Title:

Approaches for Optimising Intravenous Iron Dosing in Pregnancy: A Retrospective Cohort Study

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Contributions of Authors

AQ, BJ, and LEG conceptualised and designed the study, AQ and LEG carried out the initial analyses, LEG drafted the initial manuscript, AQ, BJ, and RMG assisted in the interpretation of results, and AQ, BJ, and RMG reviewed and revised the initial manuscript. All authors approved the final article for publication.

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Abstract

Aims: To examine the relationship between dose of intravenous iron administered during pregnancy according to different maternal body weight measures and subsequent treatment response.

Methods: Retrospective cohort study of pregnant women with confirmed iron deficiency anaemia who received intravenous iron polymaltose at a tertiary teaching hospital in Australia from January 1st, 2014 to January 31st, 2016. Diagnosis of anaemia and/or iron deficiency, infusion dosage characteristics, and haematological parameters were collected from paper-based case notes and electronic records. The dose of intravenous iron administered was examined relative to maternal total body weight [TBW], ideal body weight [IBW] (equation=45.5kg + 0.9 kg/cm for each cm over 152cm), and adjusted body weight (equation=IBW + [0.4 x (TBW – IBW)]).

Results: A total of 122 pregnancies were identified where women had confirmed iron deficiency anaemia and received a single infusion of intravenous iron polymaltose. Dose response relationships were evident between change in haemoglobin from treatment until delivery and intravenous iron dose according to adjusted body weight (adjusted beta coefficient 0.70 (95% CI 0.24 to 1.15) and pre-pregnancy total body weight (adjusted beta coefficient 0.83 (95% CI 0.36 to 1.29), but not ideal body weight (adjusted beta coefficient 0.37 (95% CI -0.04 to 0.78). Calculating iron deficit utilising adjusted body weight most closely matched that based on a physiological estimate of iron deficit according to weight-based total blood volume.

Conclusion: Optimal treatment outcomes in pregnant women requiring intravenous iron may be reached by dosing according to adjusted pre-pregnancy body weight, rather than ideal body weight.

Keywords: Anemia, Iron-Deficiency/drug therapy; Ferric Compounds/administration & dosage; Hematologic/drug therapy; Pregnancy; Dose-Response Relationship, Drug; Treatment Outcome

Main Text

Introduction

Iron deficiency is the leading cause of anaemia in pregnancy,[1] which in turn is associated with significant perinatal morbidity and mortality.[1,2] Therefore, improvements in haematological status in pregnancy through appropriate replenishment of depleted iron stores is considered important in supporting optimal perinatal outcomes.[3] Suggested approaches towards diagnosis and management of iron-deficiency anaemia in pregnancy can be found elsewhere.[4,5] According to such algorithms, intravenous iron therapy plays an important role where oral iron therapy is either not tolerated or unsuitable such as in the setting of imminent delivery, where rapid restoration of iron status is required.[4,5]

While a number of different intravenous formulations of iron have been studied in pregnancy,[6] dosing strategies are often inconsistent and there has been no examination of the optimal dosing weight to use when calculating body iron deficit and subsequent iron dose. This is of particular concern given the increasing prevalence of overweight and obesity in pregnancy, leading to confusion in what dosing weight to use.

Traditional dosing regimens have utilised the Ganzoni formula,[7] but this has been criticised for its difficulty in use, susceptibility to calculation errors, inconsistent use in clinical practice, and underestimation of total iron replacement requirements.[8] More recently, a Simplified Dosing Method has been trialled alongside the use of a new formulation of intravenous iron, ferric carboxymaltose,[9] but how doses calculated using this method compare to alternative regimens remains unclear. Therefore, this study aimed to explore the

relationship between the dose of intravenous iron administered and haematological outcomes and compare recommended doses according to different dose calculation methods.

Methods

Study Cohort and Data Collection

We conducted a retrospective cohort study of all women receiving intravenous iron polymaltose for the management of iron deficiency anaemia between January 1st, 2014 and January 31st, 2016 at Flinders Medical Centre (FMC) in Adelaide, South Australia. FMC is a tertiary level teaching hospital caring for more than 3,000 births each year. Pregnant women prescribed intravenous iron polymaltose were identified by matching the electronic pharmacy dispensing records to the electronic perinatal hospital records. We excluded women receiving IV iron who did not have anaemia. Paper-based case notes were then examined to verify that the infusion was administered and that women were indeed pregnant at the time of infusion. Women were identified as being anaemic based on a haemoglobin (Hb) value less than 110 g/L in the first trimester and 105 g/L during the second or first trimester.[10] Iron deficiency was defined as a serum ferritin less 30 mcg/L or serum transferrin ≤16%.[11] 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 from a combination of electronic and paper-based medical records.

Investigation of Dose Response Relationship

The local clinical practice guideline for intravenous iron is to calculate total iron deficit according to the Ganzoni equation:

Iron Dose = Weight x (Target Hb – Current Hb) x 0.24 + 500mg[7]

The guideline recommends a target Hb of 150g/L, but it does not specify which weight must be used when calculating the dose (i.e. whether to use pre-pregnancy or current weight). In order to investigate dose-response relationships, the prescribed dose was divided by different patient weights, including; booking weight (which was estimated to be a close approximation of pre-pregnancy weight), ideal body weight, and adjusted body weight. Ideal body weight was calculated using the following equation: 45.5kg + 0.9 kg/cm for each cm over 152cm.[12] Adjusted body weight was calculated using the following equation: IBW + [0.4 x (TBW – IBW)] [12].[13]

Response to IV iron was evaluated by exploring changes in Hb from immediately prior to IV iron infusion to 2–4 weeks post-treatment, and also at delivery. Women were classified as having treatment success if they had a Hb increase of 20g/L prior to delivery. The presence of anaemia at delivery (Hb <105g/L) was also examined.

Comparison of Dose Calculation Methods

Weight-based estimate of blood volume was determined using the equation developed by Feldschuh and Enson (1977): Blood Volume (mL) = [blood volume to body weight ratio (mL/kg)] x [body weight (kg)] = 45.2 + [25.3 x exp(-0.0198 x DDW)]. DDW is the deviation from desired weight (%) = 100 [body weight (kg) – DW (kg)]/[DW(kg)].[14] DW is desirable weight (kg) for women = 7.090 x exp[0.01309 x (body height[cm]).

The weight-based estimate of blood volume can then be used to estimate iron deficit according to Hb deficit using the following equation:

Iron deficit = [Hb deficit (g/L) x blood volume (L)] x iron content of Hb (1g Hb = 3.47 mg elemental iron). Added to this is the 500mg of elemental iron required to replenish body iron stores.[7]

The calculated iron deficit according to the weight-based estimate of blood volume was regarded as the true iron deficit and then compared to the dose of iron calculated according to the Ganzoni formula or Simplified Dosing Method (**Table 1**). For the purposes of comparison, we took a woman of average height (162cm), with varying degrees of anaemia (from 100g/L to 70g/L) and calculated iron deficits according to pre-pregnancy weight ranging from 60 to 100kg. Calculations using the Ganzoni formula were undertaken using three different dosing weights including total body weight, adjusted body weight, and ideal body weight. Calculations using the Simplified method solely rely on a weight less than or greater than or equal to 70kg.

Statistical Analysis

Adjusted differences in continuous (i.e. Hb Change) or categorical (i.e. Hb Success) outcomes according to increasing maternal intravenous iron dose (i.e. mg/kg according to ideal body weight, adjusted body weight, or total body weight) were compared using a linear regression analysis and a generalised linear model (Poisson distribution) with robust variance estimates (and resulting relative risks (RR) and 95% confidence intervals), respectively. Analyses were adjusted for possible confounders including gestation at the time of infusion, Hb status at the time of infusion, and maternal BMI. Statistical significance was defined as a two-sided p-value of <0.05. All data analysis was undertaken using Stata SE 14 (Stata, College Station, TX, USA).

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)

Results

A total of 122 pregnancies were identified where women had confirmed iron deficiency anaemia and received a single infusion of intravenous iron polymaltose. The number of women who had a repeat Hb at either 2-4 weeks post-infusion or prior to delivery was 65 and 110, respectively. There were only 9 women who did not have a repeat Hb at either time point, with characteristics of the study cohort outlined in **Table 2**.

The majority of women were of Caucasian ethnicity (65%), multiparous (67%), and had trialled oral iron prior to receiving an IV dose (79%), while a small number had documented intolerance to oral iron (20%). Approximately half were overweight or obese (54%) with a mean age of 28.5 (±5.5) years. On average, women were 33.2 (±3.6) weeks gestation with a mean Hb of 95 (±7) g/L at the time of infusion. The median dose of intravenous iron was 1400mg and ranged from 800mg to 2000mg.

Dose response relationships were evident between change in Hb from treatment until delivery and intravenous iron dose according to adjusted body weight (adjusted beta coefficient 0.70 (0.24 to 1.15) and pre-pregnancy total body weight (adjusted beta coefficient 0.83 (0.36 to 1.29), but not ideal body weight (adjusted beta coefficient 0.37 (-0.04 to 0.78) (**Table 3**).

Significant variability was evident in the calculated iron deficit and required dose according to different calculation methods (**Figure 1**). In all examples, using the Ganzoni formula and dosing according to adjusted body weight most closely estimated the iron deficit according to the weight-based total blood volume. As pre-pregnancy body weight increased (corresponding to overweight or obesity), the use of Ganzoni formula and total body weight or ideal body weight progressively led to over or under-dosing of iron respectively by as much as 200-500mg of iron, with greater discrepancy in dosing with greater anaemia severity. Similarly, calculating iron doses according to the Simplified Dosing Regimen often led to over or under-dosing of iron depending on which dosing weight was used and the severity of anaemia. When pre-pregnancy ideal body weight and total body weight were similar (i.e. when BMI <25), the dose recommended by the Simplified Dosing Method provided a close approximation to the iron deficit (±250mg). However, accuracy of dosing appeared to significantly change as total body weight increased. In the instance of mild anaemia (Hb above 100g/L), administering 1000 mg of iron according to ideal body weight (i.e. <70kg) using the Simplified Dosing Method resulted in underestimation of the iron deficit by 250-400mg in the setting of overweight/obesity. In contrast, where Hb is between 80-99g/L, administering 1500mg of iron according to ideal body weight using the Simplified Dosing Method remained within 200mg of the estimated iron deficit up to a body weight of 100kg. If given 2000mg of iron according to total body weight (i.e. ≥70 kg) using the Simplified Dosing Method, the administered dose would be 200-600mg in excess of the calculated iron deficit, representing potential overdosing. In the instance of severe anaemia (Hb around 70g/L), however, administering 1500mg of iron according to ideal body weight using the Simplified Dosing Method resulted in underestimation of the iron deficit by 200-400mg in the setting of overweight/obesity.

Discussion

The discovery of a dose-response relationship between increasing dose of intravenous iron according to total or adjusted pre-pregnancy body weight and improved haematological response is of great importance given the negative outcomes associated with anaemia in pregnancy. This, together with physiological data on estimated blood volumes, provides evidence that optimal treatment outcomes in pregnant women requiring intravenous iron may be reached by dosing according to adjusted body weight, rather than ideal body weight. Further, if using the Simplified Dosing Method to calculate iron doses (as is most commonly done with ferric carboxymaltose), significant caution must be applied when considering the appropriate dosing weight for women who are overweight or obese as the dose administered can over- or under-estimate total body iron deficit by as much as 500mg.

We are not aware of previous studies investigating the dose-response relationship for intravenous iron administration in pregnancy, nor any studies evaluating optimal dosing of iron in pregnant women who are overweight or obese. This is of significant importance given the increasing proportion of women entering pregnancy overweight or obese. Within Australia, as well as internationally, a number of clinical guidelines recommend dosing intravenous iron according to ideal body weight if the individual is overweight or obese.[15] This approach, however, does not appear to be informed by any direct evidence and appears in contrast to information provided from physiological and pharmacokinetic data. In general, medication dosing in overweight and obesity represents a common prescribing challenge as it is associated with alterations in drug pharmacokinetics.[16] These alterations can lead to requirements for changes in medication dosing regimens, but such alterations are medication specific and their resultant impact on clinical outcomes are variable and often not well studied. Given body composition varies as a function of total bodyweight, optimising dosing

in this population requires identification of size descriptors, such as adjusted body weight, that share a quantitative relationship with changes in pharmacokinetics and associated pharmacological activity. When it comes to intravenous iron, it has been previously demonstrated that pregnant women who are overweight or obese have a greater total blood volume,[17] which in turn would require a greater amount of iron to increase haemoglobin concentration relative to an individual of ideal body weight and a lower total blood volume.

Recently, studies have suggested that the administration of ferric carboxymaltose according to the Simplified Dosing Method produces superior haematological outcomes then the administration of iron sucrose according to the Ganzoni formula.[8,9] However, a key factor overlooked in these studies was that a normalised dosing weight was utilised for any individuals with a BMI>25 kg/m^2. That is, doses were capped at the weight corresponding to a BMI of 25 kg/m^2 for any individual with a BMI>25 kg/m^2. Our weight-based blood volume calculations clearly demonstrate an increase in iron requirements with increasing body weight, therefore it is not surprising that these previous studies found that capping the iron dose at a BMI of 25 kg/m^2 resulted in under-dosing. Regardless of this key factor, the findings have been routinely interpreted as superiority of the Simplified Dosing Method over the traditional Ganzoni formula and its use is now widespread in clinical practice as use of ferric carboxymaltose increases. Our dosing examples, however, clearly demonstrate the need for caution when using the Simplified Dosing Method to calculate iron doses as confusion around what dosing weight to use, which is the challenge in treating women who are overweight or obese, can lead to significant over- or under-estimate total body iron deficit. Therefore, the dosing of intravenous iron in pregnancy appears to reflect a more nuanced maternal and fetal risk versus benefit consideration. Based on current evidence, the potential

under-dosing of intravenous iron and resultant sub therapeutic treatment response would appear a more significant concern in pregnancy, especially given the increasing prevalence of overweight and obesity. That said, it must be noted that the potential harms of over-dosing iron are not well studied. This suggests that dosing of intravenous iron in pregnancy lends itself to a more individualised approach with consideration of factors such as overweight or obesity, pre-pregnancy as opposed to current body weight, time to delivery, and likelihood of further bleeding, all influencing the ideal dose to be administered. A key factor often overlooked when using the Simplified Dosing Method is that it includes 500mg to replace body iron stores. The question is whether this is required in late pregnancy, as long as haemoglobin is increased to an acceptable level then iron stores will increase by as much as 200-300mg as a result of maternal erythrocyte recycling following delivery.[18] Of course, this recycling will not occur among women who experience significant blood loss during or following delivery and represents the key challenge facing clinicians when determining the optimal dose to prescribe.

Both pregnancy and obesity are associated with dysregulation of iron metabolism. Pregnancy is associated with a reduction in the iron-regulatory hormone hepcidin, which is involved in regulating intestinal iron absorption, plasma iron concentrations, and tissue iron distribution.[19] Hepcidin levels decrease across pregnancy, with lowest levels apparent in the third trimester, and serve to alter iron homeostasis in an attempt to match increasing iron demands to meet the expansion in maternal haemoglobin mass and to satisfy the requirements for fetal growth.[4] Similarly, obesity is associated with an increased risk of iron deficiency anaemia.[20] While obesity is also associated with an increase in total blood volume and resultant dilutional hypoferremia, in contrast to pregnancy it is associated with an increase in circulating hepcidin.[20] These higher levels of hepcidin are associated with a reduction in

intestinal iron absorption (leading to inadequate absorption of dietary iron and an increased risk of treatment failure with oral iron) and resultant decrease in iron availability,[20] in addition to impaired placental iron transfer and subsequent reduced neonatal iron status[21]. While further research is required to investigate the relationship between obesity, iron status, and response to iron treatments in pregnancy, current evidence points towards the important role of optimising intravenous iron dosing in these women to enhance perinatal health outcomes.

A limitation of this study is the reliance on information obtainable from electronic or paper-based records and on tests ordered by clinicians as part of routine clinical care, with complete data on haematological outcomes not available for all women at every time point studied. We did not have data available on oral iron use following receipt of IV iron which may have influenced treatment response. Further, any suggestion for increasing intravenous iron dosing must be balanced against the unknown harms of administering too much IV iron, with any potential negative consequences on the foetus remaining undetermined. Supporting such potential concerns are data associating adverse pregnancy outcomes with high Hb concentrations.[22,23]

Conclusion

In conclusion, we observed a dose-response relationship between increasing dose of intravenous iron according to total or adjusted pre-pregnancy body weight and improved haematological response. In light of these findings, further studies investigating both maternal and neonatal outcomes according to different dosing strategies are urgently needed to optimise intravenous iron dosing. In the meantime, clinicians should be cautious about utilising Simplified Dosing Methods and lean body weight for calculating intravenous iron

doses, as these can lead to significant over- or under-dosing. Ideally, adjusted body weight should be utilised to calculate the most accurate iron deficit and then an individualised approach taken to take into account the clinical circumstances of the individual, including future bleeding risk and requirement for replacement of iron stores prior to delivery, before determining the most appropriate dose.

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Conflicts of Interest

The authors declare that they have no competing interests.

Table and Figures:

Table 1: Different Intravenous Iron Dose Calculation Methods

Table 2: Characteristics of women who received an intravenous iron polymaltose infusion for the management of iron deficiency anaemia according to whether haematological outcome data was available following the infusion until delivery.

Table 3: Dose-response relationship between intravenous iron dose relative to maternal body weight and haematological outcomes

Figure 1: Differences in calculated iron dose according to the Ganzoni formula or Simplified dosing method compared with blood volume based iron deficit for different levels of anaemia. Values were calculated for a 162 cm tall woman weighing between 60 and 100kg.

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Table 1. Different Intravenous Iron Dose Calculation Methods

A. Ganzoni Formula[7]

Iron Dose (mg) = Dosing Weight x (Target Hb – Current Hb) x 0.24 + 500mg‡

‡ Estimated amount of iron required to replenish iron stores

B. Simplified Dosing Method[9]

	Dosing Weight	
Hb Level	<70 kg	≥ 70 kg
≥100 g/L	1000 mg	1500 mg
<100 g/L	1500 mg	2000 mg

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Table 2. Characteristics of women who received an intravenous iron polymaltose infusion for the management of iron deficiency anaemia according to whether haematological outcome data was available following the infusion until delivery.

	Haematological outcome data	
	Yes	**No**
Variable	**n=113**	**n=9**
Age (Years), mean (SD)	28.5 (5.5)	28.2 (7.3)
Ethnicity, n (%)		
Caucasian	74 (65)	7 (78)
Aboriginal	11 (10)	1 (11)
Asian	8 (7)	0 (0)
Other	20 (18)	1 (11)
BMI (kg/m^2), mean (SD)	26.8 (6.9)	23.5 (3.2)
BMI Category, n (%)		
Underweight (<18.5)	11 (10)	0 (0)
Normal Weight (BMI 18.5 – 24.9)	41 (36)	8 (89)
Overweight (BMI 25-29.9)	34 (30)	0 (0)
Obese (BMI>30)	27 (24)	1 (11)
Parity > 1, n (%)	76 (67)	8 (89)
Previous Pregnancy < 1 Year Ago, n (%)	8 (7)	0 (0)
Oral Iron Trial, n (%)	89 (79)	8 (100)
Oral Iron Intolerance, n (%)	23 (20)	1 (11)
Gestational Age at Treatment (Weeks), mean (SD)	33.2 (3.6)	36.7 (1.9)
Plurality (foetal count > 1), n (%)	9 (8)	9 (0)

Haemoglobin at booking (g/L), mean (SD)	116 (13)	118 (13)
Haemoglobin at time of infusion (g/L), mean (SD)	95 (7)	94 (6)
Anaemia Severity, n (%)		
Mild	30 (27)	2 (22)
Moderate	54 (48)	4 (44)
Severe	29 (26)	3 (33)
Serum ferritin at time of infusion (mcg/L), mean (SD)	11 (13)	9 (2)
Time from Infusion to Delivery (Weeks), mean (SD)	4.9 (3.4)	3.2 (2.3)
Delivery Hb (g/L), mean (SD)	117 (13)	N/A
Treatment Success, n (%)	62 (56)	N/A
Anaemia at Delivery, n (%)	15 (14)	N/A

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Table 3. Dose-response relationship between intravenous iron dose relative to maternal body weight and haematological outcomes

		Intravenous Iron Dose in mg/kg according to:		
Outcome	**N**	**Adjusted Body Weight Adjusted Beta-coefficient[a] (95% CI)**	**Total Body Weight Adjusted Beta-coefficient[a] (95% CI)**	**Ideal Body Weight Adjusted Beta-coefficient[a] (95% CI)**
Mean change in Hb from dose until 2-4 weeks post-treatment (g/L)	**65**	**0.77 (0.25-1.30)**	**0.95 (0.40-1.51)**	0.39 (-0.09 to 0.86)
Mean change in Hb from dose until delivery (g/L)	**110**	**0.70 (0.24-1.15)**	**0.83 (0.36-1.29)**	0.37 (-0.04 to 0.78)
		Adjusted RR[a] (95% CI)	**Adjusted RR[a] (95% CI)**	**Adjusted RR[a] (95% CI)**
Treatment Success (Hb increase >20g/L)	**110**	**1.05 (1.01-1.10)**	**1.07 (1.03-1.11)**	1.02 (0.98-1.07)
Anaemia at Delivery (Hb <105g/L)	110	0.98 (0.87-1.11)	0.98 (0.86-1.12)	0.97 (0.89-1.07)

Abbreviations: aRR, adjusted relative risk; CI, confidence interval

[a] Adjusted for haemoglobin value at the time of infusion, gestational age at time of treatment, and pre-pregnancy body mass index

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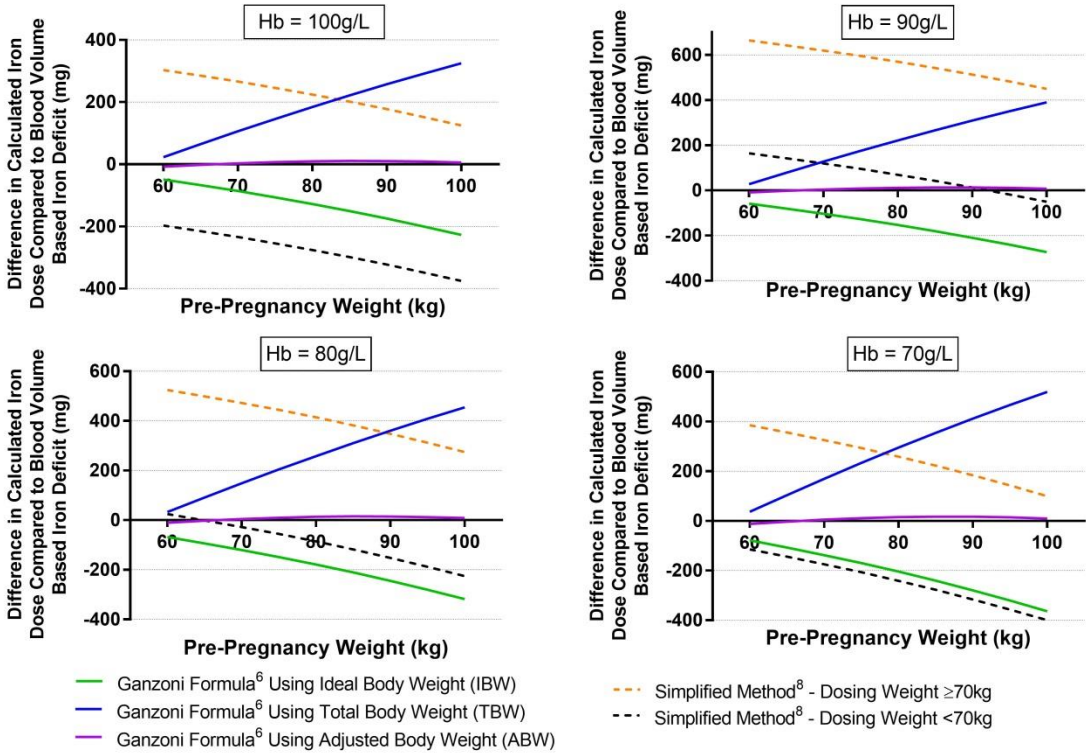

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