MATERNITY BLOOD OPTIMISATION (MBOP) GUIDELINE AND PRACTICE IMPROVEMENT STRATEGY

BACKGROUND TO THE MBOP PATHWAYS

OBJECTIVES/RATIONALE

A recent study of primary practice in Canterbury demonstrated a wide range of approaches to the management of iron-deficiency and anaemia in pregnancy and postpartum, with significant under-recognition of low iron status and under prescribing of oral iron, in the absence of clear clinical guidance[1]. A standardised approach is required to improve the prevention and management of antenatal, peripartum and postpartum iron-deficiency and anaemia. The aim is to optimize iron levels to:

1. Reduce rates of maternal iron-deficiency, anaemia and iron-deficiency anaemia (IDA).
2. Improve maternal, fetal and neonatal outcomes associated with iron-deficiency, anaemia and IDA (eg. reduced fetal growth[2-4], decreased neonatal/infant iron stores[5], neurodevelopmental delays[6] and disorders[7], increased risk of infections[8,9], poor wound healing[8,9], fatigue[10,11] and postnatal depression[11-13], impaired maternal bonding[14] and breastfeeding[14,15])
3. Improve tolerance to blood loss at birth and reduce reliance on blood transfusions[16] and post-partum intravenous (IV) iron.
4. Reduce the incidence of severe anaemia and associated morbidity.[17,18]
5. Reduce economic costs associated with severe maternal anaemia: costs of blood transfusions[19] and IV iron, prolonged hospital stays[20], and hidden costs associated with impairment of breast feeding, cognition, physical performance and work capacity.[21,22]

PREVALENCE

Anaemia in pregnancy significantly affects 52% of women in low income countries, and 25-30% in well-resourced countries.[9,17] In New Zealand, the prevalence of iron-deficiency and anaemia is largely unknown. However, CWH data from 2012 showed that of the 85% of second trimester women who had ferritin tested (n=3766), 82% were iron-deficient and 7% had IDA. Rates of postpartum anaemia are unreported in New Zealand but it is reasonable to consider they are likely to be similar to the 30% reported in the United Kingdom.[8]

TARGET POPULATION

Screening of all pregnant and postpartum women, especially high-risk women, with a targeted (non-routine) approach to iron supplementation. **High-risk women include those with: a poor diet, low socio-economic status, previous anaemia, inter-pregnancy interval < 1 year, multiple pregnancy, parity ≥ 3, vegetarians, teenage pregnancies, smokers, obesity, bariatric surgery, recent history of bleeding, high risk of obstetric bleeding (eg. placenta praevia), gastrointestinal (GI) disorders (eg. crohns, coeliac), Jehovah's Witnesses, and women from ethnic background at high-risk of haemoglobinopathies.**

USER GROUPS OF MBOP PATHWAYS

All maternity care providers, from primary to secondary care, including community midwives, general practitioners, antenatal and obstetric clinics, Birthing Suite and the Maternity Ward at Christchurch Women's Hospital.

CLINICAL GUIDANCE

ANAEMIA

Anaemia is defined in the MBOP pathways as Hb < 110 g/L in the first trimester[23], Hb < 105 g/L in the second and third trimester[24], and Hb < 100 g/L in the postpartum period.[24]

Explanation

Anaemia is defined as Hb < 2 standard deviations below the mean for a healthy matched population[24]. In the absence of a large population study, we don't know what Hb levels are normal or optimal[19] for New Zealand women. Therefore, we have adopted the above parameters, which are consistent with local data and other guidelines with similar populations[24-27].

A low haemoglobin defines anaemia, but not the cause, and requires investigation. Anaemia can be multifactorial.

- If Hb < 90 g/L at any gestation: referral to obstetric secondary care as per referral guidelines[MOH28]
- If Hb < 70g/L at any gestation: *urgent* referral to obstetric secondary care

Other obstetric referrals may be suitable for paper triage in obstetric/antenatal clinic.

Globally, the most common cause of anaemia is iron deficiency (> 60%)[17,27] usually secondary to a nutritional deficiency. There are many other causes of iron-deficiency including: increased requirements of pregnancy, decreased intestinal absorption, acute and chronic blood loss.

Other causes of anaemia[26]

- Physiological haemodilution of pregnancy – although the boundaries between physiological haemodilution and pathological anaemia of pregnancy are not well defined.[29]
- Megaloblastic anaemia due to vitamin B_{12} and folic acid deficiency, thalassaemias, acute blood loss, haemolytic states (pre-eclampsia, HELLP syndrome, sickle cell disease, malaria), helminth

infections (soil borne parasites, ie. hookworm), anaemia of chronic disease (ACD)[16] or inflammatory states including obesity.[30,31]

Classification of anaemia based on red cell indices[26]

(see Appendix 1 for overview of interpreting results)

- **Normocytic, normochromic anaemia:** normal MCV (mean cell volume) and MCH (mean corpuscular haemoglobin) and MCHC (mean corpuscular haemoglobin concentration): acute blood loss, early iron-deficiency anaemia, physiological anaemia, haemolysis, multifactorial anaemia, chronic kidney disease and anaemia of chronic disease/inflammation.
- **Microcytic, hypochromic anaemia (small, pale red blood cells):** low MCV, low MCH and/or MCHC: long term iron-deficiency anaemia, thalassaemia, and some haemoglobinopathies.
- **Macrocytic, normochromic anaemia (large red blood cells):** elevated MCV, normal MCH and MCHC: **megaloblastic anaemia** B_{12} or folate deficiency, liver disease, hypothyroidism, myelodysplasia.

Key practice point: This classification has limitations because anaemia may be multi-factorial, ie. there may be a co-existing iron-deficiency, other deficiencies (B_{12}/folate), chronic disease or thalassaemia. *Inflammation may mask an underlying iron-deficiency.*

IRON-DEFICIENCY

This guideline has adopted the diagnostic parameter for iron-deficiency as serum ferritin < 30 mcg/L[24,32] Serum ferritin < 15 mcg/mL indicates absent iron stores[24], where iron is not available for erythropoiesis (production of red blood cells). Diagnosis of iron-deficiency in the absence of inflammation (CRP < 5 mg/L) is straight forward.[30]

Explanation

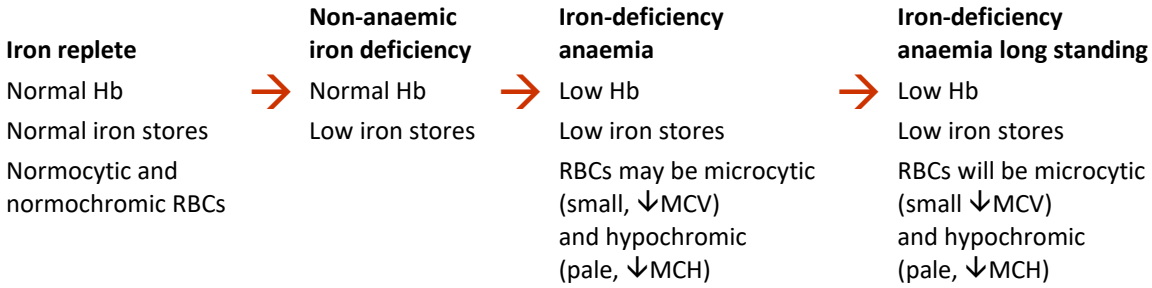
Serum ferritin is currently recognized as the best and most clinically useful measure of iron deficiency[33] despite it being an acute phase reactant or inflammatory marker which increases in the presence of inflammation (CRP > 5 mg/L). Diagnosis of iron-deficiency in the presence of inflammation requires a higher ferritin cut off[34], however this is not clearly defined[33] and may be as high as < 100 mcg/L.[30] The CDHB Obstetric Iron Infusion Guideline[35] has adopted the cut-off of < 50 mcg/L, when CRP > 5 mg/L.

Key practice points

- Iron-deficiency without anaemia progresses to IDA if untreated. IDA may be normocytic, progressing to microcytic hypochromic IDA when the anaemia is longstanding (Figure 1).
- Haemoglobin alone is an insensitive measure of iron status, missing over 90% of iron-deficiency.[36] Therefore, test for iron-deficiency with serum ferritin levels.
- Routine antenatal ferritin screening in the first and second trimester is recommended.
- Test ferritin in the third trimester if iron-deficient +/- anaemia in earlier trimesters.
- Early management of iron-deficiency reduces the risk of anaemia at birth.
- If iron–deficiency or IDA is diagnosed, the cause of the iron-deficiency must be evaluated, especially if it is persistent or difficult to treat. Pathologies may exist beyond increased iron requirements of pregnancy and low iron intake.

- If iron-deficiency (+/- microcytosis) persists, or remains unexplained, despite iron supplementation (and/or exclusion of haemoglobinopathy) then other investigations for underlying cause should be considered (ie. malabsorption from Inflammatory Bowel Disease (IBD), coeliac disease, GI tract blood loss, or other systemic disease).

FIGURE 1: THE SPECTRUM AND PROGRESSION OF IRON-DEFICIENCY ANAEMIA



SERUM FERRITIN, HEPCIDIN AND INFLAMMATION

Hepcidin is a liver hormone and master-regulator of iron-metabolism that tightly controls both iron absorption, bioavailability and iron release from stores.[30,37] The main factors that influence hepcidin levels are iron stores, erythropoiesis, hypoxia and inflammation. Hepcidin levels decrease in iron-deficiency and IDA. Hepcidin increases with inflammation, infection, and increased circulating and tissue levels of iron. When hepcidin increases, circulating iron is sequestered in macrophages, where the iron is unavailable for release (ferritin levels increase). In chronic inflammation ferritin increases and haemoglobin decreases (anaemia of chronic disease, or anaemia of inflammation).

Key practice points

- Increased hepcidin inhibits iron absorption from the gut.
- Hepcidin increases can be in response to oxidative stress or inflammation induced from high daily doses of oral iron.[38,39] This mechanism explains why intermittent doses of oral iron appear to be almost as effective as multiple daily doses in treating non-anaemic iron-deficiency, with less side effects.[38,39]
- There is no benefit in testing serum ferritin in labour and in the early postpartum (for at least 1-2 weeks[9]) due to increases in inflammatory markers associated with all births.
- A mildly raised CRP (< 15) is very common in pregnancy particularly in obese women and women with diabetes. If the CRP is elevated beyond this then enquire about maternal wellbeing and consider infection or whether a known inflammatory condition (eg. inflammatory bowel disease, arthritis) is flaring.

IRON STUDIES

- **Serum iron:** is a measure of iron available for erythropoiesis, and may increase with inflammation[30] but is of limited use viewed in isolation, except in cases of suspected iron poisoning.[27]
- **Transferrin saturation:** is a measure of iron available for erythropoiesis. A level <16% is an accepted cut off for iron-deficiency, but may increase with inflammation.[30] An elevated transferrin saturation is a sign of iron overload.[27]
- **Soluble transferrin receptor (sTFR):** levels are increased in iron-deficiency. sTFR may be useful to differentially diagnose iron-deficiency in the presence of inflammation.
- **sTFR/log ferritin ratio:** may be useful in diagnosing the presence of iron-deficiency anaemia with concurrent ACD. Despite the sTFR/log ferritin ratio being suggested as the most useful test, standardization and availability of the test is variable.[30]
- Serum hepcidin is currently a research test under investigation as a novel biomarker with potential for the diagnosis of iron disorders.

ORAL IRON (SEE MBOP PATHWAYS FOR TREATMENT PARAMETERS AND ORAL IRON DOSES)

Key practice points

- **Non-responsiveness to oral iron** is currently defined as persistent anaemia after 6-8 weeks of oral iron (< 10 g/L rise in Hb and ferritin remains low).[36]
- If daily doses of oral iron are not tolerated (usually due to side effects of nausea or constipation), consider alternative day dosing of oral iron.
- See the handout/link: **Recommended oral iron preparations for Maternity Blood Optimisation (MBOP) pathways** which includes advice for maximising absorption of oral iron.
- **Elemental iron** refers to the amount of actual iron in formulations.
- Oral iron is ineffective if inflammation and hepcidin levels are high.[30]
- A trial of oral iron is warranted in cases with inflammatory bowel disease. (IBD)
- Oral iron should not be given if Hb ≥ 130 g/L (even if iron-deficient) due to association with increased blood pressure, low birth weight and small for gestational age infants.[3]

Iron Overload is accompanied by high ferritin levels. Causes of iron overload include: genetic haemochromatosis, alcohol abuse, excessive oral iron intake, multiple blood transfusions, malignancy and haematological disease.[27]

SCREENING FOR HAEMOGLOBINOPATHIES: AN OVERVIEW

Haemoglobinopathy disorders are the most common genetic disorder worldwide (7%). Thalassaemia is an inherited disorder of the synthesis of the globin molecule – alpha and beta thalassaemia being the most common forms[26]. The prevalence of haemoglobinopathies is increasing in Australia because of recent immigration from countries where these disorders are endemic.[40] The population of birthing women in Canterbury is similarly increasing in ethnic diversity. **Women from Mediterranean countries or Southern Europe, the Middle East, India, South East Asia, Africa and the Pacific Islands are more at risk of haemoglobinopathies.** These disorders include: α- and β-thalassaemia, sickle cell

disease and globin chain variants. Clinical characteristics of haemoglobinopathies range from being asymptomatic to requirements of regular blood transfusions, and reduced life expectancy. Early screening aims to reduce the burden of disease by identifying those most at risk of haemoglobinopathies and managing their pregnancy appropriately.[40] (Appendix 2)

Key practice points:

- Haemoglobinopathy screening should be undertaken in women with microcytic indices, from high risk populations, and with unexplained anaemia.[40]
- Early screening of women and their partners allows for timely and appropriate management prior to conception or during pregnancy. Screening is a multi-step process (Appendix 2). Turn-around time of tests is usually one week but may take up to four weeks.
- The clinically significant thalassaemias have autosomal recessive inheritance where the fetus of alpha and beta major thalassaemia carriers can be affected.[26] Screening and testing should be undertaken in the first trimester if prenatal diagnosis (ie. chorionic villus sampling) is to be offered to the family.
- Carriers of thalassaemia or haemoglobinopathy may have a normal or mildly low haemoglobin.[26] Iron-deficiency or IDA may mask the diagnosis of β-thalassaemia trait. Testing for haemoglobinopathy should ideally happen when the woman is iron-replete.[41]
- Women with known haemoglobinopathy and ferritin < 30 mcg/L should be offered oral iron.[24]
- Women with unknown haemoglobinopathy status with microcytic anaemia should be commenced oral iron and screening commenced without delay.[24]

RED BLOOD CELL TRANSFUSION

A significant aim of the MBOP practice improvement strategy is to reduce reliance on red blood cell transfusions. This aim aligns with recommendations by the National Blood Authority (NBA) Patient Blood Management in Obstetrics[16] and the Australian Red Cross Blood Service (ARCBS).[32]

Key practice points

- In maternity patients who are not actively bleeding, non-transfusion therapies, including iron, should be considered as part of the treatment of anaemia.
- Intravenous iron may be more effective than blood transfusion at replenishing iron stores.
- Blood transfusion should not be dictated by Hb alone, but on assessment of the clinical status, ie. actively bleeding or risk of further bleeding,[16] imminent cardiac compromise, or symptoms requiring immediate attention.[41]
- Transfusion should be based on symptoms especially when Hb > 70 g/L.[16]. However, objective criteria for blood transfusion prescription can be challenging in the postpartum period as there may be many conflicting causes of symptoms (eg. post-birth fatigue) attributed to anaemia.[32,41]
- The risk of red cells alloimmunisation and the potential clinical impact should be considered when balancing the risks and benefits of red cell transfusion.
- **For postnatal women, not actively bleeding**:
  - Hb < 70 g/L: transfusion may be appropriate but is not always required. Consider IV iron as an alternative or adjunct to transfusion.

- Hb 70-90 g/L: consider transfusion only if there are signs and symptoms of anaemia. Consider IV iron as an alternative or adjunct to transfusion.
- Hb > 90 g/L: transfusion is usually inappropriate.
- Where indicated **transfuse a single unit** followed by clinical assessment +/- repeat Hb test.
- In patients with iron-deficiency anaemia iron therapy is required to replenish iron stores even after transfusion – **review antenatal ferritin levels as part of assessment.**

Guidelines on obstetric and maternity transfusion practice can be found at:

- CDHB Maternity Guidelines: Obstetric Intravenous Iron Infusion (Ref.233597)
- New Zealand Blood: Resources for DHBs
- Australian National Blood Authority: Patent Blood Management Guidelines: Module 5 Obstetric and Maternity

INTRAVENOUS IRON

The efficacy and superiority of IV iron at rapidly replenishing Hb and iron stores, and superiority over oral iron, has been well established in clinical trials.[41] Third generation IV iron formulations (ie. ferinject) have an acceptable low rate of immediate side effects, although long-term safety of IV iron is yet to be established.[30,41] Benefits of IV iron must outweigh risks.

Key practice points

- The **Obstetric Intravenous Iron Infusion Prescription (Antenatal & Postnatal)** can be found in the CWH Maternity guidelines at Obstetric Intravenous Iron Infusion (Ref.233597)
- An adequate trial of oral iron as first-line treatment must be documented.
- In moderate to severe postpartum anaemia (especially with underlying third trimester iron-deficiency +/- anaemia), the response to oral iron may not be rapid enough to replenish Hb and ferritin.
- Review other factors that may increase the woman's risk of ongoing anaemia, such as grand multiparity or short pregnancy interval (page 1) when considering IV iron.
- In addition to the obstetric indications, IV iron might be beneficial in the obstetric patient with co-morbidities that also increase the risk of ongoing iron-deficiency +/- anaemia e.g. IBD or gastric banding. Consultation with a haematologist, physician or medical team may be required.

APPENDIX 1: AN OVERVIEW OF INTERPRETING LABORATORY TEST RESULTS TO ASSESS IRON STATUS

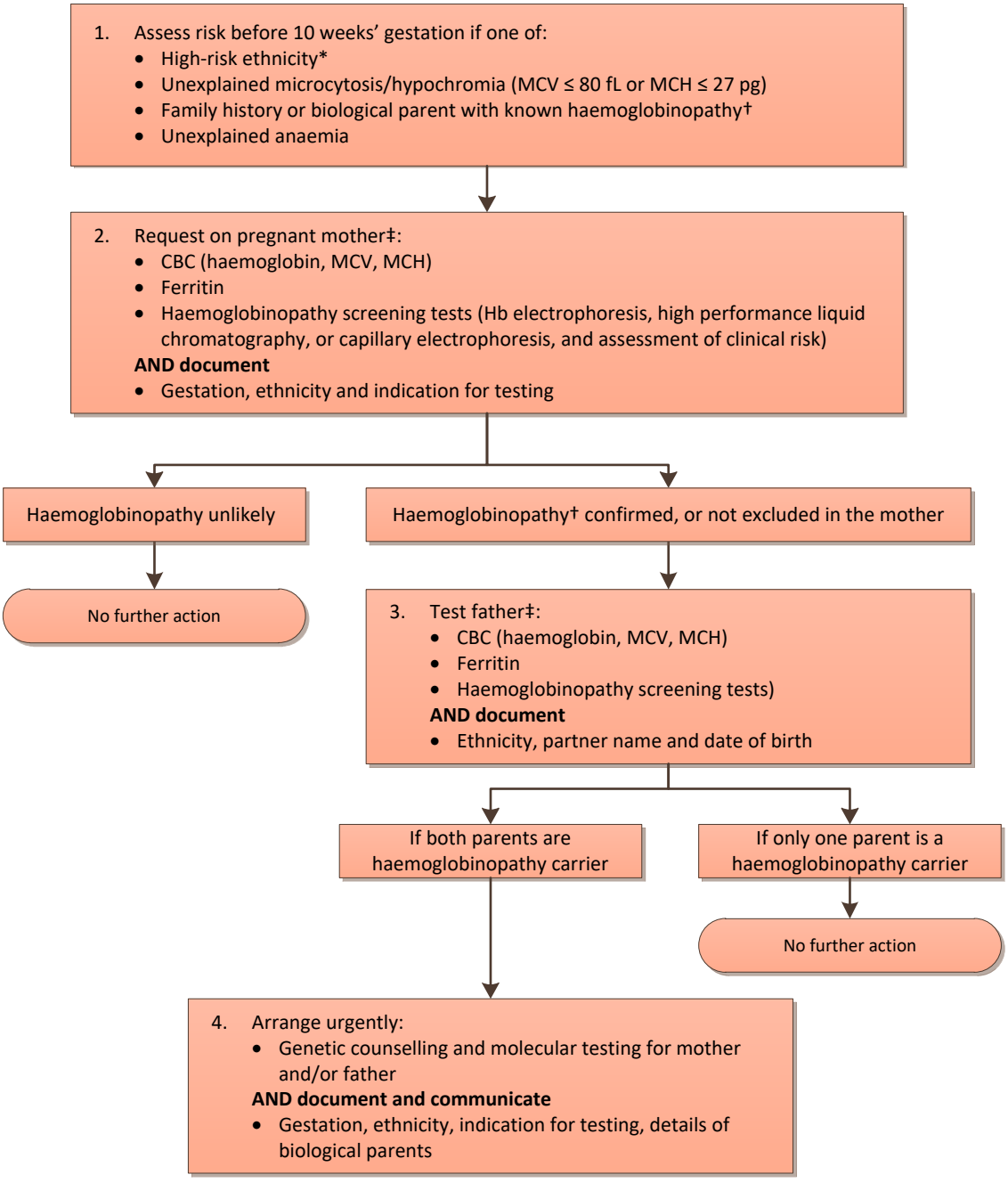
(adapted with permission[42])

DIAGNOSIS	HAEMOGLOBIN g/L	SERUM FERRITIN mcg/L	C-REACTIVE PROTEIN (CRP) mg/L	MEAN CELL VOLUME (MCV) AND MEAN CELL HAEMOGLOBIN (MCH) [and classification]
Iron replete	Normal	> 30	< 5	Normal [normocytic, normochromic]
iron-deficiency (non- anaemic)	Normal	< 15-30	< 5	Normal (or low)
iron-deficiency (non- anaemic) with inflammation	Normal	Normal or elevated (elevated ferritin does not imply elevated iron stores)	CRP > 5	Normal (maybe mildly low)
Iron-deficiency anaemia (IDA)	Low	< 15-30	< 5	Low (or normal in early IDA)
Anaemia of chronic disease (ACD) or inflammation	Low	Normal or elevated (elevated ferritin does not imply elevated iron stores)	CRP > 5	Normal (maybe mildly low)
IDA with co-existing chronic disease or inflammation	Low	Low or normal, but usually < 60-100	CRP > 5	Low [microcytic]
Thalassaemia minor	Low (or normal)	Normal or elevated		Low (or normal)
Megaloblastic anaemia (folate or vitamin B_{12} deficiency, liver disease or hypothyroidism)	Low (or normal) Platelet levels may be low			Elevated MCV Normal MCH [macrocytic, normochromic]

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APPENDIX 2: A SELECTIVE SCREENING ALGORITHM FOR ANTENATAL HAEMOGLOBINOPATHY

(reproduced with permission[40])



CBC = complete blood count; MCH = mean corpuscular haemoglobin; MCV = mean corpuscular volume

* Parent from Southern Europe, Middle East, Africa, South East Asia, Indian Subcontinent or Pacific Islands

†ß-Thalassaemia, ß⁺-thalassaemia, Óß-thalassaemia, haemoglobin Lahore, haemoglobin E, α^{o}-thalassaemia, haemoglobin H, haemoglobin S, haemoglobin C, haemoglobin D-Punjab, haemoglobin O-Arab

‡ Steps 2 and 3 are interchangeable depending on which parent has previously been tested

§ No further action is needed during pregnancy, but the child may be a carrier and should be followed up later in life

APPENDIX 3: BACKGROUND TO THE MBOP PRACTICE IMPROVEMENT STRATEGY

STRENGTHS AND LIMITATIONS OF THE EVIDENCE

The impact of anaemia and IDA on maternal health and perinatal outcomes have been well documented.[17,18,21] However, the quality of evidence in meta-analyses that demonstrates improvements in outcomes following treatment for iron-deficiency +/- anaemia is limited due to the wide heterogeneity of clinical trials.[4] Ongoing research is required to address significant evidence gaps;[43] for example, on the efficacy of IV iron versus blood transfusion in women with moderate to severe postpartum anaemia.[16] There is even debate about the definition of anaemia[44] and iron-deficiency [33] during pregnancy.

FORMULATION OF RECOMMENDATIONS

The MBOP pathways have been adapted by a multidisciplinary working group, with permission, from the ARCBS Haemoglobin Assessment and Optimisation Pathways.[32] The pathways are aligned with the NBA Patient Blood Management Guidelines and recommendations.[16] As a practice improvement strategy, the ARCBS pathways have reduced the rate of anaemia at delivery from 12% to 3%.[32] Adaptations to our setting have been made based on best available current evidence on interventions for iron-deficiency and anaemia, as well as recent scientific evidence on hepcidin-mediated iron regulation. However, the working group acknowledges that this guideline reflects a global inconsistency in guidelines for the management of IDA, which in turn reflects the unresolved complexities surrounding iron metabolism and iron deficiency, especially in the presence of inflammation.[30]

FEEDBACK/MONITORING/AUDITING

Prior to roll out of the MBOP pilot, the draft pathways were circulated widely for feedback. The pilot MBOP pathways will be audited, by comparing data on prevalence of anaemia and iron-deficiency pre and post implementation. Pathways will be amended based on feedback from clinicians and if new evidence becomes available.

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