Intravenous iron use in pregnancy: Ironing out the issues and evidence

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Iron

- Essential during pregnancy:
  - expansion of the red blood cell mass
  - growth of maternal tissues
  - fetal and placental development
- Present in all human cells
- Several vital functions, including carrying oxygen in the form of haemoglobin
- Iron is stored primarily as ferritin
- Pregnant women particularly vulnerable to ID due to high demand for iron from growth (maternal/fetoplacental)
**IV iron preparations**

**TABLE 1** Comparison of different intravenous iron preparations†

<table>
<thead>
<tr>
<th></th>
<th>Iron sucrose</th>
<th>Iron polymaltose</th>
<th>Ferric carboxymaltose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trade (brand) name</td>
<td>Venofer®</td>
<td>Ferrum H®, Ferrosig®</td>
<td>Ferinject®</td>
</tr>
<tr>
<td>Concentration of elemental iron</td>
<td>20 mg/mL</td>
<td>50 mg/mL</td>
<td>50 mg/mL</td>
</tr>
<tr>
<td>Maximum dose in single administration for patients ≥35 kg</td>
<td>100 mg</td>
<td>Up to 2500 mg</td>
<td>20 mg/kg with max. dose of 1000 mg</td>
</tr>
<tr>
<td>Total dose single infusion</td>
<td>No</td>
<td>Yes</td>
<td>No (unless total body iron deficit is ≤1000 mg)</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>Not more than three times per week</td>
<td>Not required</td>
<td>Not less than seven days apart</td>
</tr>
<tr>
<td>Infusion time for maximum dose</td>
<td>15 min</td>
<td>4-5 h</td>
<td>15 min</td>
</tr>
<tr>
<td>Approximate cost‡</td>
<td>$40/500 mg</td>
<td>$20/500 mg</td>
<td>$150/500 mg</td>
</tr>
<tr>
<td>Eligible for PBS subsidy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

PBS, Pharmaceutical Benefits Scheme.
IV iron prescriptions, Australia

Figure 1: Number of PBS parenteral iron prescriptions supplied by month
### Ferric carboxymaltose (FCM) usage among females in Australia

#### Table 2: All Patients and prescriptions by age group, national total

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>00 to 13 Years</td>
<td>155</td>
<td>289</td>
<td>462</td>
<td>168</td>
<td>323</td>
<td>529</td>
</tr>
<tr>
<td></td>
<td>14 to 19 Years</td>
<td>3,072</td>
<td>5,220</td>
<td>7,577</td>
<td>3,488</td>
<td>5,820</td>
<td>8,426</td>
</tr>
<tr>
<td></td>
<td>20 to 24 Years</td>
<td>4,556</td>
<td>7,207</td>
<td>10,316</td>
<td>5,240</td>
<td>8,103</td>
<td>11,584</td>
</tr>
<tr>
<td></td>
<td>25 to 29 Years</td>
<td>5,157</td>
<td>8,626</td>
<td>12,575</td>
<td>5,016</td>
<td>9,757</td>
<td>14,161</td>
</tr>
<tr>
<td></td>
<td>30 to 34 Years</td>
<td>6,447</td>
<td>10,807</td>
<td>15,717</td>
<td>6,025</td>
<td>12,184</td>
<td>17,392</td>
</tr>
<tr>
<td></td>
<td>35 to 39 Years</td>
<td>6,578</td>
<td>10,278</td>
<td>14,951</td>
<td>6,025</td>
<td>12,184</td>
<td>17,392</td>
</tr>
<tr>
<td></td>
<td>40 to 44 Years</td>
<td>7,561</td>
<td>10,703</td>
<td>14,528</td>
<td>6,025</td>
<td>12,184</td>
<td>17,392</td>
</tr>
<tr>
<td></td>
<td>45+ Years</td>
<td>37,158</td>
<td>50,633</td>
<td>65,479</td>
<td>50,041</td>
<td>66,565</td>
<td>84,018</td>
</tr>
<tr>
<td>Female Total</td>
<td></td>
<td>70,684</td>
<td>103,763</td>
<td>141,605</td>
<td>89,862</td>
<td>128,227</td>
<td>171,416</td>
</tr>
</tbody>
</table>
Who is prescribing IV iron?

Figure 2: Number of parenteral iron prescriptions by prescriber type and year


570%
Birth numbers, Australia
Iron studies: referrals

Medicare Item 66596 processed from July 2013 to June 2014

Medicare Item 66596 processed from July 2018 to June 2019

Ferritin: referrals

Medicare Item 66593 processed from July 2013 to June 2014

Medicare Item 66593 processed from July 2018 to June 2019

Book Your Iron Infusion Now
Iron Infusions Without The Wait

Name *

Phone *

Search
Try typing a suburb, procedure, practice or practitioner's name

Practitioner Gender:  Any  Male  Female
Practitioner Language: All

Practices offering services for Iron Infusion in Sydney, NSW
17 results found

We are located at 7 - 9 Gibbons Street in Redfern. Ideally positioned directly opposite Redfern train station
Inappropriate use of IV iron

– PBS/PHARMAC (NZ) listing:
  – FCM (Ferinject) is listed for the treatment of iron deficiency anaemia, where oral iron preparations are not tolerated, ineffective or otherwise inappropriate. The diagnosis must be based on laboratory tests

– An Adelaide study in a tertiary teaching hospital (Qassim et al., 2017 ANZJOG) found:
  – of the 213 pregnant women who received IV IPM, only 62% had iron deficiency anaemia, and 38% had non-anaemic iron deficiency
**IV iron: what is the cost?**

### Table 1: Unrestricted PBS listings of parenteral iron products

<table>
<thead>
<tr>
<th>Item</th>
<th>Name, form &amp; strength, pack size</th>
<th>Max. quantity units (mg iron)</th>
<th>Rpts</th>
<th>DPMQ</th>
<th>Brand name and manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>10104T</td>
<td>Iron (as ferric carboxymaltose) 500 mg/10 mL injection, 1 x 10 mL vial</td>
<td>2 (1000 mg)</td>
<td>1</td>
<td>$306.96</td>
<td>Ferinject® (Vifor Pharma Pty Limited)</td>
</tr>
<tr>
<td>2593L</td>
<td>Iron (as polymaltose) 100 mg/2 mL injection, 5 x 2 mL ampoules</td>
<td>5 (2,500 mg)</td>
<td>0</td>
<td>$23.16</td>
<td>Ferrosig® (Sigma Company Limited)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ferrum H® (Aspen Pharmacare Australia Pty Ltd)</td>
</tr>
<tr>
<td>10229J</td>
<td>Iron (as sucrose) 100 mg/5 mL injection, 5 x 5 mL ampoules</td>
<td>5 (2,500 mg)</td>
<td>0</td>
<td>$39.53</td>
<td>Venofer® (Aspen Pharmacare Australia Pty Ltd)</td>
</tr>
</tbody>
</table>

Source: the PBS website. Special Pricing Arrangements apply.

### Table 7: PBS benefits for parenteral iron

<table>
<thead>
<tr>
<th>Listing year</th>
<th>FCM</th>
<th>IP</th>
<th>IS</th>
<th>Total market</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1 (June 2014 to May 2015)</td>
<td>$19,292,165</td>
<td>$982,946</td>
<td>$58,953</td>
<td>$20,334,064</td>
</tr>
<tr>
<td>Year 2 (June 2015 to May 2016)</td>
<td>$34,505,573</td>
<td>$632,542</td>
<td>$22,748</td>
<td>$35,160,863</td>
</tr>
</tbody>
</table>

Special pricing arrangements apply for FCM. Source: DHS database using date of supply, which may be slightly different to publicly available Medicare Australia date of processing data, accessed November 2016.
Definition of anaemia and iron deficiency (and what are we treating)?

- Definition is variable
- No agreed normal range for Hb in Australia
  - WHO: Hb <110 g/L at any stage in pregnancy
  - UK: <110 g/L in 1st trimester and <105 g/L in 2nd and 3rd
  - USA: <110 g/L in 1st and 3rd trimesters, <105 g/L in 2nd
- No universal accepted ferritin concentration for iron deficiency
  - WHO: ferritin <15 μg/L
  - UK and Australia: <30 μg/L
Current Practice in the Diagnosis and Management of PPH

WHA Member Survey Responses

How does your hospital define and diagnose anaemia during pregnancy

Number of respondents

<table>
<thead>
<tr>
<th>Definition</th>
<th>Number of respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb &lt;100</td>
<td>6</td>
</tr>
<tr>
<td>Hb &lt;105</td>
<td>2</td>
</tr>
<tr>
<td>Hb &lt;110</td>
<td>9</td>
</tr>
<tr>
<td>Fe &lt;15 normal Hb</td>
<td>1</td>
</tr>
<tr>
<td>Trimester Specific - According to Red cross guidelines</td>
<td>3</td>
</tr>
<tr>
<td>Other guideline</td>
<td>1</td>
</tr>
<tr>
<td>No standard definition</td>
<td>0</td>
</tr>
</tbody>
</table>
Current guidelines for screening for anaemia

- **RANZCOG:**
  - assess Hb at first antenatal visit and at 28 weeks gestation, and ensure any anaemia is investigated and treated

- **National blood authority:**
  - in women at high risk of anaemia, ferritin should be tested along with FBC early in pregnancy to assess iron stores and anaemia

- **Australian Pregnancy Care Guidelines:**
  - routinely offer testing for Hb early in pregnancy (at first visit) and at 28 weeks gestation
  - in areas where prevalence of IDA is high consider testing ferritin at the first antenatal visit.
Current Practice in the Diagnosis and Management of PPH

WHA Member Survey Responses

At what gestation does your hospital routinely investigate Hb and/or iron studies?

- 16/40
- 28/40
- First trimester then 26/40
- Booking & 28/40
- Booking, 28/40, 36/40
- 12/40, 19/40, 28/40 and 36/40. More if levels are low.
- 36 Weeks
- GP arranges
Iron supplementation

- **Australia/NZ/UK:**
  - routine iron supplementation is *not recommended* for all pregnant women

- **WHO/CDC/SOGC:**
  - recommend *universal* iron supplementation for all pregnant women

- **Australia/NZ/UK:**
  - oral iron is recommended as first line therapy for women with IDA
  - IV iron is recommended when oral iron is poorly tolerated, absorption is likely to be impaired, the response to oral iron is inadequate, or when rapid restoration of Hb and iron stores is required
Current Practice in the Diagnosis and Management of PPH
WHAMember Survey Responses

What are the clinical triggers for using intravenous iron during pregnancy?

- Failed to respond to oral therapy/are intolerant/non-compliant: 90%
- Hb < 110 g/l Fe < 8: 5%
- Hb 70-110 g/l Fe < 30: 10%
- Hb < 90: 5%
- Hb < 70: 3%
- Variable and practitioner dependant: 2%
- Symptomatic: 1%
- Not given beyond 37 weeks or in first trimester: 1%

NOTE: Does not total to 100% - Multiple responses
**IDA: what is the harm?**

### Table 3 Clinical outcomes associated with maternal iron deficiency anaemia

<table>
<thead>
<tr>
<th>Maternal outcomes</th>
<th>Infant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence grade high (4)</td>
<td>Evidence grade high (4)</td>
</tr>
<tr>
<td>Evidence grade moderate (3)</td>
<td>Evidence grade moderate (3)</td>
</tr>
<tr>
<td>Postpartum infection</td>
<td></td>
</tr>
<tr>
<td>Evidence grade low (2)</td>
<td>* Low birth weight</td>
</tr>
<tr>
<td>Infection during pregnancy</td>
<td>* Preterm delivery (&lt;37wks)</td>
</tr>
<tr>
<td>Evidence grade very low (1)</td>
<td>Mean birth weight</td>
</tr>
<tr>
<td>Antepartum haemorrhage</td>
<td>Very low birth weight</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>Neurodevelopmental delay</td>
</tr>
<tr>
<td>§Postpartum haemorrhage</td>
<td>Neonatal death</td>
</tr>
<tr>
<td>Breast feeding duration</td>
<td>Congenital anomaly</td>
</tr>
<tr>
<td>Maternal wellbeing</td>
<td>Evidence grade very low (1)</td>
</tr>
<tr>
<td>Maternal death</td>
<td>Stillbirth</td>
</tr>
<tr>
<td>Maternal malaria</td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>Placental malaria</td>
</tr>
<tr>
<td></td>
<td>Transfusion</td>
</tr>
<tr>
<td></td>
<td>Premature rupture of membranes</td>
</tr>
<tr>
<td></td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td></td>
<td>Reduced cognitive ability</td>
</tr>
<tr>
<td></td>
<td>Post-partum depression</td>
</tr>
<tr>
<td></td>
<td>Emotional instability</td>
</tr>
<tr>
<td></td>
<td>Lactation failure</td>
</tr>
</tbody>
</table>

* IDA in 1st/2nd trimester

§ Antenatal anaemia associated

6.55 fold increase in PPH (Canberra study, 2018)
IDA: what is the harm?

- Most studies in low/middle income countries
- Lack of evidence on the benefits of treating mild IDA in pregnancy
- Oral iron can cause gastrointestinal adverse effects (nausea, constipation)
- The clinical effects of iron deficiency without anaemia in pregnancy on maternal and infant outcomes are unknown
Treating IDA and maternal/fetal outcomes

Question 2 (Interventional question)
In maternity patients, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion?

RBC, red blood cell
Iron therapy and haematological parameters

- **Iron therapy:**
  - Improves haematological parameters (Hb and ferritin)

- **IV iron:**
  - Increase in Hb (median) of **21 g/L at 3-4 weeks;** and **30.1 g/L at delivery**
  - IPM (34 g/L) > IS (21 g/L) > FCM (15 g/L) at 3-4 weeks

- **IV versus oral iron:**
  - Greater increase in Hb by **6 g/L at 2-4 weeks;** and **6.8 g/L at delivery**
  - Greater increase in ferritin by 38 µg/L at 4 weeks
  - Greater increase in ferritin by 43-108 µg/L at delivery (*2 studies)
## Oral iron

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| **ES2.9** | In pregnant women, oral iron reduces maternal iron deficiency anaemia (Hb < 110 g/L) at 34 weeks gestation or more compared to no treatment or placebo.  
(See evidence matrix D2.J in Volume 2 of the technical report) |
| **ES2.10** | In pregnant women, the effect of oral iron compared to no treatment or placebo on postpartum anaemia (Hb < 110 g/L) is uncertain.  
(See evidence matrix D2.J in Volume 2 of the technical report) |
| **ES2.11** | In pregnant women with iron deficiency anaemia, oral iron improves laboratory measures (Hb and ferritin) and reduces anaemia (Hb < 110 g/L) compared to no treatment or placebo.  
(See evidence matrix D2.K in Volume 2 of the technical report) |
## Oral iron

<table>
<thead>
<tr>
<th>ES2.26</th>
<th>In pregnant women, the effect of oral iron compared to no treatment or placebo on the incidence of low birth weight (&lt;2500 g), very low birth weight (&lt;1500 g) and preterm birth is uncertain. (See evidence matrix D2.U in Volume 2 of the technical report)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ES2.27</td>
<td>In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on measures of fetal outcomes (low birth weight, incidence of preterm birth and small-for-gestational age) is uncertain. (See evidence matrix D2.V in Volume 2 of the technical report)</td>
</tr>
</tbody>
</table>
## IV iron versus oral iron

| ES2.16 | In maternity patients with iron deficiency anaemia, IV iron may lead to more rapid correction of laboratory measures (Hb and ferritin) than oral iron; however, at completion of therapy Hb levels were similar in both groups but ferritin continued to be higher with IV iron. (See evidence matrix D2.M in Volume 2 of the technical report) |
| ES2.17 | In maternity patients with anaemia, the superiority of IV iron plus oral iron compared to oral iron alone in increasing Hb or ferritin levels is uncertain. (See evidence matrix D2.N in Volume 2 of the technical report) |
### IV iron versus oral iron

| ES2.38 | In maternity patients with iron deficiency anaemia, the effect of IV iron compared to oral iron on maternal and perinatal mortality is uncertain.  
(See evidence matrix D2.AB in Volume 2 of the technical report) |
| ES2.39 | In pregnant women, the effect of IV iron plus oral iron compared to oral iron alone on maternal and perinatal mortality is unknown (no evidence). |
IV iron versus oral iron: clinical outcomes

Two recent systematic reviews/meta-analyses

Systematic review/Meta-analysis

Intravenous or oral iron for treating iron deficiency anaemia during pregnancy: systematic review and meta-analysis

Alaa Cassim1,2, Rosalie M Grivell3,4, Amanda Henry5,6,7, Giselle Kidson-Gerber2,9,9, Antonia Shand9,10, Luke E Grzeskowiak2,11,12.


Intravenous compared with oral iron for the treatment of iron-deficiency anemia in pregnancy: a systematic review and meta-analysis

Adam K. Lewkowitz1 · Anjlie Gupta2 · Laura Simon3 · Bethany A. Sabol1 · Carrie Stoll2 · Emily Cooke4 · Roxanne A. Rampersad1 · Methodius G. Tuulii

https://doi.org/10.1038/s41372-019-0320-2
### IV iron versus oral iron for IDA

**Lewkowitz paper:** No difference in maternal blood transfusion (OR 1.02; 0.99-1.04)  
* NNT with IV iron to prevent one blood transfusion = 95 women (95% CI, 81-348)
Iron therapy and maternal/perinatal outcomes

- There is inconclusive evidence that iron therapy (IV or oral) for IDA improves maternal or infant clinical health outcomes, such as postpartum haemorrhage, blood transfusion*, preterm birth, gestational age, mode of delivery
- Few studies investigate maternal or perinatal outcomes, and the small study sample sizes limit the power to detect clinically relevant differences

USPST, 2015; Qassim, 2017
IV iron: is there any harm?

- Monitoring and reporting of ADRs highly variable
- **Median prevalence of ADRs:**
  - IPM 2.2%; range 0-4.5%
  - FCM 5.0%; range 0-20%
  - IS 6.7%; range 0-19.5%
- **Moderate or severe ADRs (requiring treatment or discontinuation of IV iron):**
  - IPM 14.0 per 1000 women
  - IS 7.9 per 1000 women
  - FCM 3.6 per 1000 women
- **Anaphylaxis:**
  - IS 21 per 100,000 persons
  - FCM ~0.1% (2/1775 persons)

Bregman and Goodnough, 2014; Wang, 2015; Qassim, 2017
FCM: side effects

- Results from pooled phase II/III trials (n=5799):
  - Hypersensitivity/allergic reactions (0.9%)
  - Nausea (3.1%)
  - Hypophosphataemia (1.9%)
  - Injection site reaction* (1.6%)
  - Headache (1.4%)
  - Hypertension (1.3%)
  - Dizziness (1.2%)
  - Flushing (1.0%)
  - ALT increase (1.0%)
  - Dysgeusia (0.9%)
  - Constipation (0.8%)
  - Vomiting (0.7%)
  - Diarrhoea (0.5%)
  - Hypotension (0.5%)
  * Skin staining 1.3% (4/305)

Anker, 2009; Bregman and Goodnough, 2014
Increase in notifications regarding skin staining

Previously, patients unable to tolerate oral iron formulations have received iron infusions in local hospitals. Ferinject’s key advantage is the ability to safely administer equivalent doses in a shorter time. A consequence is that these patients no longer require day admission in hospitals for infusions, but can have the equivalent dose of iron in as little as 15 minutes through an IV in general practice. Avant has received requests for information from GPs who find they are being expected to provide iron infusions in the general practice setting.

In addition, in recent months, Avant’s claims team has received a number of notifications regarding skin staining following intravenous iron infusions. The staining is long-lasting or permanent, and occurs when the compound leaks outside the vein and into the surrounding soft tissues during the infusion. While the complication is uncommon, it is a known risk. The iron leakage itself is not harmful, but the resulting stain can be aesthetically unacceptable to many patients. Some doctors are facing direct patient complaints, formal regulatory body complaints or legal action as a result of a patient’s iron ‘tattoo’ following an infusion.
Current Practice in the Diagnosis and Management of PPH

WHA Member Survey Responses

Does your hospital have a policy/guideline in relation to the use of intravenous iron during pregnancy?

- Yes: 90%
- No: 10%
- Unsure: 0%

Does your hospital use intravenous iron infusion for pregnant women who are identified as having iron deficient anaemia?

- Yes: 80%
- No: 20%
My parting thoughts on IV iron…

- Lack of demonstrated improvement in important clinical outcomes, and the potential to cause harm, should discourage widespread dissemination of this practice
- Reversal of medical practice once established is often difficult
- Oral iron should remain the first line treatment of IDA
- High-quality research studies that evaluate meaningful clinical outcomes for the mother and baby are needed (maybe WHA to take a lead in this research?)

*Aust N Z J Obstet Gynaecol* 2018; 58: 145–147

DOI: 10.1111/ajo.12794

**INVITED EDITORIAL**

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Thank you

Questions?