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Title: Use of Intravenous Iron Polymaltose in the Management of Iron Deficiency in Pregnancy: a retrospective cohort study

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Abstract

**Background:** Intravenous iron polymaltose (IPM) is commonly utilised in pregnancy when oral treatment is not tolerated or where rapid replenishment of iron stores is required, but data on use in pregnancy is scarce. **Aim:** To examine the use, safety and efficacy of intravenous IPM in pregnancy. **Methods:** Retrospective cohort study of pregnant women administered intravenous IPM between January 2014 and January 2016 at a Tertiary teaching hospital in Adelaide, Australia. Data on maternal characteristics, intravenous iron infusion details, and haematological parameters were collected from case notes and electronic records. Main outcome measures included indication for intravenous iron infusion, prevalence of infusion reactions, change in haemoglobin, and correction of anaemia prior to delivery. **Results:** Intravenous IPM was administered in 213 pregnancies, 62.0% of women with iron deficiency anaemia (IDA) and the remainder (38.0%) with non-anaemic iron deficiency. Adverse drug reactions (ADRs) occurred in 24% of women, of which 32% required infusion cessation. Anaemia was still present at delivery among 7%, and 17% of women with mild, and moderate/severe anaemia respectively. Approximately 1 in 5 anaemic women received an IV IPM dose below that recommended by the local guideline, particularly in women with a BMI $\geq 25$ kg/m$^2$ compared with $<25$ kg/m$^2$ (30.9% vs. 6.3%; $p<0.001$). Doses ‘at recommended’ resulted in a greater increase in haemoglobin from treatment until delivery than doses ‘below recommended’ (adjusted beta coefficient 8.4 g/L; 95% CI 2.7 to 14.1 g/L). **Conclusion:** Intravenous IPM is effective in treating IDA in pregnancy but is associated with a high prevalence of ADRs and treatment cessation.
Manuscript

Introduction

Iron deficiency represents the most widespread nutritional deficiency globally and is the leading cause of anaemia during pregnancy.\(^1\) Anaemia is estimated to affect 38% of pregnancies worldwide and is associated with a significantly increased risk of perinatal morbidity and mortality.\(^1,2\) Improvements in haematological status during pregnancy are associated with reduced risk of blood loss during delivery, enhanced compensatory response to blood loss during delivery, and improved iron status in the postpartum period.\(^3\)

Intravenous (IV) iron is commonly utilised when oral treatment is not tolerated or where rapid replenishment of iron stores is required. The most common types of IV iron utilised in pregnancy include iron polymaltose (IPM), ferric carboxymaltose and iron sucrose. These preparations significantly differ in some key aspects such as the maximum dose that can be administered in a single infusion, the number of infusions required to provide the total dose, total infusion time and cost, with IPM being the only type that can be utilised to provide complete iron replacement in a single infusion. Despite the commonality of use, few studies have investigated the use of IPM in pregnancy, including a total of just 164 women.\(^4-6\) Given the limited number of clinical studies on IPM in pregnant women and the routine use of this formulation in our clinical practice setting, this study aimed to examine its use, safety and efficacy in the management of iron deficiency in pregnancy.

Methods
Ethics Approval

This study was approved by the Southern Adelaide Local Health Network and University of South Australia Human Research Ethics Committee (46.16 – HREC/16/SAC/53; ID 0000035537)

Study Design and Setting

Retrospective cohort study of all pregnant women receiving IV IPM between January 1st, 2014 and January 31st, 2016 at Flinders Medical Centre (FMC) in Adelaide, South Australia. FMC is a tertiary level teaching hospital with more than 3,000 births each year. Women were identified from electronic hospital pharmacy dispensing records as receiving IPM during pregnancy. Antenatal care, including the investigation and management of anaemia in pregnancy, is provided according to the South Australian Perinatal Practice Guidelines. This includes routine complete blood examination at booking and at 28 weeks’ gestation, with iron studies undertaken using a targeted approach of at risk women.

Outcome Measures

Relevant data were collected from hard copy medical case notes and electronic pathology records. A standardised electronic data collection tool was used to collect patient demographics, obstetric and medical history, infusion related data, haematological data, iron studies, and perinatal outcomes.

Use Evaluation

Women were initially classified according to the presence or absence of anaemia at the time of IV IPM infusion (Haemoglobin <105 g/L after the first trimester7), then further classified according to the severity of anaemia, either mild (Haemoglobin 100-104 g/L), moderate
(Haemoglobin 90-99 g/L), or severe (Haemoglobin <90 g/L). The presence of iron deficiency was determined according to a serum ferritin <30 mcg/L or transferrin saturation ≤16%.

The dose of IPM prescribed was compared to that recommended by the local hospital guideline, which recommends calculating the dose based on the following equation: Iron Dose = Weight x (Target haemoglobin – Current haemoglobin) x 0.24 + 500 mg. The guideline recommends a target haemoglobin of 150 g/L, but it does not specify which weight to use when calculating the dose (i.e. whether to use pre-pregnancy or current weight). In order to evaluate the appropriateness of prescribed iron doses, the expected IV iron dose was first calculated based on the woman’s haemoglobin deficit and current weight. To allow for rounding and minor variation in dosing weights, 200 mg was subtracted from this expected value. This figure was then compared with the actual dose prescribed. Based on this comparison the doses were then classified as being either ‘At Recommended Dose’ or ‘Below Recommended Dose’.

Safety Measures
Adverse drug reactions (ADRs) were classified as either local reactions, occurring at or near the injection site, or systemic reactions which include any other reactions regardless of severity. Documentation of infusion rate modification, infusion termination or any medications used to manage reactions in the case notes were used to assess the impact of the experienced ADR. Significance of reactions leading to infusion termination were further analysed based on recommencement status: infusions recommenced on the same or an alternate day and infusions that were completely ceased.

Efficacy Measures
Response to IV iron was evaluated by exploring changes in haemoglobin from immediately prior to IV iron infusion to 2–4 weeks post-treatment, and immediately prior to delivery.
Women were classified as having treatment success if they had a haemoglobin increase of 20 g/L during the relevant time period. Anaemia status at 2-4 weeks post-infusion and immediately prior to delivery were also examined. Efficacy of IV iron based on changes in haemoglobin was examined only among those women with confirmed IDA.

**Statistical Analysis**

Data Analyses were undertaken using Stata SE 14 (Stata, College Station, TX, USA). Continuous data were compared using the Student’s t-test or paired t-test, while categorical data were compared using Chi-squared test or Fisher’s exact test as appropriate. Adjusted differences between groups with respect to continuous (i.e. haemoglobin change) outcomes were compared using a linear regression analysis. Analyses were adjusted for possible confounders including gestation at the time of infusion, haemoglobin status prior to infusion, and maternal BMI. Statistical significance was defined as a two-sided p-value of <0.05.

**Results**

**IV Iron Use**

Following linkage of the pharmacy dispensing records and perinatal statistics database, a total of 247 women were identified as receiving intravenous iron. We then excluded 34 women, 31 who received IV iron in the postnatal period, two who cancelled their appointment and did not end up receiving their IV iron despite it being dispensed, and one who was given it intramuscularly instead of intravenously. This left a total of 213 pregnancies during which IPM was administered intravenously. No women received multiple IV iron infusions during pregnancy. Prior to treatment, 132 women (62%) were identified as anaemic (Haemoglobin < 105 g/L). Of the remaining 81 non-anaemic women, iron studies were available and
confirmed iron deficiency (ferritin < 30 mcg/L) in 75 women (93%). Among anaemic women, iron studies were available for 124 women (94%) of which 122 (98%) were confirmed IDA. A total of 14 women (6%) did not have any data on iron studies prior to treatment.

Compared to non-anaemic iron deficient women, a lower proportion of anaemic women were Caucasian (66% vs. 82%; P=0.04). Anaemic women also had a later booking gestation (16.8 weeks versus 14.3; P=0.005) and were more likely to have trialled oral iron therapy prior to IV iron treatment (82% vs. 59%; P<0.001) (Table 1). Mean gestation at treatment was 33.5 weeks and 32.6 weeks for the IDA and non-anaemia iron deficiency groups. The median prescribed intravenous iron dose was 1000 mg (Range: 600 – 1500 mg) and 1400 mg (Range: 800 – 2000 mg) for women with non-anaemic iron deficiency and IDA respectively. Evaluation of the prescribed doses against the dose recommended in the local hospital clinical guideline demonstrated that a similar proportion of doses were in accordance with the recommended guideline dose in women with non-anaemic iron deficiency and IDA respectively (86% versus 81%; p=0.311).

When stratified according to maternal BMI, among women with IDA, 6% (n=4/64) with a BMI < 25 kg/m² compared to 31% (n=21/68) with a BMI ≥ 25 kg/m² received a dose below recommended (p<0.001). No such difference was seen among women with non-anaemic iron deficiency, with 12% (n=4/34) of women with a BMI < 25 kg/m² compared to 15% (n=7/47) of women with a BMI ≥ 25 kg/m² receiving a dose lower than that recommended by the guidelines (p=0.754).

Safety
Overall, 50/213 women (23.5%) experienced an ADR of which 8 (16%) were local infusion site reactions and 43 (86%) were systemic reactions (n=1 experienced both a local and a systemic reaction) (Figure 1). Treatment was ceased in 16/213 women (8%) due to intolerable adverse events. Of these 16 women, the infusion was recommenced on the same day for 8 (50%) women of which 1 required infusion rate modification. For 2/16 (13%) other women, the infusion was recommenced on a separate day with premedication (cetirizine 10mg administered in both women and additional hydrocortisone 250 mg intravenously in one) of which 1 had their infusion commenced at a slower rate. The remaining 6/16 (38%) women ceased treatment completely. Rate modification was also required in one woman without cessation of treatment at any point. In total, 23/50 (46%) women experiencing an ADR required medical treatment to manage the symptoms.

Most commonly reported reactions were local reactions (painful or swollen infusion site) (n=8; 4%), or systematic reactions including headache (n=8; 4%), and symptomatic hypotension (n=8; 4%) (Table 2). One woman experienced a severe anaphylactic reaction accompanied with wheezing, chest tightness and elevated blood pressure which required complete treatment cessation. There was no statistically significant association between the likelihood of an ADR occurrence and potential influencing factors including the dose administered (High [> 1000 mg]: 25% versus Low [≤ 1000 mg]: 21%; p=0.722), previously documented maternal allergies or adverse drug reactions (Allergy history: 25% versus No Allergy History: 23%; p=0.735), anaemia status (IDA: 26% versus Non-Anaemic Iron Deficiency: 20%; p=0.405), anaemia severity (Non-Anaemic Iron Deficiency: 20%, Mild Anaemia: 24%, Moderate Anaemia: 27%, and Severe Anaemia: 24%; p=0.739) or maternal BMI (Underweight: 40%, Normal Weight: 21%, Overweight: 21%, Obese: 26%; p=0.391).
Efficacy

Haemoglobin levels at delivery were available for 118 women (89%) in the IDA group and 73 women (90%) in the non-anaemic iron deficient group. Significant increases in haemoglobin were evident from prior to infusion until delivery among all anaemia severity levels (all p<0.001), with the largest increase seen among women with severe anaemia (Figure 2). The presence of anaemia at delivery was 1% (n=1/73), 7% (n=2/30), 16% (n=9/55), and 18% (n=6/33) among women with non-anaemic iron deficiency, mild anaemia, moderate anaemia, and severe anaemia respectively that received IV IPM.

When restricted to women with confirmed IDA (n=132), mean change in haemoglobin from prior to IV iron infusion until delivery (adjusted beta 7.9 g/L 95% CI 2.2 to 13.7 g/L; n=118) was significant greater among those who received the recommended compared to those who received a dose below recommended. Compared to women who received a below recommended dose of IV iron, women receiving the recommended dose were more likely to experience treatment success, defined as a 20 g/L increase in haemoglobin by delivery (62% versus 28%; p=0.010), but no difference in the presence of anaemia at the time of delivery (Haemoglobin <105 g/L) was evident (13% versus 16.7%; p=0.709). Further, postpartum haemorrhage and the requirement for a postnatal blood transfusion occurred in 17% (n=18/107) and 8% (n=8/107) compared with 16% (n=4/25) and 4% (n=1/25) of women who received a dose equal to or above recommended compared with dose below recommended respectively.

Perinatal Outcomes

One pregnancy in the IDA group resulted in a stillbirth, occurring 3 months following IV iron administration. The proportions of vaginal delivery (58% versus 50%), elective caesarean
section (30% versus 35%), and emergency caesarean section (12% versus 16%) were similar between IDA and non-anaemia iron deficiency groups. Similarly, prevalence of induction of labour (27% versus 32%), delivery by caesarean section (42% versus 51%), preterm birth (15% versus 16%), low birthweight (14% versus 9%), and postpartum haemorrhage (17% versus 16%) were similar between the IDA and non-anaemic iron deficiency groups. Median [range] for gestation (39 [28-41] weeks versus 39 [30-41] weeks) and birthweight (3343 [1275-4745] grams versus 3420 [1230-4705] grams) were also similar between IDA and non-anaemia iron deficiency groups. Overall, the median (range) number of days from IV iron administration to delivery was 29 (1-149) days.

Discussion

While the use of IV IPM was associated with significant improvements in haematological parameters, it was also associated with a much higher prevalence of adverse reactions than previously reported in the published literature, affecting approximately 1 in 4 women. Overall, IV IPM was highly effective in raising haemoglobin levels by time of delivery resulting in resolution of anaemia in the vast majority of pregnant women. These findings are consistent with those from previously published studies. Furthermore, it is evident that anaemia was resolved in a similar proportion of women who received a dose equal to or above recommended and those who received a dose below recommended. However, the degree of correction varied significantly as women who received a dose equal to or above recommended were more likely to have achieved a successful haemoglobin response at delivery than women given a dose lower than recommended. Consequently the mean haemoglobin at delivery was also significantly different among the two groups. Low haemoglobin level at delivery is associated with increased perinatal morbidity and mortality;
hence, adequate restoration of levels by the time of delivery is vital for optimum perinatal outcomes.

The prevalence of adverse reactions identified in this study (23.5%) was much higher than the 0% to 5% prevalence reported in the literature. When restricted to those considered moderate-severe, 32 women (15%) experienced an ADR requiring treatment cessation, rate modification, or medical treatment of symptoms. Singh et al. reported no (0%) adverse reactions among a total of 50 exposed women; however, all women were pre-treated with 25mg of intramuscular promethazine. Similarly, Sogbanmu et al. observed an ADR prevalence of 4.5% among 22 women, while all women again received pre-medication with 50mg of intramuscular promethazine. In contrast, a recent Australian study by Khalafallah et al. examining the use of IV IPM did not administer pre-medication, but reported a similarly low prevalence of ADRs (2.2%) among 92 women. Observed ADRs were urticarial reactions of which 100% required treatment cessation. While it is possible that factors such as pre-medication may have influenced the observed difference in ADRs, these have not been universally employed in previous studies. Therefore, other factors such as staff awareness of ADRs and the requirement to monitor women receiving IV iron for ADRs as part of local clinical guidelines at our hospital may explain the higher prevalence. Such a high prevalence of ADRs lends support towards consideration and use of alternative formulations of IV iron such as ferric carboxymaltose, which has been increasingly studied in pregnancy, does not require a test dose, and has been associated with a much lower risk of ADRs.

The high prevalence of use of IV IPM in the management of non-anaemic iron deficiency was unexpected, with no clinical studies to guide appropriate use of IV iron for this indication. There is evidence that low iron stores in early pregnancy has a negative impact on
pregnancy outcomes, with babies of women with non-anaemic iron deficiency weighing on average 192 grams less than those of women with normal iron stores.\textsuperscript{11} While a recent clinical practice survey of health care professionals highlighted strong interest in the identification and management of non-anaemic iron deficiency in pregnancy, clinicians had reservations on the use of intravenous iron for treatment.\textsuperscript{12} Overall, the impact and subsequent treatment of non-anaemic iron deficiency in pregnancy is poorly understood and represents a clear evidence-practice gap for future research.

Approximately 1 in 5 prescribed doses were not in accordance with the locally recommended guideline dose for managing iron deficiency anaemia, increasing to 1 in 3 prescribed doses being lower than that recommended by the guidelines for women who were overweight or obese. This is potentially suggestive of the clinician’s decision to cap or modify the dose after its calculation, or use an alternative dosing weight such as ideal body weight, potentially due to concerns relating to overdosing these women. However, there are no published studies exploring optimal dosing of IV iron in pregnancy, nor studies exploring optimal dosing of IV iron among adults who are overweight/obese. Anecdotally, it has been suggested that dosing for women who are overweight/obese should be based on ideal body weight, rather than current weight, but the optimal approach remains to be determined. Counteracting this are potential concerns relating to the unknown harms of administering excess IV iron, with any potential negative consequences on the fetus remaining undetermined. Supporting such potential concerns are data associating adverse pregnancy outcomes with high haemoglobin concentrations.\textsuperscript{13-14} Therefore, studies investigating both maternal and neonatal outcomes in this population according to different dosing strategies is urgently needed to optimise IV iron dosing.
This study has a number of strengths. With a total of 213 women, this is the largest study evaluating the use of IV IPM in pregnancy, compared to the cumulative total of 164 women included in previous publications. Case notes for 100% of women identified as being dispensed IV IPM were reviewed and a variety of resources were used, including paper-based and electronic records, to capture data as much complete data as possible on these women.

The limitations of this study are consistent with its retrospective nature. We were reliant on information obtainable from electronic or paper-based records and on tests ordered by clinicians as part of routine clinical care. For example, data on haemoglobin values at delivery were obtainable in 90% of women compared with only 54% of women at 2 to 4 weeks following the IV iron infusion. Furthermore, iron studies were not available for 7% of women, making it impossible to determine if they were truly iron deficient. In addition, we did not have data regarding oral iron use following IV iron administration. Lastly, while the high prevalence of identified adverse events suggests that poor documentation was unlikely to be a significant issue, it is still possible that represents an underestimate of total adverse reactions.

**Conclusion**

Intravenous IPM is effective in the treatment of iron deficiency anaemia in pregnancy; however, a higher rate of adverse drug reactions was noted (23.5%) in this study compared to that previously published in the literature. Despite success of treatment, a significant number of women received a dose lower than recommended by local clinical guidelines, with the dose received associated with significant differences in haematological response, highlighting the need of IV iron dose optimisation especially in overweight or obese women.
Disclosure of interests

The authors have no conflicts of interests to disclose

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Figures and Tables

Table 1. Characteristics of women receiving intravenous iron polymaltose during pregnancy

Table 2. Description of adverse drug reactions (ADRs) to intravenous iron polymaltose administration and their occurrence

Figure 1: Prevalence of adverse drug reactions (ADRs) and management outcomes associated with use of iron polymaltose in pregnancy

Figure 2. Mean (±SD) haemoglobin change across pregnancy according to anaemia severity at the time of intravenous iron polymaltose infusion
References


*One woman experience both a local and systemic ADR*
Table 1. Characteristics of women receiving intravenous iron polymaltose during pregnancy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-Anaemic Iron Deficiency (n = 81)</th>
<th>Iron Deficiency Anaemia (n = 132)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years), mean (SD)</td>
<td>29.5 (6.7)</td>
<td>28.6 (5.5)</td>
<td>0.258</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>66 (81.5%)</td>
<td>87 (65.9%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Aboriginal</td>
<td>2 (2.5%)</td>
<td>14 (10.6%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (2.5%)</td>
<td>9 (6.8%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11 (13.6%)</td>
<td>22 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>Booking BMI (kg/m²), mean (SD)</td>
<td>27.3 (6.6)</td>
<td>26.6 (6.8)</td>
<td>0.484</td>
</tr>
<tr>
<td>Parity &gt; 1, n (%)</td>
<td>59 (73%)</td>
<td>92 (70%)</td>
<td>0.624</td>
</tr>
<tr>
<td>Previous Pregnancy &lt; 1 Year Ago, n (%)</td>
<td>6 (7%)</td>
<td>8 (6%)</td>
<td>0.700</td>
</tr>
<tr>
<td>Oral Iron Trial, n (%)</td>
<td>48 (59%)</td>
<td>107 (82%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Oral Iron Intolerance, n (%)</td>
<td>21 (26%)</td>
<td>27 (21%)</td>
<td>0.328</td>
</tr>
<tr>
<td>Gestation at Treatment (Weeks), mean (SD)</td>
<td>32.6 (5.1)</td>
<td>33.5 (3.7)</td>
<td>0.144</td>
</tr>
<tr>
<td>Plurality (fetal count &gt; 1), n (%)</td>
<td>1 (1.2%)</td>
<td>10 (7.6%)</td>
<td>0.055</td>
</tr>
<tr>
<td>Booking Gestation (Weeks), mean (SD)</td>
<td>14.3 (4.9)</td>
<td>16.8 (6.7)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
**Table 2.** Description of adverse drug reactions (ADRs) to intravenous iron polymaltose administration and their occurrence

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local Reactions</strong></td>
<td></td>
</tr>
<tr>
<td>Painful, swollen infusion site</td>
<td>8 (16%)</td>
</tr>
<tr>
<td><strong>Systemic Reactions</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Symptomatic Hypotension</td>
<td>8 (16%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>7 (14%)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Heat sensation</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Blurry vision</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Itchiness</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Muscle pain</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Tingling lips</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Decrease in oxygen saturation (Asymptomatic)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Elevated Blood Pressure</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>Total number of women experiencing an ADR</strong></td>
<td>50*</td>
</tr>
</tbody>
</table>

*total number of reactions experienced do not add up to the total number of women as some may have experienced more than one adverse drug reaction.
Figure 2. Mean (±SD) haemoglobin change across pregnancy according to anaemia severity at the time of intravenous iron polymaltose infusion