ANAEMIA AND HAEMOGLOBOINOPATHIES IN PREGNANCY

This LOP is developed to guide clinical practice at the Royal Hospital for Women. Individual patient circumstances may mean that practice diverges from this LOP.

1. **AIM**
   - Assessment and management of anaemia and haemoglobinopathies to prevent fetal/maternal morbidity/mortality
   - Appropriate referral to Clinical Genetics of woman/oocyte donor and biological father at "high risk" of haemoglobinopathies

2. **PATIENT**
   - Pregnant woman with anaemia[10]
     - <20 weeks gestation haemoglobin (Hb) ≤110g/L
     - ≥20 weeks gestation Hb ≤105g/L
   - Pregnant woman/oocyte donor and biological father at risk of, or with known haemoglobinopathy

3. **STAFF**
   - Medical and midwifery staff

4. **EQUIPMENT**
   - 21-gauge needle with vacutainer
   - Blood tubes
     - EDTA - full blood count (FBC), red cell folate, haemoglobinopathy screen (if required)
     - Serum Gel - ferritin (iron studies if required) and B12, folate

5. **CLINICAL PRACTICE**

Screening

- Review woman/oocyte donor and biological father's history and any prior investigations at first pregnancy contact (usually GP) for risk for anaemia and/or haemoglobinopathies
- Perform FBC at booking visit and again at 26-28 weeks gestation
- Perform haemoglobinopathy screening (FBC, haemoglobinopathy screen and iron studies for woman/oocyte donor including gestation and ethnicity on request form) if not been screened in past or previous result is not available, and has the following risk factors (appendix 2):
  - high risk ethnicity: South East Asian, Indian, Sri Lankan, Pakistani, Bangladeshi, Middle Eastern, Mediterranean, Black African or Islander
  - mean corpuscular volume (MCV) <80fL or mean corpuscular haemoglobin (MCH) <27pg
  - known haemoglobinopathy carrier, family history of haemoglobinopathy in woman/oocyte donor's or biological father's family
- Screen for iron deficiency (ferritin < 30ug/L) with a serum ferritin level if:
  - anaemia (as defined above)
  - at high risk of iron deficiency:
    - past history of anaemia
    - multiparity (≥P3)
    - multiple pregnancy
    - inter-pregnancy interval <one year
    - last birth complicated by postpartum haemorrhage
    - vegetarian/vegan
    - teenager
    - low socioeconomic status
    - woman who will refuse transfusion or unable to access transfusion, e.g. Jehovah's Witness or red cell antibodies[2]

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Further Investigations

- Investigate anaemia as per appendix 2:
  - Review history and past investigations
  - Review blood film (microcytosis, fragmentation, sickle cells) and MCV, MCH
  - Iron Studies, vitamin B12, folic acid, red cell folate, haemoglobinopathy screen

- Screen biological father (FBC, haemoglobinopathy screen, iron studies) if any abnormalities identified on woman/oocyte donor's haemoglobinopathy screen. State woman/oocyte donor's name and MRN on biological father's form and state biological father's name and date of birth on woman/oocyte donor's form

Management

- Discuss appropriate diet to maintain iron stores and inform woman of symptoms of anaemia
- Refer haemoglobinopathy carriers to an obstetrician/haematologist for maternal management
- Refer to geneticist if both biological parents known or suspected haemoglobinopathy carriers. DNA testing, then chorionic villus sampling (CVS) or amniocentesis may be offered
- Treat iron deficiency (ferritin <30, regardless of Hb) with:
  - diet AND
  - oral iron supplementation. Advise a minimum of 80mg *elemental iron* content – the higher the better Increase to 200mg once daily, as tolerated. Refer to Table 1 below and patient handout for iron preparations
- Give woman information handout (appendix 1)
- Do not commence iron replacement without confirming iron deficiency, as low MCV or Hb may be due to haemoglobinopathy
- Discuss gastrointestinal side effects of iron supplementation and options to prevent/mitigate. If woman troubled by these side effects encourage reduction in the frequency (e.g. alternate day dosing) rather than ceasing altogether, taking iron at night, and treating constipation (if a problem) with increased fibre and fluids, and a mild laxative e.g. docusate sodium (Coloxyl®) if required
- Monitor response to oral supplementation. Hb should increase 2g within three weeks[14].
  - retest Hb in two to four weeks from commencement of supplementation if anaemic
  - retest in one month from commencement of supplementation if iron deficiency alone
  - evaluate compliance/adherence to treatment at each visit and further options if Hb not increasing[6]
  - continue replacement for three months, and until at least six weeks post-partum[6] once the Hb is in the normal range
- Consider intravenous iron in the following circumstances (see Iron deficiency in Maternity and Gynaecology/Oncology Patients LOP):
  - iron deficiency anaemia in a woman unresponsive to, or intolerant/non-compliant with oral iron, or where absorption of oral iron is likely to be impaired, e.g. inflammatory bowel disease, bariatric surgery, or where there is inadequate time for oral replacement (e.g. birth expected within three weeks, and/or severe anaemia- Hb <80)
  - symptomatic blood loss, or at high risk of significant blood loss in the antenatal or postnatal period where iron deficiency is diagnosed, with or without a reduction in Hb (Hb < 100 g/L postnatally)
  - woman at high risk of intrapartum/intraoperative blood loss, where iron deficiency or iron deficiency anaemia is diagnosed and woman is unable to achieve target ferritin (target ferritin 100 µg/L) with oral supplementation or woman is unwilling/unable to accept blood products[2]

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- Treat other specific causes of anaemia (e.g. folate or B12 deficiency)[6]
- Refer to obstetrician or haematologist if thrombocytopenia, unexplained anaemia, moderate to severe anaemia (Hb < 90g/L), significant symptoms, late gestation >34 weeks or failure to respond to a trial of oral iron

6. **DOCUMENTATION**
   - Antenatal Card
   - Medical record

7. **EDUCATIONAL NOTES**
   - Iron deficiency is the leading cause of anaemia during pregnancy. It is associated with increased risk of perinatal morbidity and mortality, low birth weight, preterm birth, transfusion, and maternal morbidity [6,12,13]
   - When discussing iron supplementation in pregnancy, awareness of the variation in elemental iron content in supplemental formulations, is important[11]

Table 1: Oral iron preparations[11]

BRAND NAME	FORMULATION	ELEMENTAL IRON CONTENT PER UNIT	OTHER ACTIVE INGEDIENTS
Ferro-Gradumet®	325 mg ferrous sulfate controlled release tablet	105 mg	Nil
Ferrograd C®	325 mg ferrous sulfate controlled release tablet	105 mg	Ascorbic acid 500 mg
Ferro-f-tab®	310 mg ferrous fumarate tablet	100 mg	Folic acid 350 mcg
Fefol®	270 mg ferrous sulfate controlled release capsule	87.4 mg	Folic acid 300 mcg
FGF®	250 mg ferrous sulfate controlled release tablet	80 mg	Folic acid 300 mcg
Ferro-tab®	200 mg ferrous fumarate tablet	65.7 mg	Nil
Ferro-Liquid®	30 mg/mL ferrous sulfate oral liquid	6 mg/mL	Nil
Maltofer Syrup®	37 mg/mL iron polymaltose complex syrup	10 mg/mL	Ethanol 3.25 mg/mL
Maltofer tablet®	370 mg iron polymaltose complex tablet	100 mg	Nil
Elevit ®	Not suggested for iron deficiency treatment as one tablet contains 60mg of elemental iron, also contains other vitamins and minerals that may reduce iron absorption[2]		

8. **RELATED POLICIES / PROCEDURES / CLINICAL PRACTICE LOP**
   - Antenatal Shared Care Protocol
   - Australian College of Midwives (AM) Guidelines for consultation and referral
   - Iron deficiency in Maternity and Gynaecology/Oncology Patients
   - Postpartum Haemorrhage – Prevention and Management
   - Blood products – Management of pregnant woman unable to use blood products

9. **RISK RATING**
   - Medium

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10. NATIONAL STANDARD

- Standard 2 – Partnering with Consumers
- Standard 4medication safety
- Standard 5 - Comprehensive care

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APPENDIX 1.
PATIENT INFORMATION:
IRON DEFICIENCY AND IRON DEFICIENCY ANAEMIA

Iron is used by all our cells. It is Important for our immune system, mental function, muscle strength, and energy. Iron is also used to make red blood cells (haemoglobin) to carry oxygen around our body. When you have low iron and low haemoglobin it is called iron deficiency anaemia.

Symptoms of iron deficiency anaemia can include:

- Feeling weak, tired, and lacking energy
- Feeling short of breath, dizzy or an irregular heartbeat
- Not able to exercise as much as usual
- Getting more infections than normal
- Finding it hard to remember things or concentrate
- Feeling irritable

Iron Deficiency. Not having enough iron is most common in teenagers, women of child-bearing age, pregnant women, vegans and vegetarians and women with heavy periods. It is also found in some people with medical problems.
Iron Deficiency Anaemia (IDA) can develop when low iron is not treated. Over time, all the stored iron is used.

Your recent blood test shows that you have anaemia (low haemoglobin, below the recommended level of 110g/L) and/or low stored iron (ferritin) levels.

You should increase your iron levels both increasing the iron in the food you eat and by taking an iron supplement. This should improve your energy levels and ensure plentiful iron is available for you (and your baby).

A. Diet:
Iron is best absorbed into the body from food that you eat.

Increase your daily intake of food with high iron content:

- **Red meat:** beef, lamb, veal, pork (the best source)
- **Chicken**
- **Fish**, especially oily fish e.g. tuna, trout, salmon
- **Tofu, soybeans, lentils, beans, baked beans**
- **Cereals**, especially wholegrain. Check the label on bread and breakfast cereals, as some are iron-fortified, e.g. Weet-Bix®, All-Bran®

Other foods also contain iron, but to a lesser extent e.g. eggs, green leafy vegetables (especially spinach), dried fruit and some other fruit and vegetables.

B. Iron Supplements
There are many iron supplements available over the counter at any pharmacy. Check for the *Elemental Iron content* – the higher the better. Take one tablet every day (see the table below for our recommended iron supplements).

To help your body absorb the iron efficiently, take the tablet away from meals – at bedtime is often the best time. Avoid consuming coffee, tea, dairy products (milk, yoghurt, cheese) and calcium supplements at the same time. Try to spread out the calcium and dairy throughout the rest of your day, as it is still very important for you and your baby.

Some women who are taking iron supplements may notice that their stool is darker in colour – this is normal. Iron can cause varied gastrointestinal symptoms including nausea (most commonly), abdominal discomfort, constipation and diarrhoea and occasionally trying a

different iron preparation may improve the symptoms. You should drink plenty of water (approximately 1.5 Litre per day) and eat foods high in fibre, such as brown grain bread and rice, fruit, and vegetables. Taking the iron at night may reduce side effects, and a mild laxative may be used if constipation is a problem.

You are recommended to continue your iron treatment for at least one month after your baby is born.

Iron tablets, like all medicines should be kept in a locked cupboard out of reach and sight of children. A small amount can be poisonous, even fatal, in infants and young children.

Certain medications e.g. thyroxine, methyldopa, antacids, and some antibiotics may improve or reduce absorption of oral iron. All medications should be taken at least 2 hours from the iron tablets.

Please discuss any concerns with your Midwife or Doctor at your next visit

TABLE 1. OVERVIEW OF ORAL PREPARATIONS OF IRON AVAILABLE IN AUSTRALIA

Brand name	**Formulation/other active ingredients**	**Elemental iron content**	**Approximate Cost***
Ferro-tab®	Ferrous fumarate immediate release 200 mg	66 mg	$5 per 30 tablets
Ferro-f-tab®	Ferrous fumarate immediate release 310 mg, folic acid 300 mcg	100 mg	$5 per 30 tablets
Ferro-gradumet®	Ferrous sulfate slow release 325 mg	105 mg	$18 per 30 tablets
Ferro-grad C®	Ferrous sulfate slow release 325 mg, ascorbic acid 500 mg	105 mg	$27 per 30 tablets
Fefol®	Ferrous sulfate, slow release 270 mg, folic acid 300 mcg	87 mg	$10 per 30 tablets
FGF®	Ferrous sulfate, slow release 250 mg, folic acid 300 mcg	80 mg	$16 per 30 tablets
Maltofer® tablets	Iron polymaltose 370 mg	100 mg	$30 per 30 tablets
Ferro-liquid®	Ferrous sulfate oral liquid 150 mg/5 mL	6 mg/mL	$1 per 100 mg (6 cents per mL)
Maltofer® syrup	Iron polymaltose oral liquid 185 mg/5 mL	10 mg/mL	$1.50 per 100 mg (15 cents per mL)

Abbreviation: OTC = over the counter (available without prescription)
* Estimated costs from online and retail pharmacies in Australia, July 2019.

Adapted from: Shand A, Austin K, Nassar N, Kidson-Gerber G. Management of anaemia in pregnancy: a review. *Journal of Pharmacy Practice and Research 2020*

APPENDIX 2

INVESTIGATIONS OF ANAEMIA AND HAEMOGLOBINOPATHY IN PREGNANCY

KNOWN HAEMOGLOBINOPATHY CARRIER
SCREEN BIOLOGICAL FATHER THEN REFER TO OBSTETRICIAN AND/OR HAEMATOLOGIST
Genetic counselling regarding potential DNA/prenatal testing may be appropriate

ANAEMIA IF:
- *Hb < 110 before 20 weeks gestation*
- *Hb < 105 after 20 weeks gestation*

INVESTIGATE CAUSE OF ANAEMIA:
- *FBC*
- *Ferritin*

TREAT CONFIRMED IRON DEFICIENCY IF:
- *Ferritin < 30 ug/L by commencing oral iron supplementation.*
- *Other causes of anaemia e.g. B12 or folate deficient.*

REFER TO OBSTETRICIAN OR HAEMATOLOGIST IF:
- *Thrombocytopenia*
- *Unexplained anaemia*
- *Hb < 90g/L*
- *Significant symptoms > 34 weeks gestation*
- *Failure to respond to oral iron supplementation - iron infusion may be indicated.*

WOMAN/OOCYTE DONOR AT HIGH RISK:
- *Ethnicities – South East Asian, Indian, Sri Lankan, Pakistani, Bangladeshi, Middle Eastern, Mediterranean, Black African, Islander*
  and/or
- *MCV < 80fL or MCH < 27pg*

IF AT HIGH RISK OF HAEMOGLOBINOPATHY, THEN REQUEST:
For woman/oocyte donor – (include gestation, ethnicity, biological father's name and date of birth on request form)
- *FBC*
- *Haemoglobinopathy screen*
- *Iron studies*

For biological father (screen simultaneously with woman/oocyte donor and include woman/oocyte donor's name and MRN on request form)
- *FBC*
- *Haemoglobinopathy screen*
- *Iron studies*

URGENTLY REFER TO GENETICIST IF:

Both biological parents known or suspected haemoglobinopathy carriers. Genetic counselling regarding potential DNA/prenatal testing may be appropriate.

Action following Antenatal Haemoglobinopathy Screen: A Guide for the Antenatal Clinic

Request Haemoglobinopathy Screen if any of:

- High risk ethnicity in woman/oocyte donor and biological father: South east Asian, Asian, Indian, Sri Lankan, Pakistani, Bangladeshi, Middle Eastern, Mediterranean, Black African, Pacific Islander
- MCV <80fL or MCH <27pg
- Known haemoglobinopathy carrier, family history of haemoglobinopathy in woman/oocyte donor and biological father's family

Request
- Full Blood Count
- Haemoglobinopathy screen
- Iron studies

Haemoglobinopathy Screen Result

Beta thalassaemia trait, δβ thalassaemia
or
Abnormal variant detected, such as HbS, HbE, HbC, HbD-Punjab, HbO-Arab, Hb Lepore
or
Hb Constant Spring
or
HbH disease, alpha thalassaemia detected

yes → *Further action required*

HbA_2: 2.0 - 3.2% → yes → MCV <80fl or MCH < 27pg → yes → Alpha thalassaemia cannot be excluded → MCV <75fl or MCH < 25pg → yes → *Further action n required*

no

HbA_2: 3.3 - 3.7% → yes → Atypical heterozygous beta thalassaemia cannot be excluded → *Further action required*

HbH bodies detected or ICT strip positive → ye → *Further action required*

Additional Comments

Molecular studies would be required Alpha thalassaemia cannot be excluded
Atypical beta thalassaemia cannot be excluded
Biological father should be screened

→ *Further action required*

Further Action

If only woman/oocyte donor's results available → then **biological father** must be **screened** with urgent haemoglobinopathy screen

If 'further action required' from **BOTH** biological parent's results → **refer urgently** to Genetics or Haematology

Contacts: **RHW St George** Prenatal Genetic Service Department of Clinical Genetics Phone: 9382 6098; 9382 6099; 9382 6042 Phone: 9113 3635 Fax 9382 6038 Fax 9113 3694

Action that occurs through Genetics or Haematology following Antenatal Haemoglobinopathy Screen, when *both biological* parents involved.

Beta globin problem in both biological parents (Box A or B)

Box A
HbA_2: 3.3 – 3.7%
Atypical heterozygous beta thalassaemia cannot be excluded
Molecular studies required

→ *Beta gene molecular testing*

Variant present

Box B
Beta thalassaemia trait
HbS, HbE, HbC, HbD-Punjab, HbO-Arab
δβ thalassaemia, Hb Lepore

→ *Urgent genetic referral*

Alpha globin problem in both biological parents (Box

Box C
MCV <75fl or MCH < 25pg
HbH bodies detected
ICT strip positive
Alpha thalassaemia cannot be excluded
Molecular studies required
HbE with % HbE <27%
HbS with MCV < 80 or HbS % <35%

→ *Alpha gene molecular*

2 gene deletion present

Box D
Hb Constant Spring
HbH disease

→ *Urgent genetic referral*