Policy

Clinical Guideline

Anaemia in Pregnancy

Policy developed by: SA Maternal & Neonatal Community of Practice
Approved SA Health Safety & Quality Strategic Governance Committee on: 19 April 2016
Next review due: 19 April 2019

Summary Clinical practice guideline on the treatment for women with anaemia in the peripartum period

Keywords anaemia in pregnancy, Iron deficiency anaemia, haemoglobin, ferritin, thalassaemia, folic acid, vitamin B12, megaloblastic, microcytic, hypochromic, CBE, iron supplementation, haemoglobinopathy, oral iron, intravenous iron, clinical guideline

Policy history Is this a new policy? **N**
Does this policy amend or update an existing policy? **Y v3.0**
Does this policy replace an existing policy? **N**
If so, which policies?

Applies to All SA Health Portfolio

Staff impact All Staff, Management, Admin, Students, Volunteers
All Clinical, Medical, Nursing, Allied Health, Emergency, Dental, Mental Health, Pathology

PDS reference CG229

Version control and change history

Version	Date from	Date to	Amendment
1.0	17 Aug 04	06 Oct 09	Original version
2.0	06 Oct 09	12 May 12	Reviewed
3.0	12 May 12	19 April 2016	Reviewed
4.0	19 April 2016	Current	Reviewed

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Note

This guideline provides advice of a general nature. This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion.

Information in this statewide guideline is current at the time of publication.

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Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation.

If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom, and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes:

- The use of interpreter services where necessary,
- Advising consumers of their choice and ensuring informed consent is obtained,
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct, and
- Documenting all care in accordance with mandatory and local requirements

Explanation of the aboriginal artwork:
The aboriginal artwork used symbolises the connection to country and the circle shape shows the strong relationships amongst families and the aboriginal culture. The horse shoe shape design shown in front of the generic statement symbolises a woman and those enclosing a smaller horse shoe shape depicts a pregnant women. The smaller horse shoe shape in this instance represents the unborn child. The artwork shown before the specific statements within the document symbolises a footprint and demonstrates the need to move forward together in unison.

 ***Australian Aboriginal Culture is the oldest living culture in the world yet Aboriginal people continue to experience the poorest health outcomes when compared to non-Aboriginal Australians. In South Australia, Aboriginal women are 2-5 times more likely to die in childbirth and their babies are 2-3 times more likely to be of low birth weight. The accumulative effects of stress, low socio economic status, exposure to violence, historical trauma, culturally unsafe and discriminatory health services and health systems are all major contributors to the disparities in Aboriginal maternal and birthing outcomes. Despite these unacceptable statistics the birth of an Aboriginal baby is a celebration of life and an important cultural event bringing family together in celebration, obligation and responsibility. The diversity between Aboriginal cultures, language and practices differ greatly and so it is imperative that Perinatal services prepare to respectively manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.***

ISBN number: 978-1-74243-062-1
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Last Revised: 19/4/2016

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Anaemia

Definition of anaemia

- World Health Organisation (WHO) define anaemia as haemoglobin (Hb) level <110 g/L in pregnancy and 100 g/L postpartum. Currently, there are no WHO recommendations on the use of different haemoglobin cut-off points for anaemia by trimester, but it is recognised that during the second trimester of pregnancy, haemoglobin concentrations diminish by approximately 5 g/L[1,2]
- US Centers for Disease Control (CDC) has established the lower limit of the normal range of haemoglobin in the latter part of the second trimester is 103 g/L (2 standard deviations [SD] below the mean of 116 g/L)[3,4]
- The populations from which both CDC and WHO definitions of normal haemoglobin and anaemia are derived are predominately from developing countries, which limit their applicability to the Australian population[3]
- There is variation in the definition of anaemia in pregnancy and no agreed normal range for pregnant women in Australia[3]. Although total red cell mass and plasma volume both increase during pregnancy, the relative changes result in haemoglobin levels slightly below those found in age-matched non-pregnant women. Maternal haemoglobin levels reach a nadir near the end of the second trimester[3]
- In view of the relative plasma expansion being particularly marked in the second trimester, it would seem reasonable to define anaemia[5] as:
    - **Hb <110 g/L in first trimester**
    - **Hb <105 g/L in second and third trimesters**
    - **Hb <100 g/L in postpartum period**
- Although data are limited, the haematological parameters of Australian Aboriginals are thought to be similar to non-Aboriginal Australians. Aboriginal and Torres Strait Islander women experience a much higher prevalence of factors that contribute to anaemia and iron deficiency, and their adverse effects.[6] Such factors include[6]:
    - Higher fertility rate (2.6% Aboriginal versus 1.9% non-Aboriginal in 2009) and higher parity
    - More frequent teenage births (21% Aboriginal versus 4% non-Aboriginal in 2009)
    - More limited access to affordable nutritious food
    - Higher rates of medical comorbidities, such as chronic renal disease, diabetes, chronic vascular disease and rheumatic heart disease

Physiological changes in pregnancy

- Both red cell mass and 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 increase in mean corpuscular volume (MCV) increasing on average 4 fl at term[7]

Causes of anaemia

- Physiological
- Iron deficiency is a common cause of anaemia in pregnancy, in both the developed and

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Last Revised: 19/4/2016

developing world

- Other causes of anaemia include megaloblastic anaemias due to vitamin B_{12} and folic acid deficiency, thalassaemias, blood loss, haemolytic states (sickle cell disease, malaria and pre-eclampsia), helminthic infection and underlying malignancy and chronic disease[3]
- The treatment of anaemia requires an accurate assessment of its underlying cause, but this can be difficult in pregnancy, where multiple factors may be responsible
- The preferred test of maternal iron status is the serum ferritin level[3], although because ferritin is an acute phase reactant, levels can be elevated in inflammatory states
- Other measures of iron status (e.g. serum iron, transferrin, transferrin receptors and erythrocyte protoporphyrin) have a limited role in pregnancy, due to restricted availability of tests, cost and interpretive difficulties arising from non-standardised reference ranges and diurnal variation[3]

Classification of anaemia

- Anaemia is often classified in the following way based on red cell indices:
    - **Normocytic, normochromic anaemia –** normal MCV, MCH and MCHC: acute blood loss, early iron deficiency anaemia, physiological (dilutional drop in haemoglobin), haemolysis, multifactorial anaemia, anaemia of chronic disease / inflammation and chronic kidney disease
    - **Microcytic, hypochromic –** low MCV, low MCH and / or MCHC: iron deficiency, thalassaemia and some haemoglobinopathies
    - **Macrocytic, normochromic anaemia –** elevated MCV, normal MCH and MCHC: **megaloblastic anaemia –** B_{12} or folate deficiency, liver disease, myelodysplasia and hypothyroidism
- It is important to note the limitations of this classification. In milder cases of iron deficiency, the MCV may not have fallen below the normal range.[5] Co-existing conditions such as combined vitamin deficiency of iron and B_{12} or folate may present with a normocytic blood picture, likewise with a co-existing thalassaemia and B_{12} or folate deficiency

Pathology testing

- All women require a complete blood examination (CBE) at the first antenatal visit to determine whether anaemia, signs of evolving anaemia or features suggestive of a thalassaemic syndrome / haemoglobinopathy are apparent. Repeat CBE at 28 weeks
- If the woman is in a risk group for thalassaemia / haemoglobinopathy according to available information, haemoglobin variant analysis and iron studies would also be indicated. See ‘Antenatal Screening Program guidelines for Thalassaemia / Haemoglobinopathy’ below

Iron deficiency anaemia

- Iron deficiency is the most common cause of anaemia in pregnancy, in both the developed and developing world
- Physiological iron requirements are 3 times higher in pregnancy than they are in the menstruating women[8], with increasing demand as pregnancy advances
- Approximately 600 mg of elemental iron is required for the increase in red cell mass during pregnancy and a further 300 mg for the fetus
- The recommended daily intake (RDI) of iron for the latter half of pregnancy is 30 mg. Absorption of iron increases three-fold by the third trimester, with iron requirements increasing from 1 – 2 mg to 6 mg per day[9]

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Iron supplementation

- Although there is an increase in iron requirements during pregnancy, the routine administration of iron supplementation to all pregnant women is not recommended, because of the lack of applicability of trials to the Australian health-care setting, and the lack of evidence for patient-centred outcomes[3]
- In non-anaemic women, an individualised approach to serum ferritin testing and iron supplementation should be based on results of blood count screening tests as well as identification of women at increased risk of iron deficiency, those at high risk of bleeding or those that decline blood transfusion e.g. Jehovah's witnesses (see table 1 below)[5]
- Risk populations for iron deficiency include women who have previously completed one or more pregnancies (at the start of any subsequent pregnancy) especially if the inter-pregnancy interval is short or their deliveries have been complicated by PPH. Other groups at special risk include adolescents, **Australian Aboriginals,** some recent immigrants and women of low socioeconomic status[3,4]

Diagnosis of iron deficiency anaemia

- 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 (see table 1)
- Complete blood examination (CBE) should be assessed at booking and at 28 weeks
- Women with haemoglobin <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 thalassaemia / haemoglobinopathy. These women should have serum ferritin checked and offered therapeutic iron if the ferritin is <30 micrograms/L[5]
- The CBE in iron deficiency may show low haemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC); a blood film may confirm presence of microcytic hypochromic red cells and characteristic 'pencil cells' of iron deficiency. However, microcytic, hypochromic indices may also occur in thalassemia / haemoglobinopathies. In addition, for milder cases of iron deficiency, the MCV may not have fallen below the normal range.[5] Note that both iron deficiency AND thalassemia / haemoglobinopathy can be present with a haemoglobin within the normal range
- Serum ferritin is the most useful and easily available parameter for assessing iron deficiency. Ferritin levels <15 micrograms/L are diagnostic of established iron deficiency.[5] A level <30 micrograms/L in pregnancy should prompt treatment.[5] C-Reactive Protein (CRP) levels may facilitate assessment when inflammatory or infective processes are suspected / present
- Serum ferritin should be checked before starting iron in women with known thalassaemia / haemoglobinopathy as there is a risk of iron overload because of dyserythropoiesis.[5] Serum ferritin should also be checked in women with likely multifactorial anaemia (e.g. with risk factors for multiple deficiencies, chronic disease / inflammation)
- Anaemic women with unknown thalassemia / haemoglobinopathy status should be offered a trial of iron whilst **thalassemia / haemoglobinopathy screening & serum ferritin are undertaken without delay**[5] in accordance with 'SA Pathology Thalassaemia / Haemoglobinopathy Screening Program' guidelines (see below) but with awareness that iron deficiency can cause some lowering of the haemoglobin A2 percentage

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TABLE 1: Indications for assessment of serum ferritin in pregnancy (adapted from 5)	
Anaemic women where estimation of iron stores is necessary	> Known thalassaemia / haemoglobinopathy > Women at risk of thalassaemia / haemoglobinopathy where ferritin is required as per SA Pathology / WCHN Screening Program Guidelines > Failure to respond to a 2 week trial of oral iron > Likely multifactorial anaemia (e.g. risk factors for multiple deficiencies, chronic disease / inflammation) > Before any parenteral iron replacement
Non-anaemic women with high risk of iron depletion	> Previous anaemia or iron deficiency > Multiparity ≥ para 3 > Consecutive pregnancy < 1 year following delivery > Vegetarians > Teenage pregnancies > ***Aboriginal and Torres Strait Islander women*** > Recent history of bleeding > Inflammatory bowel disease > Bariatric surgery
Non-anaemic women where estimation of iron stores is necessary	> High risk of bleeding for example women with bleeding disorders, anticoagulated patients and known abnormal placentation > Women who decline transfusion e.g. Jehovah's witnesses > Where the provision of compatible blood may be difficult e.g. where complex red cell antibodies or rare red cell phenotypes have been identified

Treatment

> **Dietary changes alone are insufficient** to correct iron deficiency anaemia and iron supplements are necessary

> All women should be counselled regarding diet in pregnancy including details of iron rich food sources and factors that may inhibit (tannins in tea / coffee, calcium) or promote iron absorption (vitamin C, haem iron) and why maintaining adequate iron stores in pregnancy is important.[5] This should be consolidated by the provision of an information leaflet in the appropriate language. See at URL: http://www.beefandlamb.com.au/How_to/Online_magazines/Are_you_getting_enough_iron

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Oral iron

- In iron deficiency anaemia the oral dose of iron should be 100 - 200 mg of elemental iron daily [3,5]
- In non-anaemic iron deficiency lower doses of elemental iron (e.g. 20 - 80 mg daily) may be considered, and may be better tolerated than higher doses[3]
- The response to therapy should be monitored and if inadequate, IV iron should be used.[3] For more information on parenteral iron, refer to the Iron Infusion guideline in the A to Z index at URL: www.sahealth.sa.gov.au/perinatal
- An illustrated prescribing chart with oral iron preparations for treatment of iron deficiency anaemia in Australia is available from BloodSafe SA at URL: http://www.sahealth.sa.gov.au/wps/wcm/connect/81d0f6804f7202a8b7aef774733d1f2b/OralIronDosingTreatmentAnaemia-BloodSafe-Oct2011.pdf?MOD=AJPERES&CACHEID=81d0f6804f7202a8b7aef774733d1f2b
- The table below also provides a summary of suitable preparations

Oral iron preparation	Elemental iron content in mg
Ferro tab PBS listed	65.7 mg (as ferrous fumarate) Non-controlled release tablet
Ferro F tabs PBS listed	100 mg (as ferrous fumarate) + 0.3 mg folate Non-controlled release tablet
FGF	80 mg (as ferrous sulphate) + 0.3 mg folate Controlled release tablet
Fefol	87 mg (as ferrous sulphate) + 0.3 mg folate Controlled release tablet
Ferrograd C	105 mg (as ferrous sulphate) + 500 mg ascorbic acid. Controlled release tablet
Ferrogradumet	105 mg (as ferrous sulphate) Controlled release tablet
Ferro-Liquid PBS listed	30 mg per 5 mL syrup (as ferrous sulphate)
Elevit	60 mg + other vitamins and minerals including calcium which may reduce iron absorption
Maltofer (Category B1 in pregnancy)	100 mg as iron polymaltose (for use in iron deficiency without anaemia due to slower response compared with iron salts)

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NOTE: Many iron supplements (including those for 'pregnancy / breast feeding') do not contain sufficient quantities of elemental iron (commonly only around 5 mg) to provide a therapeutic dose (100 - 200 mg) for treatment of iron deficiency anaemia

- Oral iron can cause gastrointestinal upset and exacerbate symptoms of pregnancy such as constipation, heartburn, nausea and vomiting. Advice regarding these symptoms, including blackening of stools, should be given
- Whenever iron tablets are supplied, the importance of keeping them out of the reach of children must be stressed[5]
- Patient information should be provided. Leaflets on oral iron therapy in multiple languages are available at URL: http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+programs/blood+products+and+programs/bloodsafe/bloodsafe+information+for+consumers/iron+therapy

Assessing response

- Repeat haemoglobin testing and reticulocyte response is required 2 weeks after commencing treatment for established anaemia, to assess compliance, correct administration and response to treatment[5]
- Once haemoglobin is in the normal range, replacement should continue for three months and until at least 6 weeks postpartum to replenish iron stores[5]
- In non-anaemic women, repeat haemoglobin and serum ferritin is required after 8 weeks of treatment to confirm response[5]
- If response to oral iron replacement is poor, non-compliance and concomitant causes, which may be contributing to the anaemia, such as folate deficiency or anaemia of chronic disease, need to be excluded[5] and specialist advice sought

Intravenous (IV) iron

- IV iron is preferred when rapid restoration of haemoglobin and iron stores is required, because it leads to a more rapid increase in these values than other routes of administration[3]
- In women requiring iron in the peripartum period, intravenous iron is preferred when oral iron is poorly tolerated (affecting compliance), or absorption is likely to be impaired[3]
- When IV iron is prescribed, calculation of the dose should take into consideration the iron deficit[3]
- Long-lasting brown discoloration (staining) of the skin may occur due to leakage of IV iron into the tissues around the injection site. This may be permanent. Ensure injection site is monitored and women receiving IV iron are educated to report any discomfort, burning, redness or swelling. In case of paravenous leakage STOP infusion immediately. The infusion should be completed after intravenous access is resited
- Patient information should be provided. Leaflets on IV iron therapy in multiple languages are available at URL: http://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/clinical+resources/clinical+programs/blood+products+and+programs/bloodsafe/bloodsafe+information+for+consumers/iron+therapy
- For further information regarding intravenous iron in the peripartum period, refer to 'Iron Infusion' guideline in the A to Z index at URL: www.sahealth.sa.gov.au/perinatal
- The routine use of IM iron is not advised where alternatives are available[3]
- Prompt recognition of iron deficiency in the antenatal period followed by iron therapy may reduce the subsequent need for blood transfusions. For information on transfusion refer to the 'Transfusion' section below

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Intrapartum management of anaemia[5]

Women who are anaemic at the time of birth may require additional precautions, including:

- Birth in a hospital setting
- IV access
- Group and save and haemoglobin (CBE)
- Active management of the third stage of labour
- In cases of caesarean section, where available, consider provision of cell salvage
- Either bolus oxytocin 10 IU intramuscular or 5-10 IU slowly intravenous OR consider ergot derivative if no pre-existing hypertension or preeclampsia:
    - Intramuscular Syntometrine® (oxytocin and ergometrine)
- Plans to deal with excessive bleeding (For further information see 'Postpartum haemorrhage' in the A to Z index at URL: www.sahealth.sa.gov.au/perinatal)

Postpartum management of anaemia

- Postpartum women with estimated blood loss >500 mL, uncorrected anaemia detected in the antenatal period or symptoms suggestive of anaemia postpartum should have their haemoglobin checked within 48 hours[5]
- Women who are haemodynamically stable, asymptomatic or mildly symptomatic, with haemoglobin <100 g/L should be offered elemental iron 100 - 200 mg daily for 3 months with a repeat complete blood examination (CBE) and ferritin on completion of iron therapy to ensure haemoglobin and iron stores are replete[5]

Transfusion

- The decision to transfuse 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 IV iron therapy as an alternative[5]
- 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
- Special transfusion requirements exist in this population group and specialist transfusion advice should be sought. For further information, see 'Blood transfusion' guideline in the A to Z index of the Perinatal Practice Guidelines at URL: www.sahealth.sa.gov.au/perinatal

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The National Patient Blood Management Guidelines: Module 5 - Obstetrics and Maternity (2015)[3] provides the following practice points related to transfusion:	
Women who are not actively bleeding in the peripartum period	> Red cell transfusion should not be dictated by haemoglobin alone, but should also be based on assessment of the woman's clinical status (e.g. risk of further haemorrhage). Most women in the peripartum period are otherwise healthy and can generally tolerate moderate degrees of anaemia while medical therapies take effect > Non-transfusion therapies, including iron, should be considered as part of the treatment of anaemia > Where transfusion is indicated, a single unit of red cells, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the haemoglobin level
Consideration of red cell transfusion for women in the peripartum period	> The risk of red cells alloimmunisation and potential clinical impact should be considered when balancing the risks and benefits of red cell transfusion

Direct evidence of the efficacy of red cell transfusion for treatment of anaemia is not available for women in the peripartum period

Evidence from other patient groups and the Clinical Reference Group consensus suggests that in women who are not actively bleeding, with a:

> **Haemoglobin >90 g/L,** red cell transfusion is usually inappropriate

> **Haemoglobin 70-90 g/L,** red cell transfusion is not associated with reduced mortality. The decision to transfuse peripartum women (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, the availability of other therapies for the treatment of anaemia, the expected timeframe to delivery and the presence of risk factors for haemorrhage

> **Haemoglobin <70 g/L,** red cell transfusion may be associated with reduced mortality and may be appropriate. However, transfusion may not be required in well-compensated patients, or where other specific therapy is available

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- 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 uncommon, despite the increased requirements of pregnancy, due to the extent of vitamin B_{12} stores. Other causes of vitamin B_{12} deficiency include conditions affecting the stomach (e.g. hypochlorhydria, gastrectomy, pernicious anaemia – autoimmune, rare in women of childbearing age), conditions affecting the intestines (e.g. Crohn's disease) and some medications
- 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 / haemoglobinopathy
- Vitamin B_{12} and folate measurements should be undertaken to exclude deficiencies of both haematinics. The metabolic roles of folate and vitamin B_{12} are closely linked, and deficiency of either vitamin can result in the same clinical manifestations. In addition, a low serum folate may be associated with a low serum B_{12}, in which case treatment is initiated with B_{12} therapy before adding in folate therapy[10]

Folate deficiency

- Pregnancy and lactation are associated with increased folate requirements, and preferential delivery of folate to the fetus may result in severe maternal deficiency in the presence of normal folate status in the baby. Multiparity and hyperemesis gravidarum increase the risk of developing deficiency in the mother[10]
- Routine measurement of folate is not required during pregnancy unless increased MCV or changes of megaloblastic anaemia (see below), poor diet, prolonged hyperemesis / poor oral intake in pregnancy, suspected malabsorption or gastrointestinal (GI) pathology (coeliac disease, Crohn's disease, gastric bypass etc.)[11]
- Folate deficiency in pregnancy may be difficult to diagnose early. However it should be thought of and excluded in the presence of:
    - Increasing MCV (greater than 100 fL but may be of the order of 120 fL)
    - Anaemia
    - Large hyper-segmented neutrophils (these being a late sign in pregnancy)
    - Falling platelet count (less than 100 x 10^9 / L)
    - Isolated folate deficiency without malabsorption can be secondary to increased requirements in pregnancy
- If serum folate confirmed to be low check CBE and film, ferritin, coeliac disease screen, Active vitamin B_{12} level and start folate once vitamin B_{12} confirmed normal[11]
- 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

Vitamin B_{12} deficiency

- Vitamin B_{12} is essential for infant neurodevelopment. Undiagnosed maternal vitamin B_{12} deficiency may result in irreversible neurological damage to the breastfed infant. Although maternal vitamin B_{12} deficiency is uncommon, the majority of women with deficient vitamin B_{12} levels are asymptomatic

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- Those who have had gastric surgery have a high prevalence of vitamin B_{12} deficiency[12] , and more recently, treatments for obesity including gastric banding and gastric bypass surgery also lead to vitamin deficiency[10]. For further information see 'Women with a high body mass index' in the A to Z index of the Perinatal Practice Guidelines (sub-heading 'Perinatal care after bariatric surgery') at URL: www.sahealth.sa.gov.au/perinatal

Testing for B_{12} deficiency

- Routine measurement of vitamin B_{12} is not required; however check the serum vitamin B_{12} level if [13]:
    - Increased MCV
    - Vegetarian diet. Also consider referral to dietician
    - GI pathology (coeliac disease, Crohn's disease, gastric banding / bypass etc.)
    - Family history of vitamin B_{12} deficiency or pernicious anaemia
- SA Pathology performs Total vitamin B_{12} and Active vitamin B_{12} (if indicated). Other laboratories may also have both tests available. In pregnancy Total vitamin B_{12} is reduced, however, this is not necessarily reflective of deficiency even if the value is below the reference interval. Total vitamin B_{12} is made up of biologically active (10 - 30% of Total vitamin B_{12}) and biologically inert (70 - 90% of Total vitamin B_{12}) complexes. This is determined by the protein it is bound to. In normal pregnancy the protein that complexes with vitamin B_{12} to produce the biologically inert complex (haptocorrin + vitamin B_{12} ➔ holohaptocorrin) is 'naturally' reduced, whereas the protein that complexes with vitamin B_{12} to produce the biologically active complex (transcobalamin + B_{12} ➔ holotranscobalamin) remains unchanged
- For tests requested through SA Pathology, if the Total vitamin B_{12} concentration when assayed is low / equivocal, testing of Active vitamin B_{12} is initiated automatically in both pregnant and non-pregnant women. This will determine whether a woman has normal Active vitamin B_{12} levels (no further testing needed), indeterminate levels (measure homocysteine and methylmalonic acid and discuss with a haematologist) or low levels (discuss with a haematologist)

Treatment

- For treatment of vitamin B_{12} deficiency in pregnancy, consult a haematologist / physician and refer to the product information for intramuscular (IM) vitamin B_{12} injections regarding dosing. For further information on dosing, see 'Vitamin and mineral supplementation in pregnancy' in the A to Z index of the Perinatal Practice Guideines at URL: www.sahealth.sa.gov.au/perinatal

Prevention

- Vegetarians and vegans should be supplemented with vitamin B_{12} in pregnancy and lactation. The Recommended Daily Intake of vitamin B_{12} in pregnancy is 6 micrograms per day[14]
- The following link explains what vegans believe are acceptable oral supplements http://www.vegansociety.com/resources/nutrition-health/vitamins-minerals-and-more/vitamin-b12-your-key-facts/what-every-vegan
- An alternative to oral supplementation in strict vegans is IM injection of 1,000 micrograms of vitamin B_{12} at 3 monthly intervals to prevent the development of vitamin B_{12} deficiency. For further information, see 'Vitamin and mineral supplementation in pregnancy' in the A to Z index of the Perinatal Practice Guidelines at www.sahealth.sa.gov.au/perinatal

Specific population groups:

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1. Thalassaemia / Haemoglobinopathy

- Thalassaemia is an inherited disorder associated with impaired synthesis of one or more globin chains with alpha thalassaemia and beta thalassaemia being the most common forms
- Haemoglobinopathies are a group of inherited disorders characterised by structural variations of the haemoglobin molecule, such as HbS (sickle), HbE etc
- The clinical significance of these conditions is quite variable. For carriers of thalassaemia / haemoglobinopathy, generally, there are no clinical consequences. However pregnancy increases demand on red cell production and this may worsen maternal anaemia and influence fetal growth.[15] Patients with disease, (depending on the inherited disorder), do have significant clinical requirements, including regular blood transfusions and drug therapy (sickle cell disease)

Distribution

- Thalassaemia and haemoglobinopathies are common conditions in many countries across the world but particularly concentrated through the 'malaria belt'. This stretches from the Southern Mediterranean, through parts of Africa, the Middle East, Indian Sub-Continent, parts of Asia, South East Asia and some Pacific nations
- Antenatal women with thalassaemia or haemoglobinopathy would generally be carriers. However, there is a distinct possibility for women to present with undiagnosed haemoglobin H disease (HbH), clinically variable depending on the inherited disorder, or to a lesser extent, Beta thalassaemia / intermedia or major
- It is important to note however, that the clinically significant thalassaemia syndromes have autosomal recessive inheritance, meaning that the fetus of alpha and beta thalassaemia major carrier parents can be affected. The potential for a clinically significant thalassaemia syndrome in the fetus should be identified early in the first trimester if prenatal diagnosis is to be offered to the couple. Prenatal diagnosis can only be done using molecular (DNA) analysis, is best done on chorionic villus sampling (CVS) (where DNA is not limiting as is often the case with amniocentesis) and only after full molecular workup has been completed in both parents. Full molecular workup can take 4-6 weeks, leaving a very tight timeframe for counselling, CVS and prenatal diagnosis
- Carriers of thalassaemia or haemoglobinopathy have a normal or mildly reduced haemoglobin level but often have a low to borderline low MCV and almost invariably a low MCH (occasionally borderline low) and a normal MCHC (unless iron deficiency is also apparent). Co-existence of iron deficiency can have a greater influence on the microcytic, hypochromic blood picture and possibly result in anaemia. Severe iron deficiency with a moderate to marked anaemia could mask a diagnosis of beta thalassaemia. DNA analysis in this setting to help clarify the situation would be recommended if the partner was known to be a carrier of beta thalassaemia or haemoglobinopathy
- Antenatal screening for at risk women is indicated. See 'Antenatal Screening program Guidelines for Thalassaemia / Haemoglobinopathy' for further information

2. Women of ethnic origin from countries where thalassaemias and haemoglobinopathies are endemic

- Women of ethnic origin from countries where thalassaemias and haemoglobinopathies are endemic, have a relatively high probability of being carriers of these conditions. In view of this antenatal screening for at risk women is indicated. See 'Antenatal Screening program Guidelines for Thalassaemia / Haemoglobinopathy' for further information

3. Aboriginal and Torres Strait Islander women

ISBN number: 978-1-74243-062-1
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- Aboriginal and Torres Strait Islander women are at higher risk of anaemia. Therefore, iron studies should be performed along with CBE at booking, to assess iron stores and anaemia. Other factors contributing to anaemia, such as deficiencies in folic acid and vitamin B_{12} or hookworm, should be screened for in selected women. Thalassaemia, whilst relatively uncommon, does exist in some Aboriginal groups; therefore this should also be a consideration. See section under 'thalassaemia / haemoglobinopathy'
- Incorporate holistic management to minimise anaemia in pregnancy e.g. support longer intervals between pregnancies, access to a nutritious diet, optimal management of any medical comorbidities, and treatment of hookworm if relevant
- In pregnant Aboriginal and Torres Strait Islander women, if parenteral iron is indicated, IV iron therapy should be used. The routine use of IM iron is not advised where alternatives are available
- For Aboriginal and Torres Strait Islander women in rural and remote areas who are at high risk of severe postpartum haemorrhage (PPH), have a management plan in place to minimise any delay in accessing health-care services and resources, including blood products

Antenatal screening program guidelines for thalassaemia / haemoglobinopathy

- All women at their first antenatal visit are encouraged to complete the 'Family of Origin Questionnaire' – Thalassaemia / Haemoglobinopathy (see below). If the woman has not had a recent CBE and iron studies performed at SA PATHOLOGY samples to perform these tests should be collected and forwarded with the questionnaire and a copy of any available pathology results

ISBN number: 978-1-74243-062-1
Endorsed by: South Australian Maternal & Neonatal Community of Practice
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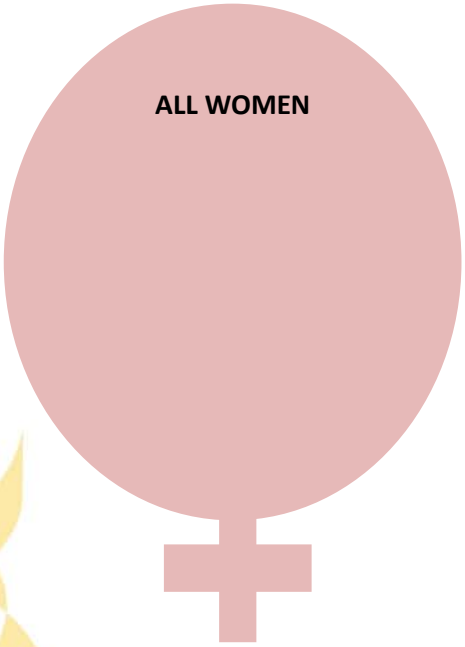
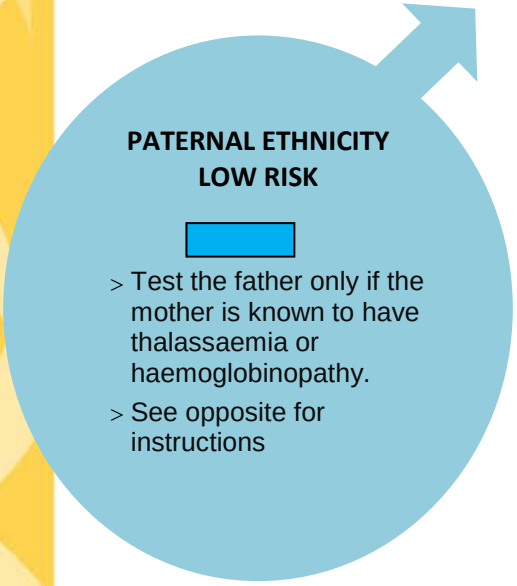
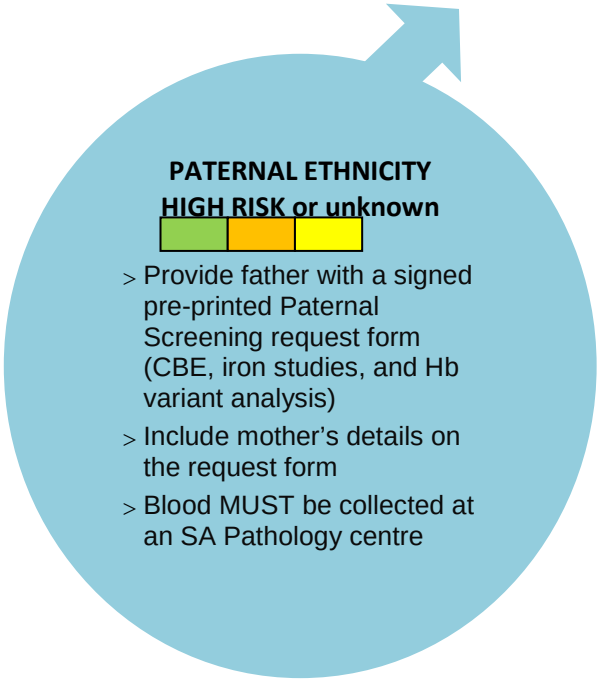
MATERNAL HAEMOGLOBINOPATHY/THALASSAEMIA SCREENING ALGORITHM



- Complete Family Origin Questionnaire
- Send CBE and serum (white top) using a pre-printed Maternal Screening request form to SA Pathology (CBE for all women. The lab will initiate iron studies and Hb variant analysis if indicated)
- Attach a copy of the questionnaire to the request form, including the father's name and date of birth. Also include any accompanying pathology results for relevant tests performed by a pathology service provider/s other than SA PATHOLOGY

PATERNAL SCREENING BASED ON FATHER'S ETHNIC ORIGIN





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Endorsed by: South Australian Maternal & Neonatal Community of Practice
Last Revised: 19/4/2016

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Family of Origin Questionnaire – Thalassaemia / Haemoglobinopathy

SA PATHOLOGY

Antenatal thalassaemia/haemoglobinopathy screening programme

Enquiries 8222 3000

Family / Ancestral Questionnaire

Patient details	Partner's details
Given name:	Given name:
Family name:	Family name:
Date of birth:	Date of birth:
Address:	Address:
Medicare number:	Medicare number:
Office Use ONLY	
EDC:	Consanguinous Couple ☐ Yes ☐ No
Gestation:	If Yes Relationship _____
UR number:	
Location: *(Hosp. Shared Services, Dr's rooms)*	

Is there a known family history of haemoglobinopathy/thalassaemia?

Patient ☐ Yes ☐ No ☐ Not sure **Partner** ☐ Yes ☐ No ☐ Not sure

What are your or your family's origins?

Please tick *all* boxes that apply. See overleaf for key and map of regions and associated countries.

	Region of family / ancestral origin	Patient	Partner
	Australia (Aboriginal / Torres Strait Islanders) / Pacific Islands	☐	☐
	South East Asia / China / Indian Sub Continent	☐	☐
	Southern Europe / Africa / Middle East / Other African Origins	☐	☐
	United Kingdom / Northern Europe / Northern Asia / Americas	☐	☐

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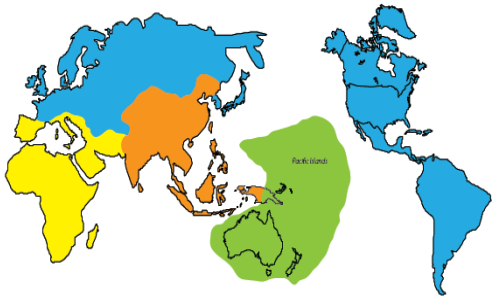
SA PATHOLOGY

Antenatal thalassaemia/haemoglobinopathy screening programme

Enquiries 8222 3000

Country key

	Australia, Torres Strait Islands
	Pacific Islands (Micronesia, Melanesia, Polynesia)
	New Guinea, Palau, Solomon Islands, Vanuatu, Fiji, New Caledonia, New Zealand, Tonga, Hawaii, other Micronesian, Melanesian, Polynesian Islands
	South East Asia, China (Asian), Indian Sub Continent
	Vietnam, Cambodia, Laos, Indonesia, Thailand, Malaysia, other South East Asian countries
	China (including Hong Kong), Taiwan, Singapore
	Afghanistan, Pakistan, India, Bangladesh, Sri Lanka, Myanmar (formerly Burma)
	Southern Europe, Africa, Other African Origins, Middle East
	Southern Europe (Mediterranean)
	Greece, Cyprus, Italy, Spain, Portugal, Turkey, Other Mediterranean Countries
	Africa
	Other African Origins
	Caribbean, North America, South America, UK, Other
	Middle East
	Iran, Iraq, Saudi Arabia, Other Middle Eastern country
	United Kingdom, Northern Europe, Northern Asia, Americas, Other
	England, Ireland, Scotland, Wales, Austria, Belgium, France, Germany, Netherlands, Russia, Mongolia, North America, South America, South Africa.



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Laboratory surveillance

- The laboratory will perform Hb variant analysis on the following pregnant women:
  - Women in the high risk group and / or those where their partner is known to have a thalassaemic syndrome
  - Women initially considered to be in the low risk group, with CBE findings that are considered suspicious, in the presence of a normal iron status
- DNA confirmation may be indicated and will be initiated by the laboratory in the following settings:
  - Some haemoglobinopathies
  - Normal Hb variant analysis (possible alpha thalassaemia, not characterised using common screening technologies) in the presence of CBE findings suggestive of a two or more alpha gene deletion and / or the partner is known to have a thalassaemic syndrome or is in a high risk group (follow up required)
- Unclassified Hb variants by standard screening methods causing CBE findings consistent with a thalassaemic syndrome and the partner is known to have a thalassaemic syndrome or is in a high risk group (follow up required)

ISBN number: 978-1-74243-062-1
Endorsed by: South Australian Maternal & Neonatal Community of Practice
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ISBN number: 978-1-74243-062-1
Endorsed by: South Australian Maternal & Neonatal Community of Practice
Last Revised: 19/4/2016

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Thalassaemia Australia: Fact sheets on Hb E, sickle cell, beta thalassaemia, alpha thalassaemia, family planning, etc. Available from URL: http://www.thalassaemia.org.au/fact-sheets

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Abbreviations

CBE	Complete blood examination
CDC	Centers for Disease Control and Prevention
DNA	Deoxyribonucleic acid
e.g.	For example
et al.	And others
fl	Femtolitres
GI	Gastrointestinal
g / L	Gram(s) per litre
Hb	Haemoglobin
HbH	Haemoglobin H disease
HELLP	Haemolysis, elevated liver enzymes and low platelets
IM	Intramuscular
IUD	Intrauterine device
IV	Intravenous
kg	Kilogram(s)
MCV	Mean corpuscularl volume
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
µg / L	Microgram(s) per litre
µmol / L	Micromol(s) per litre
mg	Milligram(s)
mL	Millilitre(s)
%	Percentage
PPH	Postpartum haemorrhage
RDI	Recommended daily intake
SA	South Australia
SD	Standard deviation(s)
US	United States
WHO	World Health Organisation

ISBN number: 978-1-74243-062-1
Endorsed by: South Australian Maternal & Neonatal Community of Practice
Last Revised: 19/4/2016

Version control and change history

PDS reference: OCE use only

Version	Date from	Date to	Amendment
1.0	17 Aug 04	06 Oct 09	Original version
2.0	06 Oct 09	12 May 12	Reviewed
3.0	12 May 12	19 April 16	Reviewed
4.0	19 April 16	Current	

ISBN number: 978-1-74243-062-1
Endorsed by: South Australian Maternal & Neonatal Community of Practice
Last Revised: 19/4/2016

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