TORONTO POLICY ON IRON DEFICIENCY ANEMIA TREATMENT IN PREGNANCY: DEVELOPED WITH INPUT FROM EXPERTS ACROSS TORONTO ACADEMIC HOSPITALS

Throughout this document, we use the term 'women' and pronouns 'she/her' to highlight important health care gaps for women. We acknowledge that these terms are exclusive, and respectfully recognize that these experiences may also apply to all people with the anatomy that allows for menstruation, pregnancy, childbirth and lactation, including girls, transgender men, and gender non-binary individuals.

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.
    - At St. Michael's Hospital in Toronto, among 1307 pregnant patients, 81% had iron deficiency (defined by a serum ferritin level <30 ug/L) and 24% had iron deficiency anemia (IDA) (defined by a ferritin <30 ug/L with a hemoglobin concentration <110g/L).[3]
- 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 women of a lower SES, and those with unrecognized and untreated IDA.[15]
- There are currently few clinical locations in Toronto that enable the administration of intravenous iron as an outpatient, partly due to lack of funding, nursing expertise and physical space for safe administration.
- 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 University of Toronto's affiliated hospitals.

Definitions:

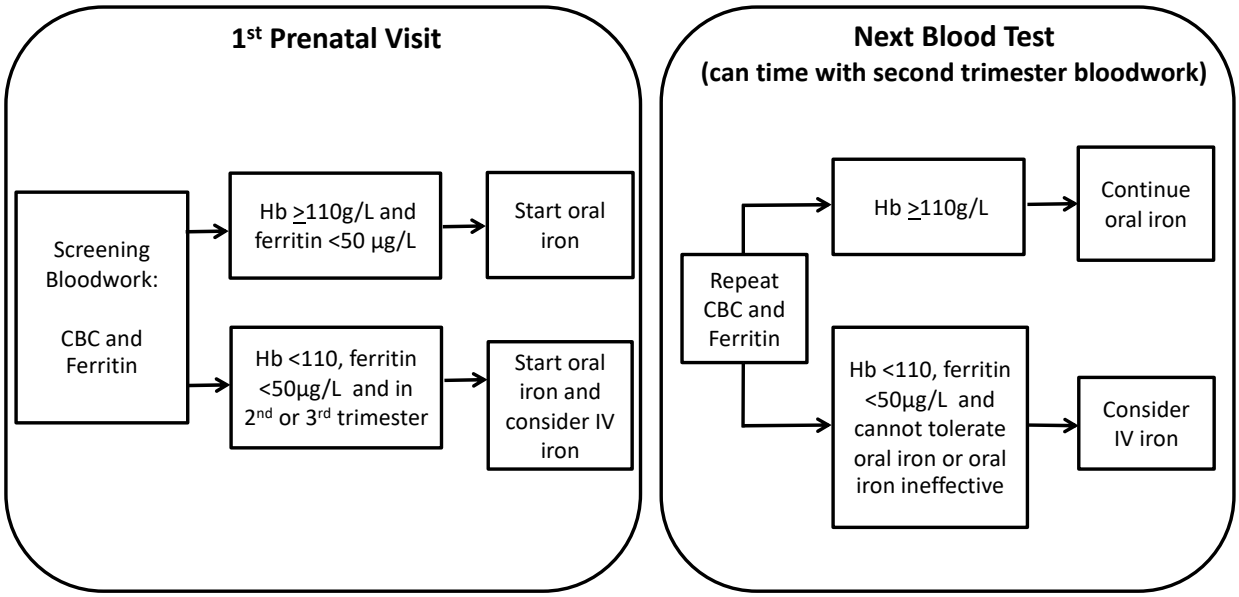
- Anemia in pregnancy is generally defined as a hemoglobin of <110 g/L in the first trimester, <105 g/L in the second trimester, and <110 g/L in the third trimester.[14,19]
- Iron deficiency in adults is generally defined as a serum ferritin <30 µg/L.[14,20]
- There is some evidence that a serum ferritin <50 µg/L is in keeping with iron insufficiency in adults.[21]

- Adult patients whose serum ferritin is ≥ 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 erythematous)

- **Normal iron stores are reflected by a serum ferritin > 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 women, 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 currently available formulation (IV iron sucrose or IV ferric derisomaltose) 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 (Monoferric) was licensed 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 Programme (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:

  i) 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

  ii) A lack of a hemoglobin response to oral iron therapy.
- As of February 26, 2021, IV ferric derisomaltose (Monoferric) was approved for patients on ODB, under the limited use (LU) code 610, permitted for patients with IDA who meet all the following criteria[35]:
  - 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 ferric derisomaltose 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 ferric derisomaltose 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](as well as unpublished data via personal correspondence with the principal investigators of ongoing trials, and physicians who have administered IV ferric derisomaltose (Monoferric) and other formulations of IV iron to thousands of patients in Europe, the US and Canada), 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 women 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 physicians for management of a pregnant woman with IDA, and those is in her 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 women 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.

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).**

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