South Australian Perinatal Practice Guidelines

Anaemia in Pregnancy

Introduction

- Iron deficiency is the most common cause of anaemia in pregnancy worldwide
- Anaemia in pregnancy may be defined as an Hb below 110 g / L in the first trimester and below 105 g / L in the second and third trimesters. Postpartum anaemia is a Hb below 100 g / L (CDC 1998; Pavord et al. 2012)
- Normal ranges of red cell indices in pregnancy:
- Haemoglobin (Hb) 110-150 g / L (Yip 2000)
- Mean cell volume (MCV) 80-100 femtolitres (fl) (a rise of 20 fl above baseline may occur in normal pregnancy but should not cause the MCV to fall outside of the normal range)
- Uncorrected anaemia increases pregnancy morbidity especially if there is postpartum haemorrhage
- Severe iron deficiency in pregnancy is associated with low birth weight, preterm birth, perinatal mortality and postnatal depression (ACOG 2008)

Physiological changes

- Both the red cell mass and the plasma volume expand from the first trimester of pregnancy. The expansion of 30 – 40 % in plasma volume exceeds the 20 – 25 % increase in red cell mass. As a consequence, there is a dilutional drop in haemoglobin concentration. This creates a low viscosity state, which promotes oxygen transport to the tissues including the placenta. This is associated with a physiological macrocytosis (increasing on average 4 fl at term) (Howells et al. 1986)
- Absence of these physiological changes indicates a failure of maternal adaptation to pregnancy. It should be seen as a warning sign for inadequate placental function

Anaemia

- A Hb below 100 g / L requires investigation and treatment
- A Hb of 100-110 g / L, particularly when normocytic and occurring only in late pregnancy, does not necessarily need further investigation or treatment
- The origin of anaemia in pregnancy falls into one of the following categories:
- Iron deficiency
- Megaloblastic anaemia (vitamin B_{12} and folate deficiency)
- Haemoglobinopathies
- Other conditions

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Iron deficiency

- Approximately 600 mg of elemental iron are required for the increase in red cell mass during pregnancy and a further 300 mg for the fetus
- Many women, particularly multiparous women and women with heavy menstrual loss, commence pregnancy with reduced iron reserves
- In uncomplicated pregnancy the mean red cell volume (MCV) usually rises by 4 fl. Therefore a fall in MCV is the earliest sign of iron deficiency. This is followed by a fall in mean corpuscular haemoglobin (MCH) and finally anaemia
- Anaemia with a low MCV that does not respond to iron supplementation should be investigated with iron studies. True iron deficiency is characterised by the following taking all parameters into account:
- Low ferritin (< 15 μg / L)
- High transferrin (> 5.56 μmol / L) concentration (transferrin levels are higher in than outside pregnancy)
- Low serum iron (< 8 μmol / L)
- Low transferrin saturation (< 10 %)

Diagnosis of iron deficiency

- Women who are pregnant should be screened for anaemia at their booking visit and again at 28 weeks of gestation (see table 1)
- Anaemia can be diagnosed with a complete blood picture
- Confirmation of iron deficiency, when required, involves measurement of serum ferritin, which can be supported by serum transferrin saturation and serum soluble transferrin receptor. NB: Serum ferritin levels are increased in the presence of active infection or inflammation (consider C-reactive protein to facilitate assessment as indicated)
- Haemoglobin levels (Hb) and mean cell volume (MCV) are used as the first screening indicators of iron deficiency. However, iron studies, including serum ferritin may be required to correctly diagnose iron deficiency anaemia if women do not respond to iron supplementation
- Haemoglobinopathy is the main differential diagnosis of microcytosis. Investigations for haemoglobinopathies should ideally occur once a patient is iron replete. However, for treatment purposes, haemoglobinopathy screening may be required in the first trimester to allow time for genetic testing

Treatment of established iron deficiency

- Treatment of iron deficiency has obvious benefits to the mother
- Oral iron supplementation is the first line of management
- A high iron diet should be recommended where possible including red meat, iron fortified cereals and drinks
- Intravenous and intramuscular iron treatments carry a small risk of anaphylactic reaction. Their use should be reserved for cases of severe iron deficiency anaemia resistant to oral iron treatment (follow link to iron infusion)

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Iron absorption

- The amount of iron absorption depends upon the amount of iron in the diet, its bioavailability and physiological requirements (3 times higher in pregnancy)
- Haem iron, found in meat, poultry and fish, is two to three times more absorbable than non-haem iron, which is found in supplements, plant-based foods and iron-fortified foods. Offal products such as liver and kidneys are particularly rich sources of haem iron (CDC 1998)
- The bioavailability of non-haem iron is strongly affected by the kind of other foods ingested at the same meal
    - **Enhancers** of iron absorption are haem iron (in meat, poultry, and fish) and vitamin C (ascorbic acid)
    - Vitamin C significantly enhances iron absorption from non-haem foods
    - **Inhibitors** of iron absorption include polyphenols (in certain vegetables e.g. spinach, rhubarb), tannins (in tea), phytates (in bran and fibre supplements), and calcium (in dairy products and supplements) (CDC 1998)
    - Avoid consuming tea and coffee during or shortly after a meal

Recommended iron dose

- For iron-deficient anaemia the recommended dose is 40-80 mg of elemental iron per day (Milman 2008; Zhou et al. 2009). Depending on the preparation taken, the total dose can be achieved with one tablet taken daily or every second day, preferably on an empty stomach one hour before meals, with a source of vitamin C such as orange juice to maximise absorption (Pavord et al. 2012)
- The treatment of iron deficiency is twofold. In addition to taking iron tablets it is recommended that each meal contains 25 to 50 mg of ascorbic acid to enhance dietary non-haem iron absorption (either in the form of vitamin C tablets or vitamin C containing juices, e.g. orange, blackcurrant)
- Do not take iron tablets with dairy products, tea / coffee or cereals as these inhibit iron absorption (Ballot et al. 1987)

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Common oral iron preparations	Elemental iron content in mg
FGF	80 (as ferrous sulphate) + 0.3 mg folate
FGF 500	105 (as ferrous sulphate) + 0.5 mg folate
Ferro F	100 (as ferrous fumarate) + 0.3 mg folate
Fefol	87 (as ferrous sulphate) + 0.3 mg folate
Ferrograd C	105 (as ferrous sulphate) + 562 mg sodium ascorbate
Ferrogradumet	105 (as ferrous sulphate)
Ferro-Liquid	6 mg per mL syrup (as ferrous sulphate)
Elevit	60 + 11 other vitamins and minerals including calcium which simultaneously increases the risk of constipation while reducing iron absorption

- Oral iron treatment is often poorly tolerated. The side-effects of oral iron can exacerbate those of pregnancy such as constipation, heartburn, nausea and vomiting
- Advice regarding these symptoms, including blackening of stools, should be given
- The choice of oral preparation of iron can be guided by its tolerability
- "Natural" iron supplements available from health food stores are unlikely to contain sufficient quantities of elemental iron to be therapeutic. For a comparison of the number of tablets needed to achieve the recommended daily dose see the table below:

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"Natural" oral iron preparations	Elemental iron content in mg	No of tablets / amount in mL to achieve recommended daily dose (48-80 mg)
Iron melts	5 (as ferrous fumarate) + 0.2 mg folate, ascorbic acid 50 mg, vit B_{12} 0.1 mg	8-16 tablets
Herron one a day iron formula	5 (as ferrous fumarate) + 0.4 mg folate, ascorbic acid 50 mg, vit B_6 10 mg, vit B_{12} 0.02 mg	8-16 tablets
Blackmore's Bio Iron	5 (as ferrous fumarate) + 0.16 mg folate, ascorbic acid 100 mg, vit B_{12} 0.05 mg, nettle herb powder 100 mg	16 tablets
Blackmore's Pregnancy and Breastfeeding Gold	5 (as ferrous fumarate) + 25 mg folate, ascorbic acid 30 mg and other vitamins and minerals	16 tablets

Iron supplementation follow up

- Re-check complete blood picture 4 weeks after starting iron supplementation and follow up with iron studies if required
- If serum ferritin is < 15 μg / L in the first trimester, re-check serum ferritin at 28 weeks of gestation
- Once the haemoglobin concentration is in the normal range, continue oral iron treatment for a minimum of 12 weeks (or until completion of breastfeeding)

Intrapartum management

- Women with anaemia at the time of delivery require:
- Intravenous access
- Group and save
- Active management of the third stage of labour
    - Either bolus Syntocinon® 10 IU intravenous and / or 10 IU intramuscular

  OR consider ergot derivative if no pre-existing hypertension or preeclampsia:

    - Intramuscular Syntometrine® (oxytocin and ergometrine). Alternatively, give bolus ergometrine 25 to 50 micrograms intravenous (draw up 250 micrograms [0.5 mL] ergometrine and dilute to 5 mL with sodium chloride 0.9 % [1 mL = 50 micrograms], may repeat after 2 to 3 minutes) or 250 micrograms intramuscular

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Postpartum management

- Women with a haemoglobin < 100 g / L in the postpartum period should be prescribed elemental iron supplementation for 3 months (Pavord et al. 2012)

Megaloblastic anaemia - folate and vitamin B12 deficiency

- Megaloblastic anaemia is the second most common nutritional anaemia seen during pregnancy
- Folate deficiency is a more common cause of megaloblastic anaemia than vitamin B_{12} deficiency
- Folate and its co-factor vitamin B_{12} are required for DNA synthesis and cell division. During pregnancy, requirements are increased approximately 5-10 fold and stores may be exhausted if increased folate intake does not occur
- Except in strict vegans, true vitamin B_{12} deficiency is unlikely despite the increased requirements of pregnancy due to the extent of vitamin B_{12} stores
- Folate stores are much smaller and more easily exhausted
- Women with anaemia in the presence of a normal MCV should have further testing to exclude folate, vitamin B_{12} deficiency or thalassaemia
- True folate deficiency in pregnancy may be difficult to diagnose early. However it should be thought of and excluded in the presence of :
  - increasing MCV (> 100 fL but may be of the order of 120 fL)
  - development of anaemia
  - development of large hyper-segmented neutrophils are a late sign in pregnancy
  - falling platelet count (< 100 x 10^9 / L)
- Vitamin B_{12} and folate measurements should be undertaken to exclude deficiencies of both haematinics
- Sole folate deficiency without malabsorption can be due to increased requirements in excess of folate intake

Treatment of megaloblastic anaemia

- In the case of folate deficiency supplemental folate is given at 5 mg per day and continued throughout the pregnancy. Lack of reticulocytosis should raise the question of folate malabsorption
- In strict vegans *give* 1,000 micrograms of vitamin B_{12} by intramuscular injection may be given at 3 monthly intervals to prevent the development of vitamin B_{12} deficiency

Haemoglobinopathies

- Inherited defects of haemoglobin, resulting from:
  - Impaired globin synthesis (thalassaemia syndromes) or
  - Structural abnormality of globin (haemoglobin variants)
- Women with known haemoglobinopathy should have serum ferritin checked and offered oral supplements their ferritin level is < 30 μg / L (Pavord et al 2012)

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Thalassaemia

- Thalassaemia trait may be first diagnosed in pregnancy
- Pregnancy will exacerbate the anaemia of thalassaemia minor (normally 100 - 120 g / L) and may result in symptoms of anaemia in the first trimester
- The MCV (55 - 65 fl) will be lower than expected for iron deficiency and the red cell count high (> 5.5 x 1012 / L)
- Co-existent iron deficiency should be excluded and treated before testing for thalassaemia, as Hb electrophoresis may be falsely negative for thalassaemia in iron deficiency
- Once the diagnosis of either alpha or beta thalassaemia is made, informed discussion with the woman must be undertaken and where possible the father of the fetus should be tested initially by complete blood picture to exclude the presence of thalassaemia trait
- Discussion with a clinical geneticist is advisable before proceeding with further characterisation of the fetus where there is a risk of thalassaemia major

Other conditions

- Other conditions may occur in pregnancy that give rise to anaemia. These are uncommon and should be managed by an experienced obstetrician and physician (haematologist or nephrologist) according to the diagnosis
- *Acute leukaemia:* 1 in 75,000 pregnancies
- *Aplastic anaemia* in pregnancy is rare
- Micro-angiopathic anaemia can occur with a spectrum of disease states notably pre-eclampsia, eclampsia, abruptio placenta, thrombotic thrombocytopenic purpura / haemolytic uraemic syndrome. Also seen in the HELLP syndrome (haemolysis, elevated liver enzymes and low platelets).

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Useful references

RANZCOG College statement.Vitamin and mineral supplementation in pregnancy
Available from URL: http://www.ranzcog.edu.au/publications/statements/C-obs25.pdf

Bloodsafe Patient information leaflet 'What you should know about iron tablets'. Available from URL:

Bloodsafe Oral iron dosing chart for clinicians: 'Oral preparations for treatment of iron deficiency anaemia (IDA) in Australia'

Chart: Oral preparations for treatment of iron deficiency anaemia (IDA) in Australia.

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
CDC	Centers for Disease Control and Prevention
DNA	Deoxyribonucleic acid
e.g.	For example
et al.	And others
fl	Femtolitres
g / L	Gram(s) per litre
Hb	Haemoglobin
HELLP	Haemolysis, elevated liver enzymes and low platelets
IUD	Intrauterine device
kg	Kilogram(s)
MCV	Mean cell volume
MCH	mean corpuscular haemoglobin
mg / L	Microgram(s) per litre
mmol / L	Micromol(s) per litre
mg	Milligram(s)
mL	Millilitre(s)
%	Percentage

Version control and change history

PDS reference: OCE use only

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1.0	17 Aug 04	06 Oct 08	Original version
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