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The effect of iron deficiency and anaemia on women's health

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Abstract:	Iron deficiency and anaemia are global health problems and major causes of morbidity in women. Current definitions of anaemia in women are historic and have been challenged by recent data from observational studies. Menstrual loss, abnormal uterine bleeding and pregnancy put women at risk of developing iron deficiency which can result in severe fatigue, reduced exercise capacity and poor work performance. Iron deficiency and anaemia during pregnancy are associated with adverse maternal and fetal outcomes, including neurocognitive deficits in children born to iron deficient mothers. Both iron deficiency and anaemia are common in women undergoing surgery but their association with poor outcomes remains uncertain. The enduring burden of iron deficiency and anaemia in women suggests that current strategies for recognition, prevention and treatment are limited in their utility. Improvements in our understanding of iron homeostasis and the development of new iron preparations, that are better absorbed with fewer side effects, may improve therapeutic effectiveness of oral iron. Intravenous iron is efficacious for correcting anaemia rapidly but high quality data on patient-centred outcomes and cost-effectiveness are currently lacking. Many recommendations for treatment of iron deficiency and anaemia in national guidelines are not supported by high quality evidence. There is a need for robust epidemiological data and well-designed clinical trials. The latter will require collaborative working between researchers and patients to design studies in ways that incorporate patients’ perspectives on the research process and target outcomes that matter to them.

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Review Article

The effect of iron deficiency and anaemia on women's health

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Summary

Iron deficiency and anaemia are global health problems and major causes of morbidity in women. Current definitions of anaemia in women are historic and have been challenged by recent data from observational studies. Menstrual loss, abnormal uterine bleeding and pregnancy put women at risk of developing iron deficiency which can result in severe fatigue, reduced exercise capacity and poor work performance. Iron deficiency and anaemia during pregnancy are associated with adverse maternal and fetal outcomes, including neurocognitive deficits in children born to iron deficient mothers. Both iron deficiency and anaemia are common in women undergoing surgery but their association with poor outcomes remains uncertain. The enduring burden of iron deficiency and anaemia in women suggests that current strategies for recognition, prevention and treatment are limited in their utility. Improvements in our understanding of iron homeostasis and the development of new iron preparations, which are better absorbed with fewer side effects, may improve therapeutic effectiveness of oral iron. Intravenous iron is efficacious for correcting anaemia rapidly but high quality data on patient-centred outcomes and cost-effectiveness are currently lacking. Many recommendations for treatment of iron deficiency and anaemia in national guidelines are not supported by high quality evidence. There is a need for robust epidemiological data and well-designed clinical trials. The latter will require collaborative working between researchers and patients to design studies in ways that incorporate patients' perspectives on the research process and target outcomes that matter to them.

Introduction

Iron deficiency is the most common cause of anaemia worldwide and affects approximately 1 billion people [1, 2]. It is the leading cause of years lived with disability burden in women [2]. The documented prevalence of iron deficiency in women ranges from 15% to 18% globally (Table 1) [3]. This problem becomes even more significant when we take into account functional iron deficiency and/or iron sequestration secondary to chronic inflammation or infection [2, 4]. Worldwide, anaemia is thought to affect 29% of non-pregnant women and 38% of pregnant women [1, 5]. In the UK, approximately 46% of women develop anaemia at some point during pregnancy [6]. Iron deficiency anaemia is now an established risk factor for poor peri-operative, maternal, fetal and neonatal outcomes [7, 8]. In this narrative review, we will discuss current definitions, causes and treatment of iron deficiency and anaemia in women.

Current definitions of iron deficiency and anaemia in women's health

Serum ferritin is currently the most reliable indicator of iron deficiency in the absence of inflammation but there is considerable variation in recommended cut-offs. This is, in part, due to variation in assay techniques and platforms used as well as limited adherence to World Health Organization (WHO) reference standards [9]. As a result, recommendations for all the guidelines are mostly based on low quality evidence. The most recent guidelines from WHO published in April 2020 recommend a ferritin cut-off of < 15 mcg.l^{-1} for diagnosing iron deficiency in adults and pregnant women in the first trimester. Guidelines from the UK on the management of iron deficiency recommend a cut-off of < 30 mcg.l^{-1} for pregnant women [10]. In many women, a ferritin of < 50 mcg.l^{-1} [11] is associated with symptoms of iron deficiency such as fatigue, alopecia and poor concentration. Laboratory ranges often quote the 95%CIs of 15–500 mcg.l^{-1} as the 'normal range' for ferritin, which is confusing for practitioners and unhelpful to women as many may be under-diagnosed and/or not get the treatment they require. Ferritin is also an acute phase protein and may be elevated as a result of inflammatory pathologies, surgery and even pregnancy itself. Therefore, a normal level does not exclude iron deficiency. Recent WHO guidance recommends a threshold of < 70 mcg.l^{-1} to diagnose iron deficiency in adults with infection or inflammation, but this too is not universally accepted [9].

Transferrin saturation is another marker of iron status that is readily available from most hospital laboratories. The WHO recommends a threshold of < 16% for iron deficiency, with a < 20% in patients with co-existing inflammation. The use of more novel markers of iron status, such as

hepcidin, soluble transferrin receptor and erythroferrone, is currently an active area of research [10, 12, 13].

The WHO has defined anaemia as haemoglobin (Hb) concentration of < 130 $g.l^{-1}$ for men, < 120 $g.l^{-1}$ for non-pregnant women, and < 110 $g.l^{-1}$ for pregnant women, irrespective of trimester, but recognises that Hb may fall physiologically by approximately 5 $g.l^{-1}$ during the second trimester [10]. These definitions were first published in the 1950s and 1960s using now outdated methods of measuring Hb in four small studies, two of which did not include pregnant women [14]. These definitions are currently under review by WHO [15]. Other national guideline groups and international expert panels have broadly similar definitions but there are inconsistencies [10, 14-17] (Table 2). The definitions, laboratory characteristics and potential treatment strategies for the various stages of iron deficiency are provided in Table 3.

When compared with men, non-pregnant women have a lower circulating blood volume, fewer red cells and lower haemoglobin mass, and are therefore at higher risk of developing anaemia and requiring transfusion in the peri-operative period [18]. The use of a lower haemoglobin threshold may lead to under-diagnosis of anaemia in women scheduled to undergo surgery [18]. Recent international consensus statements on peri-operative anaemia recommend a target Hb of > 130 $g.l^{-1}$, irrespective of sex [17]. This may potentially lead to earlier investigations and diagnosis and timely treatment of peri-operative anaemia [19], but a recent large randomised controlled trial found no evidence of an effect of this approach on clinical outcomes [20]. Similarly in obstetrics, recent data have questioned the physiological fall in Hb in pregnant women by 5 $g.l^{-1}$, with one study demonstrating a fall in the order of 14 $g.l^{-1}$, or 11% of the first trimester value [21]. Another study of 1171 healthy, pregnant women found that mean (95%CI) Hb was 124.6 (23.3–125.9) $g.l^{-1}$ [22]. These findings, if externally validated on a large scale, have significant implications for the diagnosis and management of maternal anaemia.

Iron-deficiency anaemia is a composite diagnosis based on Hb and ferritin concentrations. Anaemia is the end result of iron deficiency as erythropoiesis is often preserved until the advanced stages of iron deficiency [23]. Therefore, much of the burden of iron deficiency in women will go unrecognised if the absence of anaemia is assumed to imply adequate iron stores. The prevalence of iron deficiency is therefore much higher than iron-deficiency anaemia [23]. Small, retrospective studies suggest that peri-operative non-anaemic iron deficiency may be associated with increased hospital length of stay and fewer days alive and out of hospital [24, 25]. Current evidence, mainly of low

quality, suggests that treating non-anaemic iron deficiency with oral or intravenous iron only results in small improvements in Hb and lower self-reported fatigue scores [26, 27]. Data on improved peri-operative outcomes and objectives improvements in physical performance with iron supplementation are lacking.

Iron homeostasis

Iron is essential for synthesis of haemoglobin, cell growth and differentiation, neurotransmission, immunity and cardiopulmonary function [28-30]. Total body iron is approximately 3–4 g, of which 1–2 mg is lost daily, and an additional 1 mg is lost during menstruation each month [19]. In health, systemic iron homeostasis is controlled by the peptide hormone hepcidin, which is synthesised in the liver [31]. An overview of iron homeostasis is provided in Figure 1, and readers are referred elsewhere for more detailed insights [31-34]. Hepcidin expression results in degradation of ferroportin, the sole mammalian exporter of iron, which impairs release of iron from macrophages and duodenal enterocytes [31]. Hepcidin levels are increased in response to inflammation and high circulating levels of free iron, and are decreased in iron deficiency, hypoxia and during blood loss [31].

During pregnancy, hepcidin levels increase in the first trimester when compared with non-pregnant states, followed by a decrease in the second and third trimester. This pattern may facilitate increased absorption of dietary iron and promote release of iron from stores [33, 35]. Recent experimental data suggests that maternal hepcidin, and not embryonic hepcidin, controls embryo iron endowment under physiological conditions [36]. Suppression of maternal hepcidin therefore appears to be essential for maternal and fetal health. In contrast, non-pregnant women may exhibit the anaemia of inflammation, either as a result of underlying comorbidities or due to the inflammatory process of ageing. The underlying pathways include iron restriction mediated by hepcidin, suppression of erythropoiesis by inflammatory cytokines and reduced red cell survival [4].

Aetiology of iron deficiency

The aetiology of iron deficiency in women is multifactorial and summarised in Figure 2. Menstrual blood loss, abnormal uterine bleeding and blood loss from the gastro-intestinal tract are the most common causes of iron deficiency in women from high-income countries, whereas hookworm disease, sickle cell disorders, malaria and schistosomiasis dominate in low to middle-income countries [5]. Malabsorption of iron from the diet or dietary lack of iron (e.g. veganism) are increasingly common causes of iron deficiency. Malabsorption may be associated with gluten and

lactose intolerance and caused by villous atrophy in the stomach [37]. It is also caused by autoimmune conditions such as systemic lupus erythematous. Poor absorption, combined with greater losses due to menstrual bleeding, makes iron deficiency much more common in women. In older women, chronic kidney disease and poor nutrition are important contributors [2]. It is worth noting that the incidence of both folate and vitamin B12 deficiency is also rising. This may be dietary and also due to poor absorption, such as following gastric bypass surgery [38-40].

Approximately 45% of women enter pregnancy with low or absent iron stores [41]. During pregnancy, iron requirements increase 10-fold from 0.8 $mg.day^{-1}$ in the first trimester to 7.5 $mg.day^{-1}$ in the third trimester [33]. This is to support the increase in maternal red cell mass, maintain placental and fetal growth and allow for potential blood loss during delivery. However, the average daily absorption of iron is only 1–5 mg.

Clinical consequences

Iron deficiency can result in fatigue, poor concentration (brain fog), alopecia, ridged/brittle nails, aching and restless legs, reduced exercise tolerance, anxiety, low mood/depression and poor work performance [42]. Cognitive decline has also been reported in elderly individuals [43]. In severe cases, pica – a craving and purposive consumption for non-food items such as ice (pagophagia) and starch (amylophagia) may develop, especially in women whose serum ferritin < 10 $mcg.l^{-1}$. The prevalence of pica is greater in pregnant adolescent women of Afro-Caribbean origin [44]. Many women may be investigated for viral causes of chronic fatigue syndrome or treated with antidepressants when the diagnosis of iron deficiency has not been made.

In surgical settings, sex discrepancies exist in both elective and non-elective situations, where worse outcomes have been reported in women [17, 45, 46]. Women are more likely than men to be iron deficient pre-operatively [24] and peri-operative blood transfusion rates are higher in women [47]. However, it is unclear whether anaemia, irrespective of cause, is an independent risk factor for poor outcomes in women undergoing surgery [48].

Maternal anaemia is associated with increased mortality [49, 50], with one study demonstrating a 29% linear increase in mortality with each 10 $g.l^{-1}$ decrease in maternal Hb [51], and increased risk of developing postpartum haemorrhage [52]. Postpartum anaemia is associated with depression [53, 54], high levels of fatigue [55], poor cognition [56] and difficulties with breast feeding [57]. Maternal anaemia is a risk factor for preterm labour, low birth weight and small-for-gestational age babies,

and increased perinatal and neonatal mortality [21, 32]. Children born to mothers with iron deficiency display learning and memory impairments that persist into adulthood [58, 59]. Infants born with evidence of iron deficiency in utero, defined as a cord blood ferritin of < 75 $ng.ml^{-1}$, demonstrate poor memory, altered interactions with caregivers and abnormal neurological reflexes [60]. The underlying mechanisms contributing to these poor outcomes and the responses of the maternal-placental-fetal unit to changes in maternal iron status are the subject of current research [34, 36].

Optimisation of iron status

Indications for iron supplementation can be broadly categorised into two situations: to prevent iron-deficiency anaemia in at-risk populations or; to treat individuals with symptoms and laboratory-proven iron deficiency.

Individuals at risk of developing iron-deficiency anaemia are those with high iron requirements and include infants, preschool children, adolescents, young menstruating women, and pregnant and postpartum women. Female endurance athletes are at risk of developing iron deficiency as a result of increased hepcidin expression secondary to exercise (which reduces iron absorption), haemolysis and sweating, and may present with amenorrhoea [37]. Other healthy women at risk of developing iron deficiency anaemia include vegetarians/vegans and blood donors [2]. Obese women may also be at risk of developing iron deficiency anaemia secondary to obesity-related inflammation, which increases hepcidin expression and reduces iron absorption [37]. Prolonged use of proton-pump inhibitors such as lansoprazole or pantoprazole may also cause iron deficiency due to alteration of the normal acid environment of the stomach which greatly reduces iron absorption from the diet or from supplements.

Pregnant women at risk of developing iron deficiency, with or without anaemia, should be identified during the antenatal period, ideally at the booking visit, through detailed history and examination. Risk factors that healthcare professionals should be aware of include vegetarian or vegan diets, teenage pregnancy, previous anaemia, multiple gestation and short inter-pregnancy interval (<1 year). These women may be candidates for empirical iron supplementation and/or measurement of serum ferritin at the initial booking visit [10].

Clinical management

Initial history and examination should help identify potential underlying causes of iron deficiency and anaemia. Upper and lower gastro-intestinal investigations should be considered in postmenopausal women where iron-deficiency anaemia has been confirmed unless there is history suggestive of significant non-gastro-intestinal blood loss [11]. Dietary advice should be offered, although this is seldom sufficient to reverse established iron-deficiency anaemia. Meat, poultry and fish are rich sources of haem iron, which is more readily absorbed than non-haem (inorganic iron) iron [10]. Non-haem iron is mainly derived from plant foods and this may explain the high prevalence of iron deficiency in vegetarians. Co-ingestion with vitamin C can significantly help increase iron uptake from non-haem sources [68]. Tea and coffee contain tannins which inhibit iron absorption and therefore their consumption should be limited. Iron is absorbed from an acidic environment and therefore best taken on an empty stomach between meals, with milk and other 'alkalinising' food substances avoided for an hour before and afterwards.

Oral iron

Oral iron is a cheap and effective way of treating iron deficiency. Pre-operative oral iron should be commenced when the interval before surgery is 6–8 weeks [19]. The recommendations for oral iron dosing have largely been amended by recent studies demonstrating that once daily or alternate day dosing may be more effective and better tolerated when compared with traditional higher doses [69, 71]. A single oral dose of ferrous sulphate results in a rapid rise in circulating hepcidin, which can remain elevated for up to 48 h. Subsequent oral doses will not be effective because of this 'hepcidin block' and expose women to well-recognised side effects such as nausea, constipation and epigastric pain. Hepcidin levels are also lowest in the morning and therefore dosing is advised at this time [72]. An important caveat of these studies is that they were conducted in non-pregnant women. High-quality data on the optimal dosing schedule for oral iron are needed in pregnant women.

Once oral iron has been started, ferritin and Hb should be measured again after 6–8 weeks of treatment. Treatment should be continued if there is evidence of increments in Hb and ferritin. Once Hb has normalised, guidelines suggest checking Hb and ferritin at 3 monthly intervals for 1 year, then after a further year, and again after that if symptoms develop [11]. In the absence of improvements in Hb or iron stores, consideration should be given to checking for compliance, alternative oral iron formulations, intravenous iron and alternative pathologies.

Despite the high prevalence of maternal anaemia and its association with poor outcomes, there are insufficient data on the effectiveness and safety to recommend routine iron supplementation for all pregnant women [10, 70].

Intravenous iron

Intravenous iron is an efficacious method of treating anaemia due to iron deficiency, with or without inflammation, across a range of clinical conditions including chronic kidney disease, inflammatory bowel disease, heart failure and pregnancy [73-77]. In the presence of inflammation, intravenous iron is able to bypass the 'hepcidin block' that limits the absorption of oral iron [4], and newer iron preparations such as ferric carboxymaltose and iron isomaltoside permit delivery to reticuloendothelial system in a slow and controlled manner in order to limit the amount of toxic unbound circulating free iron [78, 79].

Current guidelines recommend pre-operative intravenous iron therapy for patients who are scheduled to undergo major surgery and who are unable to tolerate oral iron and/or if surgery is planned in less than 6 weeks [17]. However, the recent pre-operative intravenous iron to treat anaemia before major surgery (PREVENTT) trial showed no evidence of benefit of pre-operative iron in reducing peri-operative transfusion or death in patients scheduled to undergo major abdominal surgery [20]. Prespecified subgroup analyses demonstrated no evidence of an effect based on sex, age, anaemia severity, ferritin (< 100 $ng.ml^{-1}$) or transferrin saturation (< 20%). Current guidelines also recommend intravenous iron for the treatment of postoperative anaemia (Hb < 100 $g.l^{-1}$) or iron deficiency (ferritin < 100 $ng.ml^{-1}$ or ferritin < 300 $ng.ml^{-1}$ and transferrin saturation < 20%) [80], although there are no high quality data to support this recommendation [80, 81].

Intravenous iron in pregnancy should be considered for the following indications: from the second trimester onwards for women with confirmed iron-deficiency anaemia who do not respond to oral iron; for those presenting after 34 weeks' gestation with Hb 80–100 $g.l^{-1}$ and confirmed iron deficiency; and where rapid correction may be needed (e.g. advanced gestational age, Jehovah's Witness) [10]. However, to date, there is inconclusive evidence that intravenous iron therapy reduces peripartum transfusion requirements or improves maternal or perinatal outcomes.

Intravenous iron may also be administered to women with symptoms of iron deficiency and low ferritin/transferrin saturations who cannot absorb oral iron or fail to respond to a course of oral iron despite optimising dose and preparation. In such circumstances, intravenous iron usually leads to

resolution of symptoms in 6–8 weeks, although further doses may be needed depending on ongoing iron losses (e.g. menorrhagia) and intake (e.g. poor absorption).

Common side effects of intravenous iron include nausea, headaches, hypertension, flushing and injection site reactions and these can be managed by providing symptomatic care and reducing the rate of infusion. Iron is also essential for bacterial growth and caution is advised in patients with acute or chronic infection. True hypersensitivity (anaphylactic) reactions are very rare. Intravenous iron is currently only licensed to be given in specific settings (e.g. hospital outpatients or wards) where there are trained staff and equipment for managing anaphylaxis. Monitoring during and after for 15–30 min after administration is also recommended. Extravasation leading to permanent haemosiderin skin pigmentation has been reported and women should be counselled to report any pain at the infusion site [82]. It is worth highlighting that intravenous iron is considerably more expensive than oral iron, even without including the costs of nursing time and administration kits. No formal cost-effectiveness evaluations have been undertaken to date.

Allogeneic red blood cell transfusion

A final treatment option is red blood cell transfusion. Its use should be limited to major haemorrhage, or in those who are haemodynamically unstable with evidence of end-organ dysfunction. The need for iron supplementation can be reviewed once the woman has been stabilised. Women should be consented regarding the potential risks of transfusion [83], including being unable to donate blood in the future, and potential alternative treatments.

Research agendas

In order to progress the research agenda and improve outcomes in women's health, given the many areas of limited high quality data, it is vital that researchers work with the public, so that studies are designed towards outcomes that matter to women and their carers or loved ones. This will enable studies to be implemented more effectively. There is also supporting evidence that patient and public involvement improves study enrolment, especially if it includes people with lived experience of the health condition under investigation [84].

As an example of this, the primary prevention of maternal anaemia to avoid preterm delivery and other adverse outcomes (PANDA) programme is a research programme that has been recently funded by the National Institute for Health Research [85]. Patient and public involvement was key to understanding the outcomes of importance to mothers, including the study's primary outcome,

which is a composite outcome of preterm birth, stillbirth, neonatal death and small-for-gestational-age, and informing the design of the study (Box 1).

Despite the benefits of patient and public involvement, trials continue to select disease-orientated end points as their primary outcomes. Ongoing randomised controlled trials relevant to women's health are shown in Table 4. Of nine studies, seven focus on changes in haemoglobin and/or iron status as their primary outcome. These endpoints, although easy to measure, are largely irrelevant to patients especially if they do not translate into improved clinical outcomes [86]. Only one study focused on relevant patient outcome (postpartum fatigue).

Conclusion

The WHO aims to reduce the prevalence of anaemia in women of reproductive age by half between 2010 and 2025 [8], but currently available interventions such as iron therapy do not appear to be working on the scale required to meet this aim. Improvements in our understanding of the epidemiology and underlying pathophysiology of iron deficiency anaemia offer the potential for considerable improvements. Newer markers of iron status, such as hepcidin, may help to personalise iron therapy whilst also aiding sample enrichment for future clinical trials [12]. These studies should investigate innovative iron dosing schedules based on iron homeostasis, provide clearer indications for intravenous iron and provide long term data on patient-centred outcomes. Working with the public and patients will ensure that these studies are optimally designed to answer these questions, as illustrated by the example in this article.

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References

1. Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. Lancet Global Health 2013; **1**: e16-25.
2. Camaschella C. Iron deficiency. Blood 2019; **133**: 30-9.
3. Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. Lancet 2016; **387**: 907-16.
4. Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood 2019; **133**: 40-50.
5. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood 2014; **123**: 615-24.
6. Nair M, Churchill D, Robinson S, Nelson-Piercy C, Stanworth SJ, Knight M. Association between maternal haemoglobin and stillbirth: a cohort study among a multi-ethnic population in England. British Journal of Haematology 2017; **179**: 829-37.
7. Rahman MM, Abe SK, Rahman MS, et al. Maternal anemia and risk of adverse birth and health outcomes in low- and middle-income countries: systematic review and meta-analysis. American Journal of Clinical Nutrition 2016; **103**: 495-504.
8. Young MF. Maternal anaemia and risk of mortality: a call for action. Lancet Global Health 2018; **6**: e479-e80.
9. World Health Organization. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: WHO, 2020.
10. Pavord S, Daru J, Prasannan N, et al. UK guidelines on the management of iron deficiency in pregnancy. British Journal of Haematology 2019; **188**: 819-830
11. Goddard AF, James MW, McIntyre AS, Scott BB British Society of Gastroenterology Guidelines for the management of iron deficiency anaemia. Gut 2011; **60**: 1309-16.
12. Bah A, Muhammad AK, Wegmuller R, et al. Hepcidin-guided screen-and-treat interventions against iron-deficiency anaemia in pregnancy: a randomised controlled trial in The Gambia. Lancet Global Health 2019; **7**: e1564-e74.
13. Shah A, Wray K, James T, et al. Serum hepcidin potentially identifies iron deficiency in survivors of critical illness at the time of hospital discharge. British Journal of Haematology 2019; **184**: 279-81.
14. Ferguson MT, Dennis AT. Defining peri-operative anaemia in pregnant women - challenging the status quo. Anaesthesia 2019; **74**: 237-45.

15. Pasricha SR, Colman K, Centeno-Tablante E, Garcia-Casal MN, Pena-Rosas JP. Revisiting WHO haemoglobin thresholds to define anaemia in clinical medicine and public health. Lancet Haematology 2018; **5**: e60-e62.

16. The American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 95: anemia in pregnancy. Obstetrics and Gynecology 2008; **112**: 201-7.

17. Munoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017; **72**: 233-47.

18. Butcher A, Richards T, Stanworth SJ, Klein AA. Diagnostic criteria for pre-operative anaemia-time to end sex discrimination. Anaesthesia 2017; **72**: 811-4.

19. Munoz M, Laso-Morales MJ, Gomez-Ramirez S, Cadellas M, Nunez-Matas MJ, Garcia-Erce JA. Pre-operative haemoglobin levels and iron status in a large multicentre cohort of patients undergoing major elective surgery. Anaesthesia 2017; **72**: 826-34.

20. Richards T, Baikady RR, Clevenger B, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. Lancet 2020; **396**: 1353-1361.

21. Churchill D, Nair M, Stanworth SJ, Knight M. The change in haemoglobin concentration between the first and third trimesters of pregnancy: a population study. BMC Pregnancy and Childbirth 2019; **19**: 359.

22. Mei Z, Cogswell ME, Looker AC, et al. Assessment of iron status in US pregnant women from the National Health and Nutrition Examination Survey (NHANES), 1999-2006. American Journal of Clinical Nutrition 2011; **93**: 1312-20.

23. Pratt JJ, Khan KS. Non-anaemic iron deficiency - a disease looking for recognition of diagnosis: a systematic review. European Journal of Haematology 2016; **96**: 618-28.

24. Miles LF, Kunz SA, Na LH, Braat S, Burbury K, Story DA. Postoperative outcomes following cardiac surgery in non-anaemic iron-replete and iron-deficient patients - an exploratory study. Anaesthesia 2018; **73**: 450-8.

25. Miles LF, Sandhu RN, Grobler AC, et al. Associations between non-anaemic iron deficiency and outcomes following surgery for colorectal cancer: An exploratory study of outcomes relevant to prospective observational studies. Anaesthesia and Intensive Care 2019; **47**: 152-9.

26. Miles LF, Litton E, Imberger G, Story D. Intravenous iron therapy for non-anaemic, iron-deficient adults. Cochrane Database of Systematic Reviews 2019; **12**: CD013084.

27. Houston BL, Hurrie D, Graham J, et al. Efficacy of iron supplementation on fatigue and physical capacity in non-anaemic iron-deficient adults: a systematic review of randomised controlled trials. British Medical Journal Open 2018; **8**: e019240.

28. Frise MC, Robbins PA. Iron, oxygen, and the pulmonary circulation. Journal of Applied Physiology (1985) 2015; **119**: 1421-31.

29. Drakesmith H, Prentice AM. Hepcidin and the iron-infection axis. Science. 2012; **338**: 768-72.

30. Litton E, Lim J. Iron Metabolism: An Emerging Therapeutic Target in Critical Illness. Critical Care 2019; **23**: 81.

31. Ganz T. Systemic iron homeostasis. Physiology Reviews 2013; **93**: 1721-41.

32. Benson CS, Shah A, Frise MC, Frise CJ. Iron deficiency anaemia in pregnancy: A contemporary review. Obstetric Medicine 2020. Epub 7 July. https://doi.org/10.1177%2F1753495X20932426

33. Fisher AL, Nemeth E. Iron homeostasis during pregnancy. American Journal of Clinical Nutrition 2017; **106**: 1567S-74S.

34. Sangkhae V, Fisher AL, Wong S, et al. Effects of maternal iron status on placental and fetal iron homeostasis. Journal of Clinical Investigation 2020; **130**: 625-640.

35. Bah A, Pasricha SR, Jallow MW, et al. Serum Hepcidin Concentrations Decline during Pregnancy and May Identify Iron Deficiency: Analysis of a Longitudinal Pregnancy Cohort in The Gambia. The Journal of Nutrition 2017; **147**: 1131-7.

36. Sangkhae V, Fisher AL, Chua KJ, Ruchala P, Ganz T, Nemeth E. Maternal hepcidin determines embryo iron homeostasis in mice. Blood 2020; **136**: 2206-16.

37. Percy L, Mansour D, Fraser I. Iron deficiency and iron deficiency anaemia in women. Best Practice and Research Clinical Obstetrics and Gynaecology 2017; **40**: 55-67.

38. Bal BS, Finelli FC, Shope TR, Koch TR. Nutritional deficiencies after bariatric surgery. Nature Reviews Endocrinology 2012; **8**: 544-56.

39. Toh SY, Zarshenas N, Jorgensen J. Prevalence of nutrient deficiencies in bariatric patients. Nutrition 2009; **25**: 1150-6.

40. Mead NC, Sakkatos P, Sakellaropoulos GC, Adonakis GL, Alexandrides TK, Kalfarentzos F. Pregnancy outcomes and nutritional indices after 3 types of bariatric surgery performed at a single institution. Surgery for Obesity and Related Diseases 2014; **10**: 1166-73.

41. Milman N. Iron in pregnancy: How do we secure an appropriate iron status in the mother and child? Annals of Nutrition and Metabolism 2011; **59**: 50-4.

42. Haas JD, Brownlie Tt. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. The Journal of Nutrition 2001; **131**: 676S-88S.

43. Andro M, Le Squere P, Estivin S, Gentric A. Anaemia and cognitive performances in the elderly: a systematic review. European Journal of Neurology 2013; **20**: 1234-40.

44. Lumish RA, Young SL, Lee S, et al. Gestational iron deficiency is associated with pica behaviors in adolescents. Journal of Nutrition 2014; **144**: 1533-9.

45. Johnston A, Mesana TG, Lee DS, Eddeen AB, Sun LY. Sex Differences in Long-Term Survival After Major Cardiac Surgery: A Population-Based Cohort Study. Journal of the American Heart Association 2019; **8**: e013260.

46. Rucker D, Warkentin LM, Huynh H, Khadaroo RG. Sex differences in the treatment and outcome of emergency general surgery. PLoS One. 2019; **14**: e0224278.

47. Gombotz H, Schreier G, Neubauer S, Kastner P, Hofmann A. Gender disparities in red blood cell transfusion in elective surgery: a post hoc multicentre cohort study. British Medical Journal Open 2016; **6**: e012210.

48. Miles LF, Larsen T, Bailey MJ, Burbury KL, Story DA, Bellomo R. Borderline anaemia and postoperative outcome in women undergoing major abdominal surgery: a retrospective cohort study. Anaesthesia 2020; **75**: 210-7.

49. Black RE, Victora CG, Walker SP, et al. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013; **382**: 427-51.

50. Daru J, Zamora J, Fernandez-Felix BM, et al. Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis. Lancet Global Health 2018; **6**: e548-e54.

51. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Global Health 2014; **2**: e323-33.

52. Briley A, Seed PT, Tydeman G, et al. Reporting errors, incidence and risk factors for postpartum haemorrhage and progression to severe PPH: a prospective observational study. British Journal of Obstetrics and Gynaecology 2014; **121**: 876-88.

53. Wassef A, Nguyen QD, St-Andre M. Anaemia and depletion of iron stores as risk factors for postpartum depression: a literature review. Journal of Psychosomatic Obstetrics and Gynaecology 2019; **40**: 19-28.

54. Maeda Y, Ogawa K, Morisaki N, Tachibana Y, Horikawa R, Sago H. Association between perinatal anemia and postpartum depression: A prospective cohort study of Japanese women. International Journal of Gynecology and Obstetrics 2020; **148**: 48-52.

55. Lee KA, Zaffke ME. Longitudinal changes in fatigue and energy during pregnancy and the postpartum period. Journal of Obstetric, Gynecological and Neonatal Nursing 1999; **28**: 183-91.

56. Beard JL, Hendricks MK, Perez EM, et al. Maternal iron deficiency anemia affects postpartum emotions and cognition. Journal of Nutrition 2005; **135**: 267-72.

57. Rioux FM, Savoie N, Allard J. Is there a link between postpartum anemia and discontinuation of breastfeeding? Canadian Journal of Dietetic Practice and Research 2006; **67**: 72-6.

58. Congdon EL, Westerlund A, Algarin CR, et al. Iron deficiency in infancy is associated with altered neural correlates of recognition memory at 10 years. Journal of Pediatrics 2012; **160**: 1027-33.

59. Geng F, Mai X, Zhan J, et al. Impact of Fetal-Neonatal Iron Deficiency on Recognition Memory at 2 Months of Age. The Journal of Pediatrics 2015; **167**: 1226-32.

60. Doom JR, Georgieff MK. Striking while the iron is hot: Understanding the biological and neurodevelopmental effects of iron deficiency to optimize intervention in early childhood. Current Pediatrics Reports 2014; **2**: 291-8.

61. Zhang Y, Shi J, Wei H, Han V, Zhu WZ, Liu C. Neonate and infant brain development from birth to 2 years assessed using MRI-based quantitative susceptibility mapping. Neuroimage 2019; **185**: 349-60.

62. Radlowski EC, Johnson RW. Perinatal iron deficiency and neurocognitive development. Frontiers in Human Neuroscience 2013; **7**: 585.

63. Christian P, Murray-Kolb LE, Khatry SK, et al. Prenatal micronutrient supplementation and intellectual and motor function in early school-aged children in Nepal. Journal of the American Medical Association 2010; **304**: 2716-23.

64. Pasricha SR, Drakesmith H, Black J, Hipgrave D, Biggs BA. Control of iron deficiency anemia in low- and middle-income countries. Blood 2013; **121**: 2607-17.

65. Haider BA, Olofin I, Wang M, et al. Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis. British Medical Journal 2013; **346**: f3443.

66. De Pee S, Bloem MW, Sari M, Kiess L, Yip R, Kosen S. The high prevalence of low hemoglobin concentration among Indonesian infants aged 3-5 months is related to maternal anemia. Journal of Nutrition 2002; **132**: 2215-21.

67. Mireku MO, Davidson LL, Boivin MJ, et al. Prenatal Iron Deficiency, Neonatal Ferritin, and Infant Cognitive Function. Pediatrics 2016; **138**: e20161319

68. Lynch SR. Interaction of iron with other nutrients. Nutrtion Reviews 1997; **55**: 102-10.

69. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. Blood 2015; **126**: 1981-9.

70. Munoz M, Pena-Rosas JP, Robinson S, et al. Patient blood management in obstetrics: management of anaemia and haematinic deficiencies in pregnancy and in the post-partum period: NATA consensus statement. Transfusion Medicine 2018; **28**: 22-39.

71. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split

dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematology 2017; **4**: e524-e33.

72. Schaap CC, Hendriks JC, Kortman GA, et al. Diurnal rhythm rather than dietary iron mediates daily hepcidin variations. Clinical Chemistry 2013; **59**: 527-35.

73. Bonovas S, Fiorino G, Allocca M, et al. Intravenous Versus Oral Iron for the Treatment of Anemia in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Medicine (Baltimore). 2016; **95**: e2308.

74. Jankowska EA, Tkaczyszyn M, Suchocki T, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. European Journal of Heart Failure 2016; **18**: 786-95.

75. Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-analysis. American Journal of Kidney Diseases 2016; **68**: 677-90.

76. Lewkowitz AK, Gupta A, Simon L, et al. Intravenous compared with oral iron for the treatment of iron-deficiency anemia in pregnancy: a systematic review and meta-analysis. Journal of Perinatology 2019; **39**: 519-32.

77. Qassim A, Grivell RM, Henry A, Kidson-Gerber G, Shand A, Grzeskowiak LE. Intravenous or oral iron for treating iron deficiency anaemia during pregnancy: systematic review and meta-analysis. Medical Journal of Australia 2019; **211**: 367-73.

78. Kalra PA, Bhandari S. Efficacy and safety of iron isomaltoside (Monofer((R))) in the management of patients with iron deficiency anemia. International Journal of Nephrology and Renovascular Disease 2016; **9**: 53-64.

79. Keating GM. Ferric carboxymaltose: a review of its use in iron deficiency. Drugs 2015; **75**: 101-27.

80. Munoz M, Acheson AG, Bisbe E, et al. An international consensus statement on the management of postoperative anaemia after major surgical procedures. Anaesthesia 2018; **73**: 1418-31.

81. Perelman I, Winter R, Sikora L, Martel G, Saidenberg E, Fergusson D. The Efficacy of Postoperative Iron Therapy in Improving Clinical and Patient-Centered Outcomes Following Surgery: A Systematic Review and Meta-Analysis. Transfusion Medicine Reviews 2018; **32**: 89-101.

82. El-Zaatari MS, Hassan-Smith ZK, Reddy-Kolanu V. Extravasation and pigmentation post iron infusion. British Journal of Hospital Medicine 2019; **80**: https://doi.org/10.12968/hmed.2019.80.4.ii

83. Delaney M, Wendel S, Bercovitz RS, et al. Transfusion reactions: prevention, diagnosis, and treatment. Lancet 2016; **388**: 2825-36.

84. Crocker JC, Ricci-Cabello I, Parker A, et al. Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis. British Medical Journal 2018; **363**: k4738.

85. National Institute for Health Research. Funding and Awards https://www.fundingawards.nihr.ac.uk/award/NIHR200869 (Accessed 01/09/2020)

86. Shah A, Bailey CR. Outcomes following surgery: are we measuring what really matters? Anaesthesia 2019; **74**: 696-699.

Table 1. Global prevalence of iron deficiency and anaemia

	Prevalence (%)
Iron deficiency	
Children (< 2 years)	9.0
Children (3–5 years)	4.5
Adolescent girls (12–19 years)	15.6
Women (20–49 years)	15.7
Pregnant women (15–49 years)	18.0
Iron-deficiency anaemia	
General population	12.2
Hospitalised population	23.0
Anaemia	
General population	32.9
Preschool children (0–5 years)	43.0
School age children (> 5 years)	25.4
Non-pregnant women (15–49 years)	29.0
Pregnant women (15–19 years)	38.0
Men (15–60 years)	12.7
Elderly (> 60 years)	23.9

Table 2. Variations in the definitions of anaemia in guidelines

Responsible body	Patient population	Definition of anaemia	Comments
World Health Organization [15]	General	Non-pregnant women: Hb <120 $g.l^{-1}$ Pregnant women: Hb <110 $g.l^{-1}$ Men: Hb <130 $g.l^{-1}$	Consistent thresholds with no trimester specific cut-offs in pregnancy
International consensus statements for peri-operative management of anaemia [19]	Surgery	Hb <130 $g.l^{-1}$ (Pre-operative) Hb <100 $g.l^{-1}$ (Postoperative)	Same threshold irrespective of sex
British Society of Gastroenterology [11]	General	Similar to World Health Organization	Men with Hb < 120 $g.l^{-1}$ and postmenopausal women with Hb < 100 $g.l^{-1}$ should be investigated urgently for colorectal cancer
National Blood Authority, Australia [14]	Surgery	Women: Hb <120 $g.l^{-1}$ Men: Hb <130 $g.l^{-1}$	Guidelines state that it would be reasonable to assume that normal Hb in pregnancy levels lie between 103 and 146 $g.l^{-1}$
	Pregnancy	No recommendation provided as no agreed normal range for pregnant women in Australia	
British Committee for Standards in Haematology [9]	Pregnancy	First trimester: Hb < 110 $g.l^{-1}$ Second trimester: Hb < 10.5 $g.l^{-1}$ Postpartum: Hb < 100 $g.l^{-1}$	Incorporates 5 $g.l^{-1}$ drop in the second trimester into definition
American College of Obstetricians and Gynecologists [16]	Pregnancy	First trimester: Hb < 110 $g.l^{-1}$ Second trimester: Hb < 10.5 $g.l^{-1}$ Third trimester: Hb < 100 $g.l^{-1}$	Recommendations based on CDC data obtained from an iron-replete population sample

CDC, Centers for Disease Prevention and Control; Hb, haemoglobin,

Table 3. Definitions, laboratory characteristics and potential treatment strategies of the various stages of iron deficiency

Iron status	Definition	Laboratory findings	Expected hepcidin levels	Iron therapy strategies
True/absolute iron deficiency	Depletion of body iron stores, which are inadequate to maintain erythropoiesis	Low ferritin and low Tsat	Low	Oral iron, i.v. iron if poorly tolerated
Iron-deficiency anaemia	Reduced Hb and erythrocytes due to insufficient iron availability	Low Hb, low ferritin and low Tsat	Low	Oral iron, i.v. iron if poorly tolerated or rapid correction required
Functional iron deficiency	Insufficient mobilisation of iron stores due to increased demands, despite adequate iron stores	Low Tsat, variable ferritin	Variable	i.v iron, consider oral iron if low disease activity or inflammatory burden
Iron sequestration/iron-restricted erythropoiesis	Reduced supply of iron to meet erythropoietic requirements	Low Tsat, normal to elevated ferritin, elevated CRP	High	i.v. iron, consider erythropoietin

Tsat, transferrin saturation; i.v., intravenous; Hb, haemoglobin; CRP, C-reactive protein.

Table 4. Characteristics of ongoing randomised controlled trials relevant to women's health

Study details and status	Planned sample size	Participants	Intervention(s)			Primary outcome	Secondary outcome
			Arm 1	Arm 2	Arm 3		
NCT03188445; Denmark (Recruiting)	200 participants	Women aged > 18 years; Pregnant >14 weeks gestation; Ferritin < 30 $\mu g.l^{-1}$ after 4 weeks of oral iron	Iron isomaltoside 1000mg	Ferrous fumarate + ascorbic acid		Time to achieve Hb >11 $g.dl^{-1}$ (baseline to 18 weeks after treatment)	Changes in Hb and iron biomarkers
NCT04278651; USA (Recruiting)	80 participants	Singleton pregnancy, gestational age < 24 weeks, Hb 9-10 $g.dl^{-1}$ with evidence of iron deficiency anaemia	Ferumoxytol 510mg x2 doses, 3–8 days apart	Ferrous sulphate 325mg twice daily		Change in Hb at day 90 following randomisation	Anaemia resolution; anaemia at delivery; adherence; peripartum transfusion requirements; neonatal outcomes; quality of life on linear analogue scale
ACTRN12619000283178p; IRONWOMAN; Australia (Not yet open)	50 participants	Pregnant women aged > 18 years; Hb 80–105 $g.dl^{-1}$ and ferritin <30 $\mu g.l^{-1}$; between 26–33 weeks' gestation	Ferric carboxymaltose 1000mg + oral placebo capsules	Oral iron 80 mg once daily + i.v. placebo		Feasibility – adequacy of blinding	Patient and clinician acceptability; changes in SF-36 from baseline to 4 weeks; treatment side effects; oral iron compliance; proportion of women with Hb < 105 $g.dl^{-1}$ at 4 weeks; changes in Hb and iron profiles; maternal outcomes (PPH, mode of delivery, transfusion requirements); fetal outcomes (SGA, birth weight, preterm labour,

							death, NICU admission)
ACTRN12618001268235; REVAMP; Malawi (Recruiting)	862 participants	Pregnant women 13–26 weeks' gestation; Hb < 10 $g.dl^{-1}$; negative malaria test	Ferric carboxymaltose 1000mg	Ferrous sulphate 200mg x2/day for 90 days		Prevalence of Hb < 10 $g.dl^{-1}$ at time-point closest to delivery	Maternal fatigue (1 month postpartum); changes in Hb and iron profiles; incidence of PPH, length of stay post-delivery; maternal cognitive function; transfusion requirements; adverse events; neonatal outcomes (birth weight, preterm birth, still birth)
NCT04505514; IVIronPPH; Malaysia (Recruiting)	60 participants	Age > 18 years; PPH >500 ml; Hb < 10 $g.dl^{-1}$	Iron isomaltoside 1000mg + oral iron preparation (Iberet-Folic 500)	I.v. placebo + oral iron preparation (Iberet-Folic 500)		Changes in Hb, serum iron and ferritin at 6 weeks	General fatigue score; adverse events; transfusion requirements
NCT03957057; Slovenia (Recruiting)	300 participants	PPH with Hb 7–10 $g.dl^{-1}$ within 48 h after delivery	Ferric carboxymaltose 1000mg	Iron isomaltoside 1500mg	Ferrous sulphate 160mg once daily for 6 weeks	MFI score at 6 weeks postpartum	Edinburgh Postnatal Depression score; changes in Hb and iron profiles; side effects; compliance with oral iron
CTRI/2020/02/023125; India (Recruiting)	80 participants	Women age 18–45 years, postpartum Hb 8-10 $g.dl^{-1}$	Ferric carboxymaltose 1000mg	Ferrous fumarate 152mg x2/day for 6 weeks		Changes in Hb at 2 and 6 weeks postpartum	Safety and acceptability
NCT04205266; USA	76	Women aged 18-50; heavy	Ferumoxytol 510	Ferrous		Change in Hb at 60	Participant satisfaction

(Not yet recruiting)	participants	menstrual bleeding; Hb < 11 $g.dl^{-1}$	mg (2 infusion)	sulphate 325mg once daily for 60 days	days	with treatment; quality of life measured using Duke Health Profile
NCT04636060; Switzerland (Not yet recruiting)	34 participants	Non-pregnant women aged > 18 years with non-anaemic iron-deficiency, ferritin < 30 $ng.ml^{-1}$	Low dose oral iron 6mg, twice daily for 8 weeks	Dietary supplements	Changes in serum ferritin at 8 weeks	Side effects; changes in serum hepcidin

Hb, haemoglobin; I.v., intravenous; MFI, Multidimensional Fatigue Inventory; NICU, neonatal intensive care unit; PPH, postpartum haemorrhage; SGA, small for gestational age

Box 1. Examples of patient and public involvement to inform the design of the Primary prevention of maternal Anaemia to avoid preterm Delivery and other Adverse outcomes study.

Understanding the scale of the problem

- Discussions with the wider network group identified an alarming lack of awareness of the severe clinical consequences of iron-deficiency in women of reproductive age
- Tensions between healthcare professionals seeing treatment of iron deficiency as routine and trivial, and women being fearful of the side effects of taking oral iron were also identified

Informing study design

- Further discussions highlighted the importance of clear communication of risk, enabling women's choices and privacy
- Any woman-facing documentation should be tactfully and carefully worded to avoid raising more fear of adverse consequences during what is already an emotional time for women
- Study involvement must be integrated with antenatal appointments as much as possible
- Offer women a choice of formats to complete study questionnaires e.g. postal copy, email
- Long-term follow up of infants born to trial participants raised questions about data privacy related to database linkage options
- Although guidelines recommend alternate day dosing for oral iron, network members felt this would be harder to keep track of than with a daily dosing schedule. A smart phone app may be useful.

Dissemination of findings

- Multiple avenues of dissemination were identified including the media, online forums relevant to pregnancy, patient and public involvement and health care professional events

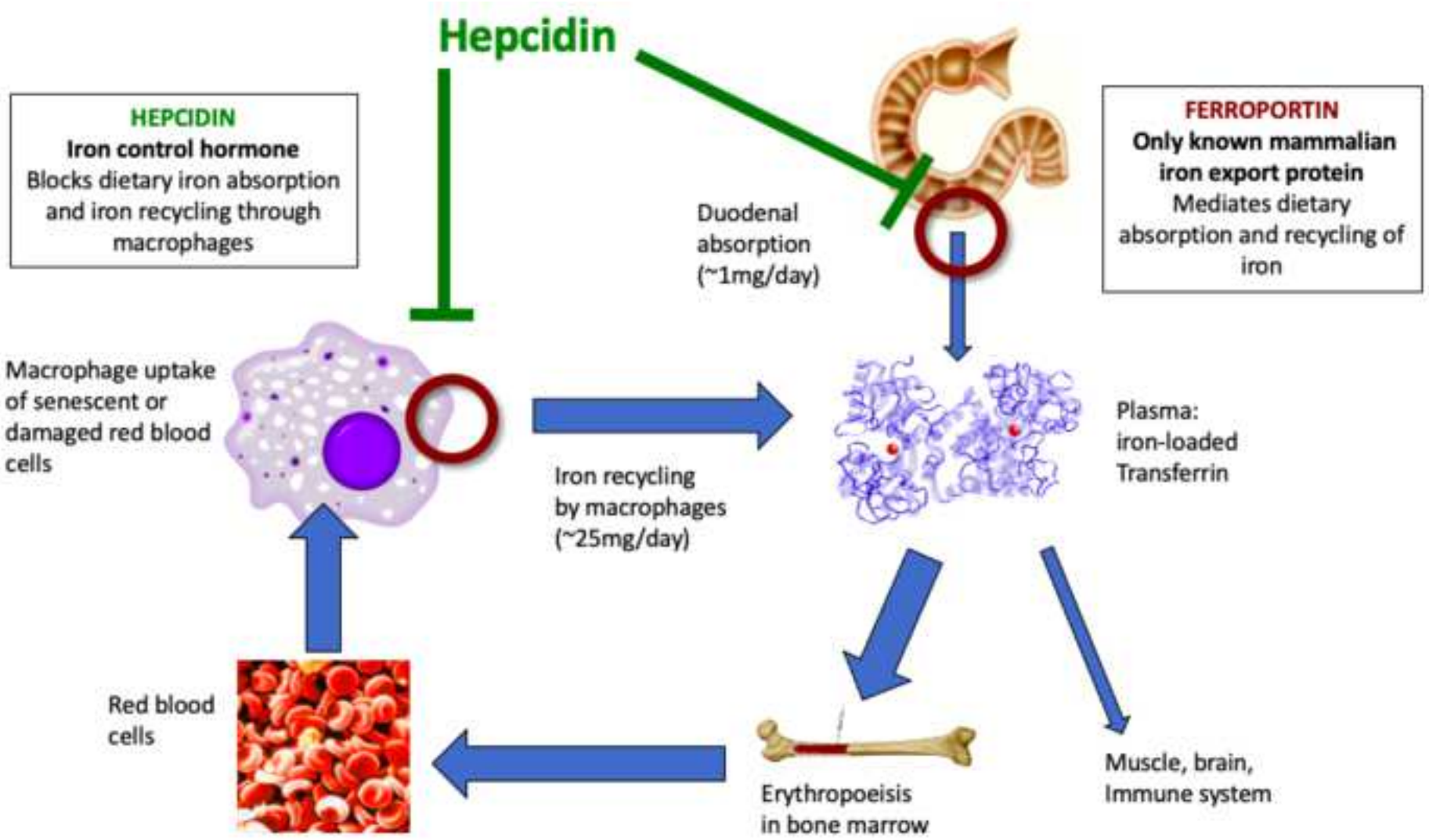
Figure legends

Fig. 1. Hepcidin-ferroportin interaction and major systemic iron pathways. Approximately 1 mg of iron is absorbed daily in the gut. Ferroportin is the sole mammalian exporter of iron and delivers stored, dietary or recycled iron to blood plasma. In plasma, iron is taken up by transferrin. A small proportion is used for muscle function and development of neural tissue, whilst the rest is used by the bone marrow for erythropoiesis. At the end of their life cycle, red blood cells are taken up by macrophages and approximately 25 mg of iron is recycled daily through this pathway. This is the major source of body iron. Hepcidin expression results in degradation of ferroportin which impairs release of iron from macrophages and duodenal enterocytes. Hepcidin levels are low in states of iron deficiency, which allows for increased absorption of iron through ferroportin.

Fig. 2. Causes of iron-deficiency anaemia.

PPI, proton pump inhibitors; H2RA, H_2 receptor antagonists; IRIDA, iron-refractory iron-deficiency anaemia; NSAIDs, non-steroidal anti-inflammatory drugs;

Figure 1



Figure