

Perinatal Anaemia and Iron Infusion

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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

Note: The words woman/women/mother/she/her have been used throughout this guideline as most pregnant and birthing people identify with their birth sex. However, for the purpose of this guideline, these terms include people who do not identify as women or mothers, including those with a non-binary identity. All clinicians should ask the pregnant person what their preferred term is and ensure this is communicated to the healthcare team.

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 woman. 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 respectfully manage Aboriginal protocol and provide a culturally positive health care experience for Aboriginal people to ensure the best maternal, neonatal and child health outcomes.

Purpose and Scope of Perinatal Practice Guideline (PPG)

To ensure that maternity clinicians have consistent information to inform diagnosis and management of perinatal anaemia. The following guideline supports the use of the Australian Red Cross Toolkit for Maternity Blood Management.



Flowchart 1 - Haemoglobin Assessment and Optimisation in Maternity, First Trimester¹

Haemoglobin Assessment and Optimisation in Maternity



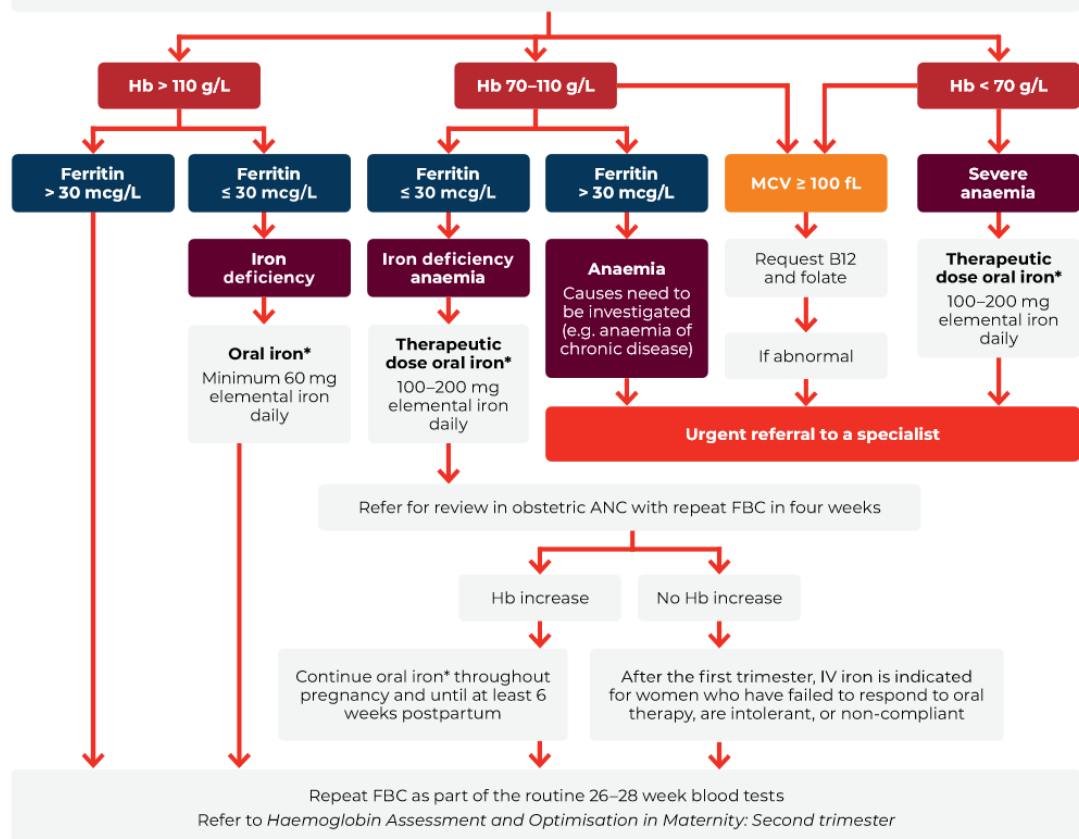
First trimester

First antenatal visit ≤ 20 weeks (booking visit)

- Document risk factors for anaemia: Previous anaemia, inter-pregnancy interval < 1 year, multiple pregnancy, parity ≥ 3, vegetarian/vegan, teenage pregnancy, recent history of bleeding, Aboriginal and Torres Strait Islander.
- **Important:** Request full blood count (FBC) and ferritin on all women if recent bloods not available.
- Perform haemoglobinopathy screening if risk factors (women with a family history of anaemia, thalassaemia or other abnormal haemoglobin variant; and any woman from a high-risk ethnic background who has not previously been tested) **or** the booking FBC shows a MCV ≤ 80 fL and/or MCH < 27 pg.

Second antenatal visit (follow-up visit)

- If a haemoglobinopathy is detected, perform partner screening as soon as possible. Add the woman's details to the request form and refer her to the obstetric antenatal clinic (ANC).
- Review booking blood results and use the flowchart to determine if iron is required.*



***If iron therapy is required:**

- Continue iron rich diet and pregnancy multivitamins.
- Provide the woman with the following handouts: Lifeblood's *Oral Iron Choices for Maternity* and Bloodsafe's *A Guide to Taking Iron Tablets*.
- Document iron preparation and dose in the patient's record.
- Assess adherence (dose and timing) and ask about side effects at every visit. Refer to Bloodsafe's *A Guide to Taking Iron Tablets* to address side effects.

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*** The SAPPGs acknowledge that Aboriginal ethnicity is not a stand-alone risk factor for anaemia, however there may be other pre-disposing factors for anaemia in this group of women including accessibility to, and affordability of fresh, iron rich foods and supplements. It is therefore reasonable to consider a lower threshold for recommending IV iron therapy for Aboriginal women with challenges around accessing an iron rich diet or oral iron supplements

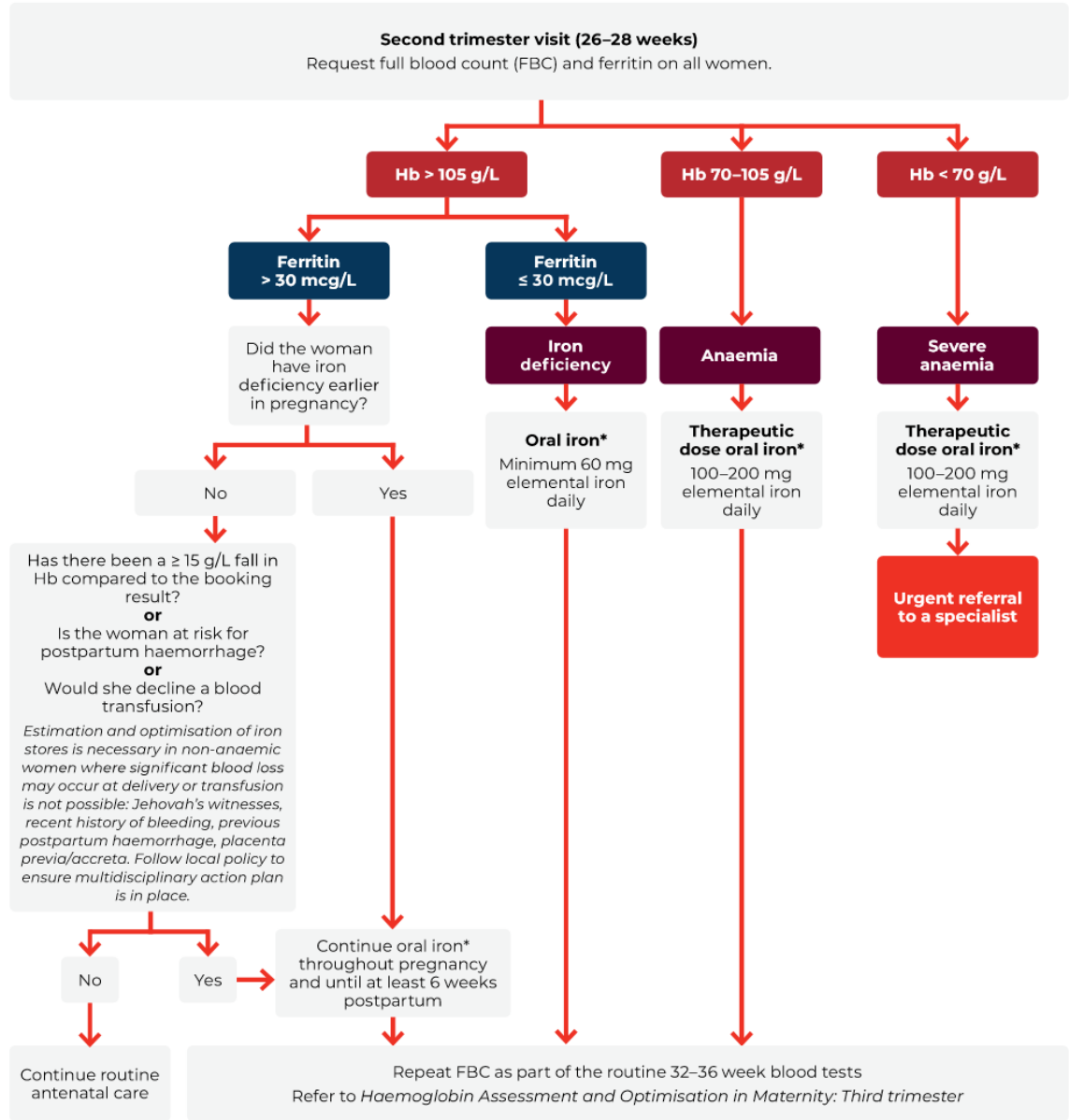
Perinatal Anaemia and Iron Infusion

Flowchart 2 - Haemoglobin Assessment and Optimisation in Maternity, Second Trimester¹

Haemoglobin Assessment and Optimisation in Maternity



Second trimester



***If iron therapy is required:**

- Continue iron rich diet and pregnancy multivitamins.
- Provide the woman with the following handouts: Lifeblood's *Oral Iron Choices for Maternity* and Bloodsafe's *A Guide to Taking Iron Tablets*.
- Document iron preparation and dose in the patient's record.
- Assess adherence (dose and timing) and ask about side effects at every visit. Refer to Bloodsafe's *A Guide to Taking Iron Tablets* to address side effects.

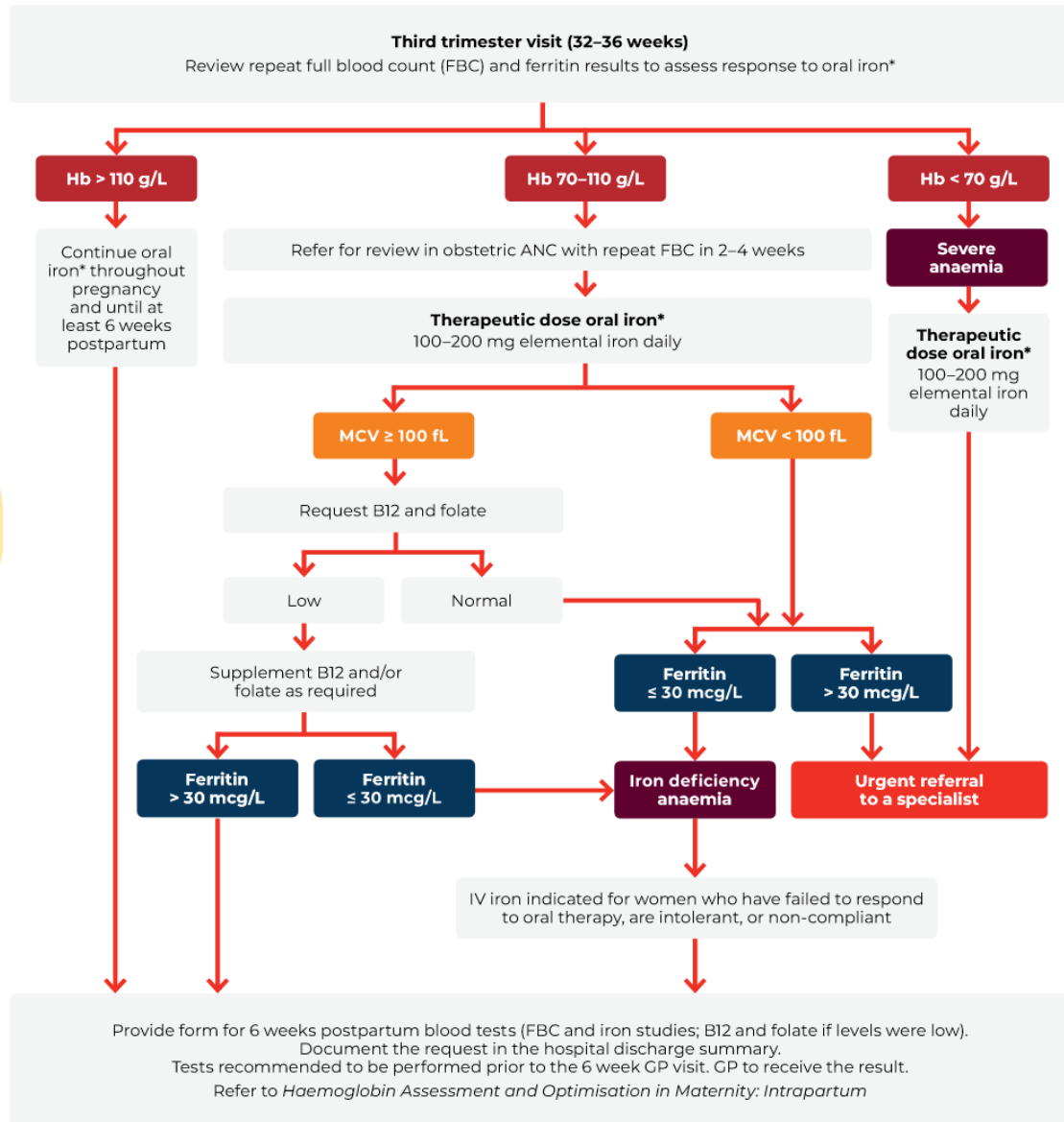
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Flowchart 3 - Haemoglobin Assessment and Optimisation in Maternity, Third Trimester¹

Haemoglobin Assessment and Optimisation in Maternity



Third trimester



***If iron therapy is required:**

- Continue iron rich diet and pregnancy multivitamins.
- Provide the woman with the following handouts: Lifeblood's *Oral Iron Choices for Maternity* and Bloodsafe's *A Guide to Taking Iron Tablets*.
- Document iron preparation and dose in the patient's record.
- Assess adherence (dose and timing) and ask about side effects at every visit. Refer to Bloodsafe's *A Guide to Taking Iron Tablets* to address side effects.

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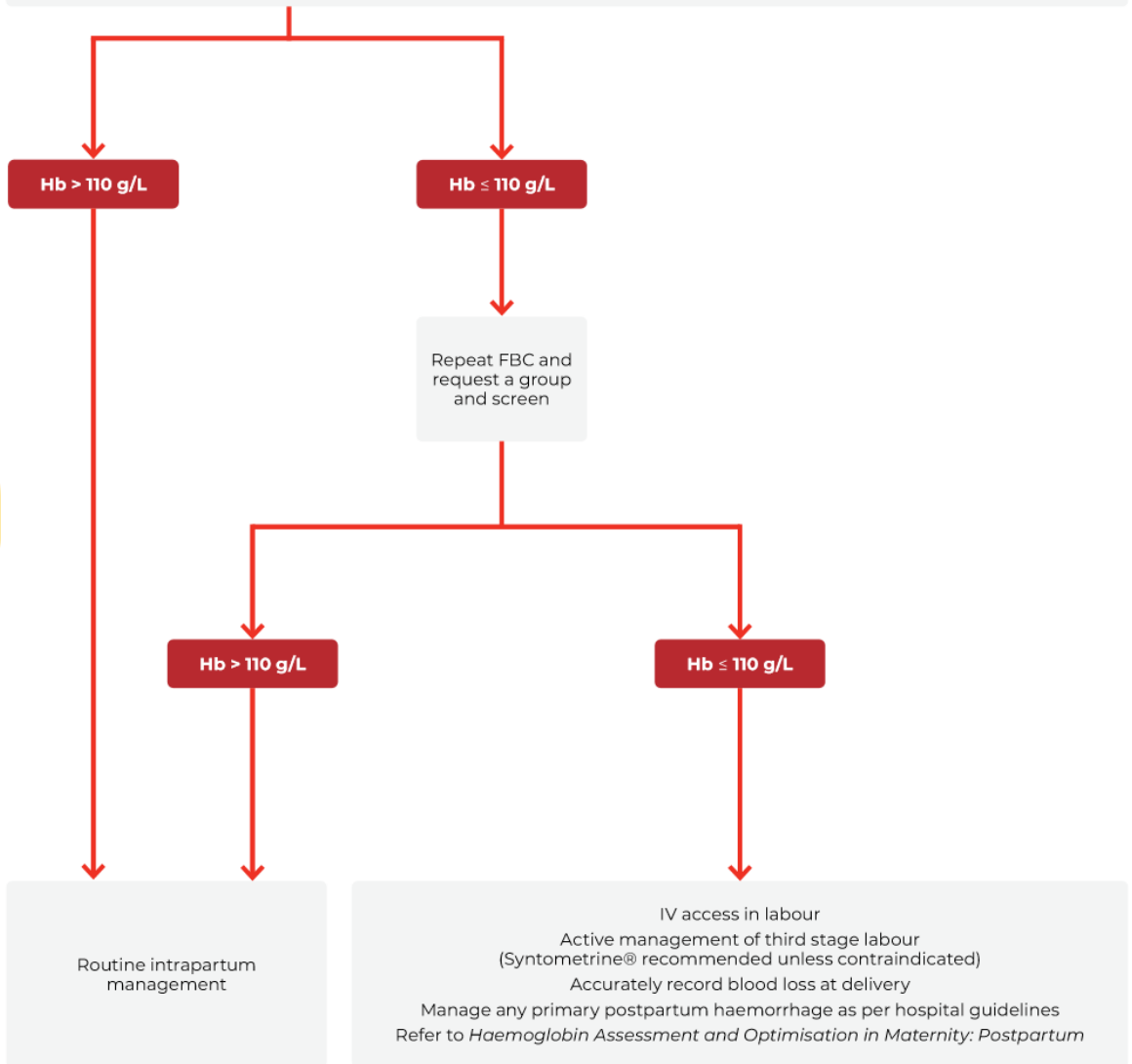
Flowchart 4 - Haemoglobin Assessment and Optimisation in Maternity, Intrapartum¹

Haemoglobin Assessment and Optimisation in Maternity



Intrapartum

Admission in labour
 Review haemoglobin (Hb) result from the last available antenatal full blood count (FBC) for all women on admission.
 Note: Women with anaemia at the time of delivery may require additional precautions.



***If iron therapy is required:**

- Continue iron rich diet and pregnancy multivitamins.
- Provide the woman with the following handouts: Lifeblood's *Oral Iron Choices for Maternity* and Bloodsafe's *A Guide to Taking Iron Tablets*.
- Document iron preparation and dose in the patient's record.
- Assess adherence (dose and timing) and ask about side effects at every visit. Refer to Bloodsafe's *A Guide to Taking Iron Tablets* to address side effects.

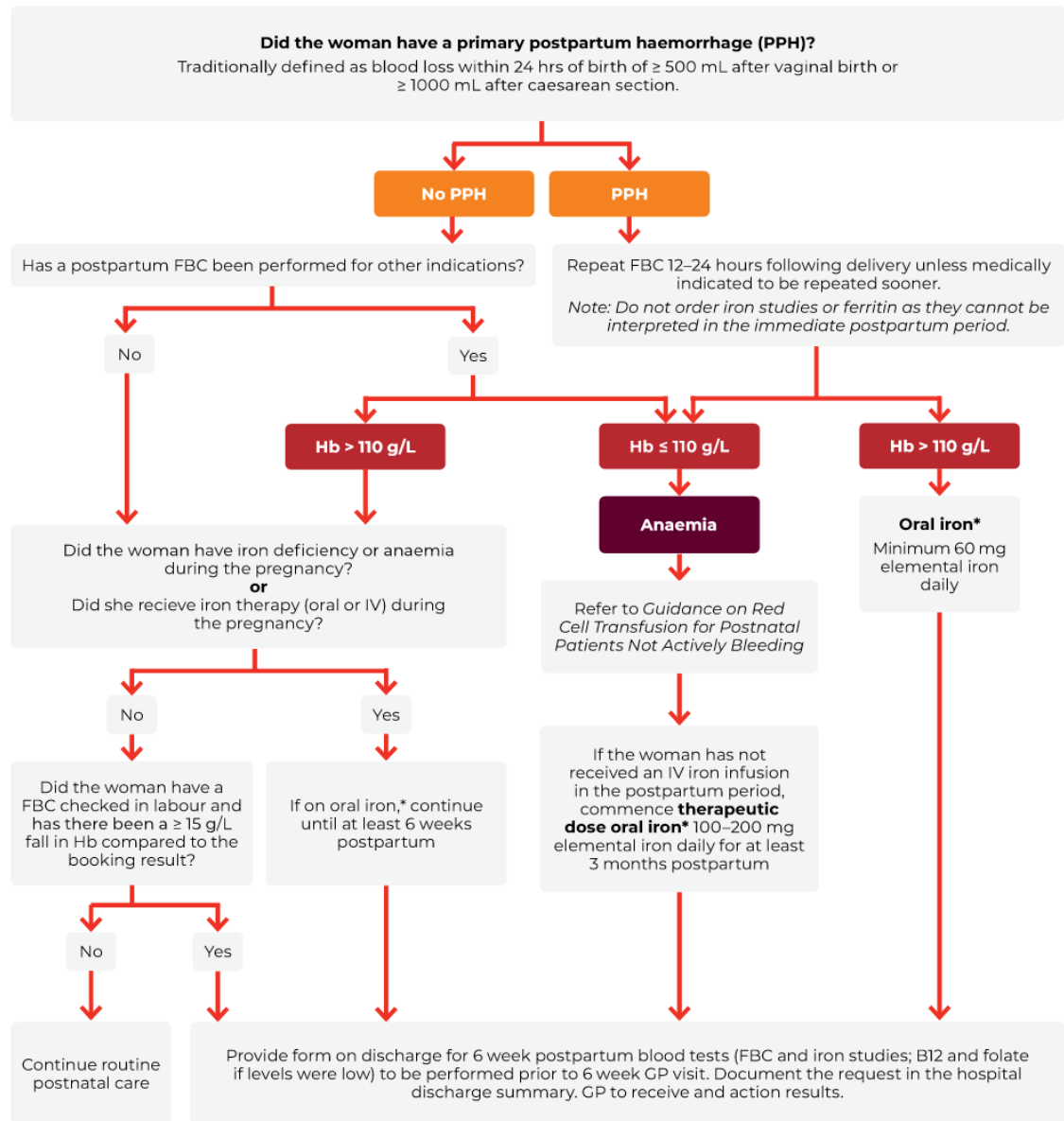
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Flowchart 5 - Haemoglobin Assessment and Optimisation in Maternity, Postpartum¹

Haemoglobin Assessment and Optimisation in Maternity



Postpartum



***If iron therapy is required:**

- Continue iron rich diet and pregnancy multivitamins.
- Provide the woman with the following handouts: Lifeblood's *Oral Iron Choices for Maternity* and Bloodsafe's *A Guide to Taking Iron Tablets*.
- Document iron preparation and dose in the patient's record.
- Assess adherence (dose and timing) and ask about side effects at every visit. Refer to Bloodsafe's *A Guide to Taking Iron Tablets* to address side effects.

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Perinatal Anaemia and Iron Infusion

Summary of Practice Recommendations

- > Complete Blood Examination (CBE) and Serum Ferritin level should be assessed at booking visit and at 28 weeks for all pregnant women¹
- > Anaemia increases the risk of postpartum haemorrhage, therefore optimisation of haemoglobin in pregnancy is important
- > Iron deficiency is common in women of childbearing age therefore all women should be assessed and commenced on treatment with guidance from the National Blood Authority guidelines on Haemoglobin assessment and optimisation in maternity guidelines²
- > Iron therapies are important in treating iron deficiency. Oral iron is recommended for mild anaemia and IV iron for moderate anaemia. There is emerging evidence that IV iron may be a viable first line treatment for postpartum anaemia³
- > Consider IV iron as first line treatment for IDA for Aboriginal women and women in rural/remote communities where accessibility and availability of iron-rich foods and supplements may be limited
- > Some anaemia may be caused by Thalassaemia or Haemoglobinopathies. A Thalassaemia PPG is being developed and will be available at www.sahealth.sa.gov.au/perinatal. All women should be assessed using the maternal and paternal Haemoglobinopathy / Thalassaemia Screening Algorithm, and be directed to complete the Family of Origin questionnaire available [here](#)

Abbreviations

CBE	Complete blood examination
CDC	Centers for Disease Control and Prevention
DNA	Deoxyribonucleic acid
e.g.	For example
et al.	And others
FBC	Full Blood Count
fl	Femtolitres
GI	Gastrointestinal
g / L	Gram(s) per litre
Hb	Haemoglobin
HbH	Haemoglobin H disease
HELLP	Haemolysis, elevated liver enzymes and low platelets
IDA	Iron deficiency anaemia
IM	Intramuscular
IUD	Intrauterine device
IV	Intravenous
kg	Kilogram(s)
MCV	Mean corpuscular 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

Perinatal Anaemia and Iron Infusion

Definitions

Anaemia	Haemoglobin (Hb) level <110g/L in pregnancy and 100g/L postpartum
Haemoglobinopathies	Inherited disorders resulting in decreased synthesis of globin chains, or altered physicochemical properties. The severity of resultant disease is dependent on the type and severity of the gene variants
Thalassaemia	An inherited disorder resulting in decreased synthesis of globin chains.
Iron deficiency	Iron loss or requirement exceeding absorption. In pregnant women, serum ferritin of less than 30 is diagnostic of iron deficiency
Iron deficiency anaemia	Iron loss or requirement exceeding absorption, resulting in anaemia (haemoglobin concentration below the reference range (specific for age, sex and gestation))

Anaemia

Context and Background

- > Anaemia affects 40% of pregnant women worldwide⁴ and is associated with significant perinatal morbidity and mortality⁵
- > Complete Blood Examination (CBE) and Serum Ferritin level should be assessed at booking visit and at 28 weeks for all pregnant women¹
- > Anaemia increases the risk of postpartum haemorrhage (PPH)⁶
- > There is great need to adequately manage anaemia and iron deficiency in pregnancy. The use of iron therapy has important neonatal and maternal outcomes. For the mother, restoration of adequate iron stores is associated with a reduction in maternal mortality, preterm birth and low birth weight⁷. Maternal anaemia can cause iron deficiency in infants which is associated with statistically significant cognitive and behavioural abnormalities as well as a poorer motor, social-emotional and neurophysiologic development⁷
- > Women who have previously completed one or more pregnancy are at higher risk of iron deficiency at the start of any subsequent gestation, especially with short inter-pregnancy interval or previous PPH
- > As well as the perinatal morbidity associated with anaemia, early postpartum anaemia has been identified as an independent risk factor for long-term atherosclerotic events^{8, 9}

Impacts of perinatal iron deficiency¹⁰

- > Odds of developing antenatal depression are 2.5 times higher
- > Increased risk of postpartum haemorrhage (PPH)⁶
- > Increased incidence of postpartum depression, fatigue, impaired cognition and altered maternal-infant bonding³
- > Increased risk of pre-term birth and low birth weight
- > Iron deficiency in babies born to Iron deficient mothers

Improved outcomes with recommended interventions¹⁰

- > 60-70% of women screened were iron deficient during LifeBlood Maternity Toolkit pilot
- > Anaemia at birth reduced by 70%
- > Number of units transfused in maternity settings reduced by 34%
- > Less low birthweight babies when iron supplements taken during pregnancy

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^{4, 11}
- > US Center [sic] 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)¹²



Perinatal Anaemia and Iron Infusion

- > 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 population²
- > There is variation in the definition of anaemia in pregnancy and no agreed normal range for pregnant women in Australia. 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 trimester²
- > In view of the relative plasma expansion being particularly marked in the second trimester, it would seem reasonable to define anaemia as²:
 - 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 Aboriginal people are thought to be similar to non-Aboriginal people. Aboriginal and Torres Strait Islander women experience a much higher prevalence of factors that contribute to anaemia and iron deficiency, and their adverse effects².
- > Such factors include²:
 - Higher fertility rate (2.6% in Aboriginal women compared with 1.9% in non-Aboriginal people in 2009) and higher parity
 - A higher rate of teenage births (21% of Aboriginal births are to teenage mothers, compared with 4% of non-Aboriginal births in 2009)
 - More limited access to affordable nutritious food especially in remote areas
 - Higher rates of medical comorbidities, such as chronic renal disease, diabetes, chronic vascular disease, cardiac anomalies, and rheumatic heart disease
 - Reduced access to culturally safe health care

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
- > Consequently, 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 term²

Causes of anaemia

- > Physiological
- > Iron deficiency is a common cause of anaemia in pregnancy, in both the developed and developing world
- > Other causes of anaemia include²:
 - megaloblastic anaemias due to vitamin B₁₂ and folic acid deficiency,
 - thalassaemias,
 - blood loss,
 - haemolytic states (sickle cell disease, malaria and pre-eclampsia),
 - helminthic infection,
 - underlying malignancy and
 - chronic disease
- > 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 level², although because ferritin is an acute phase reactant, levels can be misleadingly 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 variation²



Perinatal Anaemia and Iron Infusion

Aboriginal and Torres Strait Islander women

- > Increased incidence of co-morbidities and impacts of social determinants, place Aboriginal women at an increased risk of experiencing anaemia and/or iron deficiency. 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 B₁₂ or hookworm, should be screened for in selected groups women.
- > Thalassaemia, whilst relatively uncommon, does exist in some Aboriginal groups; therefore this should also be a consideration.
- > Incorporate holistic management to minimise anaemia in pregnancy:
 - access to contraception
 - support longer inter-pregnancy interval
 - access to a nutritious diet
 - optimal management of any medical comorbidities
 - treatment of hookworm if relevant
- > Some of the conservative treatment regimens recommended for women in pregnancy may not be practicable for Aboriginal women.
- > Consideration of IV iron therapy is suggested for these women to ensure rapid restoration of iron stores to improve perinatal outcomes and avoid additional complications.
- > For Aboriginal and Torres Strait Islander women in rural and remote areas who are at high risk of severe PPH, have a management plan in place to minimise any delay in accessing health-care services and resources, including blood products

Classification of anaemia

- > Anaemia is often classified in the following way based on red cell indices:
 1. **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
 2. **Microcytic, hypochromic** – low MCV, low MCH and / or MCHC: iron deficiency, thalassaemia and some haemoglobinopathies
 3. **Macrocytic, normochromic anaemia** – elevated MCV, normal MCH and MCHC:
 4. **Megaloblastic anaemia** – B₁₂ or folate deficiency, liver disease, myelodysplasia and hypothyroidism
- > It is important to note the limitations of this classification. In milder cases of iron deficiency anaemia, the MCV may not have fallen below the normal range². Co-existing conditions such as combined vitamin deficiency of iron and B₁₂ or folate may present with a normocytic blood picture, likewise with a co-existing thalassaemia and B₁₂ or folate deficiency

Antepartum management of anaemia

See the flow charts available at the beginning of this PPG relevant to each trimester of pregnancy which contain Hb and Ferritin thresholds for treatment, and treatment modalities in each trimester of pregnancy:

- Flowchart 1 - Haemoglobin Assessment and Optimisation in Maternity, First Trimester¹
- Flowchart 2 - Haemoglobin Assessment and Optimisation in Maternity, Second Trimester¹
- Flowchart 3 - Haemoglobin Assessment and Optimisation in Maternity, Third Trimester¹

Pathology testing

- > First antenatal visit:
 - All women require a complete blood examination (CBE) at the first antenatal visit to determine whether anaemic²
 - Check serum Ferritin level at first antenatal visit to determine if iron deficiency is present independently or is causing anaemia²
 - If the woman is in a risk group for thalassaemia / haemoglobinopathy (women with a family history of anaemia, thalassaemia or other abnormal haemoglobin variant; any woman from a high-risk ethnic background who has not previously been tested OR if the booking CBE shows a MCV \leq 80 f/L and/or MCH $<$ 27 pg²



Perinatal Anaemia and Iron Infusion

- > 28 weeks
 - Repeat CBE and serum ferritin at 28 weeks²

Additionally, testing is recommended at 36 weeks for women who identify as Aboriginal or Torres Strait Islander. The *Minymaku Kutju Tjukurpa: Women's Business Manual* outlines culturally appropriate care for rural and remote Aboriginal women and recommends additional Hb and serum ferritin testing at 36 weeks.

<https://remotephcmanuals.com.au/document/30938.html?publicationid=#8>

Intrapartum management of anaemia¹³

- > Women who are anaemic at the time of birth (last Hb \leq 110g/L) may require additional precautions due to their increased risk of PPH, including:
 - Birth in a hospital setting
 - IV access
 - Blood Group and Antibody Screen and Complete Blood Examination (CBE)
 - Active management of the third stage of labour
 - For caesarean section, consider using cell salvage if available.
 - Either bolus oxytocin 10 units, intramuscular or 5-10 units, slowly intravenous OR consider ergot derivative if no pre-existing hypertension or preeclampsia:
 - Consider 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)
- > See **Flowchart 4 - Haemoglobin Assessment and Optimisation in Maternity, Intrapartum1** outlining the Hb and Ferritin thresholds for intrapartum treatment and ongoing management

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 hours²
- > 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 replete². Discharge planning includes timely communication with primary care services including GPs and Aboriginal Community Controlled Health Services
- > Intravenous iron is more effective in treating postpartum anaemia, with haemoglobin concentrations higher in women receiving IV iron versus oral.¹⁴ There is emerging evidence that IV iron is a viable first-line treatment for postpartum anaemia³. IV iron may be offered to women at risk of not continuing with oral iron
- > See
- > **Flowchart 5 - Haemoglobin Assessment and Optimisation in Maternity, Postpartum1** outlining the Hb and Ferritin thresholds for postpartum treatment and management
- > Access to contraception in the postpartum period, and inter-pregnancy monitoring of iron levels can assist with optimising maternal health in the next pregnancy

Management of anaemia and the indications for various treatment modalities are discussed extensively in

Iron deficiency anaemia. Transfusion is generally only used to treat acute blood loss anaemia as a result of postpartum haemorrhage in specific circumstances. A brief summary of indications and considerations are listed below, however detailed information is available in 'Postpartum Haemorrhage' and 'Blood Transfusion' PPGs, available at www.sahealth.sa.gov.au/perinatal



Perinatal Anaemia and Iron Infusion

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 alternative²
- > 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 women who are pregnant or immediately postpartum. Seek specialist transfusion advice where necessary
- > 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

The National Patient Blood Management Guidelines: Module 5 - Obstetrics and Maternity (2015)². This information relates only to women who are not actively bleeding

Women who are <u>NOT actively bleeding</u> in the peripartum period	<ul style="list-style-type: none"> > 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. Clinical assessment will determine appropriateness of repeating Hb
Considerations for red cell transfusion	<ul style="list-style-type: none"> > 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



Perinatal Anaemia and Iron Infusion

Megaloblastic anaemia - folate and vitamin B₁₂ deficiency

Megaloblastic anaemia is the second most common nutritional anaemia seen during pregnancy

- > Megaloblastic anaemia can be caused by B12 or Folate deficiency
- > Folate and its co-factor vitamin B₁₂ 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 B₁₂ deficiency is uncommon, despite the increased requirements of pregnancy, due to the extent of vitamin B₁₂ stores.
- > Other causes of vitamin B₁₂ deficiency include conditions affecting the stomach (e.g. hypochlorhydria, gastrectomy, gastric bypass, 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 B₁₂ deficiency or thalassaemia / haemoglobinopathy
- > Vitamin B₁₂ and folate measurements should be undertaken to exclude deficiencies of both haematinics. The metabolic roles of folate and vitamin B₁₂ 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 B₁₂, in which case treatment is initiated with B₁₂ therapy before adding in folate therapy¹⁵

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 mother¹⁵
- > Folate supplementation is recommended in all pregnancies, as per the *Antenatal Care PPG*, available at www.sahealth.sa.gov.au/perinatal
- > 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.)¹⁶
- > 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 120fL)
 - Anaemia
 - Large hyper-segmented neutrophils (these being a late sign in pregnancy)
 - Falling platelet count (less than $100 \times 10^9 / L$)
 - 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 B₁₂ level and start folate once vitamin B₁₂ confirmed normal¹⁶
- > 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 B₁₂ deficiency

- > Vitamin B₁₂ plays a fundamental role in the formation of blood and normal functioning of the brain and nervous system¹⁷. It is essential for infant neurodevelopment.
- > Undiagnosed maternal vitamin B₁₂ deficiency may result in irreversible neurological damage to the breastfed infant. Although maternal vitamin B₁₂ deficiency is uncommon, the majority of women with deficient vitamin B₁₂ levels are asymptomatic



Perinatal Anaemia and Iron Infusion

- > Vitamin B₁₂ Deficiency is most commonly seen in:
 - Pernicious anaemia where there is an autoimmune destruction of gastric parietal cells causing loss of intrinsic factor,
 - Total or subtotal gastrectomy and gastric bypass procedures,
 - Exocrine pancreatic failure,
 - Loss or disease of the permanent ileum,
 - Intestinal bacterial overgrowth (may consume B₁₂)
- > Those who have had gastric surgery have a high prevalence of vitamin B₁₂ deficiency¹⁸, and more recently, treatments for obesity including gastric banding and gastric bypass surgery also lead to vitamin deficiency¹⁵. 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 B₁₂ deficiency

Routine measurement of vitamin B₁₂ is not required; however check the serum vitamin B₁₂ level if ^{17, 19}:

- Increased MCV,
 - Vegetarian or Vegan diet. Also consider referral to dietician,
 - GI pathology / procedures (coeliac disease, Crohn's disease, bariatric surgery such as gastric banding / bypass etc.),
 - Family history of vitamin B₁₂ deficiency or pernicious anaemia,
 - History of excessive alcohol consumption,
 - Medications that impeded B₁₂ absorption, such as H₂ receptor antagonists, proton pump inhibitors or metformin),
 - Have had a gastric or small intestine resection.
- > SA Pathology performs Total vitamin B₁₂ and Active vitamin B₁₂ (if indicated). Other laboratories may also have both tests available. In pregnancy Total vitamin B₁₂ is reduced, however, this is not necessarily reflective of deficiency even if the value is below the reference interval. Total vitamin B₁₂ is made up of biologically active (10 - 30% of Total vitamin B₁₂) and biologically inert (70 - 90% of Total vitamin B₁₂) complexes. This is determined by the protein it is bound to. In normal pregnancy the protein that complexes with vitamin B₁₂ to produce the biologically inert complex (haptocorrin + vitamin B₁₂ → holohaptocorrin) is 'naturally' reduced, whereas the protein that complexes with vitamin B₁₂ to produce the biologically active complex (transcobalamin + B₁₂ → holotranscobalamin) remains unchanged
 - > For tests requested through SA Pathology, if the Total vitamin B₁₂ concentration when assayed is low / equivocal, testing of Active vitamin B₁₂ is initiated automatically in both pregnant and non-pregnant women. This will determine whether a woman has normal Active vitamin B₁₂ 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 B₁₂ deficiency in pregnancy, consult a haematologist / physician and refer to the product information for intramuscular (IM) vitamin B₁₂ 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 Guidelines at URL: www.sahealth.sa.gov.au/perinatal

Prevention

- > Vegetarians and vegans should be supplemented with vitamin B₁₂ in pregnancy and lactation. The Recommended Daily Intake of vitamin B₁₂ in pregnancy is 6 micrograms per day²⁰
- > The following link²¹ explains the consequences of B12 deficiency in pregnancy, with specific information for those on a plant based diet. <https://nutritionfacts.org/video/the-optimal-vitamin-b12-dosage-for-kids-pregnancy-and-seniors/>
- > An alternative to oral supplementation in strict vegans is IM injection of 1,000 micrograms of vitamin B₁₂ at 3 monthly intervals to prevent the development of vitamin B₁₂ 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



Perinatal Anaemia and Iron Infusion

Iron deficiency anaemia

Iron in pregnancy

- > Iron is essential during pregnancy to support expansion of blood cell mass, and for growth of maternal, fetal, and placental tissue²²
- > Iron deficiency is the most common cause of anaemia in pregnancy, in both the developed and developing world. Iron deficiency anaemia in pregnancy is associated with increased maternal and perinatal morbidity and mortality including neurocognitive deficits in children²³
- > Physiological iron requirements are 3 times higher in pregnancy than they are in the menstruating women²⁴, with increasing demand as pregnancy advances
- > 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. Identified vulnerable groups include; adolescents, women who identify as **Aboriginal**, some immigrants groups and women of low socioeconomic status^{2, 12}
- > The use of iron therapy has important neonatal and maternal outcomes. For the mother, restoration of adequate iron stores is associated with a reduction in maternal mortality, preterm birth and low birth weight⁷. Maternal anaemia can cause iron deficiency in infants which is associated with statistically significant cognitive and behavioural abnormalities as well as a poorer motor, social-emotional and neurophysiologic development⁷. The need for adequately managing anaemia and iron deficiency in pregnancy cannot be underestimated. Risks of non-compliance with oral iron therapy should be discussed with the pregnant woman to ensure that she understands the importance of resolving her anaemia and/or iron deficiency. **Aboriginal women can ensure better health outcomes for their babies if they have control over their experiences during pregnancy. Support from an Aboriginal healthcare worker is recommended**
- > 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 day²⁵
- > See **Flowchart 1 - Haemoglobin Assessment and Optimisation in Maternity**. This contains flowcharts outlining the Hb and Ferritin thresholds for treatment in each trimester of pregnancy, as well as intrapartum and postpartum treatment and management

Diagnosis of iron deficiency anaemia

- > Universal Serum Ferritin testing is recommended for all women at their first antenatal visit and repeated at 28 weeks gestation¹⁰
- > Women with haemoglobin <110 g/L before 12 weeks or <105 g/L, and/or serum ferritin <30micrograms/L beyond 12 weeks are anaemic and should be offered a trial of therapeutic iron replacement.
- > Women known to have a thalassaemia / haemoglobinopathy should only be offered therapeutic iron if the ferritin is <30 micrograms/L^{2, 26}
- > 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 thalassaemia / haemoglobinopathies. In addition, for milder cases of iron deficiency, the MCV may not have fallen below the normal range²⁶. Note that both iron deficiency AND thalassaemia / 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 in the general population²⁶. A level <30 micrograms/L in pregnancy should prompt treatment^{2, 26}.
- > Serum ferritin should be checked before starting iron in women with known thalassaemia / haemoglobinopathy as there is a risk of iron overload because of dyserythropoiesis²⁶. Serum ferritin should also be checked in women with likely multifactorial anaemia (e.g. with risk factors for multiple deficiencies, chronic disease / inflammation)



Perinatal Anaemia and Iron Infusion

- > Anaemic women with unknown thalassemia / haemoglobinopathy status should be offered a trial of iron whilst **thalassemia / haemoglobinopathy screening & serum ferritin are undertaken without delay**²⁶
- > Further information regarding screening for thalassaemia and haemoglobinopathies is outlined in the Thalassaemia and Haemoglobinopathies PPG available soon at www.sahealth.sa.gov.au/perinatal

Management and 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 important²⁶. This should be consolidated by the provision of an information leaflet in the appropriate language.
- > 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 outcomes²
- > Treatment of iron deficiency anaemia occurs by 2 main modalities:
 - Oral iron replacement therapy, and;
 - Intravenous iron infusion.

Oral iron

Oral iron supplementation is an inexpensive and effective means of restoring iron balance. For most women with iron deficiency and iron deficiency anaemia (IDA) in the peripartum period, oral iron supplementation can be used.

- > **See Appendix** for examples of oral iron preparations
- > For women with iron deficiency anaemia, the oral dose of iron should be 100 to 200 mg of elemental iron daily²
- > In non-anaemic iron deficiency lower doses of elemental iron (e.g. 20-80mg daily) may be considered and may be better tolerated than higher doses²
- > The response to therapy should be monitored and if inadequate, intravenous iron should be used from second trimester²
- > NOTE: Many multi-vitamin 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 stressed²⁶. Ensure that education materials are culturally appropriate with use of pictorial aids and translation where needed.
- > Patient information should be provided. Leaflets on oral iron therapy in multiple languages are available at URL:
<https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/conditions/blood+organ+and+tissue/iron+deficiency+and+iron+therapy>



Perinatal Anaemia and Iron Infusion

Assessing response

- > In anaemic women, repeat haemoglobin testing and reticulocyte response is required 2 weeks after commencing treatment for established anaemia, to assess compliance, correct administration and response to treatment²⁶
- > Once haemoglobin is in the normal range, replacement should continue for three months and until at least 6 weeks postpartum to replenish iron stores²⁶
- > In iron deficient, non-anaemic women; refer to **Flowchart 1 - Haemoglobin Assessment and Optimisation in Maternity** as management varies, dependent stage of perinatal period.
- > If response to oral iron replacement is poor explore factors that may be contributing to the anaemia such as:
 - non-compliance
 - concomitant causes- folate deficiency or anaemia of chronic disease
- > Seek specialist advice where necessary
- > Consider intravenous iron infusion, as per **Flowchart 1 - Haemoglobin Assessment and Optimisation in Maternity**

IV Iron replacement

Intravenous Iron replacement therapy is an effective and widely used treatment for iron deficiency anaemia in pregnancy and postpartum. Iron infusion is discussed extensively in

Intravenous Iron, and each medication infusion regimen is outlined in **Appendix 2 – Intravenous Iron Infusion** Regimens.



Perinatal Anaemia and Iron Infusion

Intravenous Iron

Background

- > For women with confirmed iron deficiency that fail to respond to, or are intolerant of oral supplementation, or where rapid restoration of haemoglobin and iron stores is required, intravenous iron may be considered from the second trimester and during the postpartum period^{2, 26}.
- > There is increasing evidence^{2, 27, 28} that intravenous iron is more effective, provides more rapid correction of haemoglobin and iron stores and is better tolerated than oral iron in treating iron deficiency anaemia during pregnancy.
- > The *National Patient Blood Management Guidelines - Obstetric and Maternity: Module 5* provides recommendations and practice points on the use of intravenous iron in the peripartum setting²⁹ – See Flowchart 1 - Haemoglobin Assessment and Optimisation in Maternity
- > Intravenous iron reduces the use of blood products. In some cases, rapid correction of anaemia with red blood cells may be required to restore oxygen carrying capacity (such as in decompensated and/or acutely bleeding patients). Iron therapy should always follow transfusion to replenish deficient iron stores² (for further information see the *Blood transfusion* PPG in the A to Z index at www.sahealth.sa.gov.au/perinatal)
- > Intravenous iron treatment circumvents the natural gastrointestinal regulatory mechanisms to deliver non-protein bound iron to the red cells²⁶.
- > The routine use of IM iron is not advised where alternatives are available

General administration information

- > Facilities and staff trained in management of anaphylaxis should be available. IV iron should not be administered to pregnant women outside a hospital setting unless there is capacity for full resuscitation in the event of anaphylaxis, and staff trained in the management of obstetric patients. This includes; adrenaline, oxygen, airway adjuncts and AED. See also 'Anaphylaxis (maternal)' PPG available at www.sahealth.sa.gov.au/perinatal. Appropriate maternal positioning is imperative to ensure displacement of uterus. This is achieved by a left lateral tilt or by placing a wedge under the woman's right hip.
- > When IV iron is prescribed, calculation of the dose should take into consideration the iron deficit².
- > Brown staining of the skin (potentially permanent) may occur due to leakage of the drug into the tissues around the injection site. Distant skin discolouration has also been reported.
- > Monitor injection site and educate women to immediately report any discomfort, burning, redness or swelling. In case of paravenous leakage STOP infusion immediately³⁰. Refer to each product later in this document for information regarding flushing the line.
- > Iron polymaltose (Ferrosig[®]), iron sucrose (Venofer[®]), ferric carboxymaltose (Ferinject[®]), and ferric derisomaltose (Monofer[®]) are the parenteral iron formulations currently available in Australia.
- > A "total-dose" infusion (where iron stores can be repleted in a single treatment episode) can be administered with iron polymaltose (Ferrum H[®] or Ferrosig[®]).
- > In women with mild iron deficiency anaemia, a single dose of ferric carboxymaltose (Ferinject[®]) may be sufficient to fully replete iron stores but 2 doses (at least a week apart) are required in more severe anaemia
- > The choice of iron infusion will depend on SA Medicines Formulary guidelines, logistics, availability and individual patient factors.
- > Iron sucrose (Venofer[®]) can only be given as multiple small intermittent doses over days to weeks not as a large or 'total dose' infusion
- > Ferric derisomaltose (Monofer[®]), became available in Australia in 2017 and was PBS listed in 2019. Whilst it allows a large dose to be given in a short time, there is a lack of adequate and well-controlled trials of ferric derisomaltose (Monofer[®]) in pregnant women and therefore an administration guide is not provided within this PPG. Refer to the product information. It is important to beware that it has a similar sounding name to ferric carboxymaltose (Ferinject[®]). Whilst dosing and infusion rates between the 2 preparations are similar, they are NOT the same.



Perinatal Anaemia and Iron Infusion

Indications

- > Refer to: Flowchart 1 - Haemoglobin Assessment and Optimisation in Maternity or website <https://transfusion.com.au/node/2234> for Haemoglobin Assessment and Optimisation in Maternity for guidance²⁹
- > Oral iron (therapeutic doses) is first line therapy for most maternity patients with iron deficiency or iron deficiency anaemia (note that the woman does not need to be anaemic to have an iron deficiency). The response to therapy should be monitored and if inadequate, intravenous iron should be used²
- > In maternity patients with iron deficiency anaemia, intravenous iron is preferred when rapid restoration of haemoglobin and iron stores is required, because it leads to a more rapid increase in these values when compared to other routes of administration²
- > In maternity patients requiring iron, intravenous iron is preferred when oral iron is poorly tolerated (affecting compliance), or absorption is likely to be impaired²

Contraindications

- > First trimester of pregnancy
- > Known hypersensitivity to intravenous or intramuscular iron (discuss choice of intravenous iron preparation and indication with an expert such as haematologist, perinatal physician, nephrologist, or other specialist)
- > Haemochromatosis or anaemia that is not due to iron deficiency or associated with low iron stores (seek advice if cause of anaemia is unclear)
- > Cases of women with asymptomatic thalassaemia minor (normal or mildly reduced haemoglobin level) and coexisting iron deficiency with indications for intravenous iron may rarely occur (see 'Indications' for intravenous iron above). Intravenous iron is not contraindicated so long as the presence of iron deficiency is confirmed by a low serum ferritin level. If in doubt seek specialist advice
- > Women with thalassaemia / haemoglobinopathy requiring regular or intermittent blood transfusions (e.g. thalassaemia major or intermedia) may have or be at future risk of iron overload. They should not receive intravenous iron unless recommended by a haematologist (after assessment of the phenotype of their disease and current iron stores)
- > Active systemic infection/bacteraemia

Precautions

- > **⚠ WARNING** *Intravenous iron can cause hypersensitivity reactions (including anaphylactoid), which may be fatal and can occur after previous uneventful doses. Cardiopulmonary resuscitation facilities MUST be available. Stop immediately if signs of allergy or intolerance. Observe for at least 30 minutes post infusion.*
- > Significant hepatic dysfunction (discuss risks / benefits with gastroenterologist), avoid in women with hepatic dysfunction where iron overload is a precipitating factor, in particular porphyria cutanea tarda
- > Use with caution in acute or chronic infection after assessing risks / benefits and seek expert advice. Avoid during active systemic infection / bacteraemia
- > Use with caution in asthma, eczema, or other atopic allergies
- > Paravenous leakage may cause permanent skin staining
- > IV iron (particularly ferric carboxymaltose®) can cause hypophosphataemia, which is usually mild, transient, and clinically irrelevant.
 - Ferric carboxymaltose (Ferinject®) has also been associated with a rare risk of severe, symptomatic hypophosphataemia and with rare reports of hypophosphataemic osteomalacia. In clinical trials, the minimum serum phosphate values were obtained after approximately 2 weeks, and in most cases returned to baseline by 12 weeks following treatment. Follow up at-risk patients (refer to PI) and consider hypophosphataemia as a potential reason for a patients' symptoms after use of ferric carboxymaltose.



Perinatal Anaemia and Iron Infusion

Calculation of total body iron deficit

⚠️ WARNING *This section is for calculation of the woman's total body iron deficit (cumulative amount of iron required to replete body iron stores) NOT the allowable iron dose per infusion which is DIFFERENT for each product. Refer to the specific product information and administration guidelines for information on the maximum iron dose per infusion for each product*

- > Calculation of total body iron deficit is based on body weight and haemoglobin as per product information or calculated by the Ganzoni formula below. Seek expert advice if in doubt.
- > The total body iron deficit is expressed as milligrams of **elemental iron**

Ganzoni formula:

Total body iron deficit (mg) =

$$\text{body weight (kg)}^* \times (\text{target Hb} - \text{actual Hb in g/L}) \times 0.24^{**} + \text{iron depot (mg)}^{***}$$

***Use ideal body weight (non-pregnant) in overweight women.** If underweight, use actual body weight (see ideal body weight calculator in Australian Medicines Handbook)

******The factor 0.24= 0.0034 x 0.07 x 1,000.

- For this calculation the iron content of haemoglobin = 0.34%, blood volume = 7% of the bodyweight and 1,000 is the conversion from gram (g) to milligram (mg)

*******Iron depot:

- > 15 mg/kg for body weight less than 35 kg
- 500 mg for those with a body weight greater than or equal to 35 kg

OR;

A Simplified Method for estimating the total body iron deficit (for adult patients of body weight \geq 35 kg) can be found in table form in the appendices of this document for each preparation. Alternatively, refer to the Australian product information.

Administration

⚠️ WARNING *Infusion rates, maximum dose per infusion and dilution are NOT interchangeable between IV iron products. Beware of similar names! Refer to the specific product information and administration guidelines outlined in Appendix 2 – Intravenous Iron Infusion Regimens*

- > All iron preparations can only be mixed with 0.9 % sodium chloride
- > Use a dedicated intravenous line and do not add any other medications
- > Administer through infusion pump
- > Anaphylactoid reactions occur most frequently within the first several minutes of administration and are generally characterised by sudden onset of respiratory difficulties, tachycardia and hypotension
- > Adrenaline, oxygen and steroids should be available for immediate use during administration to treat possible anaphylactic reaction For further information see *Anaphylaxis (maternal)* PPG in the A to Z index at www.sahealth.sa.gov.au/perinatal
- > Oral iron is not required after IV iron is given if the total iron deficit has been (or will be) replenished with IV iron therapy

For women with a history of systemic allergy to parenteral iron; consult an expert regarding the nature of the reaction, indication and alternatives to IV iron, and the most suitable choice of preparation eg. use of iron sucrose.



Perinatal Anaemia and Iron Infusion

NB: Brown staining of the skin (potentially permanent) may occur due to leakage of the drug into the tissues around the injection site. Potentially permanent staining has occurred in the absence of obvious extravasation³¹. Monitor injection site and educate women to immediately report any discomfort, burning, redness or swelling or other indicators, which include: taut skin above or below insertion site, fluid leaking at insertion site, coolness/ blanching around insertion site, numbness or tingling above or below insertion site³².

In case of paravenous leakage STOP infusion immediately. Minimise the risk of injection site leakage by flushing with sodium chloride 0.9% before and after administration

NB: Test doses are no longer recommended at the beginning of an iron infusion as there is no evidence of any protective effect³³. However, caution should be taken with each even if previous infusions have been well tolerated. **Monitor for signs of hypersensitivity during infusion, and for at least 30 minutes after completion of the infusion.**

Adverse Reaction

- > Stop the infusion immediately
- > Institute emergency care and notify medical officer to review as soon as possible
- > Lie the woman flat (If uterine size is greater than 20 weeks of gestation avoid aortocaval compression by using a left lateral wedge / tilt)
- > Oxygen at > 6 L / minute (preferably 12-15 L / minute via non-rebreathing mask.
- > If anaphylaxis is suspected, follow care as per *Anaphylaxis (maternal)* PPG in the A to Z index at www.sahealth.sa.gov.au/perinatal
- > For nonspecific and minor side effects, close observation using the 'Rapid Deterioration and Response' (RDR) chart with frequent observations including pulse oximetry, blood pressure and respirations until symptoms resolve (at least 1 hour). Appropriate medical review as identified by RDR criteria. Do not recommence infusion
- > Adverse reaction reporting for anaphylaxis:
- > Document adverse reaction in patients' medical records
- > Report to the SA Health Safety Learning System (SLS)
- > Reporting adverse event via Advisory Committee on the Safety of Medicines (ACSOM) where appropriate. Further information available at URL: <https://www.tga.gov.au/reporting-adverse-events>

Discharge Planning

- > Discharge after medical review
- > Advise the woman that delayed systemic reactions may include:
 - dizziness, syncope
 - sensation of stiffness in arms, legs or face
 - chest and back pain
 - arthralgia, chills, fever, rash
 - urticaria, angioneurotic oedema
 - generalised lymphadenopathy
- > Ensure the woman has been given the appropriate patient information including when / how to seek medical attention / advice if required as per the patient leaflet 'Intravenous (IV) iron infusions' which is available in multiple languages at URL: <https://www.sahealth.sa.gov.au/wps/wcm/connect/public+content/sa+health+internet/conditions/blood+organ+and+tissue/iron+deficiency+and+iron+therapy>



Perinatal Anaemia and Iron Infusion

Useful Websites

Royal College of Obstetrics and Gynaecology (RCOG): Management of Beta Thalassaemia in pregnancy (Green top 66). Available at: <https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg66/>

Royal College of Obstetrics and Gynaecology (RCOG): Sickle cell disease in pregnancy-management of (Green top No. 61). Available at: <https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg61/>

BloodSafe:

Patient information leaflets in 18 languages:

- > 'What you should know about iron tablets'
- > 'Intravenous (IV) iron infusions'

And, oral iron dosing chart for clinicians:

- > 'Oral preparations for treatment of iron deficiency anaemia (IDA) in Australia'

Available at: [Iron deficiency and iron therapy | SA Health](#)

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Oral Iron Choices for Maternity

Woman's name _____

Today's date _____

Date of blood test _____

Haemoglobin (g/L) _____










Ferritin (µg/L) _____

Health professional's signature: _____

It is recommended you begin taking a daily dose of
 60–100 mg of elemental iron ≥ 100 mg of elemental iron
for the remainder of your pregnancy and for a minimum of six weeks after the birth of your baby. Continue taking pregnancy multivitamins.

Follow up with your:

- Maternity Care Provider for a repeat blood test at _____ weeks.
- GP for a repeat blood test six weeks after the birth of your baby.

Recommended iron preparations	Elemental iron	Dosage information
<input type="checkbox"/>  Ferro-grad Ferrous sulfate 325 mg tablets	105 mg per tablet	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
<input type="checkbox"/>  Ferro-grad C Ferrous sulfate 325 mg tablets	105 mg per tablet	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
<input type="checkbox"/>  Ferro-F-Tab Ferrous fumarate 310 mg tablets	100 mg per tablet	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
<input type="checkbox"/>  Maltofer Iron polymaltose 370 mg tablets	100 mg per tablet	Take one tablet with food: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
<input type="checkbox"/>  Maltofer Syrup Iron polymaltose 370 mg/10 mL oral liquid	100 mg/10 mL	Take _____ mL with food, through a straw to avoid staining teeth.
<input type="checkbox"/>  Ferro-grad F Ferrous sulfate 250 mg tablets	80 mg per tablet	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
<input type="checkbox"/>  Fefol Iron & Folate Supplement Ferrous sulphate 270 mg capsules	87.4 mg per capsule	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
<input type="checkbox"/>  Ferro-Tab Ferrous fumarate 200 mg tablets	65.7 mg per tablet	Take one tablet on an empty stomach: <input type="checkbox"/> once a day <input type="checkbox"/> twice a day <input type="checkbox"/> on alternate days
<input type="checkbox"/>  Ferro-Liquid Ferrous sulphate 30 g/mL oral liquid	60 mg/10 mL	Take _____ mL with food, through a straw to avoid staining teeth.





Taking iron

Take iron products (except for Maltofer) 1 hour before or 3 hours after meals – ideally with juice (not milk). If this isn't possible, it's better to take iron with food than not at all.

Iron is better absorbed if taken with orange juice due to the vitamin C content.

Discuss the timing of any other medications with your healthcare professional, especially those for treating reflux. Keep iron products safely out of reach of children and pets.

Side effects

Side effects may include darkened bowel motions, indigestion, nausea, constipation or diarrhoea.

If you are experiencing indigestion or nausea, try changing the timing so you take your iron supplement with food.

If you are experiencing additional mild symptoms, do not stop taking iron, but try spacing the doses out instead and discuss with your healthcare professional.

Recommended iron preparations vs over-the-counter multivitamins

Over-the-counter multivitamins **DO NOT** contain enough iron to treat iron deficiency anaemia.

	Recommended iron preparation	Over-the-counter multivitamins		
Number of tablets required to meet the daily therapeutic dose for treatment of iron deficiency	1	2	10	20
Product	Ferro-grad	Elevit Pregnancy	Floradix Iron and Herbs	Elevit Women's Multi
Elemental iron equivalent	1 tablet = 105 mg	1 tablet = 60 mg <i>(plus other vitamins and minerals including calcium which reduce iron absorption and can increase risk of constipation)</i>	10 mL dose = 10 mg	1 tablet = 5 mg

Important: The information on this page is for illustration purposes only to compare common over-the-counter multivitamins with the recommended iron preparations. Follow instructions on the front page.



Perinatal Anaemia and Iron Infusion

Appendix 2 – Intravenous Iron Infusion Regimens

Check the approved indications for using these products within your health service

Ferric carboxymaltose (Ferinject®)³⁴

- **⚠ WARNING** *This protocol is for the administration of ferric carboxymaltose (Ferinject®) ONLY.*
- *Maximum dose per infusion, rate and dilution are NOT interchangeable between iron preparations – beware of similar names.*
- *Women with systemic allergy to other IV iron preparations must not receive ferric carboxymaltose (Ferinject®) as cross reactivity may be possible - consult an expert regarding the nature of the reaction, indication and alternatives to IV iron and choice of preparation (eg. Iron sucrose (Venofer®))*

Presentation	• 50 mg per mL (100mg / 2 mL, 500mg / 10 mL, and 1000mg / 20 mL vials)
Route	• Intravenous infusion
Dosage	<ul style="list-style-type: none"> • Calculation of total body iron deficit is based on body weight and haemoglobin. This has been simplified in the table below. • The treating doctor should prescribe the required dose and document verbal consent for the procedure in the case notes • Maximum single dose of 1,000 mg or 20 mg/kg, whichever is less • A second dose at least a week later to make up the remainder of the calculated total body iron deficit may be required (not exceeding 20 mg/kg up to 1,000 mg per infusion) • Dose should be prescribed as milligrams of elemental iron

PREGNANCY DOSING TABLE

Total body iron deficit & dosage per infusion of ferric carboxymaltose (Ferinject®)

Hb (g/L)	*Body weight 35 to <50 kg	*Body weight ≥50 kg	*Body weight ≥70 kg
#Hb <90g/L	Total iron deficit: 1,400 mg 1 st dose: 700 mg [§] 2 nd dose: 700 mg [§]	Total iron deficit: 1,500 mg 1 st dose: 1,000 mg 2 nd dose: 500 mg [^]	Total iron deficit: 2,000 mg 1 st dose: 1,000 mg 2 nd dose: 1,000 mg
*Hb ≥90g/L	Total iron deficit: 1,000 mg 1 st dose: 500 mg 2 nd dose: 500 mg	Total iron deficit: 1,000 mg 1 st dose: 1,000 mg 2 nd dose: not required	Total iron deficit: 1,500 mg 1 st dose: 1,000 mg 2 nd dose: 500 mg [^]

+ If Hb is within the normal range for pregnancy, a dose of 500mg of iron (replacement of iron stores) may be sufficient. However, if significant further iron demand or iron loss (bleeding) is expected, consider giving the first dose from the Hb ≥90 g/L section of the table above

If Hb is <70 g/L calculate the total body iron deficit more precisely using Ganzoni formula in the product information. The first dose can be guided by the Hb <100 g/L section of the table above

^ In patients with ongoing blood loss or impending delivery / surgery associated with substantial expected blood loss, consider giving 1,000 mg for 2nd dose

§ Where dose is >500 mg and <1,000 mg use 500 mg vial (PBS listed) and discard excess

*Use ideal body weight (non-pregnant) in overweight patients (see ideal body weight calculator in Australian Medicines Handbook). If underweight, use actual body weight.



Perinatal Anaemia and Iron Infusion

Infusion set up	<ul style="list-style-type: none"> • Add the calculated dose to sodium chloride 0.9% as per instructions below • To ensure stability of infusion, do not dilute the required dose to concentration less than 2 mg/mL (with sodium chloride 0.9%) • After dilution, infuse immediately using a volumetric infusion pump
Administration	<ul style="list-style-type: none"> • Flush cannula with sodium chloride 0.9% before infusion to confirm patency • Add the prescribed dose to 100 mL sodium chloride 0.9% and infuse over a minimum of 15 minutes • Monitor injection site and educate women to immediately report any discomfort, burning, redness or swelling. In case of paravenous leakage STOP infusion immediately <p>CAUTION: Brown staining of the skin (potentially permanent) may occur due to leakage of the drug into the tissues around the injection site.</p> <ul style="list-style-type: none"> • On completion, infuse 50 mL sodium chloride 0.9% to ensure the drug is flushed completely • Do NOT administer more than 1000mg of ferric carboxymaltose (Ferrinject®) per week.
Observations	<ul style="list-style-type: none"> • Check for any pre-existing skin rashes • Monitor vital signs before the infusion, 5 minutes after commencing the infusion and on completion of the infusion • Check if patient is symptomatic (i.e. ensure patient does not feel faint upon mobilisation) • Patient should be observed for at least 30 minutes following each infusion • Antenatal: confirm presence of fetal heart rate on admission and before discharge
Side effects	<p>Common ($\geq 1/10$, $< 1/10$), Uncommon ($\geq 1/1,000$, $< 1/100$), Rare ($\geq 1/10,000$, $< 1/1,000$) Anaphylactoid reactions (rare): ($\geq 1/10,000$, $< 1/1,000$) Hypersensitivity:(uncommon): ($\geq 1/1,000$, $< 1/100$)</p> <p>Other side effects</p> <p>Vascular: Common: hypertension, flushing. Uncommon: hypotension. Gastrointestinal: Common: nausea. Uncommon: vomiting. CNS: Common: headache, dizziness. Musculoskeletal: Uncommon: myalgia, back pain, arthralgia. Respiratory: Uncommon: dyspnoea. Dermatological: Uncommon: pruritus, urticaria, rash. General: Common: injection / infusion site reactions. Uncommon: pyrexia, fatigue, peripheral oedema. Metabolism and Nutritional Disorders: Common: hypophosphataemia.</p>

Perinatal Anaemia and Iron Infusion

Iron polymaltose complex (Ferrosig®)^{31, 35, 36}

<p>⚠ WARNING <i>This protocol is for administration of iron polymaltose (Ferro-sig®) ONLY. Maximum dose per infusion, rate and dilution are NOT interchangeable between iron preparations – beware of similar names! Women with systemic allergy to other IV iron preparations must not receive iron polymaltose (Ferrosig®) as cross reactivity may be possible - consult an expert regarding the nature of the reaction, indication and alternatives to IV iron and choice of preparation e.g. iron sucrose (Venofer®)</i></p>										
Presentation	<ul style="list-style-type: none"> 50 mg per mL, (100mg / 2 mL ampoule) 									
Route	<ul style="list-style-type: none"> Intravenous infusion 									
Dosage	<ul style="list-style-type: none"> Calculation of the total body iron deficit is determined by body weight and haemoglobin according to the Ganzoni formula or using the nomogram in the product information or alternatively the simplified table below <u>Simplified Method</u> for estimating the total body iron deficit (for women of body weight ≥ 35 kg) <p>Estimated total body iron deficit³⁷</p> <table border="1"> <thead> <tr> <th>Hb g/L</th> <th>*Body weight 35 kg to <70 kg</th> <th>*Body weight ≥70 kg</th> </tr> </thead> <tbody> <tr> <td>#Hb <100 g/L</td> <td>1,500 mg</td> <td>2,000 mg</td> </tr> <tr> <td>+Hb ≥100 g/L</td> <td>1,000 mg</td> <td>1,500 mg</td> </tr> </tbody> </table> <p># If Hb is <70 g/L calculate the total body iron deficit more precisely using Ganzoni formula in the product information + If Hb is within the normal range for pregnancy then 500 mg (replacement of iron stores) may be sufficient or use Ganzoni formula in the product information to calculate the iron deficit more precisely</p> <p>Use ideal body weight (non-pregnant) in overweight women. If underweight, use actual body weight (see ideal body weight calculator in Australian Medicines Handbook)</p> <ul style="list-style-type: none"> The treating doctor should prescribe the required dose and document verbal consent for the procedure in the case notes The total calculated body iron deficit (up to 2,500 mg) may be given in a single infusion Dose should be prescribed as milligrams of elemental iron 	Hb g/L	*Body weight 35 kg to <70 kg	*Body weight ≥70 kg	#Hb <100 g/L	1,500 mg	2,000 mg	+Hb ≥100 g/L	1,000 mg	1,500 mg
Hb g/L	*Body weight 35 kg to <70 kg	*Body weight ≥70 kg								
#Hb <100 g/L	1,500 mg	2,000 mg								
+Hb ≥100 g/L	1,000 mg	1,500 mg								

Perinatal Anaemia and Iron Infusion

Infusion set up	<ul style="list-style-type: none"> • Draw up iron using a filtered needle (e.g. 18 gauge BD blunt filter needle 5 microns). Change to a suitable needle (e.g. 21 gauge BD precision glide needle) before adding the calculated dose to 500 mL of sodium chloride 0.9 % (up to 2,500 mg may be given in 500 mL) • After dilution infuse immediately using a volumetric infusion pump (if prepared by pharmacy, check expiry date and time is not exceeded)
Administration	<ul style="list-style-type: none"> • Flush cannula with sodium chloride 0.9% before infusion to confirm patency • The first 50 mL should be given slowly at 20 to 40 mL per hour • If well tolerated after 50 mL, the rate may be increased to 120 mL per hour, until completion³⁵ * • Monitor injection site and educate women to immediately report any discomfort, burning, redness or swelling. In case of paravenous leakage STOP infusion immediately <p>NB: Brown staining of the skin (potentially permanent) may occur due to leakage of the drug into the tissues around the injection site.</p> <ul style="list-style-type: none"> • On completion, infuse 50 mL sodium chloride 0.9% (at the current rate) to ensure the drug is flushed completely³⁴
Observations	<ul style="list-style-type: none"> • Check for existing skin rashes before administration • Monitor vital signs before the infusion, at 5 minutes, then every 15 minutes for the first two hours. Continue monitoring hourly until 30 minutes after the completion of the infusion • Antenatal: confirm presence of fetal heart rate on admission and before discharge
Side Effects	<ul style="list-style-type: none"> • Anaphylactoid reactions (uncommon): 1:100 to 1:1,000 <p>Other side effects</p> <ul style="list-style-type: none"> • Headache • Nausea • Joint pain • Tachycardia • Flushing, sweating • Chest and back pain • Urticaria • Bronchospasm with dyspnoea • Hypotension, dizziness • Low blood phosphate levels

NB: *AIDH³¹ outlines information on more rapid infusions of iron polymaltose. Given the limited available safety data on accelerated infusion rates, these are not considered suitable for this patient population and the standard rates outlined above are recommended



Perinatal Anaemia and Iron Infusion

Iron sucrose (Venofer®)³⁸

<p>⚠️ WARNING</p> <p><i>This protocol is for administration of iron sucrose (Venofer®) ONLY. Maximum dose per infusion, rate and dilution are NOT interchangeable between iron preparations – beware of similar names!</i></p> <p><i>If there is a history of systemic allergy to parental iron, consult an expert regarding nature of reactions, indication and alternatives to IV iron and choice of preparation e.g. Venofer® before proceeding</i></p>										
Presentation	<ul style="list-style-type: none"> 20 mg per mL (100mg / 5 mL vial) 									
Route	<ul style="list-style-type: none"> Intravenous infusion 									
Dosage	<ul style="list-style-type: none"> Calculation of total cumulative iron sucrose dose, equivalent to the total iron deficit (mg), is determined by the body weight and haemoglobin according to the Ganzoni formula OR using the nomogram in the product information, OR alternatively, use the following simplified method: <u>Simplified Method</u> for estimating the total body iron deficit (for women of body weight ≥ 35 kg) <p>Estimated total body iron deficit³⁷</p> <table border="1"> <thead> <tr> <th>Hb g/L</th> <th>*Body weight 35 kg to <70 kg</th> <th>*Body weight ≥70 kg</th> </tr> </thead> <tbody> <tr> <td>#Hb <100 g/L</td> <td>1,500 mg</td> <td>2,000 mg</td> </tr> <tr> <td>+Hb ≥100 g/L</td> <td>1,000 mg</td> <td>1,500 mg</td> </tr> </tbody> </table> <p>The estimated total body iron deficit can be rounded up or down to the nearest 200 mg because it is commonly given as separate 200 mg doses (no more than 3 times per week - see below)</p> <p># If Hb is <70 g/L calculate the total body iron deficit more precisely using Ganzoni formula in the product information.</p> <p>+ If Hb is within the normal range for pregnancy then 500 mg (replacement of iron stores) may be sufficient or use Ganzoni formula in the product information to calculate the iron deficit more precisely.</p> <p>*Use ideal body weight (non-pregnant) in overweight women (see ideal body weight calculator in Australian Medicines Handbook). If underweight, use actual body weight.</p> <p>⚠️ WARNING Iron sucrose can only be given as small doses (maximum 500 mg per infusion) so multiple intermittent doses are required to cumulatively replace the total body iron deficit</p> <ul style="list-style-type: none"> The treating doctor should prescribe the required dose and document verbal consent for the procedure in the case notes Maximum infusion dose per day, given not more than once per week: <ul style="list-style-type: none"> Women above 70 kg: 500 mg iron sucrose Women ≤ 70 kg: Calculate maximum dose according to body weight i.e. 7 mg iron sucrose per kilogram of body weight Iron sucrose doses of 200 mg should be given no more than 3 times per week Doses must be expressed as milligrams of elemental iron For more information see: http://www.medsafe.govt.nz/profs/datasheet/v/venoferinf.pdf 	Hb g/L	*Body weight 35 kg to <70 kg	*Body weight ≥70 kg	#Hb <100 g/L	1,500 mg	2,000 mg	+Hb ≥100 g/L	1,000 mg	1,500 mg
Hb g/L	*Body weight 35 kg to <70 kg	*Body weight ≥70 kg								
#Hb <100 g/L	1,500 mg	2,000 mg								
+Hb ≥100 g/L	1,000 mg	1,500 mg								

Perinatal Anaemia and Iron Infusion

Infusion set up	<ul style="list-style-type: none"> For stability reasons, dilutions lower than 1 mg/mL Venofer® concentration are not permissible¹⁰ After dilution, infuse immediately using a volumetric infusion pump
Administration	<ul style="list-style-type: none"> 200 mg: Infuse 200 mg iron sucrose (10 mL Venofer®) in 100 mL sodium chloride 0.9% over at least 30 minutes 300 mg: Infuse 300 mg iron sucrose (15 mL Venofer®) in 100 mL sodium chloride 0.9% over at least 1.5 hours 400 mg: Infuse 400 mg iron sucrose (20 mL Venofer®) in 100 mL sodium chloride 0.9% over at least 2.5 hours 500 mg: Infuse 500 mg iron sucrose (25 mL Venofer®) in 500 mL sodium chloride 0.9% over at least 3.5 hours Monitor injection site and educate women to immediately report any discomfort, burning, redness or swelling. In case of paravenous leakage STOP infusion immediately <p>CAUTION: Brown staining of the skin (potentially permanent) may occur due to leakage of the drug into the tissues around the injection site. If this occurs ice may be applied to cause local vasoconstriction and decrease fluid absorption; avoid massage to the area</p> <ul style="list-style-type: none"> On completion, infuse 50 mL of sodium chloride 0.9% (at the current rate) to ensure the drug is flushed completely³⁴⁹ <p>⚠️ WARNING Rapid infusion of the maximum iron sucrose dose (500 mg) can lead to severe hypotension</p>
Observations	<ul style="list-style-type: none"> Check for existing skin rashes before administration Monitor vital signs before the infusion, then every 5 minutes for 15 minutes, then 30 minutely until / and on completion Patients should be observed for adverse effects for at least 30 minutes after completion of the infusion Antenatal: confirm presence of fetal heart rate on admission and before discharge
Side effects	<ul style="list-style-type: none"> Anaphylactoid (rare): (≥ 1/10,000, < 1/1,000) <p>Other side effects</p> <ul style="list-style-type: none"> Metallic taste Nausea Fever Shivering Hypotension Low blood phosphate levels

NB: The Australian Product Information (April 2020) indications are for patients undergoing chronic haemodialysis receiving 100 mg doses only. The NZ Medsafe Venofer® Data Sheet with information regarding other doses is more relevant in this population. For further information see URL: <http://www.medsafe.govt.nz/profs/datasheet/v/venoferinf.pdf>



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Perinatal Anaemia and Iron Infusion

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