

LONDON HEALTH SCIENCES CENTRE and ST. JOSEPH HEALTH CARE CENTRE POLICY ON IRON DEFICIENCY ANEMIA TREATMENT IN PREGNANCY
(Adapted with permission from the 2023 TORONTO WORKING GROUP ON TREATMENT OF IRON DEFICIENCY ANEMIA IN PREGNANCY)

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Background, Prevalence and Clinical Implications:

- Iron deficiency often results in anemia, due to insufficient iron stores to support red blood cell (RBC) production.^{1,2}
- Iron deficiency is common in pregnancy and there is an increase in iron requirement (about 1000 mg total) during pregnancy, parturition and lactation.
- Anemia in pregnancy is associated with a higher risk of blood transfusion, preterm birth, and postpartum depression, in addition to potential neonatal neurocognitive aberrations that may persist later in childhood.⁴⁻¹³
- IDA is more common among individuals of lower socioeconomic status (SES), who are also less likely to be tested for iron deficiency in pregnancy.¹⁴
 - In a retrospective study at Sunnybrook Health Sciences Centre in Toronto, blood transfusion around birth was more likely in patients of a lower SES, and those with unrecognized and untreated IDA.¹⁵
- Treatment of IDA in pregnancy, whether by oral or intravenous routes, is effective and safe.¹⁶⁻¹⁸
- **To date, there is no evidence that one form of oral or intravenous iron preparation is safer in pregnancy than any other iron formulation. Certainly, oral iron is less expensive, but not always tolerated or efficacious, as discussed below.**

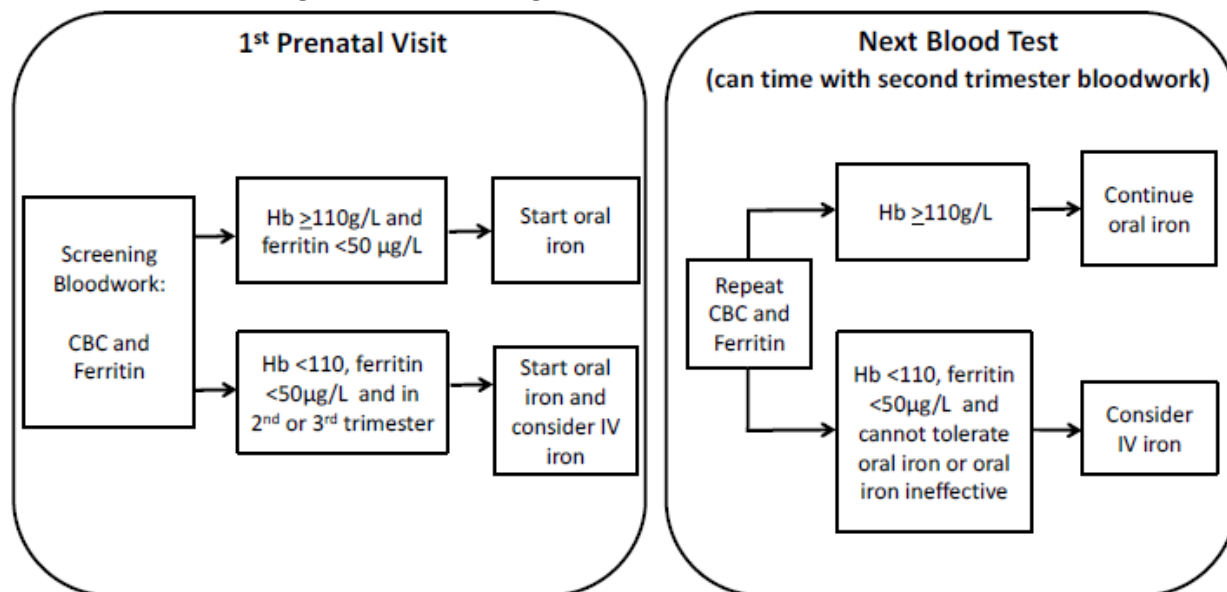
Purpose: To facilitate proper testing and treatment of IDA in pregnancy, based on consensus expertise at the London Health Sciences Centre and St. Joseph's Healthcare Centre.

Definitions:

- Anemia in pregnancy is generally defined as a hemoglobin of less than 110 g/L in the first trimester, less than 105 g/L in the second trimester, and less than 110 g/L in the third trimester.^{14,19}
- Iron deficiency in adults is generally defined as a serum ferritin less than 30 µg/L.^{14,20}
- There is some evidence that a serum ferritin less than 50 µg/L is in keeping with iron insufficiency in adults.²¹
- Adult patients whose serum ferritin is great than or equal to 30 µg /L, and who have concomitant inflammation, should have full iron studies ordered (i.e., serum iron, TIBC, and transferrin saturation).²²
 - Ferritin is a positive acute phase reactant that rises with inflammation even in presence of iron deficiency.²³
 - In this context, a transferrin saturation below 20% is in keeping with iron deficiency.
 - Examples of inflammatory states are:
 - Acute and chronic infections
 - Metabolic syndrome
 - Chronic kidney disease
 - Autoimmune conditions (e.g., systemic lupus erythematosus)

- Normal iron stores are reflected by a serum ferritin above 50 µg/L in those without concomitant inflammation.

Recommended Screening and Treatment Algorithm:



Management:

- Oral iron is first line therapy for IDA or a low serum ferritin (see Table 1).
- Oral iron may not be tolerated by some pregnant patients, or may not be effective, in pregnancy.
- Gastrointestinal side effects (nausea, constipation, diarrhea, indigestion, and metallic taste) may reduce treatment adherence.^{8,24}
- In pregnancy, decreased bowel motility caused by elevated progesterone and the enlarging uterus pressing on the rectum is sometimes made worse by oral iron.^{8,25}
- Iron salts (ferrous gluconate, sulfate or fumarate) should be used as first line oral iron supplements, as they are less expensive and there is no evidence that their more expensive counterparts are more effective.

Table 1. Oral Iron Preparations Adapted from Malinowski et al.¹⁶

Generic Name	Daily or alternate day dosing	Dose per tab, mg	Elemental iron, mg/tab	Daily estimated cost, \$
Ferrous gluconate	1 to 2 tabs	300	35	0.10
Ferrous sulfate	1 tab	300	60	0.20
Ferrous fumarate	1 tab	300	100	0.25
Ferrous bisglycinate	1 tab	25	25	0.30
Polysaccharide iron complex	1 tab	150	150	0.75
Heme iron polypeptide	2 to 3 tabs	11	11	2.40

- **Intravenous (IV) iron can be used in the 2nd and 3rd trimester of pregnancy in those who do not tolerate oral iron, when a trial of oral iron has been ineffective, or in the context of malabsorption (e.g., gastric bypass or active inflammatory bowel disease).**
 - Adverse effects with IV iron are rare (about in 1 in 200), and include self-limited acute hypersensitivity reactions (“Fishbane reaction”), such as flushing and acute chest or back tightness, without hypotension, wheezing, stridor, or periorbital edema.^{26,27}
 - Most occur within 1-2 hours of the IV iron infusion, are self-limited, resolve without treatment, and rarely recur with rechallenge.²⁷
 - They may be mistaken for anaphylaxis, but are distinct from it, and typically resolve with stopping the infusion. They do not recur when the infusion is re-initiated at a slower rate.^{28,29}
 - Risk of anaphylaxis following IV iron is rare (<1 in 200,000).^{28,30} This is in contrast to a risk of anaphylaxis of 1 in 40,000 with a red cell transfusion.³¹
- Management of a severe hypersensitivity reaction during administration of IV iron should foremost be to support the pregnant patient, including monitoring of maternal blood pressure, heart rate, respiratory rate, oxygen saturation and temperature, and only followed by fetal heart rate monitoring when available.
- **There is no evidence that one formulation of IV iron is safer than another. Thus, administration of either of the currently available formulations, IV iron sucrose or IV ferric derisomaltose (FDI), can be considered.**
- Blood transfusions should be reserved for emergency indications and settings only.

Additional information on currently available IV iron formulations in Canada:

- Current practice includes the use of IV iron sucrose as a safe and well tolerated treatment.
- Although IV iron sucrose (Venofer, generic) has been used for many years, its licensed indication is for the treatment of IDA in patients with chronic kidney disease.³²
- IV ferric derisomaltose (FDI), also known as IV iron isomaltoside, was licensed as Monoferric in Canada in June 2018, with a broader indication for the treatment of IDA in adult patients who have are intolerant or unresponsive to oral iron therapy.³³
- IV iron sucrose (Venofer, generic) is funded under the Ontario Drug Benefit Program (ODB) exceptional access program (EAP)³⁴, and restricted to cases with a documented diagnosis of IDA, confirmed by laboratory testing; and either of the following:
 - A demonstrated intolerance to oral iron therapy (requiring documentation of the name of the oral iron preparation, and its dose, duration of therapy and response),
 - OR
 - A lack of a hemoglobin response to oral iron therapy.
- As of February 26, 2021, Monoferric was approved for patients on ODB, under the limited use (LU) code 610, permitted for patients with IDA who meet all the following criteria³⁵:
 - A documented diagnosis of IDA confirmed, by laboratory testing;

- Failure to respond to, documented intolerance of, or contraindication to, an adequate trial (i.e. at least 4 weeks) of oral iron therapy; AND
- No history of hemochromatosis or other iron storage disorders; AND
- Administration in a setting where appropriate monitoring and management of hypersensitivity reactions can be provided to the patient.
- A major challenge with providing IV iron sucrose during pregnancy is a lack of resources – time, personnel and a physical space to administer the IV iron treatment. The maximum dose of IV iron sucrose is 300 mg over 1.5 to 3 hours per day, and a patient may require 1 or 2 repeat doses.
- IV FDI offers an advantage over IV iron sucrose, as up to a 1000-1500 mg dose can be provided per infusion, requiring 30 to 60 minutes of infusion time for a given visit.
 - The product monograph for IV FDI states that doses up to 1000 mg should be administered over 20 mins or more; while doses exceeding 1000 mg should be administered over 30 mins or more. In addition, single doses above 1500 mg are not recommended.³³
- **Both types of IV iron are efficacious. However, there is a likely benefit in providing a single larger iron dose over a shorter duration of time, given the healthcare resources required for each infusion.**

While clearly based on no strong evidence, the current Product Monograph language regarding pregnancy for available forms of IV iron in Canada are as follows:

Monoferric Product Monograph (Pfizer – revision date 03Nov2022) (below is direct wording from the product monograph):

“There are no studies of MONOFERRIC in pregnant women.

Based on findings in nonclinical (animal) studies, MONOFERRIC should not be used during pregnancy; if pregnancy occurs, the patients should be informed of the potential risk. MONOFERRIC should not be used in women of childbearing potential not using adequate contraception[...]

Do not become pregnant while taking MONOFERRIC. It may harm your unborn child.

- Use effective methods of birth control while taking MONOFERRIC.

- Tell your healthcare professional right away if you are pregnant, become pregnant, think you are pregnant or are planning on becoming pregnant. You can have a serious allergic reaction while receiving MONOFERRIC, which can cause serious harm to your unborn baby. They may develop an unusually slow heart rate. This usually lasts for a short time. If you are receiving this medicine while pregnant, your healthcare professional should carefully monitor your unborn baby.”

Venofer Product Monograph (American Regent – revision date 23Jan2019) (below is direct wording from the product monograph):

“Special Populations Pregnant Women: There are [...] no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, VENOFER should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. [...] It is unlikely that significant fetal iron overload would occur in iron deficient pregnant women receiving therapeutic doses of VENOFER to correct iron deficiency (see General).”

Our Working Group’s Response to the Aforementioned IV Iron Product Monographs:

Based on the existing published evidence^{27,36,40,41} (as well as the guidelines from the Toronto group), there is no evidence that IV iron sucrose (Venofer) is either safer or more effective in the second or third trimester of pregnancy than IV ferric derisomaltose (Monoferric). Accordingly, we unanimously agree

that, for the treatment of IDA in patients who are in their second or third trimester of pregnancy, and who are otherwise refractory to, or intolerant of, oral iron, there are two equal options for IV iron replacement therapy:

IV iron sucrose (Venofer, generic) at a 300 mg dose can be given. The number of necessary doses should be based on an estimation of the iron deficit (generally 3-5 doses).

IV ferric derisomaltose (Monoferric) at a 1000 mg dose can be given: The number of necessary doses should be based on an estimation of the iron deficit (generally 1-2 doses).

Ethical and Equity considerations:

The general approach among Toronto prescribers for management of a pregnant patient with IDA who is in the second or third trimester of pregnancy, and not a candidate for oral iron, is the administration of IV iron sucrose (Venofer, generic). This practice raises ethical issues pertaining to both health equity and priority setting: A disproportionate number of pregnant patients with IDA are vulnerable, marginalized, and from a low socio-economic demographic.^{14,15,37} The ability of this patient population to attend 2 to 5 appointments to complete IV iron sucrose administration can be challenging (e.g., child care, work absenteeism, cost of transit, etc.). The number of doses required with IV iron sucrose introduces unnecessary deterrence and barriers to this vulnerable group.^{38,39} Limiting access to a mode of treatment with double the number of visits, compared to IV ferric derisomaltose (Monoferric), is expected to magnify already existing health equity issues.

In a publicly funded health system, such as Canada's, resources constraints are perennial; including health human resources, space and funding. In the wake of a global pandemic, now more than ever our health system is experience shortages. Consequently, an option to administer a medication requiring significantly fewer doses/visits provides benefits to our health system by offsetting the burden to the system.

LITERATURE SEARCH ON IV FERRIC DERISOMALTOSE IN PREGNANCY:

Investigator sponsored studies:

1. Wesström J. et al. Iron deficiency anemia during pregnancy- is it safe to give intravenous iron isomaltoside (IMS)? [Abstract] *Int J Gynecol Obstetr.* 2018; 143 Suppl 3:185

Summary: Retrospective study, 2013-2018, with N=213 pregnant women matched to equal number of pregnant women not receiving IV iron. IV iron isomaltoside up to 1000-1500 mg in a single dose. A total of 10 (4.7%) ADRs occurred during administration. All ADRs were mild hypersensitivity reactions, abated spontaneously within a few minutes, and did not recur on rechallenge. No association between the dose of iron isomaltoside and frequency of ADRs was noted. Maternal and fetal outcomes were similar between case and control group.

2. Brownell A. et al. Review of intravenous iron isomaltoside in service in pregnant women at Queens Hospital Romford [Abstract]. *Transfus Med.* 2017; 27 Suppl 2:53

Summary: Retrospective study, Sep 2014-Apr 2017, with N=121 pregnant women received IV iron in 2nd and 3rd trimesters. No comparison group. IV iron isomaltoside in single doses of up to 20mg/kg infused with mean (range) 1173mg (600-2000), and 59.3% received >1000mg. 4 non-serious ADRs of hypersensitivity – none were serious or severe. In 2/4 cases patients agreed to be rechallenged with iron once symptoms abated; the infusions completed successfully and patients received their total dose.

3. Faulds J, Ralph C. The introduction of total dose iron, to the obstetric population, as part of an established patient blood management program [Abstract]. *Transfusion Med.* 2013; 23 Suppl 2:53

Summary: Retrospective study, from Oct 2012, N=83, all women with Hb<80 g/L or symptomatic pre and post delivery with Hb<90g/L received 400 mg ferric derisomaltose IV as a single dose. Only 19 were prenatal infusions. No adverse drug reactions were observed during administration.

4. Steven Fein, Dayne Alonso, Gloria Campos, Kimberly Strohfus, Isabel Duran, Adam K Lewkowitz, Gina Peralta, Nicole Peralta; Efficacy, Safety, and Tolerability of Iron Infusions in Pregnant Women: A Retrospective Chart Review [Abstract]. *Blood* 2023; 142 (Supplement 1): 2381. doi: <https://doi.org/10.1182/blood-2023-185521>

Summary: Retrospective study, N=1,383 pregnant women in their 2nd or 3rd trimester with iron deficiency without anemia (IDWA) (n=69) or iron deficiency anemia (IDA) (n=1,314) received a total of 2,971 iron infusions between June 2021 and June 2023, including Ferric Derisomaltose (FDI) 1000 mg single dose (n=417), two Ferumoxytol (FM) 510 mg doses (n=510), four Iron Sucrose (IS) 200 mg doses (n=1,661) or two IS 400 mg doses (n=383). No routine pre-medications were used. Among these pregnant women who received iron infusions, 94% reported improvement of one or more symptoms (shortness of breath, fatigue, or ice craving/ice chewing). Two weeks after the final infusion, 87% were found to have iron saturation greater than 15%, 83% were found to have ferritin above 30, and 88% were found to have increased hemoglobin compared to their pre-infusion hemoglobin. The average hemoglobin increase was 1.2 g/dL. IDA patients had higher hemoglobin increases than IDWA patients but similar increases in iron saturation and ferritin, regardless of iron formulation received. Iron infusions were usually well tolerated. The overall incidence of infusion reactions occurring during infusions, including CARPA reactions, was 4.5% (9.8% for FDI, 4.9% for FM, 1.4% for IS 200 mg doses, and 0.5% for IS 400mg doses). Five pregnant women (0.17%) discontinued iron treatments because of infusion reactions. The overall incidence of post-infusion discomfort symptoms was 22.5% (9.5% for FDI, 18.8% for FM, 31.3% for IS 200 mg doses, and 26.7% for IS 400 mg doses), including tiredness, headache, low back pain, leg swelling, or shortness of breath. Two women were evaluated in hospital ER's, one for hypotension during an iron infusion and one for hives after an iron infusion. There were no adverse events that impacted a woman's pregnancy.

Industry sponsored studies:

1. PREG-01 - Intravenous ferric derisomaltose (FDI) versus oral iron for persistent iron deficient pregnant women: a randomised controlled trial. Hansen R et al. *Arch Gynecol Obstet* 2022

Summary: A single centre, open label, randomised controlled trial at a Danish tertiary hospital was conducted to compare IV FDI (1000mg IV) and oral iron (ferrous fumarate 100mg elemental iron daily) treatment for the prevention of anaemia (Hb <11.0 g/dL) in pregnant women with persistent ID (ferritin <30 ng/mL after four weeks of routine oral iron treatment). The primary endpoint was the proportion of non anaemic (Hb ≥11.0 g/dL) women at each visit throughout the follow up period. Secondary endpoints included changes in haematological parameters (Hb, ferritin, TSAT) and PROs at Weeks 3, 6, 12, and 18. Mean Hb and proportion of non anaemic patients were similar between the FDI (n=100) and oral iron (n=101) groups at baseline. The estimated proportion of non anaemic women at all follow up visits was significantly higher in the FDI group compared with the oral iron group (91% versus 73% [difference 18%; 95% CI: 10, 25; p<0.001]). Increase in Hb was significantly greater with FDI versus oral iron at Week 6 (p<0.001), Week 12 (p<0.001) and Week 18 (p=0.01). Increase in ferritin was significantly greater with FDI versus oral iron in the first 12 weeks (p<0.001), while the increase in TSAT was significantly greater with FDI versus oral iron in the first 6 weeks (p<0.001). Greater improvements in FACIT Fatigue Scale scores were seen with FDI versus oral iron at Weeks 3 and 6 (p≤0.01). Greater improvements in psychological well-being were seen with FDI versus oral iron in the first 6 weeks and in physical well-being in the first 3 weeks (p<0.05).

THE BOTTOM LINE:

- **As with any medication, the benefits and small risks of oral or IV iron should be shared with a patient prior to its administration (see attached patient information sheet). Nevertheless, the risk to a pregnant person or the fetus is extremely low, countered by the likely benefits to both.**
- **IV iron can be used in the 2nd and 3rd trimester of pregnancy in those who do not tolerate oral iron, when oral iron has been ineffective, or in the context of malabsorption.**
- **When indicated, IV ferric derisomaltose (Monoferric) may be the preferred form of IV iron to efficiently administer in the second or third trimester of pregnancy. This opinion is furthered upon considering issues around system delivery, and health equity.**
- **IV iron sucrose (Venofer, generic) remains an equal alternative to IV ferric derisomaltose (Monoferric).**
- **Age limitations: Currently, given the lack of data of IV iron utilization in the pediatric population, these recommendations will only apply to adult pregnant who are 18 years of age or over.**

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