Anaemia in pregnancy

Anaemia is the most common haematological disorder seen in pregnancy. Early recognition and effective management will help to reduce adverse maternal and fetal outcomes.

Anaemia is a manifestation of a broad spectrum of conditions, arising from either suppressed bone marrow production or loss of red cells from the circulation through bleeding or haemolysis. The most common causes of anaemia in pregnancy are iron deficiency and congenital haemoglobinopathies but other causes are also important to recognize and manage effectively. This article will focus on haematinic deficiencies, including iron, vitamin B_{12} and folate deficiency.

Definition

Anaemia has been defined by various limits in pregnancy. The World Health Organization defines anaemia as a haemoglobin level of <110 g/litre antenatally and <100 g/litre postnatally. The British Committee for Standards in Haematology guideline defines anaemia as haemoglobin of <110 g/litre in the first trimester, <105 g/litre in the second and third trimesters and <100 g/litre in the postpartum period, in recognition of the physiological haemodilution which is maximal in the second trimester (Pavord et al, 2012).

Prevalence

Globally, anaemia affects 1.62 billion people, which corresponds to 24.8% of the population. The highest prevalence is in pre-school children at 47.4% and pregnant women at 41.8% (de Benoist et al, 2008). Even in the developed world, the estimated prevalence is 30–40% in the pregnant population.

Regulation of iron in the body

The normal iron content of the body is approximately 3–4 g. It exists in the forms listed in *Table 1*.

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The regulation of iron metabolism involves the following main processes (*Figure 1*):

Intestinal iron absorption

This function is tightly controlled, since there is no physiological means of excreting iron from the body once it is absorbed.

Iron cycling

Ferroportin functions as a major exporter of iron, transporting iron from mother to fetus, transferring absorbed iron from enterocytes into the circulation, and allowing macrophages to recycle iron from damaged red cells back into the circulation.

Hepcidin

The hormone which is responsible for the regulation of iron is hepcidin, which degrades ferroportin, suppressing release of iron from cells into the circulation. This control of iron cycling through ferroportin is post-transcriptional.

Iron loss

Iron is lost in sweat, shed skin cells, and gastrointestinal loss at a rate of approximately 1 mg/day.

Causes of anaemia in pregnancy

The commonest cause of anaemia in pregnancy is iron deficiency. The development of anaemia and the speed with which it progresses depends on the individual's initial iron stores. This in turn depends on age, nutrition and balance of iron absorption and losses.

Table 1. Distribution of iron content in body

Form of iron	Amount
Haemoglobin in circulating red blood cells and developing erythroblasts	2.5 g
Plasma transferrin-bound iron	3–7 mg
Iron-containing proteins (e.g. myoglobin, cytochromes, catalase)	400 mg
Storage as ferritin or haemosiderin	Remainder

Iron stores for adult women are generally low as a result of the composite effect of menstrual losses, poor dietary intake and iron losses associated with pregnancy and lactation (approximately 1000 mg each for pregnancy, delivery and breast feeding).

Dietary intake

Dietary iron has two main forms: haem and non-haem. Plants and iron-fortified foods contain non-haem iron only, whereas meat, seafood and poultry contain both haem and non-haem iron (Aggett, 2012). Haem iron has a higher bioavailability than non-haem iron (Bott, 2001).

The average daily iron intake from food for women in Great Britain is 10.5 mg (Gregory et al, 1990). Approximately 10–15% of dietary iron is absorbed. Physiological iron requirements are three times higher in pregnancy than they are in menstruating women with increasing demand as pregnancy advances (Tapiero et al, 2001), giving a recommended daily allowance in pregnancy of nearly 30 mg iron per day.

Awareness of dietary requirements and the iron content of various foods is essential. The US Department of Agriculture's (2016) Nutrient Database website lists the nutrient content of many foods and provides a comprehensive list of foods containing iron arranged by nutrient content and by food name.

Dietary absorption

There are a number of foods and medications that impair iron absorption (*Table 2*). A new diagnosis of malabsorption is rare in pregnancy. Patients with coeliac disease are known to be iron deficient and refractory to oral iron therapy but are unlikely to first manifest in pregnancy.

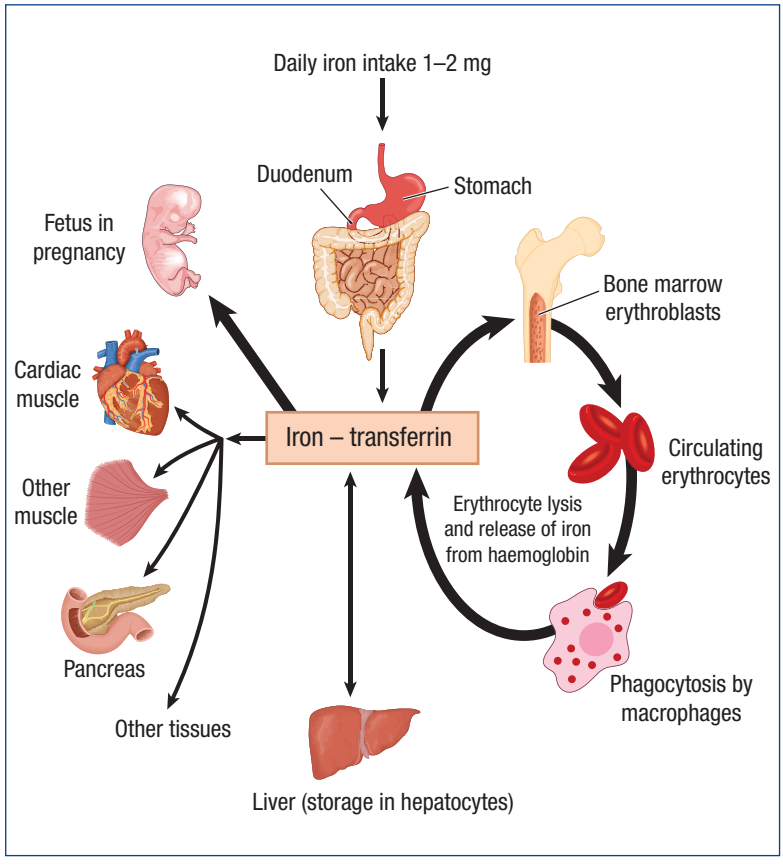
Chronic disease

Chronic infection, inflammation and neoplastic disease commonly cause anaemia. Chronic kidney disease and inflammatory bowel disease are frequent examples. Anaemia of chronic disease is usually mild to moderate. The main treatment is that of the underlying condition (Weiss and Goodnough, 2005), although iron supplementation and/or agents to stimulate erythropoiesis can be helpful. Inflammation may be associated with a functional iron deficiency, with raised hepcidin levels, causing failure of absorbed iron to be released from the intestinal cell to the circulation. Iron administered parenterally increases haemoglobin levels to a greater extent and is associated with fewer side effects than oral iron supplementation in these patients (Cavill et al, 2006).

Effects of anaemia in pregnancy

Undiagnosed and untreated iron deficiency anaemia has its impact on maternal and fetal health. Chronic iron deficiency affects the general wellbeing of the mother and leads to fatigue and reduced working capacity. It can also cause pallor, breathlessness, palpitations, headaches, dizziness and irritability.

Figure 1. Pathways involved in iron homeostasis. From Andrews (2000).



Rarely pica develops, where there is a craving for non-food items such as ice and dirt. Iron deficiency anaemia may also impair temperature regulation and cause pregnant women to feel colder than normal. Stored iron is depleted before a fall in haemoglobin and as iron is an essential element in all cells, symptoms may occur even without anaemia, including fatigue, irritability, poor concentration and hair loss.

Table 2. Factors influencing iron absorption

Absorption of haem iron	Amount of haem iron, especially in meat		
	Content of calcium in the meal (calcium impairs iron absorption)		
Absorption of non-haem iron	Iron status		
	Amount of potentially available non-haem iron		
	Balance between positive and negative factors	Positive factors	Ascorbic acid
			Meat or fish (factors in meat other than haem iron enhance absorption of non-haem iron)
		Negative factors	Phytate (in bran, oats, rye, fibre)
			Polyphenols (in tea, some vegetables and cereals)
			Dietary calcium
			Soy protein

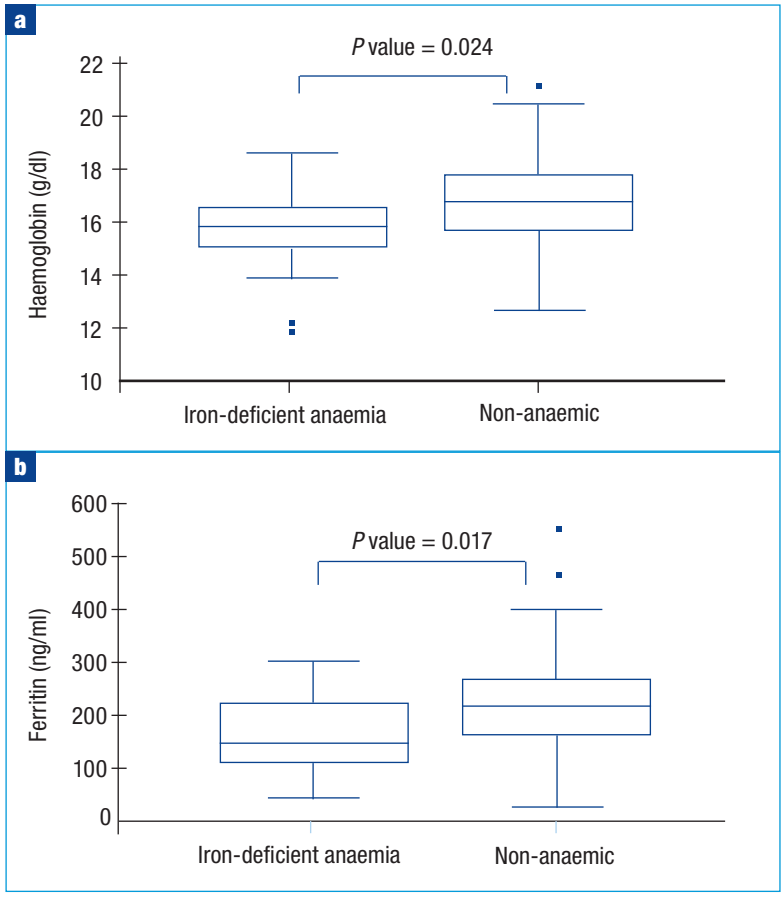
Severe anaemia in pregnancy, especially if not detected and/or not corrected, may warrant intravenous iron therapy or even blood transfusion. This may be required antenatally or postnatally. Blood transfusion is associated with various risks including acute transfusion reactions, incorrect transfusions, infections and sensitization leading to future maternal fetal alloimmunisation.

Maternal morbidity and mortality

Pregnant women with anaemia have a higher rate of preterm birth than non-anaemic women. Iron-deficient anaemic women have twice the rate of pre-term births compared to non-anaemic women. These results were obtained in a prospective study (Scholl et al, 1992) after controlling for maternal age, parity, ethnicity, prior low birth-weight or pre-term delivery, bleeding in early pregnancy, gestational age at initial blood tests, smoking, and pre-pregnancy body mass index. Inadequate gestational weight gain was also significantly higher in the iron-deficient anaemic women, which in turn is associated with preterm delivery (Viteri, 1994).

There is an increased incidence of complications in labour, placental abruption and postpartum haemorrhage in anaemic women and up to 600 000 maternal deaths occur every year in the peripartum period, mainly in the developing world. Anaemia is a direct cause in at least 8–16% of these deaths and is a major contributory factor in mortality from infection, haemorrhage, eclampsia, abortion and obstructed labour (Guidotti, 2000). The risk of maternal death increases dramatically with severe anaemia, and has been quoted as up to 20% in the peripartum period if the haemoglobin level is <50 g/litre (Harrison, 1982).

Figure 2. Box plots of **(a)** haematological profile and **(b)** ferritin parameters in newborns according to anaemia and iron status of the mothers. *P* values are from the Mann–Whitney test. From Terefe et al (2015).



Effects on fetus and neonate

There is evidence to suggest a significant correlation between severity of anaemia, premature birth and low birth weight. This in turn affects perinatal mortality (Viteri, 1994). Maternal iron depletion increases the risk of iron deficiency in the first 3 months of life, by a variety of mechanisms (Puolakka et al, 1980; Colomer et al, 1990).

Figure 2 demonstrates haematological profiles in newborns according to anaemia and iron status of the mothers, in a cross-sectional study carried out in Ethiopia (Terefe et al, 2015).

Various studies have followed up neonates into infancy and pre-school age. After controlling for background variables including maternal IQ, Home Observation for Measurement of the Environment (HOME), and infant lead level, pre-school groups with moderate iron-deficiency anaemia showed lower test scores on performance IQ (Lozoff et al, 2006). The iron-deficient anaemic groups also tested lower in IQ, psycho-educational abilities, visual motor integration and language abilities. They were also more neurologically immature, as assessed by a highly skilled neurologist.

Iron administration

The first line of management should be oral iron. The optimal dose has not been established but it has become standard to prescribe 100–200 mg of elemental iron daily. Absorption is maximized by administration 1 hour before meals on an empty stomach, with a glass of orange juice or other form of vitamin C.

Intolerance and poor compliance can limit efficacy. Iron salts may cause gastric irritation and up to a third of patients may develop dose-limiting side effects, including nausea and epigastric discomfort (Breymann, 2002). Titration of dose to a level where side effects are acceptable or a trial of an alternative preparation may be necessary. Enteric coated or sustained release preparations should be avoided as the majority of the iron is carried past the duodenum, limiting absorption. The relationship between dose and altered bowel habit (diarrhoea and constipation) is less clear and other strategies, such as use of laxatives, are helpful. Dietary advice to optimize iron intake should be tailored to the individual, according to dietary, religious or cultural preferences.

Routine iron administration

Given the prevalence and consequences of iron-deficiency anaemia in pregnancy, the value of routine iron administration to all pregnant women has been considered.

In the UK, early screening is considered preferable to routine supplementation. Guidance from the National Institute for Health and Care Excellence (2008) states that all pregnant women should have a full blood count at booking and at 28 weeks. This enables selective oral iron supplementation in those with anaemia or at risk of anaemia from factors such as vegetarianism, multiple pregnancy and a short interval (<1 year) between pregnancies. Systems should be in place for rapid review of blood results and appropriate follow up. Patients with haemoglobinopathy need their serum ferritin level checked before starting empirical iron supplements, to exclude iron overload from their condition.

In the developing world, the above may not be easily feasible. Hence daily oral iron supplementation of 60 mg/day is routinely recommended by the International Nutritional Anaemia Consultative Group guidelines for the use of iron supplements in pregnancy to treat and prevent iron deficiency anaemia (Stoltzfus and Dreyfuss, 1998).

Routine daily supplementation may potentially cause a high haemoglobin concentration in mid and late pregnancy, which can be associated with an increased risk of having premature birth and/or a low birth weight baby (Peña-Rosas et al, 2015), as a result of placental insufficiency.

Intravenous iron

Oral iron is the preferred first-line therapy for most patients with iron deficiency anaemia but many women experience gastrointestinal side effects and compliance with treatment is poor. The Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (2013) advises that parenteral iron produces a more rapid response and better repletion of iron stores in several clinical situations such as severe anaemia in late pregnancy, iron deficiency in patients with inflammatory bowel disease and patients on renal dialysis.

Blood transfusion

Blood transfusion should only be used in non-bleeding patients when there is risk of imminent cardiac compromise. The risks of blood transfusion include circulatory overload, transfusion reactions (1 in 7000 acute reactions), sensitization to antigens like Kell and c, posing a risk of fetal haemolytic disease in a future pregnancy, and incompatible transfusions (1 in 180 000) – 5–10% of which are fatal. It is crucial to discuss risks, benefits and alternative treatments with the patient and gain consent for blood transfusion. It is important that the patient is re-evaluated after each unit to avoid unnecessary transfusion. It would be unusual to require more than one unit in this setting as further management could be completed with oral or intravenous iron.

Other causes of anaemia

In severe unexplained anaemia, folate or vitamin B_{12} deficiency should be considered.

“Oral iron is the preferred first-line therapy for most patients with iron deficiency anaemia but many women experience gastrointestinal side effects and compliance with treatment is poor.”

Typical blood film appearances are of oval macrocytes, hypersegmented neutrophils and circulating megaloblasts. The bone marrow shows megaloblastic change. Mean cell volume is usually elevated, unless there is concomitant iron deficiency; however, it is not a specific indicator (Galloway and Hamilton, 2007) as there is a normal physiological increase in pregnancy and it may also be affected by alcohol, thyroid dysfunction or liver disease.

Folate deficiency usually results from imbalance between demand in pregnancy and supply from oral intake. It is easily managed by oral folate supplements. Serum vitamin B_{12} levels often fall in pregnancy and return to normal in the postpartum period. Therefore results can be misleading and testing should be avoided, unless there are risk factors for vitamin B_{12} malabsorption such as gastrectomy or gastrointestinal disease, or significantly raised mean cell volume not explained by folate deficiency, or suspicious neurological symptoms. Genuine vitamin B_{12} deficiency is rare in pregnancy, in part because stores last for several years, and partly because the condition is associated with infertility. Furthermore, pernicious anaemia, the most common cause of vitamin B_{12} deficiency, is usually a disease of older patients.

Treatment of established cobalamin deficiency should follow the schedules of the British National Formulary.

Anaemia in pregnant patients with HIV

Anaemia is prevalent in HIV-seropositive pregnant women, particularly when disease is advanced (Nandlal et al, 2014). The use of antiretroviral drugs such as zidovudine either for prevention of mother-to-child transmission of HIV or in combination with other antiretrovirals has been implicated in the development of more severe anaemia (Spiga et al, 1999).

HIV infection can cause anaemia through changes in cytokine production and altered erythropoietin response (Gangopadhyay et al, 2011). Co-existing chronic diseases such as tuberculosis and malaria, nutritional status, immunity and antiretrovirals are contributory factors in the severity of anaemia.

A Cochrane review (Martí-Carvajal et al, 2011) evaluated the evidence for use of recombinant human erythropoetin alfa and concluded that it does not reduce mortality, does not reduce transfusion requirements, does not increase haemoglobin levels, and does not improve quality of life in HIV-infected patients with anaemia. Hence in the absence of further high quality evidence, the World Health Organization (2003) recommends daily supplementation of folic acid 400 µg and of oral iron 60 mg

KEY POINTS

- Anaemia is defined as a haemoglobin level <110 g/litre in the first trimester, <105 g/litre in the second and third trimesters, and <100 g/litre in the postpartum period.
- Prompt detection of anaemia in pregnancy is essential. This allows effective intervention to prevent avoidable serious sequelae to mother and fetus.
- Adequate and appropriate counselling of patients is crucial to ensure compliance with and tolerance of medication and improve efficacy of treatment.
- Effective management will also reduce the need for blood transfusion and prevent overuse of intravenous iron therapy.
- In patients with severe unexplained anaemia, it is important to consider folate deficiency.
- Clinicians should also be careful not to over-diagnose vitamin B_{12} deficiency.

to prevent anaemia in HIV-positive pregnant women. However, iron supplements are known to interact with integrase strand transfer inhibitor drugs such as raltegravir and dolutegravir. This can be minimized by administration at least 2 hours before or 6 hours after oral iron. More information about HIV drug interactions can be found at www.hiv-druginteractions.org/

Conclusions

Recognition of anaemia and its treatment in pregnancy is a simple means of improving maternal and fetal wellbeing. Iron deficiency anaemia is the commonest cause and should be treated with oral iron as first line. Where there is absolute intolerance or non-compliance, intravenous iron is helpful. Blood transfusion should be reserved for urgent cases where there is risk of imminent cardiac compromise. **BJHM**

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