

1. Introduction and who the guideline applies to:

This guideline is aimed at all Health Care Professionals involved in the management of women with severe anaemia in pregnancy and the initial postnatal period.

Background:

Iron deficiency is the most common form of malnutrition in the world affecting more than 2 million people. Oral iron therapy and advice regarding dietary iron intake, are the simplest measures which can be employed to improve the haemoglobin (Hb) level. However, in the event that this is not possible there are alternatives. Although iron absorption from the diet increases three-fold in pregnancy, iron requirements increase even further and an iron deficit builds up.

Maternal anaemia has implications in pregnancy and postpartum period. 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).

It has been shown to increase the risk of postpartum haemorrhage (PPH). In a large prospective observational study at 2 maternity services in the UK found that 60% of women with Hb <85g/l sustained PPH, with a quarter progressing to severe PPH. One explanation is impaired uterine contractility due to reduced oxidative capacity. (Briley *et al*, 2014).

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)

Ferinject® can be used as a second line treatment when oral therapy is deemed inappropriate or has failed.

Intravenous iron is the chosen method of treatment for severe iron deficiency anaemia in pregnancy and the postnatal period.

Ferinject® usage in pregnancy is limited. However, Ferinject® is now licensed for use in the second and third trimester of pregnancy

Related documents:

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| Booking bloods and urine test guideline |
| Guidelines for Antenatal Sickle Cell and Thalassaemia (haemoglobinopathy) Screening |
| UHL aseptic technique for invasive procedures |
| UHL hand hygiene policy |
| MHRA Drug Safety Update, Volume 7, Issue 1 August 2013: Intravenous iron and serious hypersensitivity reactions: new strengthened recommendations to manage and minimise risk |

Definition:

There is variation in definition of normal haemoglobin levels in pregnancy. UK guidelines from the BCSH suggest definitions of anaemia as <11g/dl in the first trimester and <10.5g/dl in the second and third trimesters. Postpartum anaemia is defined as a haemoglobin <10g/dl.

2. Recommendations:

1. All women in pregnancy should have been screened for Haemoglobinopathies at booking as per the guidelines for Sickle Cell and Thalassaemia. All women in pregnancy should have a full blood count taken at booking and at around 28 week's gestation.
2. **Women with anaemia should have a clinical history taken by the health care professional and should be offered a trial of oral iron, without delay.** Non-anaemic women considered to be at risk of iron deficiency should have serum ferritin taken
3. First line treatment for anaemia should be oral iron supplement. Women should be advised on the correct method of administration and also receive dietary advice.
4. Once treatment has been commenced a repeat full blood count (FBC) should be taken after 2 weeks. If the Hb is improving treatment should continue. Further FBC monitoring may be necessary depending on compliance, tolerance and Hb level.
5. If there is no response after two weeks, referral should be made to secondary care. If tolerance is poor an alternative preparation with lower iron content can be tried.
6. If there is absolute intolerance or non-compliance with oral iron, IV iron should be considered providing iron deficiency has been confirmed with a low serum ferritin. The decision to prescribe Ferinject® should be made by the Clinician following this guidance. Ferinject® **MUST NOT** be given in the first trimester of pregnancy.

7. The dose of Ferinject® should be calculated according to the woman's booking weight.
8. Administration can only be undertaken in a clinical area where emergency equipment is available as there is a risk of anaphylaxis and should be controlled via an infusion pump. (see Appendix 1)
9. If the woman is symptomatic in the postnatal period, but there is no ongoing bleeding and there is no cardiovascular compromise Ferinject® can be considered in an attempt to reduce transfusion of red cells. However, if there is ongoing blood loss or any haemodynamic compromise iron supplementation may well not be sufficient and the need for a blood transfusion should be discussed with the Obstetric Lead Clinician or the Haematological Team.

Recommendation One:

All women in pregnancy should have been screened for Haemoglobinopathies at booking as per the guidelines for Sickle Cell and Thalassaemia. All women in pregnancy should have a full blood count taken at booking and at around 28 week's gestation.

- **All women** should have a screen for haemoglobinopathies at the first booking visit. The result should be reviewed and documented in the health record.
- Women with known haemoglobinopathy should have assessment of serum ferritin and folate before supplements are commenced.
- All women should have a FBC taken at booking and at 28 weeks in accordance with NICE guidelines. The results should be clearly documented in the health care records at next antenatal clinic visit.

Recommendation Two:

Women with anaemia should have a clinical history taken by the health care professional and should be offered a trial of oral iron without delay.
Non-anaemic women considered to be at risk of iron deficiency should have serum ferritin taken

- All anaemic women should be contacted to assess wellbeing and if symptomatic clinical review arranged and given oral iron.
- **At risk women who are not yet anaemic should be given oral iron if ferritin level is <30ug/l**

The clinical symptoms of iron deficiency anaemia in pregnancy are non-specific. Fatigue is the most common symptom but women may also present with pallor, weakness, headache, palpitations, dizziness, dyspnoea irritability, and restless legs. A craving for non-food items such as ice (pagophagia) and soil (pica) may develop (Lumish et al, 2014).

Recommendation Three:

First line treatment for anaemia should be an oral iron only supplement such as Pregaday. Women should be advised on the correct method of administration and also receive dietary advice.

- Women who are confirmed on venous sampling to be anaemic and who do not have a known haemoglobinopathy should be commenced on oral iron therapy.
- Women who have either Thalassaemia trait or sickle cell trait should only be commenced on oral therapy if they have evidence of iron deficiency i.e. low serum ferritin.
- All women should be instructed regarding the correct way to take oral iron and dietary advice should be given. (see Anaemia leaflet)
- Oral iron should be taken on an empty stomach 1 hour before or after food and should be taken with a vitamin C rich drink.
- If a woman is iron deficient prior to delivery and on iron therapy, she should continue oral iron for at least 3 months post partum.

The recommended daily intake is double during pregnancy more recent studies suggest that lower doses or intermittent supplementation (Cochrane - Pena-Rosas 2015) may be advantageous. Therefore, it maybe more reasonable to suggest daily or alternate daily dosing compared to twice daily dosing (Moretti 2015)

Higher doses potentially increase side effects such as gastric irritation, nausea and disturbed bowel function affecting compliance (Smith G. 2014 Cochrane database).

Recommendation Four:

Once treatment has been commenced a repeat FBC should be taken after 2 weeks. If the Hb is improving treatment should continue. Further assessments of FBC may be required if there is concern about compliance, tolerance or significant anaemia.

- All women commenced on oral iron therapy should have their FBC checked 2 weeks after commencing oral iron.
- These results should be clearly documented in the woman's health care records.

Recommendation Five:

If there is no response after two weeks, referral should be made to secondary care. If tolerance is poor an alternative preparation with lower iron content can be tried.

- If after 2 weeks the FBC is not improving because there has been intolerable side effects limiting compliance, the woman should be given a different preparation of oral iron therapy e.g. Ferrous Sulphate or Sytron.
- If the woman has symptomatic anaemia, is over 34 week's gestation or is not tolerating any oral therapy then her Obstetric Lead Clinician should be consulted. If the Obstetric Clinical Lead is unavailable then the Haematological Team should be consulted for further advice.

Recommendation Six:

If there is absolute intolerance or non-compliance with oral iron, IV iron should be considered providing iron deficiency has been confirmed with a low serum ferritin. The decision to prescribe Ferinject® should be made by the Clinician following this guidance. Ferinject® **MUST NOT** be given in the first trimester of pregnancy

Indications for Ferinject ®:

- Women with confirmed iron deficiency anaemia with a serum ferritin of <30ug/L who:
 1. Are intolerant to oral iron preparations or
 2. Fail to respond to oral iron therapy or
 3. Have malabsorption of oral iron

All care providers should discuss the option to use Ferinject® with either the Lead Obstetric Clinician or the Haematological Obstetric Team.

Recommendation Seven:

The dose of Ferinject® should be calculated according to the woman's booking weight

- The **booking** weight should be used to dose Ferinject®.
- Ferinject® should only be prescribed on the drug chart.

The regime that should be used is:

| PATIENT WEIGHT | MAXIMUM DOSE OF FERINJECT® |
|-----------------------|-----------------------------------|
| < 50kgs | 20mgs / kg |
| >50kgs | 1000mgs |

Recommendation Eight:

Ferinject® should be administered as an infusion. (see Appendix 1) Ferinject® should be diluted in 250mls of 0.9% saline and be given over 15 minutes. A pump should be used to control the rate of infusion.

- Administration can only be undertaken in a clinical area where emergency equipment is available as there is a risk of anaphylaxis.
- The risk of anaphylaxis is very rare but it is recommended that Hydrocortisone, Chlorpheniramine and Adrenaline should be available in case of severe reaction.
- Patients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after every administration of an IV iron product.
- Caution is needed with every dose of intravenous iron that is given ,even if previous administrations have been well tolerated.

Need for ongoing iron supplements should be reviewed, depending on clinical circumstances. Further supplements should not be administered within a week of IV Ferinject®.

Recommendation Nine:

If the woman is symptomatic in the postnatal period, but there is no ongoing bleeding and there is no cardiovascular compromise Ferinject® can be considered in an attempt to reduce transfusion of red cells. However, if there is ongoing blood loss or any haemodynamic compromise iron supplementation may well not be sufficient and the need for a blood transfusion should be discussed with the Obstetric Lead Clinician or the Haematological Team.

3. Education and training:

None

4. Supporting References (maximum of 3)

1. Briley et al., reporting errors, incidence & risk factors for PPH (prospective observational study) BJOG 214;121:876-888
2. Pena-Rosas, Juan Pablo, Luz Maria De-Regil, H. Malave Gomez, Monica C. Flores-Urrutia, and Therese Dowswell. "Intermittent oral iron supplementation during pregnancy." (2015): CD009997-CD009997.
3. Shinar S J, A Skornick-Rapaport, S Maslovitz. Iron supplementation in singleton pregnancy: Is there a benefit to doubling the dose of elemental iron in iron-deficient pregnant women? a randomized controlled trial. Journal of Perinatol 2017; 37: 782-786

5. Key Words:

Anaemia in pregnancy ferritin folate Ferinject®

| CONTACT AND REVIEW DETAILS | |
|--|---------------------------------|
| Guideline Lead (Name and Title) N Archer | Executive Lead A Furlong |
| Details of Changes made during review: Update to references and background. Pregaday replaced with oral iron supplement. Recommended daily intake of iron now double in pregnancy as new evidence. Higher doses may increase side effects | |

Appendix I:

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

| Combined iron and folate preparation | Iron salt and dose per tablet | Elemental iron content per tablet | Folic acid content per tablet |
|--------------------------------------|-------------------------------|-----------------------------------|-------------------------------|
| Pregaday | Fumarate 305mg | 100 mg | 350 mcg |
| Fefol | Sulphate 325 mg | 47 mg | 500 mcg |
| Galfer FA | Fumarate 305 mg | 100 mg | 350 mcg |
| Systron | Feredetate 190mg/5 mls elixir | 27.5mg/ 5mls elixir | None |
| Ferrous Sulphate | 200 mg | 65 mg | None |

Summary of intravenous iron preparations available in the UK

| | Cosmofer iron (III) hydroxide dextran complex | Venofer iron (III) hydroxide sucrose complex | FerinJect Iron(III) carboxymaltose | Monofer Iron (III) isomaltoside |
|---|--|--|--|--|
| Dose of elemental iron | 50mg/ml | 20mg/ml | 50mg/ml | 100mg/ml |
| Test dose required as per manufacturer | Yes, before every intravenous dose, once before intramuscular treatment | First dose new patients only | No | No |
| Routes of administration | Slow intravenous injection Intravenous infusion of total dose Intramuscular injection total dose | Slow intravenous injection Intravenous infusion | Slow intravenous injection Intravenous infusion | Slow intravenous injection Intravenous infusion |
| Able to administer total dose | Yes (up to 20mg/kg body weight over 4-6 hours) | No | Yes (up to 15mg/kg body weight maximum of 1000mg/week over 15mins) | Yes (up to 20mg/Kg body weight over 1 hour) |
| Half life | 5 hours | 20 hours | 7-12 hours | 5 hours |

| | | | | |
|------------------------------------|---|---|--|--|
| Dosage | 100-200mg per IV injection up to 3 times a week. Total dose infusion up to 20mg/kg body weight over 4-6 hours) (100mg IM into alternate buttocks daily in active patients in bed ridden up to 3 times a week) | Total IV single dose no more than 200mg, can be repeated up to 3 times in 1 week | 200mg per IV injection up to 3 times a week. Total dose infusion up to 15mg/kg body weight. Maximum weekly dose of 1000mg that can be administered over 15mins. | 100-200mg per IV injection up to 3 times a week. Total dose infusion up to 20mg/Kg body weight per week. Doses up to 10mg/Kg body weight can be administered over 30mins, doses greater than 10mg/kg body weight should be administered over 60 mins. |
| Use in pregnancy | No adequate data for use in pregnant women, contra-indicated in first trimester thereafter risk benefit based on clinical need | Not in first trimester | Not for use in first trimester | No adequate data for use in pregnant women, contra-indicated in first trimester thereafter risk benefit based on clinical need |
| Lactation | Risk not known | Unlikely to pass to maternal milk no clinical trials | <1% iron passed into milk unlikely to be significant | Risk not known |
| Adverse drug related events | 5% patients may experience minimal adverse events (dose related) Risk of severe anaphylaxis <1/10 000 Risk of anaphylactoid symptoms >1/1000<1/100 | 0.5-1.5% of patients may experience adverse events. Risk of anaphylactoid reaction >1/10 000 <1/1000 | 3% of patients may experience adverse events. Risk of anaphylactoid reaction >1/1000 <1/100 | More than 1% of patients may experience adverse events Risk of anaphylaxis <1/10 000 >1/1000 to <1/100 Anaphylactoid reactions |

Appendix 2:

Equipment required for administration of Ferinject®:

Ferinject® doses 1000mg in 250 mls normal saline 0.9% given in 15 mins.

1 steret
1 green Venflon.
Tape or cannula dressing
Vacutainer blood bottles- FBC.
2 White needles.
1 x 5 ml syringe
1 x 10 ml syringe
5mls of normal saline (to flush the cannula)
1 bag of 0.9% normal saline 250 mls.
Giving set (appropriate giving set to use with correct pump)
Gauze.

Procedure for administration of Ferinject infusion.

Baseline observations:

Prepare infusion of ferinject.

Prepare the skin in accordance with the aseptic non touch technique policy.

Insert venflon according to UHL guidelines.

Secure cannula in position with tape or cannula dressing.

Take blood as required via the cannula.

Flush with 2mls of normal saline.

Connect infusion of ferinject and infuse via pump calculated to the correct rate for the infusion.

Observe patient for any adverse events.

Remove cannula following completion of infusion.

Post infusion observations.

Intravenous Chlorpheniramine, Hydrocortisone and Adrenaline should be available for immediate use in the event of a severe adverse drug reaction.

Appendix 3:

Indications for assessment of serum ferritin

Anaemic women where estimation of iron stores is necessary

- Known Haemoglobinopathy
- Prior to parenteral iron replacement

Non-anaemic women with high risk of iron depletion

- Previous anaemia
- Multiparity \geq P3
- Consecutive pregnancy $<$ 1year following delivery
- Vegetarians
- Teenage pregnancies
- Recent history of bleeding

Non-anaemic women where estimation of iron stores is necessary

- High risk of bleeding
- Jehovah's witnesses