Iron deficiency anaemia in pregnancy

How best to treat, and why

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Pregnant women with iron deficiency anaemia (IDA) are at greater risk of blood transfusion, life-threatening bleeding, fetal growth restriction, preterm birth and perinatal death. Pregnancy-related IDA can usually be managed in a primary care setting with oral iron supplements, although sometimes intravenous iron is required. New maternity guidelines and clinical resources are available.

Anaemia in pregnancy is defined by the recently updated NHMRC maternity guideline as a haemoglobin (Hb) level of less than 110 g/L before 20 weeks' gestation or less than 105 g/L at or after 20 weeks' gestation.[1] Iron deficiency anaemia (IDA) is a condition characterised by both iron deficiency (diagnosed with a low serum ferritin) and anaemia. Varying thresholds for iron deficiency are used; however, a ferritin level of less than 30 mcg/L is widely accepted.[1] Iron deficiency (ID) alone is defined by a haemoglobin level that is within normal limits with a serum ferritin level below 30 mcg/L.[1] Iron deficiency is a precursor to IDA.

KEY POINTS

- Iron deficiency anaemia (IDA) is a common condition in pregnancy that can have significant adverse effects on the health of the mother and baby.
- Iron deficiency alone is defined by a haemoglobin level that is within normal limits with a serum ferritin level below 30 mcg/L and is a precursor to IDA.
- Routine screening for IDA by measuring haemoglobin level +/- ferritin level should occur at the first antenatal appointment and at 28 weeks' gestation.
- A haemoglobin level of less than 110 g/L before 20 weeks' gestation or less than 105 g/L at or after 20 weeks' gestation is considered abnormal.
- First-line treatment for IDA is oral iron supplementation. Intravenous iron supplementation should only be considered when oral iron therapy has failed, is not tolerated or rapid replacement is required to optimise iron stores and haemoglobin level.
- GPs are in a unique situation to identify, treat and monitor adherence to IDA treatment in pregnancy and postpartum to improve outcomes for the mother and baby.
- Excellent resources for clinicians and women are available from the Australian Red Cross Blood Service Toolkit for Maternity Blood Management (www.transfusion.com.au/maternity).

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The estimated prevalence of IDA among pregnant women in Australia is 11 to 18%, which equates to about 40,000 mothers affected each year.[2] Most IDA in pregnancy is related to the increased demands of pregnancy, although many women start pregnancy with iron deficiency with or without anaemia, mainly due to menstrual losses, previous pregnancies and/or dietary intake. Clinicians should always take a detailed patient history and consider other causes of inadequate iron absorption, inadequate oral intake or excessive iron loss.[3,4] If a pregnant woman has anaemia, appropriate further investigations include a full blood count, serum ferritin level and specific (fasting) tests for folate and vitamin B12 levels if the mean cell volume is high.[1] Thalassemia screening should also be considered, depending on the patient's ethnicity and mean cell volume.[5] Other causes of anaemia are beyond the scope of this article but should be considered when clinically appropriate.

Physiology and prevention of IDA

Iron demands increase in pregnancy due to maternal changes (with a 35% increase in red cell mass), the developing fetus (red cell mass and muscle) and the placenta.[6] This maternal iron deficit increases throughout advancing gestation, particularly in the third trimester.[6] The recommended daily dietary intake of iron in pregnancy is 30 mg/day.[7] Foods high in iron include lean red meat, fish and shellfish, poultry, iron-fortified breakfast cereals, eggs, cooked legumes such as chickpeas, lentils, kidney and lima beans and green vegetables such as broccoli, cabbage and spinach.[1]

Women who are particularly at risk of IDA and its consequences during pregnancy are those who have increased iron demands (e.g. multiple pregnancy), low dietary intake of iron (e.g. vegetarian, vegan and restricted eating patterns), an increased risk of blood loss (e.g. a history of postpartum haemorrhage or risk factors for it, blood transfusion, IDA or placenta praevia) or a short interpregnancy interval. Groups that are particularly at risk include teenagers, women of lower socioeconomic status, Indigenous Australian women, recent migrants and women for whom transfusion is not a medical option due to religious or ethical beliefs.[8,9]

Routine universal iron supplementation for pregnant women without ID or IDA is currently not recommended in Australia.[1] Pregnant women with risk factors for ID or IDA should be advised to follow a diet high in iron-containing foods and consider low-dose oral iron supplementation.[1] In pregnant women with iron deficiency alone, low-dose elemental iron (20 to 80 mg daily or alternate daily doses of 60 mg) should be considered.[9,10]

Maternal and fetal implications of iron deficiency anaemia

Women with IDA have increased levels of fatigue or malaise, lower performance at work and higher rates of depression, particularly postnatally.[4] Postpartum haemorrhage (≥500 mL of blood loss at birth) affects about 8% of all women giving birth.[11] Women with IDA have a higher risk of postpartum haemorrhage, increased severity of bleeding and needing a blood transfusion.[12] Although rare, women with IDA also have an increased risk of death from postpartum haemorrhage and women with severe anaemia have an increased risk of cardiac compromise.[13] Postnatal effects of IDA include reduced breastfeeding, higher rates of puerperal sepsis and poor wound healing.[12] Effects of IDA on the fetus and infant include low birthweight, preterm birth, being small for gestational age, childhood anaemia and perinatal death.[12,14,15] There is some evidence that iron deficiency in pregnancy may be associated with adverse neurodevelopment in offspring.[16]

Testing required for anaemia in pregnancy

Routine screening for anaemia is recommended at the first antenatal appointment, and at 28 weeks' gestation.[1] Repeat testing at 36 weeks may also be required for women who have symptoms or risk factors for IDA.[1] In addition, in areas where the prevalence of IDA is high, or in women who have risk factors for IDA, testing ferritin at the first antenatal appointment should be considered.[1,9]

Treatment of IDA in pregnancy

First-line therapy for IDA involves oral iron supplements.[1,10] Oral iron treatment options in Australia are outlined in Table 1. A holistic approach to therapy is recommended by the Australian Government pregnancy care guidelines.[1] Consideration of the availability of iron-rich foods appropriate to the woman's cultural practices and preferences should always be considered. A referral to a dietitian may be considered, but diet alone is insufficient to treat IDA, particularly in pregnancy.[8] In addition, discussing the benefits of treatment, possible side effects and ways to manage them and affordability of iron supplements may assist adherence.[1]

Oral treatment

Therapeutic oral iron supplementation, containing 100 to 200 mg of elemental iron daily, is considered first-line treatment for IDA in pregnant women.[9] The recently revised maternity guidelines, state that low-dose iron supplementation (60 to 100 mg) can be as effective as high dose, with fewer side effects.[1] If a rapid increase in haemoglobin is not required, alternate daily or intermittent (two to three times weekly) doses of 60 to 100 mg may lead to improved adherence and have a lower side-effect profile with similar results.[17] Women with iron deficiency alone may benefit from daily or alternate daily doses of 60 mg of elemental iron.[10] Most pregnancy multivitamins do not contain sufficient iron for treatment of IDA.[10] In addition, they may contain vitamins or minerals that impair absorption of oral iron.

As shown in Table 1, the elemental iron in supplements varies between brands, as does the cost. The aim is to use a supplement that is well balanced in terms of

TABLE 1. ORAL PREPARATIONS OF IRON AVAILABLE IN AUSTRALIA[10]

Brand name	Formulation/other active ingredients	Elemental iron content	Approximate cost*	Quantity (availability)†
Ferro-tab	Ferrous fumarate immediate release 200 mg	66 mg	$5 per 30 tablets	60 tablets (OTC or PBS restricted)
Ferro-f-tab	Ferrous fumarate immediate release 310 mg, folic acid 300 mcg	100 mg	$5 per 30 tablets	60 tablets (OTC or PBS restricted)
Ferro-gradumet	Ferrous sulfate slow release 325 mg	105 mg	$18 per 30 tablets	30 tablets (OTC)
Ferro-grad C	Ferrous sulfate slow release 325 mg, ascorbic acid 500 mg	105 mg	$27 per 30 tablets	30 tablets (OTC)
Fefol	Ferrous sulfate, slow release 270 mg, folic acid 300 mcg	87 mg	$10 per 30 tablets	30 tablets (OTC)
FGF	Ferrous sulfate, slow release 250 mg, folic acid 300 mcg	80 mg	$16 per 30 tablets	30 tablets (OTC)
Maltofer tablets	Iron polymaltose 370 mg	100 mg	$30 per 30 tablets	30 tablets (OTC)
Ferro-liquid	Ferrous sulfate oral liquid 150 mg/5 mL	6 mg/mL	$1 per 100 mg (6 cents per mL)	250 mL bottle (OTC or PBS listed)
Maltofer syrup	Iron polymaltose oral liquid 185 mg/5 mL	10 mg/mL	$1.50 per 100 mg (15 cents per mL)	150 mL bottle (OTC)

Abbreviation: OTC = over the counter.
* Estimated costs from online and retail pharmacies in Australia, July 2019.
† Restricted benefit for treatment of a patient identifying as Aboriginal or Torres Strait Islander.

cost and tolerance. There is limited evidence comparing the tolerability and effectiveness of different types of oral iron supplements.[18]

Oral iron should ideally be given one hour before or two hours after food, to improve absorption. Medications that can interfere with absorption include calcium, antacids, thyroid medications and some antibiotics. Foods and drinks that may interfere with absorption include tea, coffee, milk chocolate and cola.[10] Common side effects of oral iron include constipation, diarrhoea, abdominal discomfort or pain, discolouration of stools and nausea.[19] Higher acidity in the stomach may improve iron absorption, hence vitamin C is included in some preparations, or orange juice could be used; however, the practical effect is marginal. Constipation may be treated or prevented with increased dietary fibre and/or fluids, plus a mild laxative. Abdominal discomfort and nausea may be reduced by taking iron at night or with food, and/or taking lower doses of iron less often.[10] Oral polymaltose comprises iron attached to a large carbohydrate moiety and is absorbed throughout the gastrointestinal tract. It is said to be better tolerated than iron salts, and in contrast to other iron supplements, is best taken with food.

Oral iron should be continued until the haemoglobin is in the normal range, and for six to eight weeks after this time, to correct iron stores. Haemoglobin levels are expected to improve by about 20 g/L every three weeks.[3]

A survey of women in Australia who were pregnant or had recently given birth found that 80% initially took the iron preparations prescribed for them, but 42% did not inform their clinician when they ceased supplementation. Reasons for stopping included forgetfulness and side effects, with a few women stating cost was a factor.[20] Discussion with care providers improved adherence.[20] Patient information leaflets can be used if language is a barrier. Leaflets in a variety of languages are available from the Australian Red Cross Blood Service.[10]

Reviewing treatment efficacy with repeat haemoglobin measurement is recommended three to four weeks after starting treatment. Women with IDA who do not respond adequately to oral therapy or who are unable to tolerate oral therapy, those with severe anaemia or those presenting late in the pregnancy should be given intravenous (IV) treatment.[9] Women who do not respond adequately to oral or IV therapy should be reviewed by an obstetrician, an obstetric medicine physician or a haematologist.

Intravenous iron treatment

Use of IV iron in Australia has increased rapidly in women of reproductive age with recent reports suggesting it is effective therapy for both IDA and iron deficiency without anaemia.[21,22] The IV iron formulations available in Australia are shown in Table 2.[23] Newer preparations such as ferric carboxymaltose and ferric derisomaltose

TABLE 2. COMPARISON OF INTRAVENOUS IRON PREPARATIONS AVAILABLE IN AUSTRALIA[23]

	Iron sucrose	Iron polymaltose	Ferric carboxymaltose	Ferric derisomaltose
Brand name	Venofer	Ferrosig	Ferinject	Monofer
Elemental iron concentration	20 mg/mL	50 mg/mL	50 mg/mL	100 mg/ml
Infusion time for maximum dose	15 minutes	4 to 5 hours	15 minutes for dose of 500 to 1000 mg Do not exceed single doses of 1000 mg, or more than 1000 mg a week	20 minutes for doses up to 1000 mg 30 minutes for doses exceeding 1000 mg Do not exceed single doses of 1500 mg
Approximate cost	$40 per 500 mg	$20 per 500 mg	$150 per 500 mg	$150 per 500 mg
PBS subsidised	Yes	Yes	Yes	Yes

have shorter infusion times, compared with the older preparations such as iron polymaltose. However, the newer preparations are more expensive in terms of direct medication costs (Table 2), although this cost may be offset by reduced time and costs for administration. This rapid uptake in IV iron use has occurred with limited clinical trial evidence of better maternal and clinical outcomes (as distinct from haematological parameters) or cost-effectiveness.[23]

A recent meta-analysis found that intravenous iron compared with oral iron in pregnancy was associated with a higher maternal haemoglobin level at birth, a nonclinically significant higher birthweight, and a lower rate of gastrointestinal side effects.[24] A further meta-analysis comparing the effects of IV iron and oral iron on blood transfusion rates is due to be published shortly.[25] There is insufficient knowledge of the effect of IV iron on important outcomes such as health-related quality of life or maternal, fetal and neonatal outcomes including breastfeeding rates.

It is important to note that IV iron may have side effects including allergic reactions and, rarely, anaphylaxis.[23] The rate of moderate or severe adverse reactions requiring treatment or discontinuation of IV iron has been reported as 1.4% for iron polymaltose, 0.8% in iron sucrose and 0.36% for ferric carboxymaltose.[23] Skin staining, due to extravasation, has led to a number of notifications to medical indemnity organisations; it may be permanent, although some cases have been treated with laser. IV iron is contraindicated in the first trimester. Parenterally administered iron preparations can cause hypophosphataemia, which in most cases is transient and without clinical symptoms. Patients should be given written information about potentially serious side effects before the administration, and clinicians should take steps to reduce these complications.[10]

Postpartum

The role of iron supplementation and need for follow up should be considered for all women after birth, especially when there has been postpartum haemorrhage or IDA in pregnancy.[10] A full blood count and iron studies, when required, should ideally be performed before a woman's six-week postpartum check, so that a timely action plan may be made. A recent systematic review of randomised trials found that haemoglobin concentrations at six weeks postpartum were almost 10 g/L higher in women who received IV iron compared with those taking oral iron.[26] As such, IV iron may be considered a suitable treatment for significant postpartum IDA; however, the clinical importance of this increase in haemoglobin level is not known.

Where can I obtain more information?

Further information for clinicians and patients can be obtained from the Australian Red Cross Blood Service Toolkit for Maternity Blood Management website.[10] This includes patient information leaflets about how to take oral iron tablets, health professional and patient information on intravenous iron, and a haemoglobin assessment and optimisation action plan. The site links to the recently released iTransfuse app and a BloodSafe e-learning course, both of which are excellent resources for clinicians.[10]

Conclusion

IDA is a common pregnancy-related problem encountered by GPs, and all pregnant women should be screened and treated for IDA during pregnancy. Routine oral iron supplementation is not recommended. However, women at high risk for IDA should be tested for iron deficiency with serum ferritin. Processes should be in place to follow up results and to review adherence and response to therapy. IV iron therapy may be considered if there is insufficient response to oral iron therapy in patients with IDA after adherence is ensured. Recognition and treatment of IDA in pregnancy (or preferably before pregnancy) may improve health outcomes for mothers and their babies in the short and long term. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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