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IRON DEFICIENCY IN FEMALE HEALTH PART 2: Pregnancy



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About the Expert



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This article provides an overview of iron deficiency and iron-deficiency anaemia in pregnancy. [Part 1](#) of this mini-series discusses iron deficiency in the context of heavy menstrual bleeding. This article is supported by an educational grant from Aspen New Zealand.

Pregnancy causes a marked increase in iron requirements.¹ Iron deficiency (ID) is the most common cause of anaemia during pregnancy, and is associated with some serious adverse maternal and foetal outcomes.²

According to the 2015 WHO report on anaemia, approximately 20% of pregnant women in developed countries have anaemia related to ID.³ A recent Australian study reporting a 25% rate of iron deficiency anaemia (IDA) in pregnant women is consistent with IDA affecting at least one in five pregnancies.⁴

Iron requirements

The need for iron varies throughout a woman's life, including being markedly higher in pregnancy compared with the non-pregnant state.^{5,6} Although iron demand is reduced during the first trimester due to the absence of menstruation, demand increases almost 10-fold from the first trimester to the end of pregnancy as the plasma volume and red blood cell mass expand and more iron is diverted to the growing foetus and placental structures (**Figure 1**).

In terms of quantifying iron requirements during pregnancy:

- The overall increased iron requirement due to pregnancy is about 1200mg.⁷
- Daily iron requirements increase from approximately 0.8 mg/day in the first trimester to >6 mg/day at the end of pregnancy.⁵

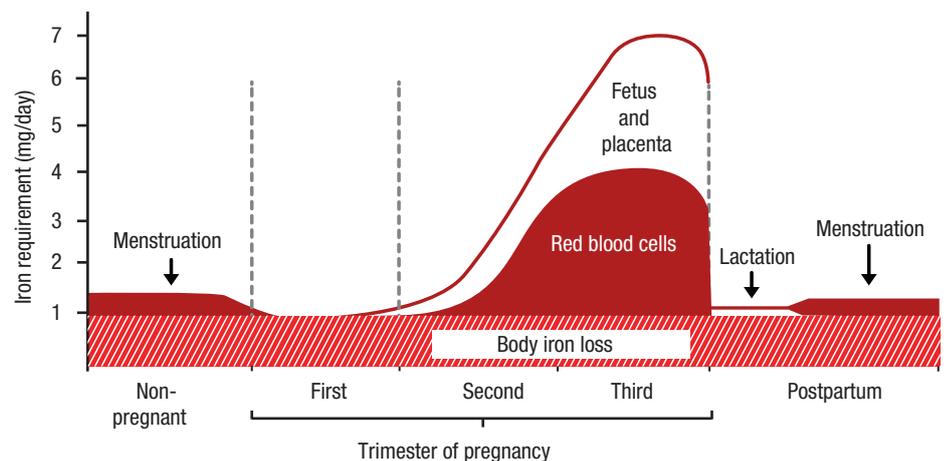


Figure 1. Estimated daily iron requirements during pregnancy.⁵

The ability to meet the increased requirement for iron in the later stage of pregnancy depends on the magnitude of iron stores at conception and on the quantity of dietary iron that can be absorbed during pregnancy.^{5,6}

However, it has been estimated that only 20–35% of women have sufficient body iron stores (serum ferritin level >70 µg/L; equivalent to ≥500mg iron) to complete a pregnancy without iron supplementation,⁸ and the iron demands during pregnancy are not always met by dietary iron intake.⁹ Consequently, iron supplementation is often necessary in pregnant women.

In the postpartum period, iron requirement is lower but remains slightly elevated to meet iron needs during lactation.⁶

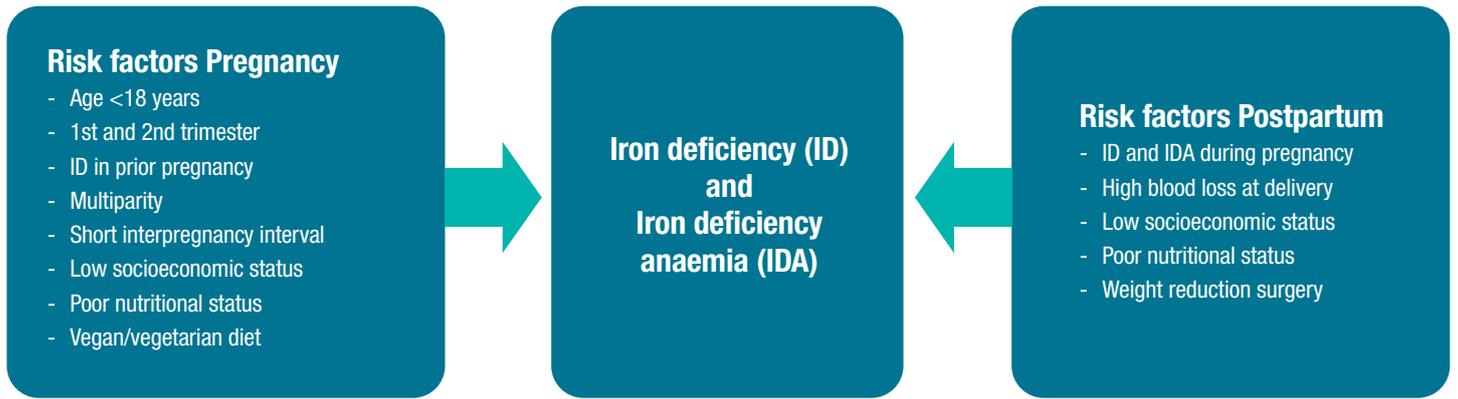


Figure 2. Summary risk factors for the development of ID and IDA during pregnancy and postpartum.^{2,10}

Risk factors

Risk detection is important in helping to reduce rates of ID and IDA in pregnancy.¹⁰

As part of pre-conception counselling or early antenatal care, risk factors that increase the likelihood of ID developing during pregnancy or postpartum (**Figure 2**), such as younger age, multiparity, and low socioeconomic status, should be considered and their identification serve as a prompt for early diagnosis and treatment of ID.^{2,10}

In general, pregnant women who have previously been anaemic, are multiparous, have had a consecutive pregnancy within one year following a delivery, or have a recent history of bleeding are at increased risk of ID and IDA.⁷

Consequences

IDA in pregnancy is associated with adverse maternal, foetal, and neonatal outcomes (**Table 1**).

Maternal consequences of IDA	Foetal-neonatal consequences of maternal IDA
<ul style="list-style-type: none"> • Reduced physical and mental performance • Cardiovascular strain • Increased risk of infection • Increased risk of obstetric haemorrhage • Mortality with high blood loss • Reduced peripartum blood reserves • Increased risk of peripartum blood transfusion • Increased risk of postpartum haemorrhage • Insufficient milk syndrome^a in postpartum anaemia 	<ul style="list-style-type: none"> • Intrauterine growth retardation • Increased risk of prematurity • Death in utero • Increased morbidity, including infection • Foetal programming (foetoplacental miss ratio)^b • Physical and cognitive development delay

^a Reduced capacity to breast feed and/or reduced quantities of breast milk.

^b Influence of external factors, such as effect of ID on foetal gene expression (epigenetics).

Table 1. Summary of the maternal and foetal consequences of ID and IDA in pregnancy.^{2,6}

Women during pregnancy or the postpartum period are especially susceptible to the consequences of ID.⁶ In addition to the general symptoms of ID, such as fatigue, IDA during pregnancy can lead to serious maternal complications including increased susceptibility to infections, increased risk and morbidity of obstetric haemorrhage, increased risk of postpartum haemorrhage, and requirement for peripartum blood transfusions.⁶ Furthermore, ID or IDA during the postpartum period has been linked to lower milk production and truncation of lactation periods.⁶

Neonates are also adversely affected by IDA during pregnancy including an increased risk of preterm labour and low birthweight (due to premature birth or foetal growth restriction), impaired physical and neurocognitive development, and increased morbidity.^{6,11}

Moreover, because neurodevelopment continues after birth, infants that did not receive adequate iron *in utero* and received low dietary iron postpartum have also been shown to have deficits in neurocognitive development as well as behavioural abnormalities and an increased risk of failing to reach educational milestones later in life.^{2,12} ID has been estimated to be present in 7% of newborns and 14% of infants and toddlers suggesting that ID is prevalent in young children in NZ.^{13,14}

There is also a potential indirect consequence of ID in pregnancy on infant development – ID-induced maternal tiredness and depression can adversely affect the mother-child relationship.⁶

The potential adverse outcomes related to IDA are preventable by accurate diagnosis and timely treatment.¹⁵

Diagnosis

Guidelines on testing for ID during the antenatal period generally lack consensus.¹⁶ In NZ, there are no national guidelines for testing of maternal iron status.¹⁷ However, several District Health Board (DHB) guidelines have been developed.¹⁸⁻²⁰

UK guidelines on antenatal care advocate testing for anaemia at booking and at 28 weeks, with haemoglobin (Hb) levels <110 g/L at first antenatal visit and <105 g/L during the second or third trimester requiring investigation and iron replacement therapy considered if indicated.^{21,22} Indeed, many existing guidelines for detection and treatment of ID in pregnancy recommend routinely testing for anaemia during pregnancy but not routinely testing for ID.¹⁶ The Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines for general antenatal assessment recommend measurement of Hb levels in the absence of ferritin levels at first visit.²³

However, screening for anaemia alone is not sufficient to diagnose ID in pregnancy.¹ Iron-deficient mothers are at risk of delivering iron-deficient neonates, irrespective of anaemia, and ID in pregnancy precedes anaemia



and significant morbidity can occur in the absence of anaemia. Screening only for anaemia will miss all the cases of ID without anaemia.^{1,16}

There is now evidence that first-trimester serum ferritin level is superior to Hb level in predicting pre-delivery anaemia, with ferritin being the most discriminatory measure.¹⁶ Ferritin has been demonstrated to predict anaemia at the time of delivery in the first, but not the second, trimester of pregnancy.

A complicating factor in screening specifically for ID during pregnancy is the lack of an accepted diagnostic definition, with serum ferritin cut-off values ranging from <10 µg/L to <30 µg/L.¹⁶ Because stainable bone marrow iron stores are generally absent histologically when the serum ferritin level is <30 µg/L, this value has been adopted as the preferred cut-off value for ID in guidelines that recommend ferritin testing.¹⁶ Local pathways recommend both Hb and ferritin with 'booking bloods' for a pregnant woman at various times up to 28 weeks of gestation, with variation in the cut-off levels indicating the need to commence oral or IV iron therapy.^{18,19,24}

There is an added complication in the diagnosis of ID: the presence of an inflammatory state can cause ferritin levels to be elevated.^{2,6} If a 'false normal' ferritin level is a suspected, concurrent measurement of serum levels of the inflammatory biomarker C-reactive protein (CRP) may be helpful in interpreting iron status, and is recommended by some guidelines for the management of ID in pregnancy.

Prevention

Maternal iron stores at conception are a predictor of maternal iron status and risk of ID and IDA during pregnancy.²⁵

The following prevention strategies should contribute to iron stores at the time of birth and hence help to reduce the risk of ID and IDA developing during pregnancy:^{2,5}

- A diet high in bioavailable iron.
- Adequate intervals between pregnancies.
- Minimising or avoiding severe blood loss postpartum.

However, the only effective intervention for ID that develops during pregnancy is iron replacement therapy.^{2,5}

Treatment

As is the case with testing for maternal ID (see **Diagnosis**), there is a lack of consensus on how to optimally treat ID during pregnancy.^{1,16} In the absence of standard NZ guidelines, a local DHB algorithm for management of antenatal ID in the first trimester is provided as an example (**Figure 3**).¹⁹

The implications of a lack of national guidelines for the testing and treatment of ID in pregnancy are to some extent revealed by a retrospective study that identified wide ranging practice in the testing and management of maternal IDA among NZ midwives and that a high proportion of pregnant women in NZ approach delivery with low iron levels or an unknown iron status.¹⁷

Oral iron

Oral iron is first-line therapy for ID during pregnancy.^{1,2,6} However, oral iron is not always optimal for treatment of ID in pregnancy because it is often poorly tolerated.

Ongoing use of oral iron is restricted by gastrointestinal (GI) adverse effects, such as nausea, heartburn, vomiting, and constipation, which are especially burdensome for pregnant women who are likely to already be experiencing GI symptoms associated with pregnancy.⁶ The GI adverse effects of oral iron can compromise treatment adherence leading to an inadequate response to iron therapy.

A definition of non-responsiveness to oral iron is persistent anaemia after 6–8 weeks of oral iron (<10 g/L increase in Hb and ferritin remains low).²⁰ If oral iron is not tolerated, alternate-day dosing of oral iron should be considered.

Ferrous salts are preferred to ferric salts due to the poorer absorption and bioavailability of the ferric salts, which include ferrous fumarate, ferrous sulphate, and ferrous gluconate. The amount of elemental iron is important and varies by preparation (**Table 2**).²⁶ Multivitamins and over-the-counter preparations usually do not contain sufficient iron to correct anaemia and may contain other minerals that interfere with iron absorption.

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Brand of iron supplement	Type of iron	Elemental iron dose	Amount required to get at least 65mg	Other ingredients	Price OTC at chemist*	PHARMAC subsidised
Ferro-F-Tab	Ferrous fumarate 310mg	100mg	1 tablet	Folic acid 0.35mg	\$9.99/60 tabs	Yes \$4.68 per 60 tabs
Ferro Tab	Ferrous fumarate 200mg	65mg	1 tablet		\$8.49/60 tabs	Yes \$3.09 per 100 tabs
Ferrograd	Ferrous sulphate 325mg	105mg	1 tablet		\$10.99/30 tabs	Yes \$2.06 per 30 tabs
Ferro-Grad C	Ferrous sulphate 325mg	105mg	1 tablet	Vitamin C 500mg	\$14.99/30 tabs	No
Maltofer tablets	Iron polymaltose 370mg	100mg	1 tablet		\$29.99/30 tabs	No
Maltofer syrup	Iron polymaltose 185mg	50mg per 5mL	6.5mL		\$29.99/150mL	No
Floradix Tonic	Ferrous gluconate	7.5mg per 10mL	9 x 10mL doses	Yeast B vitamins Vitamin C	\$28.99/250mls	No
Spatone	Ferrous iron rich water	5mg per 25mL sachet	13 sachets		\$38.17/28 sachets	No
Elevit w/ iodine	Ferrous fumarate 183mg	60mg	1 tablet	Folic acid 800mg Iodine 250mg	\$94.99/100 tabs	No

Table 2. Summary of over-the-counter (OTC) oral iron preparations for supplementation.

*RRP prices from www.pharmacydirect.co.nz/ [accessed 22/08/20] and personal communication from Aspen, AFT, and Mylan. All trademarks mentioned in this review are the property of their respective owners.



Prevention and management of ID and IDA

FIRST ANTENATAL VISIT

- Dietary advice, prescribe iodine & folic acid
- Check full blood count & ferritin

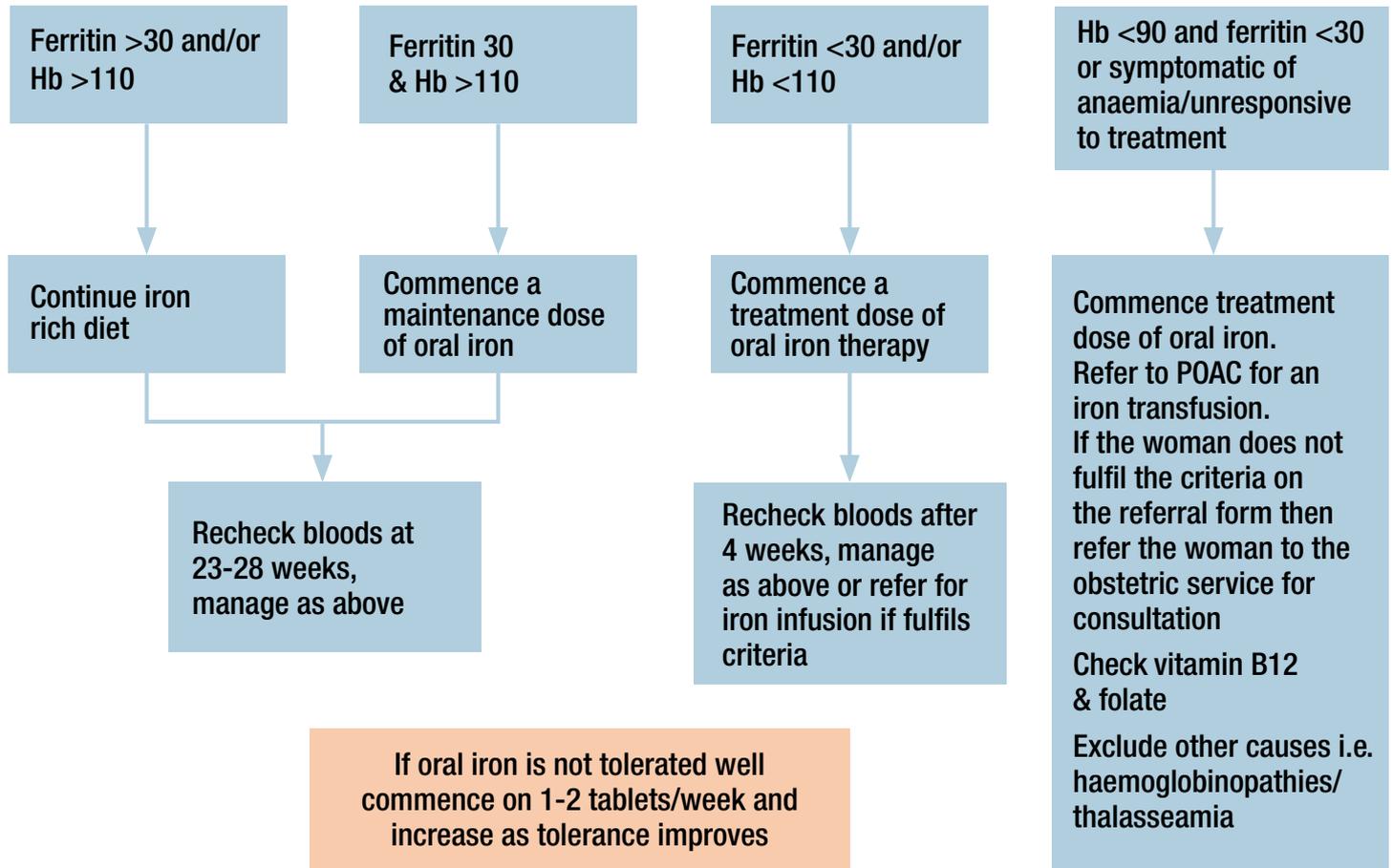


Figure 3. Example of an approach to the management of ID in the first trimester pregnancy.¹⁹

IV iron

IV iron provides rapid replacement of iron and avoids the risks associated with blood transfusion.⁶ IV iron is generally recommended for use in the latter stages of pregnancy; for example, in the third trimester or second trimester if oral iron has been ineffective or poorly tolerated,¹ and after 34 weeks gestation when there would be insufficient time for oral iron to restore iron levels prior to delivery.⁶

With published evidence having consistently demonstrated IV iron to be effective and well tolerated, and reports of serious adverse events being rare,^{1,2} the use of IV iron early in the treatment paradigm for ID in pregnancy has been advocated.¹ The use of IV iron in the first-trimester, however, is not recommended due to a lack of safety data in first-trimester pregnancies.²

Meta-analyses of randomised controlled trials comparing IV and oral iron have demonstrated that pregnant women receiving IV iron achieved target Hb more often, had an increased Hb after 4 weeks, and experienced fewer side effects.²⁶ A single dose of IV iron has been shown to be more effective than oral iron in relieving fatigue after postpartum haemorrhage, and to be as effective as blood transfusions in the management of severe anaemia.²⁷

As a novel IV iron formulation, ferric carboxymaltose can be rapidly administered at high dose due to tighter binding of elemental iron to the carbohydrate polymer shell.²⁸ The higher stability also results in a more favourable tolerability profile due to reduced probability that free iron is released.

An example of local DHB criteria for the antenatal and postnatal use of IV iron using ferric carboxymaltose appears in **Table 3**.²⁹ Ferric carboxymaltose is funded by PHARMAC under [Special Authority](#).

Expert commentary: access to IV iron through the community is variable and it is important for practitioners in their area to understand how this works. If the criteria for IV iron is met, women can access treatment through their GP under the POAC scheme – sometimes approval for this is needed from specialists in the domicile DHB (obstetricians) via a liaison midwife. Alternatively, other DHBs provide iron transfusions through haematology day-stay units at the local hospital; again, specialist approval is needed for this to occur.



Postnatal anaemia

Postnatal anaemia is defined as a Hb level <100 g/L in UK guidelines developed by the British Society for Haematology.²⁶

The UK guidelines recommend that Hb should be checked within 48 hours of delivery in all women with post-partum blood loss >500mL and in women with uncorrected anaemia in the antenatal period or symptoms suggestive of postpartum anaemia. Women with a Hb level <100 g/L, who are haemodynamically stable, asymptomatic, or mildly symptomatic should be offered oral elemental iron 40–80mg daily for ≥3 months. Use of IV iron for postpartum anaemia should be considered in women previously intolerant of, or unresponsive to, oral iron and/or where the severity of symptoms requires prompt management. Local criteria for the postnatal use of IV iron are detailed in **Table 3**.²⁹

ANTENATAL

- Iron deficiency anaemia, Hb < 100g/L, and ferritin < 20 mcg/L (or ferritin < 50 mcg/L if CRP > 5 mg/L) with other deficiencies excluded or corrected (vitamin B12 and folate)

AND one or more of the following:

- Fetal compromise, eg. intrauterine growth restriction
Failure of a trial of oral iron therapy due to side effects, high iron requirements, or persistent anaemia after 6-8 weeks (< 10 g/L rise in Hb and ferritin remains low)
- 36 weeks gestation
- Severe iron deficiency anaemia, Hb < 85 g/L ferritin < 20 mcg/L (or ferritin < 50 mcg/L if CRP > 5 mg/L) with other deficiencies excluded or corrected (vitamin B12 and folate) in the second or third trimester.

POSTNATAL

- Following postpartum haemorrhage and hemodynamically stable, Hb < 85 g/L +/- blood transfusion aim for blood transfusion to achieve Hb plus iron infusion to replenish iron stores

Table 3. Criteria for IV iron infusion using ferric carboxymaltose.²⁹

EXPERT COMMENTARY

The detection and early treatment of ID and IDA in NZ is critical to reducing preventable adverse maternal, foetal, and neonatal outcomes.

Oral iron supplementation has historically been associated with unpleasant GI side effects affecting its popularity with patients and clinicians alike. Oral iron (preferably 65mg elemental iron) should be taken on an empty stomach preferably with a glass of orange juice. Many foods impair the absorption of iron and these include soy protein, drinks with tannates (tea/coffee), and foods high in calcium and phosphates. Women taking aspirin and calcium for the prevention of preeclampsia need to take the calcium tablet at a different time of the day to iron.

The absorption of iron is not improved with a higher dose of elemental iron or dosing more than once a day and, in fact, a less is more approach has changed iron treatment. Alternate day dosing of iron is superior to increasing the dose and reduces the risk of side effects associated.

I advocate for the addition of laxatives when prescribing oral iron and also the use of antiemetics if necessary.

IV iron has revolutionised the treatment of ID and IDA in pregnancy but it is expensive and not without risk. Symptoms may include headaches, and nausea. The use of IV iron is recommended for women with a ferritin of <15 µg/L, Hb <100 g/L and demonstrable intolerance to oral iron, unresponsiveness to iron, or an inability to utilise iron (for example, severe renal failure).

Well written information pamphlets for maternity patients around the issues of ID and IDA in pregnancy would also boost compliance with iron therapy.

In conclusion, the key to optimal care in any pregnancy is ensuring a woman is iron replete in between and entering a pregnancy and I would recommend testing a mother for both ferritin and haemoglobin at her baby's 12-month immunisation as a proactive measure.

TAKE-HOME MESSAGES

- IDA may affect at least one in five pregnancies.
- ID and IDA in pregnancy and postpartum can lead to serious health complications for mother and baby.
- First-trimester serum ferritin is preferable to Hb alone in detecting candidates for iron therapy during pregnancy.
- A serum ferritin level <30 µg/L in early pregnancy, before the second trimester, is commonly used to detect ID in pregnancy.
- CRP levels should be obtained at the same time as serum ferritin levels if inflammation is present or suspected.
- Oral iron is currently considered first-line therapy for ID in pregnancy but its efficacy can be undermined by GI adverse effects.
- IV iron is generally recommended for use in the second or third trimester of pregnancy, specifically when:
 - Oral iron therapy has been ineffective; or
 - Oral iron therapy has resulted in dose-limiting intolerance; or
 - Rapid correction of IDA is required.
- Earlier intervention with IV iron is supported by published evidence demonstrating that:
 - IV iron rapidly improves iron stores and Hb levels in pregnant women with accompanying improvements in quality of life.
 - IV iron is generally well tolerated with serious adverse events rarely reported.
- Prompt identification and management of ID in the antenatal period may reduce the risk of postpartum anaemia.



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INITIAL APPLICATION - serum ferritin less than or equal to 20 mcg/L

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Prerequisites (tick boxes where appropriate)

- Patient has been diagnosed with iron-deficiency anaemia with a serum ferritin level of less than or equal to 20 mcg/L
- and
- Patient has been compliant with oral iron treatment and treatment has proven ineffective
- or
- Treatment with oral iron has resulted in dose-limiting intolerance
- or
- Rapid correction of anaemia is required

INITIAL APPLICATION - iron deficiency anaemia

Applications only from an internal medicine physician, obstetrician, gynaecologist, anaesthetist or any other medical practitioner on the recommendation of an internal medicine physician, obstetrician, gynaecologist or anaesthetist. Approvals valid for 3 months.

Prerequisites (tick boxes where appropriate)

- Patient has been diagnosed with iron-deficiency anaemia
- and
- Patient has been compliant with oral iron treatment and treatment has proven ineffective
- or
- Treatment with oral iron has resulted in dose-limiting intolerance
- or
- Patient has symptomatic heart failure, chronic kidney disease stage 3 or more or active inflammatory bowel disease and a trial of oral iron is unlikely to be effective
- or
- Rapid correction of anaemia is required



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