with evidence of ID in utero have been demonstrated to have abnormal neural maturation, poor memory, altered interactions with caregivers and an increased incidence of abnormal neurological reflexes.<sup>65,67</sup> Low ferritin levels in utero have also been linked with lower IQ, worse language ability and poorer tractability at up to 5 years of age.<sup>68</sup> Studies addressing the effects of iron supplementation have yielded mixed results. In one study in Nepal, prenatal iron supplementation for women at high risk of developing ID resulted in improved intellectual and fine motor functioning in subsequent children aged 7–9 years.<sup>69</sup> However, in other studies, the effects of iron supplementation on children whose mothers have established ID have been less clear,<sup>70</sup> implying that timing of the intervention is critical; earlier supplementation during the antenatal period may be necessary for a beneficial effect on the developing brain. Future maternal intervention trials should incorporate neurodevelopmental outcomes of offspring.

### Treatment strategies

The recommendations from the most recent BCSH guidelines<sup>34</sup> are summarised in Table 1. Guidelines from other countries make broadly similar recommendations, with some modifications tailored towards their respective population.<sup>71–73</sup>

### Prenatal

A careful history is required to identify women at risk of developing ID with or without anaemia (Table 2). All women should be offered dietary advice, though this is invariably insufficient to correct established ID. Dietary iron is absorbed in two forms – non-haem (inorganic) iron and haem-bound iron. Non-haem iron exists predominantly in the oxidised ferric (Fe<sup>3+</sup>) form and needs to be reduced to the ferrous (Fe<sup>2+</sup>) form in order to be absorbed efficiently.<sup>34</sup>

**Table 1.** Summary of key recommendations from the 2019 UK guidelines on the management of iron deficiency anaemia.

Recommendation	Grade of recommendation
<i>Antenatal</i>	
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, with implications for infant neurocognitive development	2B
Haemoglobin should be routinely measured at booking and at around 28 weeks' gestation	1D
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
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 less than 30 µg/L in pregnancy is indicative of iron deficiency. Levels higher than this do not rule out iron deficiency or depletion	2C
The optimal dose of elemental oral iron of 40–80 mg every morning is suggested, checking haemoglobin at 2–3 weeks to ensure an adequate response. Further research is warranted.	2C
For nausea and epigastric discomfort, alternate day dosing or preparations with lower iron content should be tried.	1A
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 is poor, compliance should be checked, and consideration given to alternative causes of anaemia	1A
Intravenous iron should be considered in women who present after 34 weeks' gestation with confirmed iron deficiency anaemia and an Hb of less than 100 g/L	1C
<i>Intrapartum and postpartum</i>	
Women with iron deficiency anaemia with an Hb of less than 100 g/L should deliver in an obstetrician-led unit and should have active management of the third stage of labour	1D
After delivery, women with blood loss greater than 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 less than 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 intravenous 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

Hb: haemoglobin.

**Table 2.** Risk factors for developing iron deficiency anaemia during pregnancy.

<b>Lifestyle factors</b>	
• Vegetarian or vegan diets	
• Diets low in haem iron or high in substances impairing iron absorption	
<b>Patient factors</b>	
• Previous anaemia	
• Malabsorptive conditions (e.g. inflammatory bowel disease, coeliac disease)	
• Known haemoglobinopathy	
• Jehovah's Witness	
<b>Obstetric factors</b>	
• Multiparity	
• Multiple gestation (e.g. twins)	
• High risk of bleeding during pregnancy or during labour	
• Short interpregnancy interval (less than 1 year)	

Meat, fish and poultry are rich sources of haem iron, which is absorbed much more readily than non-haem iron. Non-haem iron is predominantly derived from plant-based foods, where it is complexed in insoluble forms, which significantly contributes to the high prevalence of ID observed in societies that consume vegetarian diets. Iron absorption is inhibited by tannins in tea and coffee, and phytate, a substance found in cereals and legumes. Co-ingestion of vitamin C

(ascorbic acid) significantly increases iron uptake from non-haem sources.<sup>74</sup>

**Oral iron.** Oral iron is an effective, cheap and safe way to treat ID. The large systematic review discussed earlier found that prenatal iron increased maternal Hb by a mean of 46 g/L (95% Confidence Interval (CI): 37–55 g/L), with concomitant reductions in the RR of developing (1) anaemia (RR 0.50; 95% CI: 0.42–0.59); (2) ID (RR 0.59; 95% CI: 0.46–0.79) and (3) iron-deficiency anaemia (RR 0.40; 95% CI: 0.26–0.60).<sup>60</sup>

Current pregnancy guidelines recommend 40–80 mg of elemental oral iron once daily each morning,<sup>34</sup> which differs from previous guidance recommending 100–200 mg daily.<sup>74</sup> The WHO recommendations on antenatal care for a positive pregnancy experience recommend 30–60 mg of oral iron once daily or intermittent doses of 120 mg if daily iron is not acceptable due to side effects.<sup>75,76</sup> These recommendations have largely been driven by recent advances in our understanding of iron homeostasis. Studies in non-pregnant women have shown that a once daily or alternate day dosing strategy may be more effective and better tolerated by women compared with the traditional higher total daily doses.<sup>77,78</sup> Oral ingestion of a single dose of ferrous sulphate results in a rapid rise in circulating hepcidin, which can take up to 48 h to return to normal.<sup>77</sup> Subsequent oral doses may not be absorbed during this period because of this 'hepcidin block', and may expose women to well-recognised gastrointestinal side effects such as nausea, constipation and epigastric pain. A recent meta-analysis reported an incidence of up to 70% associated

with oral iron.<sup>79</sup> Since hepcidin levels are also lowest in the morning, dosing at this time is advised.<sup>80</sup>

Ferrous salts such as ferrous sulphate, ferrous fumarate and ferrous gluconate (Table 3) are preferable to ferric salts due to better oral bioavailability but differ with respect to available elemental iron. Multivitamins and 'off the shelf' preparations are not recommended as they contain insufficient amounts of iron and may include other substances, particularly calcium, that impair iron absorption. Slow release and enteric-coated formulations are undesirable as the majority of iron in these preparations is carried past the duodenum and therefore not absorbed.<sup>81</sup>

Once commenced on oral iron, Hb should be measured after 2–3 weeks to assess response. Once Hb has normalised, replacement should continue for three further months, and, if near term, up to 6 weeks postpartum.<sup>34</sup> If the response is poor, compliance should be explored. Other causes for failure to respond to oral therapy include iron sequestration driven by elevated hepcidin as a result of inflammation or infection; ongoing blood loss and other causes of anaemia such as folate deficiency.

**Intravenous iron.** Intravenous iron is efficacious in replenishing iron stores and treating anaemia in a wide range of clinical situations with or without the presence of inflammation.<sup>82,83</sup> Intravenous iron should be considered from the second trimester for women with confirmed IDA who do not respond to, or who fail to tolerate, oral iron. Given the proximity to delivery, it should also be considered for women presenting after 34 weeks' gestation with Hb < 100 g/L and confirmed ID.<sup>34</sup>

Recent systematic reviews have shown intravenous iron to be more effective at improving maternal Hb (WMD 6.6 g/L; 95% CI: 3.1–10.1 g/L) and ferritin (WMD 45.6 µg/L; 95% CI: 26.21–65.16 µg/L) at delivery when compared with oral iron supplementation; intravenous therapy is also associated with fewer mild medication reactions than oral treatment (RR 0.34; 95% CI: 0.20–0.57).<sup>84,85</sup> Intravenous iron is also associated with higher neonatal birthweight (WMD 58 g; 95% CI: 6–111 g). However, there was no evidence of an effect of intravenous iron to reduce maternal blood transfusion requirements or improve neonatal Hb. It is worth noting that the majority of the studies included in these systematic reviews were small and of low methodological quality, as evidenced by the wide confidence intervals. There was also heterogeneity with regards to the timing and dosage of iron supplementation and a lack of reporting of maternal and neonatal-centred outcomes.

Four intravenous iron preparations are currently available in the UK. The properties of these are summarised in Table 4. **[AQ2]** Newer iron preparations such as ferric carboxymaltose (Ferinject<sup>®</sup>) and iron isomaltoside (Monofer<sup>®</sup>) form stable carbohydrate complexes that permit controlled delivery of iron to the reticuloendothelial system (liver macrophages, spleen and bone marrow).<sup>86,87</sup> Iron is subsequently delivered in a slow and controlled manner to iron binding proteins such as ferritin. These mechanisms limit the amount of

freely available and potentially toxic unbound iron circulating in the bloodstream, while also bypassing the 'hepcidin block' in inflammatory states.<sup>87</sup>

Newer preparations also enable delivery of higher doses of iron over short time frames, typically 15–20 min (Table 4) and are increasingly being offered in an outpatient setting. True anaphylaxis and severe hypersensitivity reactions are rare with these modern intravenous iron preparations,<sup>88,89</sup> but facilities and staff trained in the management of anaphylaxis should be present. Common side effects include nausea, headaches, dizziness, hypertension, flushing and injection/infusion site reactions. These are managed by slowing the infusion rate and providing symptomatic care, such as antiemetics. Transient hypophosphataemia has been reported in several studies, and this may be more pronounced in pregnant compared with non-pregnant women.<sup>90,91</sup> Whether this hypophosphataemia has any clinically relevant consequences is uncertain. Permanent haemosiderin skin pigmentation has been reported from extravasation,<sup>92</sup> and women should therefore be advised to report any pain at the infusion site. An increased risk of infection was a concern with older intravenous iron preparations, driven by the availability of unbound circulating iron for invading bacterial pathogens. Recent systematic reviews, which have included critically ill patients at high risk of sepsis, have demonstrated no increased risk of bacterial infection.<sup>93,94</sup>

Intravenous iron preparations are considerably more expensive than oral iron, even without including the costs of administration such as infusion kits and staff time. Although trials have reported costs of treatment, no formal cost-effectiveness analysis has been undertaken comparing intravenous iron with oral iron in pregnant women. Given the improved effectiveness and favourable side-effect profile of newer intravenous iron preparations discussed above, it remains possible that the overall economic cost might favour intravenous therapy in this setting.

## During labour and postpartum

Women who enter labour with IDA are at increased risk of postpartum haemorrhage and have lower iron stores in reserve to support compensatory erythropoiesis following significant blood loss. Mode of delivery should be determined by obstetric indications but appropriate intravenous access, availability of a group and screen, birth in an obstetrician-led unit and active management of the third stage of labour should be considered.<sup>34</sup>

Appropriate management of IDA in the antenatal period reduces the likelihood of developing postpartum anaemia. Current guidelines recommend measuring Hb within 48 h of delivery in women with uncorrected anaemia in the antenatal period, blood loss of over 500 mL, or signs and symptoms suggestive of anaemia. Oral iron may be sufficient in women without active bleeding and asymptomatic or mildly symptomatic anaemia. The recommended daily dose is 40–80 mg of elemental iron for 3 months.<sup>34</sup>

**Table 3.** Characteristics of different oral iron formulations.

	Ferrous sulphate	Ferrous fumarate	Ferrous gluconate
Brand name	Feospan <sup>®</sup> , FeroSul <sup>®</sup> Ferrograd <sup>®</sup>	Galfer <sup>®</sup>	Fergon <sup>®</sup> , Ferralet <sup>®</sup>
Preparation, mg	200	210	300
Elemental iron, mg	65	65	35
Common side effects	Constipation; diarrhoea; nausea; gastrointestinal discomfort		
Uncommon side effects	Discolouration of stools; decreased appetite		
Product cost per 28 packet tablet,	1.60	1.00	3.35
NHS indicative price as per BNF, £			

BNF: British National Formulary; NHS: UK National Health Service. **[AQ4]**

**Table 4.** Characteristics of different intravenous iron formulations available in the UK.

	Ferric carboxymaltose	Iron isomaltoside	Iron (III) hydroxide sucrose	Iron (III) hydroxide dextran
Brand name	Ferinject®	Monofer®	Venofer®	CosmoFer®
Iron content, mg/mL	50	100	20	50
Labile iron (% injected dose)	0.6	1.0	3.5	3.5
Route of administration	Intravenous, slow infusion	Intravenous, slow infusion	Intravenous, slow infusion	Intravenous, slow infusion; intramuscular (gluteal)
Test dose required	No	No	First dose for new patients	Yes, before every dose
Maximal single dose	20 mg/kg diluted in 100 mL 0.9% saline. Maximum weekly dose of 1000 mg	20 mg/kg diluted in maximum 500 mL 0.9% saline	200 mg, can be repeated up to three times in 1 week	20 mg/kg, diluted in maximum 500 mL 0.9% saline or 5% glucose
Half-life	7–12 h	5 h	6 h	20 h
Infusion time, minimum	15 min	15 min, Doses greater than 1000 mg should be administered over greater than 30 min	30 min	Over 4–6 h
Use in pregnancy	Avoid in first trimester	Avoid in first trimester	Avoid in first trimester	Avoid in first trimester
Lactation	Less than 1% iron passed into breastmilk; doubtful clinical significance	Low transfer into breastmilk; doubtful clinical significance	No available data	No available data
Adverse drug reactions	Common: nausea (2.9%) headache, dizziness, injection site reactions, transient hypophosphataemia	Common: nausea, injection site reactions	Common: nausea, injection site reactions, hypotension, hypertension	Approximately 5% will experience dose-dependent adverse reactions
Anaphylactic reactions	Rare ( $\geq 1/10,000$ to $< 1/1000$ )	Rare ( $\geq 1/10,000$ to $< 1/1000$ )	Rare ( $\geq 1/10,000$ to $< 1/1000$ )	Rare ( $\geq 1/10,000$ to $< 1/1000$ )
Product cost per 1000 mg, NHS indicative price as per BNF, £	154.23	169.50	109.09	159.40

BNF: British National Formulary; NHS: UK National Health Service.

Women requiring urgent correction of symptomatic anaemia, or those who are intolerant of oral iron, should be offered intravenous iron. A recent systematic review demonstrated a mean improvement of 9 g/L (95% CI: 4–13 g/L) at 6 weeks postpartum in women who received intravenous iron compared with oral iron.<sup>59</sup> The reported rate of anaphylaxis in women receiving intravenous iron was 0.6%. Low-quality evidence suggests that intravenous iron may lower fatigue and depression scores at up to 12 weeks postpartum.<sup>95</sup> There is a need for well-designed, adequately powered, randomised controlled trials.

Allogeneic red blood cell transfusion should be reserved for women with severe active bleeding, imminent cardiac compromise or symptoms of anaemia requiring urgent attention. Women should be fully consented regarding the potential risks of transfusion,<sup>96</sup> including being unable to donate blood in the future, and potential alternative treatments.

## Conclusion and directions for future research

ID remains the most common cause of maternal anaemia worldwide, with detrimental consequences for both mother and baby. Large-scale epidemiological studies have demonstrated that antenatal anaemia is a risk factor for maternal mortality, perinatal mortality, preterm labour, low birthweight infants and postpartum haemorrhage. Maternal ID may also be associated with poor infant

neurodevelopmental outcomes. Postpartum anaemia is linked with lactation failure and low maternal quality of life scores.

The WHO aims to reduce the prevalence of anaemia in women of reproductive age by 50% between 2010 and 2025.<sup>6</sup> Currently, interventions such as oral or intravenous iron do not appear to be working at the scale required to meet the WHO aims. This may be partly due to uncertainty regarding how best to investigate, prevent and treat maternal anaemia. Importantly, few trials so far have reported maternal and neonatal-centred outcomes; the vast majority have instead focused on haematological parameters. Despite this limitation being highlighted in a systematic review in 2012,<sup>97</sup> little progress appears to have been made since. Advances in our understanding of iron physiology have led to the potential for considerable improvement by altering the dosing strategy for oral iron. Newer laboratory indices of iron status such as hepcidin may ultimately help to guide iron therapy, but a recent study found no benefit of using a hepcidin-guided screen-and-treat approach when compared with the WHO's recommended regimen.<sup>98</sup>

Over a 5-year period, the Primary prevention of maternal ANaemia to avoid preterm Delivery and other Adverse outcomes (PANDA)<sup>99</sup> research programme, recently funded by the National Institute for Health Research (NIHR), will attempt to address some of the research uncertainties highlighted in this review. Initial work will include identifying barriers and enablers to iron supplementation, development of a behavioural intervention to promote compliance and a feasibility randomised controlled trial to identify the optimal dosing schedule for oral iron. This will be followed by a larger, two-arm, multicentre trial of oral-iron supplementation versus placebo



which will aim to enrol 11,020 pregnant women across 20 maternity units. The primary outcome is a composite of preterm birth, still birth, neonatal death and SGA infants. Long-term maternal and infant neurodevelopmental outcomes will also be evaluated. Future research is also needed to identify effective screening strategies during the antenatal and postnatal periods; determining the optimal dose of oral iron treatments; developing core outcome sets; and exploring the utility of universal iron supplementation to prevent maternal IDA.

### Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: AS is currently being supported by an NIHR Doctoral Research Fellowship (DRF-2017–10-094).

### Ethical approval

Not applicable.

### Informed consent

Not applicable.

### Guarantor


CSB is the guarantor of the present work.

### Contributorship

CJF and MCF conceived the idea for the review. The literature searches, drafting and editing of all article versions were undertaken by CB and AS. All authors have contributed to, reviewed and approved the final version of the draft.

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