

Ferumoxytol for the treatment of iron deficiency and iron-deficiency anemia of pregnancy

Jesse Gerb, William Strauss, Richard Derman, Vanessa Short, Ben Mendelson, Huzefa Bahrain and Michael Auerbach 

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Abstract

Introduction: A litany of recent evidence supports the morbidity of intra-natal iron-deficiency anemia and its prodrome, iron deficiency. Oral iron administered during second and third trimesters does not get to the developing fetus if the mother is iron deficient. This is especially concerning as the rapidly developing fetal brain is in particular need of iron sufficiency. Intra-natal iron deficiency is associated with autism, schizophrenia and abnormal brain structure. The obstetrical literature reports an unacceptably high incidence of gastrointestinal adverse events with oral iron. The time iron honored standard in the United States for intravenous iron replenishment in gravidas is iron sucrose. While safe and effective, four to seven visits are required to accomplish what newer formulations can achieve with one.

Methods: Ferumoxytol is a superparamagnetic iron oxide linked to polyglucose sorbitol carboxymethylether-binding elemental iron tightly allowing administration of complete replacement doses in 15–30 min. Herein, we report the results of 131 consecutive, non-selected, iron-deficient second- and third-trimester pregnant women who received either 510 mg of intravenous (IV) ferumoxytol twice or 1020 mg once.

Results: Hemoglobin and iron parameter increments were highly statistically significant. No adverse events were reported. We report how a single infusion is safe and effective as the same dose over two visits, saving an unnecessary visit and IV placement, while reducing cost.

Conclusion: Ferumoxytol represents an efficacious and safe method of administration of IV iron which improves convenience for patients and practitioners, and is cost saving due to fewer visits.

Keywords: intravenous iron, iron deficiency, pregnancy, total dose infusion

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Correspondence to:
Michael Auerbach
Auerbach Hematology and
Oncology, 5233 King Ave
Suite 308, Baltimore, MD
21237, USA

Department of Medicine,
Georgetown University
School of Medicine,
Washington, DC, USA
[mauerbachmd@
abhemonc.com](mailto:mauerbachmd@abhemonc.com)

Jesse Gerb
Ben Mendelson
University of Maryland,
College Park, MD, USA

William Strauss
AMAG Pharmaceuticals,
Waltham, MA, UK

Richard Derman
Associate Provost for
Global Affairs, Thomas
Jefferson University,
Philadelphia, PA, USA

Vanessa Short
Department of Obstetrics
and Gynecology, Thomas
Jefferson University,
Philadelphia, PA, USA
Thomas Jefferson
University, Philadelphia,
PA, USA

Huzefa Bahrain
Auerbach Hematology
and Oncology, Baltimore,
MD, USA

Plain language summary

One or two infusions of intravenous iron for iron deficiency or iron-deficiency anemia of pregnancy simplifies care

This study was conducted to highlight the inconvenience of multiple doses of IV iron and how administering the same dose in one or two infusions simplifies care. We report how a single infusion is as safe and effective as the same dose over two visits, saving an unnecessary visit and IV placement, while reducing cost. This study supports a growing body of evidence, to date, unreported, with ferumoxytol in pregnancy, reporting improved convenience and decreased costs with higher doses of IV iron in one or two visits.

Introduction

The magnitude of morbidity of iron-deficiency anemia (IDA), and its prodrome iron deficiency, is becoming more and more apparent in pregnancy with a litany of high-quality publications in the recent literature. In a prospective study of 2400 iron-deficient women supplemented with oral iron,¹ mothers' parameters improved; however, 45% of the neonates were iron deficient, based on cord-blood ferritin concentrations. A more recent, particularly poignant report of a cohort of 532,232 Swedish individuals² testing the hypothesis that 'anemia diagnosed in mothers during pregnancy is associated with an increased risk of autism spectrum disorders,' reported anemia at any time during pregnancy was associated with a statistically significant risk. Among the multifactorial etiologies of anemia in pregnancy, iron deficiency is the overwhelmingly most common. Supporting the urgency of addressing iron deficiency and consistent with the result of the Swedish study, a recent review in the American Journal of Obstetrics and Gynecology³ noted that the rapidly developing fetal brain is at particular risk of iron deficiency, which can occur as a proximate result of maternal iron lack. This review cogently reported low maternal gestational iron intake is associated with autism, schizophrenia, and abnormal brain structure in the offspring with documented deficits which can be measured with validated tools of recognition memory, slower speed of processing and poorer bonding, which persist after postnatal iron repletion. These daunting observations stress the importance of intra-natal iron sufficiency in deference to postnatal repletion.

It is self-evident to write that treatment of iron deficiency of pregnancy is iron replacement. The frontline standard, oral iron, is inexpensive, widely available and in the non-gravid state, often effective when taken and tolerated. Sadly, this duet is the exception rather than the rule. A high-quality meta-analysis of 6831 patients, many of whom were pregnant, reported greater than 70% of those to whom oral iron was prescribed reported unacceptable gastrointestinal perturbation,⁴ and the obstetrical literature has numerous reports of unacceptably high incidences of gastrointestinal side effects.^{5,6} These data have led to recommendations that intravenous (IV), and not oral iron, be frontline therapy for gravidas in the second trimester, with hemoglobin concentrations <10.5 g/dl and for all anemic women in the third trimester.^{7,8} The recently revised United Kingdom

guidelines are consistent with these recommendations⁹ ("IV iron should be considered from the second trimester onwards for women with confirmed IDA who are intolerant of, or do not respond to, oral iron" (2B). IV iron should be considered for women who present after 34 weeks' gestation with confirmed IDA and hemoglobin of <100 g/dl (1C).

Multiple formulations of IV iron are available for commercial use in North America, Europe, and Asia. Iron sucrose, the often standard formulation for iron repletion in pregnancy, is safe and effective. However, unlike newer formulations with carbohydrate shells which bind elemental iron more tightly, allowing complete replacement of iron deficits in 15–30 min, doses of iron sucrose exceeding 200–250 mg are proscribed¹⁰ due to an unacceptably high incidence of vasoactive reactions.

One of these newer formulations, ferumoxytol (Feraheme, AMAG Pharmaceuticals, Waltham, MA, USA) is a superparamagnetic iron-oxide compound linked to polyglucose sorbitol carboxymethylether.¹¹ This complex carbohydrate coating binds elemental iron tightly, allowing administration of large doses in 15–30 min. Ferumoxytol was approved in the United States in 2009 for use in iron deficiency associated with chronic kidney disease. The original label allowed a single vial of 510 mg in 17 ml, to be infused very rapidly in as fast as 17 s (1 ml/s). This approach was associated with an unacceptably high incidence of infusion reactions, likely due to complement activation by labile free iron.^{12,13} In 2015, the US Food and Drug Administration (FDA) issued a change in the label for administering ferumoxytol as a slower 510 mg infusion over 15 min, with a second infusion approximately 1 week later. To obtain a broader label, the manufacturer performed a double-blind comparison of ferumoxytol with ferric carboxymaltose (another formulation which allows a large dose to be administered over a short period of time) in 1997 patients.¹⁴ Two vials (1020 mg) of ferumoxytol were compared with two vials (1500 mg) of ferric carboxymaltose administered according to FDA labeling, with safety as the primary endpoint. A blinded, independent safety monitoring board assessed all potential reports for toxicity–hypersensitivity reactions, including anaphylaxis or hypotension. No difference in adverse events was noted, nor was there a clinically significant difference in change in hemoglobin

concentration at 5 weeks, despite the higher dose of ferric carboxymaltose. As a result, in February of 2018, ferumoxytol was granted a broad label for use in all causes of IDA after oral iron intolerance, or for those conditions in which oral iron is ineffective or harmful.

In 2017, we published the first prospective study of intravenous iron performed in the United States in 74 oral-iron-intolerant, iron-deficient second- and third-trimester gravidas.¹⁵ A highly statistically significant increase in hemoglobin concentration and iron parameters was reported, as well as a statistically significant increment in patient-reported outcomes using a Visual Linear Analog Scale analysis. The formulation and administration method used was 1000 mg of low-molecular-weight iron dextran administered over 1 h. No serious adverse events were observed, and the authors concluded that a total dose infusion of intravenous iron represented an improved method of iron repletion in pregnancy, and was safe, effective, associated with fewer side effects than oral iron, more convenient, and less expensive than those formulations requiring multiple infusions. Subsequently, after thousands of infusions of ferumoxytol administered in our practice as 510 mg in two intravenous infusions on different days, according to the FDA label, the insurance carriers of the bulk of our patient population were approached. We had previously published the safety, efficacy and felicitousness of a single 1020 mg infusion of ferumoxytol given in 15 min¹⁶ in a 60-patient pilot study, as well as an updated safety and efficacy analysis of our experience in 184 consecutive, non-selected iron-deficient patients across a wide spectrum of disorders, who received 1020 mg of ferumoxytol as a single 30 min infusion.¹⁷ Of these 184, 33 were pregnant and in the second or third trimester. In both series, no serious adverse events were observed, with an efficacy defined as ≥ 1 g increment in hemoglobin concentration over a minimum of 4 weeks that approached 100%. Since that publication, we have treated hundreds of pregnant women with a total dose infusion of 1020 mg ferumoxytol in 30 min without a single serious adverse event. Herein, we report the results of the first 131 consecutive, non-selected, iron-deficient gravidas referred to our practice for treatment of IDA of pregnancy, who received either a single 1020 mg or two 510 mg infusions of ferumoxytol.

Methods

The electronic medical records of 131 consecutive, non-selected pregnant women in the second or third trimester referred to a community hematology practice for the evaluation and treatment of IDA were reviewed. The start date was chosen with the administration of the first total dose infusion of 1020 mg ferumoxytol following the initial insurance approval, by Maryland Blue Cross Blue Shield CareFirst, for the total dose infusion. While off label, this method of administration is standard in our practice and all demographic data were redacted, such that institutional review board approval and informed consent was obviated. A secure patient portal website was utilized to access data. Baseline de-identified demographic information (age, week of gestation at time of treatment, gravidity, and parity) was obtained. Baseline laboratory data were obtained within 4–5 weeks of administration of ferumoxytol, along with the ferumoxytol dosing regimen. Follow-up data consisted of hemoglobin concentration and iron indices at approximately 4 weeks (window 3–5 weeks). Where available, pregnancy outcomes and neonatal statuses were obtained. Any, and all, adverse events, occurring during or immediately after administration of IV iron, as well as any reported in the following week were collected, including any treatment administered or pre-medication and resolution of the event.

Consecutive, non-selected pregnant women referred for treatment of IDA in the second or third trimester of pregnancy, received either two infusions of 510 mg of ferumoxytol over 15 min on separate days, 3–8 days apart (according to label), or 1020 mg as a single infusion over 30 min (as permitted by insurance). No pre-medication was administered, unless there was a history of multiple drug allergies or asthma ($n = 4$), in which case methylprednisolone and ranitidine were administered intravenously prior to the infusion. The decision to administer IV iron was made on the basis of a serum ferritin < 30 ng/ml and/or a percent transferrin saturation (TSAT = serum iron/total iron-binding capacity) $< 20\%$ irrespective of hemoglobin concentration (although hemoglobin results were captured).

Participant demographic and pregnancy characteristics, and baseline and follow-up laboratory values were described overall and within each

Table 1. Demographic and pregnancy characteristics.

	Total <i>n</i> = 131	510 mg <i>n</i> = 79	1020 mg <i>n</i> = 52	<i>p</i> value ^a
Maternal age, years, mean (SD)	29.6 (5.8)	29.8 (5.8)	29.3 (5.9)	0.60
Gravida, mean (SD)	3.1 (1.7)	3.0 (1.6)	3.3 (1.9)	0.32
Gravida, <i>n</i> (%)				
1	23 (18.4)	14 (18.7)	9 (18.0)	0.91
2	31 (24.8)	20 (26.7)	11 (22.0)	
3	22 (17.6)	12 (16.0)	10 (20.0)	
4+	49 (39.2)	29 (38.7)	20 (40.0)	
Parity, mean (SD)	1.2 (1.0)	1.2 (1.1)	1.1 (0.9)	0.59
Parity, <i>n</i> (%)				
0	36 (29.0)	23 (31.1)	13 (26.0)	0.52
1	47 (37.9)	25 (33.8)	22 (44.0)	
2+	41 (33.1)	26 (35.1)	15 (30.0)	
Gestational age at first treatment, weeks, mean (SD)	29.4 (5.7)	30.0 (5.3)	28.4 (6.1)	0.11
^a <i>p</i> value from Chi-square test or <i>t</i> test of 510 mg versus 1020 mg. SD, standard deviation.				

study group. Means and standard deviations were produced for continuous variables, and frequency counts and percentages were generated for describing variables that were dichotomous or polytomous in nature. The balance of characteristics between the 510 mg and the 1020 mg groups were compared using two-sample *t* tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Changes in laboratory values from baseline to follow up were calculated, and the mean change in values was compared using *t* tests.

Results

A total of 52 subjects received 1020 mg as a single 30 min infusion, and 79 as 510 mg in two 15 min infusions on different days. Demographic and pregnancy characteristics of all subjects and by type of infusion (510 mg or 1020 mg) are found in Table 1. The mean age for all subjects was 29.6 years with a range of 19–42 years. The mean gestational age was 29.4 weeks with a range of 14–38 weeks. A total of 18 women were in the

second trimester and 107 in the third. The mean gravidity was 3.1, with a range of 1–10 (Table 1).

The mean time to follow up following the initial infusion was 13.7 weeks (range 4–29 weeks). The mean change in hemoglobin from baseline to follow up was 1.9 g/dl ($p < 0.0001$). A similar benefit was observed for both TSAT (mean change 17.1%; $p < 0.0001$) and serum ferritin (mean change 113.3 ng/ml; $p < 0.0001$).

Baseline and follow-up lab values of all subjects and by type of infusion (510 mg or 1020 mg) are shown in Tables 2 and 3, respectively. The mean change in hemoglobin from baseline to follow up was 1.8 g/dl and 2.3 g/dl for the 510 mg and 1020 mg groups, respectively ($p = 0.80$). The mean change in TSAT from baseline to follow up was 19.1% and 14.3% for the 510 mg and 1020 mg groups, respectively ($p = 0.30$). The mean change in ferritin from baseline to follow up was 134.9 ng/ml and 79.2 ng/ml for the 510 mg and 1020 mg groups, respectively ($p = 0.03$). The mean change in mean corpuscular volume from

Table 2. Baseline hemoglobin and iron parameters.

	Total <i>n</i> = 131 mean (SD)	510 mg <i>n</i> = 79 mean (SD)	1020 mg <i>n</i> = 52 mean (SD)	<i>p</i> value ^a
Hemoglobin, g/dl	10.0 (0.9)	10.0 (0.9)	9.9 (0.1)	0.76
Ferritin, ng/ml	17.2 (26.3)	18.9 (32.8)	14.6 (10.4)	0.28
TSAT, %	12.1 (7.1)	12.4 (6.7)	11.7 (7.7)	0.58
MCV, fl	81.6 (7.3)	82.3 (7.0)	80.7 (7.7)	0.24

^a*p* value from *t* test of 510 mg versus 1020 mg.
MCV, mean corpuscular volume; SD, standard deviation; TSAT, transferrin saturation.

Table 3. Follow-up hemoglobin and iron parameters.

	Total <i>n</i> = 75, mean (SD)	510 mg, <i>n</i> = 48 mean (SD)	1020 mg, <i>n</i> = 27, mean (SD)	<i>p</i> value ^a
Hemoglobin, g/dl	11.9 (1.2)	11.8 (1.4)	12.1 (0.9)	0.36
Ferritin, ng/ml	129.6 (110.1)	151.6 (114.2)	94.9 (95.4)	0.04
TSAT, %	29.2 (18.7)	31.7 (19.5)	25.1 (16.9)	0.16
MCV, fl	84.0 (12.5)	83.0 (14.9)	85.7 (6.5)	0.28

^a*p* value from *t* test of 510 mg versus 1020 mg.
MCV, mean corpuscular volume; SD, standard deviation; TSAT, transferrin saturation.

baseline to follow up was 1.8 fl and 5.2 fl for the 510 mg and 1020 mg groups, respectively ($p = 0.29$).

Among all infusions of 1020 mg or 510 mg, minor infusion reactions were observed in 19, of which 11 occurred with the 510 mg infusion, and 8 with the 1020 mg infusion (Table 4). These reactions consisted of pressure in the chest and/or back, facial flushing, or nasal congestion. All were self-limited, resolved within minutes, and all but one (patient refused) received the planned dose. There were no serious adverse events, episodes of hypotension or hospitalizations. Prior to resumption of the planned therapy, 16 women received methylprednisolone and either ranitidine or famotidine without recurrence of the reaction. For the 72 in whom post-partum data were available, none reported adverse events at delivery.

Discussion

Recently published evidence reports statistically significant increments in neurodevelopmental disorders in children born with iron deficiency

compared with those sufficient. Failure to insure intra-natal iron sufficiency is associated with immediate¹⁸ and long-term deficits and with an increased risk of postnatal iron deficiency despite oral iron supplementation of the mother.^{19,20} These data shift the emphasis on iron repletion to intra-natal iron sufficiency rather than post-natal repletion. Additionally, iron deficiency is associated with preterm labor, peripartum hemorrhage and a small but measurable increment in maternal mortality. Oral iron, the current frontline therapy for iron deficiency of pregnancy is associated with gastrointestinal adverse events in the majority of women, with resultant poor adherence, informing on a need for IV iron. While iron sucrose, the time-honored standard for IV iron repletion in pregnancy is effective and safe, four to seven visits, each requiring the placement of an IV access device, are required. Therefore, there is need to add to the armamentarium of IV iron formulations that are more easily administered. In this report of 131 iron-deficient pregnant women with anemia, we report on the safety and efficacy of IV ferumoxytol, 79 of whom received two 510 mg doses and 52, 1020 mg once. Efficacy was

Table 4. Adverse reactions for 510 mg and 1020 mg ferumoxytol infusions.

	Subject	Symptom
510 mg	1	Flushing and chest pain (infusion stopped) then restarted and completed; flushing, SOB (infusion stopped and then completed)
	2	Abdominal pain, headache, flush, chest tightness
	3	Nasal congestion 10 min after ferumoxytol
	4	Lightheadedness
	5	Chest pressure, SOB, flushing, back pain
	6	SOB and chest pressure
	7	Flushing, chest pressure; resolved with fluids
	8	Chest tightness
	9	Nausea and nasal congestion
	10	Facial itching
	11	Flushing and nausea
1020 mg	1	Lightheadedness
	2	Flushing, infusion stopped, restarted at slower rate; completed without further difficulty
	3	Tightness in chest and SOB
	4	Fatigue
	5	Flushing, nausea after ranitidine and methylprednisolone
	6	Facial flushing; subsided when infusion stopped
	7	Cough, scratchy throat
	8	Cough

Adverse reactions for 510 mg: $n=11$; 1020 mg: $n=8$.
SOB, shortness of breath.

demonstrated by a mean hemoglobin increment of 1.9 g/dl (1.8 g/dl in the 510 mg given twice, and 2.3 g/dl in the 1020 mg infused once, cohorts, respectively). No serious adverse events were observed.

Consistent with these data, is a prospective study of 60 oral-iron-intolerant patients who received 1020 mg of ferumoxytol administered in 15 min.¹⁶ The primary endpoint was safety and tolerability, with secondary endpoints, change in hemoglobin concentration and TSAT. No serious adverse events were observed. The mean increments at 4 weeks and 8 weeks were 2.1 g/dl and 2.6 g/dl,

respectively. In a retrospective analysis of 176 consecutive, non-selected patients, 33 of whom were pregnant in the second and third trimester, all received 184 infusions of 1020 mg of ferumoxytol. No serious adverse events were observed.¹⁷

The approximate 2 g/dl increase in hemoglobin in this current series was comparable with the efficacy previously demonstrated with the 1020 mg administration,^{16,17} in populations with a diverse etiology of IDA, as well as what has been reported in the literature with the FDA-approved regimen of 510 mg given twice.^{14,21,22} Likely of even greater interest to practitioners is the safety and tolerability

of ferumoxytol given during the second or third trimester. Few adverse events, none serious, and all self-limited, occurred with either administration paradigm. This experience with the tolerability of ferumoxytol mirrors what we have noted with the use of several thousand doses of ferumoxytol in the authors' practice, as well as with the several other IV iron formulations we have employed.

The preponderance of published evidence supports an increased use of IV iron for iron deficiency of pregnancy. In this series of 131, we demonstrate the safety and efficacy of ferumoxytol in pregnancy. The ability to administer a full replacement dose of IV iron in 15–30 min, increases convenience to both practitioners and patients, decreases cost, and improves adherence.

Conflict of interest statement

Jesse Gerb, Vanessa Short, Ben Mendelson, and Huzefa Bahrain had no disclosures. William Strauss is a former employee of and consultant to AMAG Pharmaceuticals. Richard Derman is a consultant to AMAG Pharmaceuticals. Michael Auerbach received research funding from AMAG Pharmaceuticals, and contributed in educational, non-promotional programs for Pfizer and Pharmacosmos.

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ORCID iD

Michael Auerbach  <https://orcid.org/0000-0003-0707-8647>

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