UK guidelines on the management of iron deficiency in pregnancy

British Committee for Standards in Haematology.

Address for correspondence:

BCSH Secretary
British Society for Haematology
100 White Lion Street
London N1 9PF
e-mail bcsh@b-s-h.org.uk

Writing group:

S Pavord¹, B Myers², S Robinson³, S Allard⁴, J Strong⁵, C Oppenheimer⁶

Disclaimer: While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Date of BCSH approval: July 2011

¹ University Hospitals of Leicester
² United Lincolnshire Hospitals Trust
³ Guy’s and St Thomas’ Hospital, London
⁴ Bart’s and the London NHS Trust & NHS Blood and Transplant
⁵ Leicester Royal Infirmary
⁶ Leicester Royal Infirmary
Introduction

Iron deficiency is the most common deficiency state in the world, affecting more than 2 billion people globally. Although it is particularly prevalent in less-developed countries, it remains a significant problem in the developed world, even where other forms of malnutrition have already been almost eliminated. Effective management is needed to prevent adverse maternal and pregnancy outcomes, including the need for red cell transfusion. The objective of this guideline is to provide healthcare professionals with clear and simple recommendations for the diagnosis, treatment and prevention of iron deficiency in pregnancy and the postpartum period. This is the first such guideline in the UK and may be applicable to other developed countries. Public health measures, such as helminth control and iron fortification of foods, which can be important to developing countries, are not considered here.

The guidance may not be appropriate to all patients and individual patient circumstances may dictate an alternative approach.

Methods

The guideline group was selected by the British Society for Haematology, Obstetric Haematology Group (BSH OHG) and British Committee for Standards in Haematology (BCSH), to be representative of UK-based medical experts. MEDLINE and EMBASE were searched systematically for publications from 1966 until 2010 using the terms iron, anaemia, transfusion and pregnancy. Opinions were also sought from experienced obstetricians and practice development midwives. The writing group produced the draft guideline which was subsequently considered by the members of the BSH Obstetric Haematology Group and revised by consensus by members of the General Haematology Task Force of the BCSH. The guideline was then reviewed by a sounding board of approximately 50 UK haematologists, the BCSH and the BSH Committee and comments incorporated where appropriate. Criteria used to quote levels of recommendation and grades of evidence are as outlined in the Procedure for Guidelines Commissioned by the BCSH.

Summary of key recommendations

- Anaemia is defined by Hb <110g/l in first trimester, <105g/l in second and third trimesters and <100g/l in postpartum period
- Full blood count should be assessed at booking and at 28 weeks
- All women should be given dietary information to maximise iron intake and absorption
• Routine iron supplementation for all women in pregnancy is not recommended in the UK

• Unselected screening with routine use of serum ferritin is generally not recommended although individual centres with a particularly high prevalence of “at risk” women may find this useful

• For anaemic women, a trial of oral iron should be considered as the first line diagnostic test, whereby an increment demonstrated at two weeks is a positive result

• Women with known haemoglobinopathy should have serum ferritin checked and offered oral supplements if their ferritin level is <30 ug/l

• Women with unknown haemoglobinopathy status with a normocytic or microcytic anaemia, should start a trial of oral iron (1B) and haemoglobinopathy screening should be commenced without delay in accordance with the NHS sickle cell and thalassaemia screening programme

• Non-anaemic women identified to be at increased risk of iron deficiency should have a serum ferritin checked early in pregnancy and be offered oral supplements if ferritin is <30 ug/l

• Systems must be in place for rapid review and follow up of blood results

• Women with established iron deficiency anaemia should be given 100-200mg elemental iron daily. They should be advised on correct administration to optimise absorption

• Referral to secondary care should be considered if there are significant symptoms and/or severe anaemia (Hb<70 g/l) or late gestation (>34 weeks) or if there is failure to respond to a trial of oral iron.

• For nausea and epigastric discomfort, preparations with lower iron content should be tried. Slow release and enteric coated forms should be avoided

• Once Hb is in the normal range supplementation should continue for three months and at least until 6 weeks postpartum to replenish iron stores

• Non-anaemic iron deficient women should be offered 65mg elemental iron daily, with a repeat Hb and serum ferritin test after 8 weeks

• Anaemic women may require additional precautions for delivery, including delivery in a hospital setting, available intravenous access, blood group-and-save, active management of the third stage of labour, and plans for excess bleeding. Suggested Hb cut-offs are <100g/l for delivery in hospital and <95g/l for delivery in an obstetrician-led unit
• Women with Hb <100g/l in the postpartum period should be given 100-200mg elemental iron for 3 months

• Parenteral iron should be considered from the 2nd trimester onwards and during the postpartum period for women with confirmed iron deficiency who fail to respond to or are intolerant of oral iron

• Blood transfusion should be reserved for those with risk of further bleeding, imminent cardiac compromise or symptoms requiring immediate attention. This should be backed up by local guidelines and effective patient information

1. DEFINITION AND PREVALENCE OF IRON DEFICIENCY ANAEMIA IN PREGNANCY

1.1 Definition

Iron deficiency represents a spectrum ranging from iron depletion to iron deficiency anaemia. In iron depletion, the amount of stored iron (measured by serum ferritin concentration) is reduced but the amount of transport and functional iron may not be affected. Those with iron depletion have no iron stores to mobilize if the body requires additional iron. In iron-deficient erythropoiesis, stored iron is depleted and transport iron (measured by transferrin saturation) is reduced further; the amount of iron absorbed is not sufficient to replace the amount lost or to provide the amount needed for growth and function. In this stage, the shortage of iron limits red blood cell production and results in increased erythrocyte protoporphyrin concentration. In iron-deficiency anaemia, the most severe form of iron deficiency, there is shortage of iron stores, transport and functional iron, resulting in reduced Hb in addition to low serum ferritin, low transferrin saturation and increased erythrocyte protoporphyrin concentration.

Anaemia is defined as Hb less than 2 standard deviations below the mean for a healthy matched population. However there is variation in what are considered normal values for pregnancy. The World Health Organisation (WHO) defines anaemia in pregnancy as a haemoglobin concentration of <11g/dL (WHO, 2001) whereas large studies in Caucasians have found a range between 10.4g/dL and 13.5g/dL in early third trimester, in women receiving iron supplements (Milman et al, 2007). In view of the relative plasma expansion being particularly marked in the second trimester, it would seem reasonable to take 10.5g/dL as the cut-off from 12 weeks, as suggested by the US Centers for disease control and prevention (CDC) (Dowdle, 1989; Ramsey et al, 2000). However there is a racial difference in normal Hb levels and the optimum Hb may be lower in those of African origin than in Europeans (Garn et al, 1981).

The WHO defines postpartum anaemia as Hb <10.0g/dl.
Recommendation: There is variation in definition of normal Hb levels in pregnancy. A level of $\geq 110\text{g/l}$ appears adequate in the first trimester and $\geq 105\text{g/l}$ in the second and third trimesters (1B).

Postpartum anaemia is defined as Hb <100g/l (2B).

1.2 Prevalence

Anaemia affects 1.62 billion people globally, corresponding to 24.8% of the world population (McLean et al, 2009). Iron deficiency is the most common cause and even in the developed world an estimated 30-40% of preschool children and pregnant women have iron depletion (WHO, 2008).

2. CLINICAL EFFECTS OF IRON DEFICIENCY

Tissue enzyme malfunction occurs even in the early stages of iron deficient erythropoiesis and significant effects of iron deficiency anaemia have been described on maternal morbidity and mortality, fetal and infant development and pregnancy outcomes.

2.1 Maternal morbidity and mortality

Iron deficiency may contribute to maternal morbidity through effects on immune function with increased susceptibility or severity of infections (Eliz et al, 2005), poor work capacity and performance (Haas et al, 2001) and disturbances of postpartum cognition and emotions (Beard et al, 2005). There is little information regarding the Hb thresholds below which mortality increases, although this may be as high as 8.9g/dl, which was associated with a doubling of the maternal death risk in Britain in a 1958 study (Brabin et al, 2001). However severe anaemia is likely to have multiple causes and the direct effect of the anaemia itself is unclear.

2.2 Effects on the fetus and infant

The fetus is relatively protected from the effects of iron deficiency by upregulation of placental iron transport proteins (Gambling et al, 2001) but evidence suggests that 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). Impaired psychomotor and/or mental development are well described in infants with iron deficiency anaemia and may also negatively contribute to infant and social emotional behaviour (Perez et al, 2005) and have an association with adult onset diseases, although this is a controversial area (Beard et al, 2008; Insel et al, 2008).
2.3 Effects on pregnancy outcome

There is some evidence for the association between maternal iron deficiency and preterm delivery, (Scholl et al, 1994), low birth weight (Cogswell et al, 2003), possibly placental abruption and increased peripartum blood loss (Arnold et al, 2009). However further research on the effect of iron deficiency, independent of confounding factors, is necessary to establish a clear causal relationship with pregnancy and fetal outcomes.

3. DIAGNOSIS OF IRON DEFICIENCY

3.1 Clinical symptoms and signs

Clinical symptoms and signs of iron deficiency anemia in pregnancy are usually non-specific, unless the anaemia is severe. Fatigue is the most common symptom. Patients may complain of pallor, weakness, headache, palpitations, dizziness, dyspnoea and irritability. Rarely pica develops, where there is a craving for non-food items such as ice and dirt. Iron deficiency anemia may also impair temperature regulation and cause pregnant women to feel colder than normal.

Storage iron is depleted before a fall in Hb and as iron is an essential element in all cells, symptoms of iron deficiency may occur even without anaemia: These include fatigue, irritability, poor concentration and hair loss.

3.2 Laboratory tests

3.2.1 Full blood count, blood film and red cell indices

A full blood count is taken routinely in pregnancy and may show low Hb, mean cell volume (MCV), mean cell haemoglobin (MCH), and mean cell haemoglobin concentration (MCHC); a blood film may confirm presence of microcytic hypochromic red cells and characteristic ‘pencil cells’. However, microcytic, hypochromic indices may also occur in haemoglobinopathies. In addition, for milder cases of iron deficiency, the MCV may not have fallen below the normal range.

Some analysers will give a percentage of hypochromic red cells present. This is said to be a sensitive marker of functional iron deficiency, but is not available on all analysers, and there is little information on its use in pregnancy.

Other tests either assess iron stores or the adequacy of iron supply to the tissues.

3.2.2 Serum ferritin

Serum ferritin is a stable glycoprotein which accurately reflects iron stores in the absence of inflammatory change. It is the first laboratory test to become abnormal as iron stores decrease and it is not affected by recent iron ingestion. It is generally
considered the best test to assess iron-deficiency in pregnancy, although it is an acute phase reactant and levels will rise when there is active infection or inflammation.

During pregnancy, in women with adequate iron stores at conception, the serum ferritin concentration initially rises, followed by a progressive fall by 32 weeks to about 50% pre-pregnancy levels. This is due to haemodilution and mobilisation of iron. The levels increase again mildly in the third trimester (Asif et al, 2007). Even though the ferritin level may be influenced by the plasma dilution later in pregnancy, a concentration below 15 μg/l indicates iron depletion in all stages of pregnancy. In women of reproductive age, a level <15 μg/l has shown specificity of 98% and sensitivity of 75% for iron deficiency, as defined by no stainable bone marrow iron (Hallberg et al, 1993).

There are a variety of levels for treatment, quoted in different studies but in general, treatment should be considered when serum ferritin levels fall below 30 μg/l, as this indicates early iron depletion which will worsen unless treated. Van den Broek et al found that serum ferritin is the best single indicator of storage iron provided a cut-off point of 30 mg/l is used, with sensitivity of 90%, and specificity 85% (van den Broek et al, 1998). Concurrent measurement of the C-reactive protein (CRP) may be helpful in interpreting higher levels, where indicated. The CRP concentration seems to be independent of pregnancy and gestational age, although some studies describe a mild increase.

3.2.3 Serum Iron (Fe) and total iron binding capacity (TIBC)

Serum Fe and TIBC are unreliable indicators of availability of iron to the tissues because of wide fluctuation in levels due to recent ingestion of Fe, diurnal rhythm and other factors such as infection. Transferrin saturation fluctuates due to a diurnal variation in serum iron and is affected by the nutritional status (Adams et al, 2007). This may lead to a lack of sensitivity and specificity.

3.2.4 Zinc protoporphyrin (ZPP)

ZPP increases when iron availability decreases, as zinc, rather than iron, is incorporated into the protoporphyrin ring. This gives an indication of availability of iron to the tissues. Serum ZPP has the advantage of not being influenced by the plasma dilution and levels rise in the third trimester. It is affected by inflammation and infection although less so than is the serum ferritin. Red blood cell ZPP has greater sensitivity and specificity for iron depletion (Schifman et al, 1989) but is rarely performed.

3.2.5 Soluble transferrin receptor (sTfR)

| P a g e | 7 |
Measurement of sTfR is reported to be a sensitive measure of tissue iron supply and is not an acute-phase reactant (Choi et al., 2000). The transferrin receptor is a transmembrane protein which transports iron into the cell. Circulating concentrations of sTfR are proportional to cellular expression of the membrane-associated TfR and therefore give an accurate estimate of iron deficiency. There is little change in the early stages of iron store depletion, but once iron deficiency is established, the sTfR concentration increases in direct proportion to total transferrin receptor concentration. However, this is an expensive test which restricts its general availability, and there is little data on its use in pregnancy.

3.2.6 Reticulocyte haemoglobin content and reticulocytes

Iron deficiency causes a reduction in reticulocyte number and reticulocyte haemoglobin concentration. Using an automated flow-cytometry technique, measurements of reticulocyte cellular characteristics allow extremely early and objective information to be collected on erythropoietic activity in anaemia. This again is not widely available, and there is no data in pregnancy.

3.2.7 Bone Marrow iron

A bone marrow sample stained for iron has been considered the gold standard for assessment of iron stores; however, this test is clearly too invasive and not practical for any but the most complicated cases in pregnancy, where the underlying cause or causes of anaemia are not identifiable by simpler means.

3.2.8 Trial of Iron therapy

A trial of iron therapy is simultaneously diagnostic and therapeutic. Ferritin should be checked first if the patient is known to have a haemoglobinopathy but otherwise microcytic or normocytic anaemia can be assumed to be caused by iron deficiency until proven otherwise. Assessment of response to iron is both cost and time effective. A rise in Hb should be demonstrable by 2 weeks and confirms iron deficiency. If haemoglobinopathy status is unknown, it is reasonable to start iron whilst screening is being performed. Screening should be carried out immediately, in accordance with the NHS sickle cell and thalassaemia screening programme guidelines. Although severe anaemia can affect the results of haemoglobinopathy testing, with a reduction in HbA₂ of up to 0.5%, there is no justification for delay (Ryan et al., 2010). An effective system of reviewing results is imperative. If there has been no improvement in Hb by two
weeks, referral should be made to secondary care to consider other causes of anaemia, such as folate deficiency.

Recommendations

A trial of oral iron should be considered as the first line diagnostic test for normocytic or microcytic anaemia. An increase in Hb must be demonstrated at 2 weeks, otherwise further tests are needed (1B).

Serum ferritin should be checked prior to starting iron in patients with known haemoglobinopathy (1B).

Anaemic women with unknown haemoglobinopathy status should be offered a trial of iron (1B) and haemoglobinopathy screening should be undertaken without delay in accordance with the NHS sickle cell and thalassaemia screening programme guidelines (1A) but with awareness that iron deficiency can cause some lowering of the haemoglobin A2 percentage.

The serum ferritin level is the most useful and easily available parameter for assessing iron deficiency. Levels below 15 μg/l are diagnostic of established iron deficiency. A level below 30 μg/l in pregnancy should prompt treatment (2A).

Where available, ZPP or sTfR measurements may be helpful adjuncts. Serum C-reactive protein levels may facilitate assessment when inflammatory or infective processes are suspected/present (2B).

4. MANAGEMENT OF IRON DEFICIENCY

4.1 Dietary Advice

The average daily iron intake from food for women in Great Britain is 10.5mg (Gregory et al, 1990). Approximately 15% of dietary iron is absorbed. Physiological iron requirements are 3 times higher in pregnancy than they are in the menstruating women (Tapiero et al, 2001), with increasing demand as pregnancy advances. The recommended daily intake (RDA) of iron for the latter half of pregnancy is 30mg. Absorption of iron increases three-fold by the third trimester, with iron requirements increasing from 1-2mg to 6mg per day (Bothwell, 2000).

The amount of iron absorption depends upon the amount of iron in the diet, its bioavailability and physiological requirements. The main sources of dietary haem iron are haemoglobin and myoglobin from red meats, fish and poultry. Haem iron is absorbed 2-3 fold more readily than non-haem iron. Meat also contains organic compounds which promote the absorption of iron from other less bioavailable non-haem iron sources (Skikne et al, 1994). However approximately 95% of dietary iron intake is
from non-haem iron sources (Ryan et al., 2010). Vitamin C (ascorbic acid) significantly enhances iron absorption from non-haem foods (Lynch, 1997), the size of this effect increasing with the quantity of vitamin C in the meal. Germination and fermentation of cereals and legumes improve the bioavailability of non-haem iron by reducing the content of phytate, a food substance that inhibits iron absorption. Tannins in tea and coffee inhibit iron absorption when consumed with a meal or shortly after (Table 1).

Education and counselling regarding diet may improve iron intake and enhance absorption but the degree of change achievable, especially in poorer individuals, remains in question.

Recommendation: All women should be counselled regarding diet in pregnancy including details of iron rich food sources and factors that may inhibit or promote iron absorption and why maintaining adequate iron stores in pregnancy is important. This should be consolidated by the provision of an information leaflet in the appropriate language (1A).

4.2 Oral Iron Supplements

4.2.1. Oral iron preparations

Once women become iron deficient in pregnancy it is not possible to ensure repletion through diet alone and oral supplementation is needed. Oral iron is an effective, cheap and safe way to replace iron. Ferrous salts show only marginal differences between one another in efficiency of absorption of iron. Ferric salts are much less well absorbed. The recommended dose of elemental iron for treatment of iron deficiency is 100-200mg daily. Higher doses should not be given, as absorption is saturated and side effects increased.

Available ferrous salts include ferrous fumarate, ferrous sulphate and ferrous gluconate. The amount of elemental iron in each salt varies as detailed in the Table 2. Combined iron and folic acid preparations may also be used (Table 3) but it should be noted that use of these preparations does not obviate the need to take the recommended dose of folic acid for prevention of neural tube defects preconception and during the first 12 weeks of pregnancy.

Oral iron supplementation should be taken on an empty stomach, as absorption is reduced or promoted by the same factors that affect absorption of dietary non-haem iron.

Recommendation:

Dietary changes alone are insufficient to correct iron deficiency anaemia and iron supplements are necessary. Ferrous iron salts are the preparation of choice. The oral dose for iron deficiency anaemia should be 100-200mg of elemental iron daily (1A).
Women should be counselled as to how to take oral iron supplements correctly. This should be on an empty stomach, 1 hour before meals, with a source of vitamin C (ascorbic acid) such as orange juice to maximise absorption. Other medications or antacids should not be taken at the same time (1A).

4.2.2 Indications for oral iron supplementation

In keeping with the NICE guidance for routine antenatal care, all women should have a full blood count taken at the booking appointment and at 28 weeks (NICE, 2008). This enables selective iron supplementation early in pregnancy but depends on effective systems in place for rapid review of blood results and appropriate follow up to avoid delays in management.

Women with a Hb < 110g/l up until 12 weeks or <105g/l beyond 12 weeks should be offered a trial of therapeutic iron replacement. In the presence of known haemoglobinopathy, serum ferritin should be checked and women offered therapeutic iron replacement if the ferritin is <30 µg/l.

Treatment must begin promptly in the community. Referral to secondary care should be considered if there are significant symptoms and/or severe anaemia (Hb<70g/l) or advanced gestation (>34 weeks) or if there is no rise in Hb at 2 weeks.

Women with a Hb >110g/l up until 12 weeks gestation and Hb >105g/l beyond 12 weeks are not anaemic. However experience in the UK suggests iron store depletion without anaemia is not well identified. In non-anaemic women at increased risk of iron depletion such as those with previous anaemia, multiple pregnancy, consecutive pregnancies with less than a year’s interval between and vegetarians, a serum ferritin should be considered (Table 4). Other patients to consider include pregnant teenagers, women at high risk of bleeding and Jehovah’s witnesses.

If the ferritin is <30 µg/l, 65mg elemental iron once a day should be offered. FBC and ferritin should be checked 8 weeks later.

Unselected screening with routine use of serum ferritin is generally not recommended, as this is an expensive use of resources, may be misused to exclude iron deficiency and may cause delay in response to blood count results. However local populations should be considered and where there is a particularly high prevalence of “at-risk” women, this practice may be helpful.

Recommendation:

Full blood count should be assessed at booking and at 28 weeks (1A).
Women with a Hb <110 g/l before 12 weeks or <105 g/l beyond 12 weeks are anaemic and should be offered a trial of therapeutic iron replacement, unless they are known to have a haemoglobinopathy (1B).

Women with known haemoglobinopathy should have serum ferritin checked and offered therapeutic iron if the ferritin is <30 µg/l (1B).

Treatment should start promptly in the community and referral to secondary care should be considered if anaemia is severe (Hb <70 g/l) and/or associated with significant symptoms or advanced gestation (>34 weeks) (2B). In these cases the starting dose should be 200mg elemental iron daily.

In non-anaemic women at increased risk of iron depletion, serum ferritin should be checked. If the ferritin is <30 µg/l, 65mg elemental iron once a day should be offered (1B).

Unselected screening with routine use of serum ferritin is generally not recommended although it may be useful for centres with a particularly high prevalence of “at-risk” women (2B).

Systems must be in place for rapid review and follow up of blood results (1A).

Whenever iron tablets are supplied, the importance of keeping them out of the reach of children must be stressed (1A).

4.2.3 Response to oral iron

The haemoglobin concentration should rise by approximately 20 g/l over 3-4 weeks (British National Formulary, 2010). However, the degree of increase in Hb that can be achieved with iron supplements will depend on the Hb and iron status at the start of supplementation, ongoing losses, iron absorption and other factors contributing to anaemia, such as other micronutrient deficiencies, infections and renal impairment.

Compliance and intolerance of oral iron preparations can limit efficacy. Iron salts may cause gastric irritation and up to a third of patients may develop dose limiting side effects (Breymann, 2002), including nausea and epigastric discomfort. 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 (Tapiero, 2001). The relationship between dose and altered bowel habit (diarrhoea and constipation) is less clear (Tapiero et al, 2001) and other strategies, such as use of laxatives are helpful.

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

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

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

Once the haemoglobin concentration is in the normal range replacement should continue for three months and until at least 6 weeks postpartum to replenish iron stores (1A).

In non-anaemic women repeat Hb and serum ferritin is required after 8 weeks of treatment to confirm response (2B).

If response to oral iron replacement is poor, concomitant causes which may be contributing to the anaemia, such as folate deficiency or anaemia of chronic disease, need to be excluded and the patient referred to secondary care (1A).

4.2.4 Postnatal anaemia

The WHO define postnatal anaemia as Hb <10g/dl. FBC should be checked within 48 hours of delivery in all women with an estimated blood loss greater than 500ml and in women with uncorrected anaemia in the antenatal period or symptoms suggestive of postpartum anaemia.

Women with Hb<100 g/l, who are haemodynamically stable, asymptomatic, or mildly symptomatic, should be offered elemental iron 100-200mg daily for at least 3 months and a repeat FBC and ferritin to ensure Hb and iron stores are replete.

Recommendation:

Postpartum women with estimated blood loss >500ml, uncorrected anaemia detected in the antenatal period or symptoms suggestive of anaemia postnatally should have Hb checked within 48 hours (1B).

Women who are haemodynamically stable, asymptomatic or mildly symptomatic, with Hb <100 g/l should be offered elemental iron 100-200mg daily for 3 months with a repeat FBC and ferritin at the end of therapy to ensure Hb and iron stores are replete (1B).

4.3 Parenteral Iron Therapy

4.3.1 Parenteral iron therapy is indicated when there is absolute non-compliance with, or intolerance to, oral iron therapy or proven malabsorption (RCOG, 2007). It
circumvents the natural gastrointestinal regulatory mechanisms to deliver non-protein bound iron to the red cells.

Several authors have now reported on their experience with use of parenteral iron therapy for iron deficiency anaemia in pregnancy, with faster increases in Hb and better replenishment of iron stores in comparison with oral therapy, particularly demonstrated for iron sucrose (Al et al, 2005; Bhandal et al, 2006) and iron (III) carboxymaltose (Van Wyk et al, 2007; Breymann et al, 2007). A large retrospective study reported fewer postpartum transfusions in the group treated with intravenous (IV) iron (Broche, 2005). However, there is a paucity of good quality trials that assess clinical outcomes and safety of these preparations (Reveiz et al, 2007).

As free iron may lead to the production of hydroxyl radicals with potential toxicity to tissues, iron deficiency should be confirmed by ferritin levels before use of parenteral preparations. Contraindications include a history of anaphylaxis or reactions to parenteral iron therapy, first trimester of pregnancy, active acute or chronic infection and chronic liver disease (Perewusnyk et al, 2002). Facilities and staff trained in management of anaphylaxis should be available.

The intravenous iron preparations currently available in the UK and their properties are summarised in Table 5 (British National Formulary, 2010). The different preparations have not been compared to each other in pregnancy. Iron sucrose has a higher availability for erythropoiesis than iron dextran and experience suggests a good safety profile in pregnancy (Bayoumeu et al, 2005). Its use is limited by the total dose that can be administered in one infusion, requiring multiple infusions. The newer preparations, iron III carboxymaltose and Iron III isomaltoside aim to overcome this problem, with single dose administration in an hour or less (Lyseng-Williamson et al, 2009; Gozzard, 2011).

### 4.3.2 Fast acting intravenous iron preparations

Iron III carboxymaltose (Ferrinject) is a ferric hydroxide carbohydrate complex, which allows for controlled delivery of iron within the cells of the reticuloendothelial system (primarily bone marrow) and subsequent delivery to the iron binding proteins ferritin and transferrin. It is administered intravenously, as a single dose of 1000mg over 15 minutes (maximum 15mg/kg by injection or 20 mg/kg by infusion). Randomised controlled trials have shown non-inferiority (Van Wyk et al, 2007; Breymann et al, 2007) and superiority (Seid et al, 2008) to oral ferrous sulphate in the treatment of iron deficiency anaemia in the postpartum period, with rapid and sustained increases in Hb. Animal studies have shown it to be rapidly eliminated from the plasma, giving minimal risk of large amounts of ionic iron in the plasma. By 28 days, in iron deficient rats most of the iron has been incorporated into new erythrocytes (Funk et al, 2010).
Iron III isomaltoside (Monofer) is an intravenous preparation with strongly bound iron in spheroid iron-carbohydrate particles, providing slow release of bioavailable iron to iron binding proteins. There is rapid uptake by the reticuloendothelial system and little risk of release of free iron. An erythropoietic response is seen in a few days, with an increased reticulocyte count. Ferritin levels return to the normal range by 3 weeks as iron is incorporated into new erythrocytes. Doses >1000mg iron can be administered in a single infusion (Gozzard, 2011), although there is little data on its use in the obstetrics setting (Table 5).

### 4.3.3 Intramuscular preparations

The only preparation available in the UK that may be given intramuscularly (IM) is low molecular weight iron dextran. Compared with oral iron, IM iron dextran has been shown in a randomised controlled trial to reduce the proportion of women with anaemia (Komolafe et al, 2003). However injections tend to be painful and there is significant risk of permanent skin staining. Its use is therefore generally discouraged (Pasriche et al, 2010, Solomons et al, 2004) but if given, the Z-track injection technique should be used to minimise risk of iron leakage into the skin. The advantage of IM iron dextran is that, following a test dose, it can be administered in primary care, although facilities for resuscitation should be available as there is a small risk of systemic reaction.

### 4.3.4 Other considerations

A recent Cochrane review on treatments for iron deficiency in anaemia (Reviez et al, 2007) highlighted the need for good quality randomised controlled trials in this setting, in particular to assess clinical outcomes and adverse events. Pending further good quality evidence, there is a need for centres to review their policies and systems for use of parenteral therapy in iron deficiency anaemia in pregnancy.

**Recommendations:**

Parenteral iron should be considered from the 2nd trimester onwards and postpartum period in women with iron deficiency anaemia who fail to respond to or are intolerant of oral iron (1A).

The dose of parenteral iron should be calculated on the basis of pre-pregnancy weight, aiming for a target Hb of 110 g/l (1B).

The choice of parenteral iron preparation should be based on local facilities, taking into consideration not only drug costs but also facilities and staff required for administration.

All centres should undertake audit of utilisation of intravenous iron therapy with feedback of results and change of practice where needed (1A).
Women should be informed of potential side effects and written information should be provided.

5. MANAGEMENT OF DELIVERY IN WOMEN WITH IRON DEFICIENCY ANAEMIA

With good practice this situation should generally be avoided; however there are instances when women book late, have recently come from abroad or have not engaged with antenatal care. In these situations it may be necessary to take active measures to minimise blood loss at delivery. Considerations should be given to delivery in hospital, intravenous access and blood group and save. Whilst this should be done on an individual basis, a suggested cut off would be Hb <100g/l for delivery in hospital, including hospital-based midwifery-led unit and <95 g/l for delivery in an obstetrician-led unit, with an intrapartum care plan discussed and documented.

Clear evidence from randomised trials supports active management of the third stage of labour as a method of decreasing postpartum blood loss (Prendiville et al, 1988; Rogers et al, 1988). This should be with intramuscular syntometrine/syntocinon and in the presence of additional risk factors such as prolonged labour or instrumental delivery, an intravenous infusion of high dose syntocinon continued for 2-4 hours to maintain uterine contraction. Where injectable uterotonic are not available, misoprostol may be a useful alternative (Alfirevic et al, 2007).

Recommendations:

Women still anaemic at the time of delivery may require additional precautions for delivery, including delivery in an hospital setting, available intravenous access, blood group-and-save, active management of the third stage of labour and plans to deal with excessive bleeding. Suggested Hb cut-offs are <100g/l for delivery in hospital and <95g/l for delivery in an obstetrician-led unit (2B).

6 INDICATIONS FOR AND RISKS OF BLOOD TRANSFUSION

Concerns about safety, high costs and availability of donor blood have promoted greater scrutiny of blood transfusion practice (Dept of Health, 2007). Potential dangers of transfusion are numerous but most commonly arise from clinical and laboratory errors. In addition, specific risks for women in child-bearing years include the potential for transfusion- induced sensitisation to red cell antigens, conferring a future risk of fetal haemolytic disease.

Massive Obstetric Haemorrhage (MOH) is widely recognised as an important cause of morbidity and mortality and requires prompt use of blood and components as part of appropriate management (Lewis, 2007). The RCOG green top guidelines (RCOG,
2009) comprehensively cover the multidisciplinary approach required, together with the implementation of intra-operative cell salvage in this setting as a transfusion sparing strategy. However outside the massive haemorrhage setting, audits indicate that a high proportion of blood transfusions administered in the postpartum period may be inappropriate, with underutilisation of iron supplements (Parker et al, 2009; Butwick et al, 2009; So-Osman et al, 2010).

Clinical assessment and haemoglobin concentration is necessary postpartum to consider the best method of iron replacement. Where there is no bleeding, the decision to transfuse should be made on an informed individual basis. In fit, healthy, asymptomatic patients there is little evidence of the benefit of blood transfusion (ASATF, 1996), which should be reserved for women with continued bleeding or at risk of further bleeding, imminent cardiac compromise or significant symptoms requiring urgent correction.

If, after careful consideration, elective transfusion is required, women should be fully counselled about potential risks, including written information and consent should be obtained.

**Recommendation:**

Blood and components in massive obstetric haemorrhage should be used as indicated in a local multidisciplinary guideline and this should also include provision of intra-operative cell salvage where appropriate to reduce the use of donor blood (1A).

In addition to guidelines for MOH, obstetric units should have guidelines for criteria for red cell transfusion in anaemic women who are not actively bleeding (1A).

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

Women receiving red cell transfusion should be given full information regarding the indication for transfusion and alternatives available. Consent should be sought and documented in the clinical notes (1A).

Prompt recognition of iron deficiency in the antenatal period followed by iron therapy may reduce the subsequent need for blood transfusions (1A).

**7. PREVENTION OF IRON DEFICIENCY**
7.1 Universal supplementation

Two groups, the International Nutritional Anemia Consultative Group (INACG) and the World Health Organization (WHO) recommend universal supplementation with 60 mg/d of elemental iron, from booking, (WHO) or from the second trimester (INACG) (Stolzfus et al., 1998; WHO, 2001). Evidence for this approach was first provided by the MotherCare Project in 1993, who reviewed the results of 24 well conducted world-wide trials (Sloan et al., 1995). Virtually all studies demonstrated a positive effect of supplementation on maternal iron status. The Cochrane database confirmed these results, reviewing 49 trials involving 23,200 pregnant women. Although heterogeneity made results difficult to quantify between the studies, relative risk-reduction of anaemia at term was 30-50% for those receiving daily iron supplements, with or without folic acid (Pena-Rosas et al., 2006; Pena-Rosas et al., 2009).

However the studies reviewed in the Cochrane database provided insufficient information to draw conclusions about the impact on maternal and fetal outcomes and randomised controlled studies have found conflicting evidence that maternal or neonatal health will benefit from correcting these deficits (Palma et al., 2008; Cogswell et al., 2003).

There are also other potential downsides to routine supplementation, to consider:

7.1.1. Non-compliance

Whilst studies of routine iron supplementation have shown improvements in Hb and ferritin, at present there is no good evidence of benefit when implemented as a large-scale program through the primary health care system. Significant discrepancy exists between the impact of iron supplementation reported in the clinical trials’ setting and that observed in large-scale public health programs. This is likely to be a combination of patients’ and carers’ behaviour; with, respectively, poor compliance due to lack of patient knowledge and concern about maternal anaemia and inadequate counselling about the need for iron supplementation and its potential benefits and side-effects. Research has shown that drug compliance is inconsistent and often poor, despite relatively simple regimes and even where there is obvious life-threatening disease. It is worse in situations where there is no obvious ill health. In contrast, during clinical trials, patients are closely supervised, counselled and non-compliance kept to a minimum.

7.1.2. Clinical hazards of routine supplementation
There are potential clinical hazards of iron supplementation in already iron replete women, including raised Hb with risk of placental insufficiency and secondary haemochromatosis in women with iron loading states. However these are mainly theoretical rather than practical considerations for short term iron administration.

Raised Hb

The rheological status (haemoconcentration and elevated red cell aggregation) appears to have an important influence on the outcome of pregnancy (Heilmann, 1987, Sagen et al, 1982). There is a risk of elevated Hb, with the use of iron supplements in non-anaemic women and particularly those given daily regimes from an early gestational age <20 weeks (Pena-Rosas et al, 2009). This could represent excessive erythropoiesis but may have more to do with changes in plasma volume than with iron therapy. A U-shaped association has been observed between maternal Hb concentrations and birth weight. A large observational study of 54,382 pregnancies showed higher rates of perinatal death, low birth weights and preterm delivery in women with high (Hb >13.2g/dl) compared to intermediate Hb levels, at 13-19 weeks' gestation (Murphy et al, 1986). Furthermore, a booking Hb of >14.5g/dl was associated with a 42% risk of subsequent hypertension in primiparips.

Oxidant stress

When products of oxygen are brought into contact with transition metals capable of changing valence, such as iron (Fe$^{2+}$ → Fe$^{3+}$), reactive free radicals, the hydroxyl radicals are formed, which have the potential to damage cells and tissues (Halliwell et al, 1999). Thus tissue iron excess contributes to producing and amplifying the injury caused by free radicals as well as to modulating various steps involved in the inflammatory lesion.

The placenta is particularly susceptible to oxidative stress, being rich in mitochondria and highly vascular. Markers of oxidant stress (such as malondialdehyde) have been found to be significantly elevated in the placenta of women with regular iron supplementation in pregnancy (Devrim et al, 2006).

The intestinal mucosa is also vulnerable to oxidative damage, caused by the continuous presence of a relatively small amount of excess iron intake (Lund et al, 2001) and iron accumulation leading to intestinal abnormalities and injury has been observed in patients receiving therapeutic iron (Abraham et al, 1999). Previously iron-deficient pregnant women are potentially more susceptible, due to excessive iron absorption, particularly when given daily pharmacological doses of iron (Viteri, 1997).

7.1.3. Practical difficulties

There are clear logistical problems associated with widespread use. These include cost and supply of iron tablets, cost and ability to deliver adequate supportive care and the
potential risk of accidental overdose by children in the home. Iron ingestion has been the most common cause of paediatric poisoning deaths and doses as low as 60 mg/kg have proved fatal (Baker, 1989).

### 7.2 Alternative regimens

To avoid constant exposure of the intestinal mucosal cells to unabsorbed iron excess and oxidative stress and the risk of side effects and raised Hb with daily iron supplements, researchers have considered intermittent regimes, taken weekly or on alternate days. These appear to be as efficacious as daily regimes (Institute of Medicine, 1993; Anderson, 1991). However the extent to which these findings can be generalized needs to be determined and it may be that the response is not the same for all locations, depending upon variability in other background factors. Success has also been obtained with low dose daily regimes, such as 20mg elemental iron (Makrides et al, 2003) given under controlled trial conditions.

**Recommendations:**

**Routine iron supplementation for all women in pregnancy is not recommended in the UK (1B).**

**An individual approach is preferable, based on results of blood count screening tests as well as identification of women at increased risk (1A).**

**Acknowledgements and declarations of interest**

All authors have contributed to the guideline and none have declared a conflict of interest. Acknowledgements also to Filipa Barroso, Clinical Research Fellow at Barts and the London & NHSBT and to Pauline Coser, Obstetric Haematology Midwife at University Hospitals of Leicester, who made contributions to the guideline.

**References**


<table>
<thead>
<tr>
<th>Factors that inhibit iron absorption</th>
<th>Factors that enhance iron absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods rich in calcium</td>
<td>Heme iron</td>
</tr>
<tr>
<td>Tannins in tea</td>
<td>Ferrous iron (Fe(^{2+}))</td>
</tr>
<tr>
<td>Phytates in cereals</td>
<td>Ascorbic acid</td>
</tr>
</tbody>
</table>
### Table 2  Dose and elemental iron content per tablet of oral iron preparations

<table>
<thead>
<tr>
<th>Iron Salt</th>
<th>Dose per tablet</th>
<th>Elemental iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous Fumarate</td>
<td>200mg</td>
<td>65mg</td>
</tr>
<tr>
<td>Ferrous Gluconate</td>
<td>300mg</td>
<td>35mg</td>
</tr>
<tr>
<td>Ferrous Sulphate (dried)</td>
<td>200mg</td>
<td>65mg</td>
</tr>
<tr>
<td>Ferrous Sulphate</td>
<td>300mg</td>
<td>60mg</td>
</tr>
<tr>
<td>FerrousFeredetate (Sytron)</td>
<td>190mg / 5ml elixir</td>
<td>27.5 mg / 5ml</td>
</tr>
</tbody>
</table>

Table adapted from BNF 2010

### Table 3  Dose and elemental iron content per tablet of combined oral iron and folate preparations

<table>
<thead>
<tr>
<th>Combined iron and folate preparation</th>
<th>Iron salt and dose per tablet</th>
<th>Elemental iron content per tablet</th>
<th>Folic acid content per tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregaday</td>
<td>Fumarate 305mg</td>
<td>100 mg</td>
<td>350 mcg</td>
</tr>
<tr>
<td>Fefol</td>
<td>Sulphate 325 mg</td>
<td>47 mg</td>
<td>500 mcg</td>
</tr>
<tr>
<td>Galfer FA</td>
<td>Fumarate 305 mg</td>
<td>100 mg</td>
<td>350 mcg</td>
</tr>
</tbody>
</table>
### Table 4  Indications for assessment of serum ferritin

<table>
<thead>
<tr>
<th>Anaemic women where estimation of iron stores is necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known Haemoglobinopathy</td>
</tr>
<tr>
<td>Prior to parenteral iron replacement</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-anaemic women with high risk of iron depletion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous anaemia</td>
</tr>
<tr>
<td>Multiparity $\geq P3$</td>
</tr>
<tr>
<td>Consecutive pregnancy $&lt;1$ year following delivery</td>
</tr>
<tr>
<td>Vegetarians</td>
</tr>
<tr>
<td>Teenage pregnancies</td>
</tr>
<tr>
<td>Recent history of bleeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-anaemic women where estimation of iron stores is necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk of bleeding</td>
</tr>
<tr>
<td>Jehovah’s witnesses</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td><strong>Iron (III) complex</strong></td>
</tr>
<tr>
<td><strong>Dose of elemental iron</strong></td>
</tr>
<tr>
<td><strong>Test dose required as per manufacturer</strong></td>
</tr>
<tr>
<td><strong>Routes of administration</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Able to administer total dose</strong></td>
</tr>
<tr>
<td><strong>Half life</strong></td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td><strong>Dosage</strong></td>
</tr>
<tr>
<td><strong>Use in pregnancy</strong></td>
</tr>
<tr>
<td><strong>Lactation</strong></td>
</tr>
<tr>
<td><strong>Adverse drug related events</strong></td>
</tr>
<tr>
<td>Risk of severe anaphylaxis related</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>&lt;1/10 000</td>
</tr>
<tr>
<td>&gt;1/1000&lt;1/100</td>
</tr>
</tbody>
</table>

Anaphylactoid reactions