

## How I treat anemia in pregnancy: iron, cobalamin, and folate

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**Anemia of pregnancy, an important risk factor for fetal and maternal morbidity, is considered a global health problem, affecting almost 50% of pregnant women. In this article, diagnosis and management of iron, cobalamin, and folate deficiencies, the most frequent causes of anemia in pregnancy, are discussed. Three clinical cases are considered. Iron deficiency is the most common cause. Laboratory tests defining iron deficiency, the recognition of developmental delays and cognitive**

**abnormalities in iron-deficient neonates, and literature addressing the efficacy and safety of IV iron in pregnancy are reviewed. An algorithm is proposed to help clinicians diagnose and treat iron deficiency, recommending oral iron in the first trimester and IV iron later. Association of folate deficiency with neural tube defects and impact of fortification programs are discussed. With increased obesity and bariatric surgery rates, prevalence of cobalamin deficiency in pregnancy is rising.**

**Low maternal cobalamin may be associated with fetal growth retardation, fetal insulin resistance, and excess adiposity. The importance of treating cobalamin deficiency in pregnancy is considered. A case of malarial anemia emphasizes the complex relationship between iron deficiency, iron treatment, and malaria infection in endemic areas; the heightened impact of combined etiologies on anemia severity is highlighted. (*Blood*. 2017;129(8):940-949)**

### Introduction and epidemiology

Anemia of pregnancy is a well-recognized global health problem, affecting almost half of pregnant women.<sup>1</sup> The World Health Organization (WHO) defines anemia of pregnancy as hemoglobin (Hb) <11 g/dL, or hematocrit <33%, at any time during the pregnancy.<sup>1</sup> The Centers for Disease Control and Prevention (CDC) define anemia of pregnancy as Hb <11 g/dL, or hematocrit <33% during the first and third trimesters, and <10.5 g/dL or a hematocrit <32% in the second trimester.<sup>2</sup> The WHO defines severe anemia in all persons as a Hb of <7 g/dL and very severe anemia as a Hb of <4 g/dL.<sup>3</sup>

Physiologic anemia of pregnancy reflects an expansion of plasma volume of 50% relative to the increase in the red blood cell (RBC) mass of 25%.<sup>4</sup> Globally, the most common cause for anemia of pregnancy is iron deficiency, arising from maternal-fetal transfer of iron, frequently aggravated by decreased maternal iron reserves.<sup>5</sup> The Nutrition Impact Model Study, a systematic analysis of 257 population-representative data sources from 107 countries, estimated the global prevalence of anemia in pregnancy at 43% in 1995 and 38% in 2011.<sup>6</sup>

hippocampus.<sup>9</sup> Children born to iron-deficient mothers demonstrate learning and memory impairments that may persist into adulthood.<sup>10</sup> Folic acid deficiency, especially at the time of conception, is strongly correlated with increased neural tube defects (NTDs).<sup>11</sup> Low maternal RBC folate is also associated with LBW, and an increased risk for SGA.<sup>12</sup> Maternal vitamin B12 (cobalamin) status affects fetal growth and development. Low cobalamin is associated with an increased fetal risk of low lean mass and excess adiposity, increased insulin resistance, and impaired neurodevelopment.<sup>13</sup> Maternal risks include fatigue, pallor, tachycardia, poor exercise tolerance, and suboptimal work performance.<sup>14</sup> Depleted blood reserves during delivery may increase the need for blood transfusion,<sup>15</sup> preeclampsia,<sup>16</sup> placental abruption,<sup>17</sup> cardiac failure, and related death.<sup>18</sup> In this article, we present 3 cases to address how we treat the most common nutritional causes of anemia of pregnancy: iron, cobalamin, and folate deficiencies.

### Outcomes/consequences of anemia during pregnancy

Anemia is an important risk factor for both maternal and fetal morbidity. Iron-deficiency anemia is associated with higher rates of preterm birth, low birth weight (LBW), and small-for-gestational age (SGA) newborns.<sup>7</sup> Maternal iron deficiency affects iron concentrations in umbilical cord blood.<sup>8</sup> Fetal-neonatal iron deficiency causes diminished auditory recognition memory in infants, a reflection of its impact on the developing

### Case 1

A 35-year-old woman presented to clinic 35 weeks pregnant, with fatigue that started early in pregnancy, dyspnea on exertion, and restless sleep. There was a history of Crohn ileitis, longstanding menorrhagia, and a previous preterm delivery due to severe preeclampsia. Her pulse was 109; her blood pressure was 145/96 mmHg. Complete blood count revealed: leukocytes,  $10.9 \times 10^9/L$ ; Hb, 8.8 g/dL; hematocrit (Hct), 28.1%; mean corpuscular volume (MCV), 71 fL; platelets,  $270 \times 10^9/L$ ; red cell distribution width, 17.1. A month earlier (for Hb, 8.5g/dL; Hct, 26.9%; and MCV, 76 fL), oral iron was started by an obstetrician and caused severe constipation.

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## Case 2

A 28-year-old Gravida 2 para 1 woman at 29 weeks' gestation presented with chronic fatigue, dyspnea, and palpitations. Her counts were: Hb, 9.1 g/dL; Hct, 28.0%; MCV, 83 fL; and platelets,  $192 \times 10^9/L$ . There was a history of conversion of an adjustable gastric band to Roux-en-Y gastric bypass 1 year before, complicated by persistent nausea. Physical examination revealed a gravid uterus but was otherwise unremarkable.

## Case 3

A 27-year-old woman at 34 weeks' gestation was admitted to a hospital in Jos, Nigeria with 1 week of fever, vomiting, and chills. She had completed prenatal antimalarial prophylaxis with sulphadoxine-pyrimethamine. No prenatal iron was prescribed. She was febrile, pale, and icteric, tachycardic (110 beats per minute), tachypneic (24 breaths per minute), and had splenomegaly. Her counts were: Hb, 5.3 g/dL; MCV, 80 fL; platelets,  $480 \times 10^9/L$ ; and white blood cells,  $18.0 \times 10^9/L$ .

## Iron requirements in pregnancy

In a typical pregnancy, maternal iron requirements include 300 to 350 mg for the fetus and the placenta, 500 mg for the expansion of the maternal RBC mass, and 250 mg associated with blood loss during labor and delivery.<sup>19</sup> The requirement for iron increases gradually from 0.8 mg per day in the first trimester to 7.5 mg per day in the third.<sup>20</sup> Yet, the average daily absorption of iron from western diets is only 1 to 5 mg.<sup>5</sup> Therefore, women cannot fulfill their iron needs from normal food intake, and must draw upon iron stores, increasing the risk of iron-deficiency anemia. The CDC recommends that all pregnant women begin a 30 mg per day iron supplement at the first prenatal visit,<sup>2</sup> the WHO suggests 60 mg per day for all pregnant women,<sup>1</sup> whereas British guidelines do not recommend any routine iron supplementation in pregnancy.<sup>21</sup>

## Diagnosis of iron-deficiency anemia

The laboratory diagnosis of iron-deficiency anemia may be especially difficult during pregnancy because the changes in maternal physiology may affect the serum levels of biochemical markers of iron status (Figure 1).

### Hemoglobin level

Maternal Hb declines progressively during pregnancy due to hemodilution and may be accentuated by iron-deficient erythropoiesis, with a nadir reached at 24 to 32 weeks' gestation.<sup>4,22</sup> Due to considerable variation in Hb level, it cannot be used as a single parameter to estimate iron status.

### Ferritin

Ferritin reflects total body iron stores. Iron deficiency is the only clinical situation associated with extremely low values of ferritin. Ferritin

declines gradually during pregnancy, reaches a nadir during weeks 35 to 38, and increases during the month before delivery. The nadir is about 15 ng/mL without iron supplementation and 20 ng/mL with it.<sup>23</sup> Studies correlating the presence or absence of stainable marrow iron with serum ferritin indicate that the 12 ng/mL threshold of ferritin is only 25% sensitive for detecting iron deficiency.<sup>24</sup> Instead, a ferritin of 30 ng/mL or less has a 92% sensitivity and 98% specificity for diagnosing iron deficiency.<sup>24</sup> Ferritin is a more sensitive and specific marker for iron deficiency than serum iron, transferrin saturation, and erythrocyte protoporphyrin values<sup>25</sup> and is the best test for iron deficiency in pregnancy if low.

In the absence of active comorbidity, ferritin values  $>100$  ng/mL indicate adequate iron stores and a low likelihood of iron-deficiency anemia.<sup>26</sup>

### Mean corpuscular volume

MCV is an unreliable marker of iron deficiency in pregnancy. Stimulation of erythropoiesis leads to a physiologic increase in MCV during gestation that counterbalances the microcytosis of iron deficiency.<sup>27</sup> A low MCV, defined as an MCV  $<80$  fL, is highly sensitive,<sup>26</sup> but not specific, for iron-deficiency anemia.

### Iron, transferrin, and transferrin saturation

Serum iron circulates bound to its transport protein, transferrin. The serum iron reflects both iron recycling from macrophages and iron absorbed from the diet. It demonstrates diurnal variation, with a rise in the morning and fall at night<sup>28</sup>; serum iron is also influenced by recently ingested meals. Therefore, no single value is diagnostic of iron deficiency.<sup>29</sup> Serum iron should be drawn after an overnight fast. Total iron-binding capacity (TIBC) and transferrin are measurements of iron transport proteins that increase in iron deficiency. Inflammation, chronic infection, malignancies, liver disease, nephrotic syndrome, and malnutrition can lower TIBC, whereas pregnancy can raise it, in the absence of iron deficiency.<sup>27</sup>

Plasma transferrin saturation is the ratio of plasma iron to transferrin. A saturation of  $<15\%$  suggests an inadequate supply of iron,<sup>30</sup> either because of low total body iron (iron deficiency) or due to trapping of iron in macrophages (anemia of inflammation).

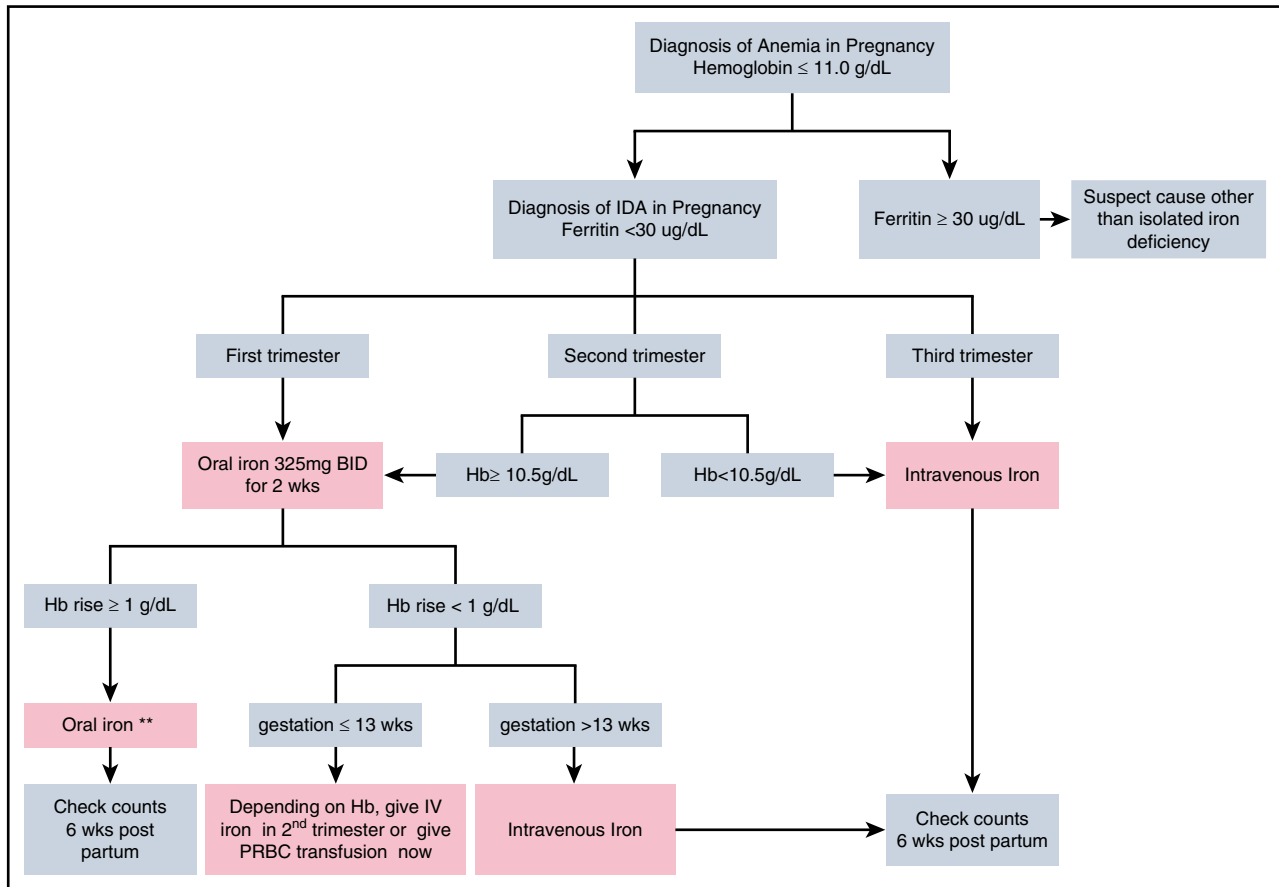
### Soluble transferrin receptor

The soluble transferrin receptor (sTfR) is a truncated fragment of the membrane receptor. In iron deficiency, synthesis of transferrin receptors, and sTfR, is increased.<sup>31</sup> Unlike TIBC and ferritin, sTfR concentrations are not affected by inflammation.<sup>24</sup> A meta-analysis of 10 studies of sTfR showed that the assay had a sensitivity of 86% and a specificity of 75%.<sup>32</sup> However, the assay is not standardized and is not used in routine diagnosis of iron-deficiency anemia.

### Hepcidin

Hepcidin is the master regulator of systemic iron bioavailability. Hepcidin decreases as pregnancy progresses, with the lowest hepcidin levels seen in the third trimester.<sup>33</sup> Pregnant women with undetectable serum hepcidin transfer more maternally ingested iron to their fetus than women with detectable hepcidin, indicating that maternal hepcidin in part determines the iron bioavailability to the fetus.<sup>34</sup> Hepcidin is currently being evaluated as a biomarker in pregnancy.<sup>35</sup>

In summary, Hb, the percentage of transferrin saturation, and plasma ferritin are adequate to assess iron status in the majority of pregnant women, and the combination of anemia and ferritin  $<15$  to 30 ng/mL is diagnostic of iron deficiency.<sup>1</sup>



**Figure 1. Algorithm of suggested approach to diagnosis and management of iron-deficiency anemia in pregnancy.** \*\*Oral iron treatment should not be interrupted once normal Hb values are achieved, but rather supplementation should continue to replenish iron stores (generally for at least 2-3 months, and until 6 weeks postpartum). BID, twice a day; IDA, iron-deficiency anemia; PRBC, packed red blood cells.

## Returning to patient 1: diagnosis and management

Additional laboratory data in our 35-year-old patient at 36 weeks' gestation included: serum iron, 24  $\mu\text{g/dL}$ ; TIBC, 623  $\mu\text{g/dL}$ ; and ferritin, 6  $\mu\text{g/L}$  (ng/mL), establishing a diagnosis of iron-deficiency anemia.

Iron repletion can be achieved with either oral or IV iron. The choice of therapy depends on the degree of anemia, the stage of pregnancy, and factors that influence gastrointestinal absorption of iron.

Oral iron is the frontline therapy for iron-deficiency anemia. It is inexpensive, readily available, and effective. However, up to 70% of patients experience significant gastrointestinal side effects (nausea, constipation, diarrhea, indigestion, and metallic taste) that prevent adherence to treatment.<sup>36</sup> In pregnancy, decreased bowel motility caused by elevated progesterone and the enlarging uterus pressing on the rectum is made worse by oral iron.<sup>37,38</sup>

Recommendations for dosing oral iron vary from 60 to 200 mg of elemental iron per day.<sup>2,21</sup> This can be achieved with 325-mg tablets (each containing 50-65 mg of elemental iron) given once to 3 times daily. The acid pH of the stomach favors solubility of iron by the conversion of ferric ( $\text{Fe}^{3+}$ ) to ferrous ( $\text{Fe}^{2+}$ ) iron for duodenal uptake. Iron absorption is facilitated by ascorbate (which facilitates  $\text{Fe}^{3+}$  to  $\text{Fe}^{2+}$ ), amino acids, and iron deficiency, and is retarded by phytates, tannins, antacids, and iron overload. The most commonly prescribed iron preparations are ferrous sulfate, ferrous gluconate, and ferrous fumarate. Prolonged-released ferrous sulfate (ferrous sulfate-polymeric

complex) is the best tolerated oral preparation, and is associated with good compliance,<sup>39</sup> although delayed release compromises absorption. An iron-deficient patient absorbs up to 28% of oral iron, if taken without food.<sup>40</sup> The total iron absorbed increases with increasing doses to a maximum of 160 mg per day. However, oral iron acutely increases hepcidin and recent data suggest that twice and thrice daily supplementation may have little added benefit over once-daily dosing.<sup>41</sup> Two weeks after starting oral iron, a Hb increase of 1 g or more suggests adequate absorption.<sup>42</sup> Replacement should be continued until iron stores are replenished (generally 2-3 months), and 6 weeks postpartum.

IV iron circumvents gastrointestinal absorption and is therefore the preferred agent for patients with gluten sensitivity, inflammatory bowel disease, gastrointestinal malabsorption, after gastric bypass surgery, hyperemesis gravidarum, or a history of oral iron intolerance. IV iron is superior to oral iron in achieving a sustained Hb response, reducing the need for packed RBC transfusions and improving quality of life for chronic heart failure,<sup>43</sup> inflammatory bowel disease,<sup>44</sup> chronic kidney diseases and hemodialysis,<sup>45</sup> and cancer-related anemia.<sup>46</sup>

Several authors have reported that parenteral iron therapy in pregnancy and postpartum is associated with a more rapid increase in Hb and/or better replenishment of iron stores than is oral therapy.<sup>18,47-54</sup> Patient 1 had Crohn ileitis, a history of menorrhagia, and may have started the pregnancy with suboptimal iron stores. At 32 weeks' gestation, we would recommend treatment with IV iron.

In the first trimester, we treat iron deficiency with oral iron, reserving IV iron for after the 13th week. This is in keeping with recommendations

**Table 1. IV iron preparations**

Generic name	Preparations					
	Iron sucrose	Sodium ferric gluconate	LMW iron dextran	Ferumoxytol	FCM	Iron isomaltoside
Trade (brand) name	Venofer	Ferlecit	INFeD, CosmoFer	Feraheme	Ferinject, Injectafer,	Monofer (Europe only)
Manufacturer	American Regent Inc	Sanofi Aventis Inc	Watson Pharma	AMAG Pharmaceuticals	Luitpold Pharmaceuticals	Pharmacosmos
Carbohydrate	Sucrose	Gluconate	LMW iron dextran	Polyglucose sorbitol carboxymethylether	Carboxymaltose	Isomaltoside
Concentration of elemental iron	20 mg/mL	12.5 mg/mL	50 mg/mL	30 mg/mL	50 mg/mL	100 mg/mL
TDI	No	No	Yes	No	Yes	Yes
Test dose required	No	No	Yes	No	No	No
Recommended max dose	Multiple doses of 200-300 mg	Multiple doses of 125-187.5 mg	Multiple doses of 100 mg or single infusion of 1000 mg	2 infusions of 510 mg given 3-8 d apart or a single dose of 1020 mg	2 doses of 750 mg, given 7 or more days apart (weight <50 kg) 2 doses of 15 mg/kg (or 1000 mg) given 7 or more days apart if weight >50 kg	A single infusion, at a dose of 20 mg/kg (or 1000 mg) or up to 3 doses of 500 mg given over 7 d
Infusion time	Over a period of at least 15 min	1 h	1 h	15 min	15 min	15 min
Pregnancy category	B	B	C	C	C	Not listed

FDA pregnancy categories: B, Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. C, Animal reproductive studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

TDI, total dose infusion.

of the European Medicine Agency's Committee of Medicinal Products for Human Use (CHMP).<sup>55</sup> The US Food and Drug Administration (FDA) does not explicitly restrict the use of IV iron until after the first trimester. Because IV iron has been shown to improve Hb more rapidly than oral iron,<sup>45,51</sup> we preferentially treat patients with IV iron in the second half of pregnancy. Some investigators report additional advantages of IV over oral iron beyond the more rapid increase in Hb. Breyman and colleagues enrolled 252 woman in the second and third trimester (weeks 16-33), randomly assigning them to oral ferrous sulfate or IV ferric carboxymaltose (FCM). Hb improvements and newborn outcomes were similar in both groups, but vitality and social functioning were better with IV iron.<sup>53</sup>

All available IV iron formulations consist of iron-carbohydrate complexes of small spheroidal iron-carbohydrate particles (Table 1). The carbohydrates serve as a shell around a core iron-hydroxide gel, permitting slow release of elemental iron while the remaining particles stay in colloid suspension.<sup>56,57</sup> Currently available IV iron formulations are of acceptable safety and equivalent effectiveness in the general population.<sup>58,59</sup> All IV formulations may be associated with allergic reactions characterized by nausea, hypotension, tachycardia, chest pain, dyspnea, and edema of the extremities that mostly occur within 24 hours of the infusion. These minor infusion reactions are self-limited, do not require treatment,<sup>60</sup> and should not be misread as anaphylaxis,<sup>61</sup> and they rarely recur with rechallenge. Empiric use of steroids prior to retreatment may diminish minor reactions that occur the next day.<sup>62</sup> Patients may also experience self-limited arthralgia, myalgias, and/or headache within a few days of infusion that generally respond to nonsteroidal anti-inflammatory drugs.

A meta-analysis of 103 randomized controlled trials, comparing 10 391 patients treated with IV iron to 4044 who received oral iron, 1329 with no iron, and 3335 with placebo showed that neither serious adverse events nor infections were increased with IV iron.<sup>63</sup>

Iron sucrose and sodium ferric gluconate are assigned to FDA pregnancy category B based on safety studies in pregnancy. Both high-molecular weight (HMW) and low-molecular-weight (LMW) iron dextrans retain a pregnancy category C designation despite evidence suggesting that adverse events ascribed to iron dextran are mostly associated with the HMW formulation.<sup>64</sup> Notably, these studies did not include pregnant women. HMW iron dextran has been linked to an increased risk of anaphylaxis and is no longer available.<sup>65</sup> An observational study of 189 women treated with LMW iron dextran in second and third trimester reported no severe adverse events and only 2% transient infusion reactions.<sup>66</sup> These results corroborated outcomes in other studies showing safety of LMW iron dextran,<sup>67,68</sup> which allows complete replacement of IV iron in a single infusion over 15 to 60 minutes. Despite well-established safety, LMW iron dextran still requires a test dose.

The newer IV iron formulations, ferumoxytol, FCM, and iron isomaltoside are all based on carbohydrates with reduced immunogenic properties; although it is not established that these decreased allergic reactions, a test dose is not required. Nevertheless, FCM and ferumoxytol are also assigned FDA pregnancy category C. FCM has been shown to be efficacious and safe in pregnancy (Table 2). In a prospective study, Froessler and colleagues treated 65 pregnant women with FCM and reported no serious adverse effects and no change in fetal heart monitoring.<sup>69</sup> Furthermore, Christoph et al evaluated 206 pregnant women in a comparison study of iron sucrose and FCM and showed equivalent safety profiles in both drugs.<sup>70</sup> We recommend that pregnant women with any degree of iron deficiency be treated to correct anemia and replete ferritin as early in pregnancy as possible.

Patient 1 was 35 weeks pregnant and was treated with LMW iron dextran without incident. Had she presented before the 13th week of pregnancy and been able to tolerate oral iron, we would have treated with oral iron with follow-up 2 weeks later (and after the 13th week

**Table 2. Examples of trials of IV iron formulations and dosing in pregnancy**

Reference/ study ID	Design	Iron formulation	Participants	Dosing
<b>Iron sucrose</b>				
47	RCT	IS vs oral	271 anemic women, 148 late pregnancy	400 mg of IS divided into two 200-mg infusions of 30-min duration, given a minimum of 24 h apart
48	RCT	IS vs oral	100 pregnant patients, weeks 24-34	IS divided doses of 200 mg on alternate days
113	RCT	IS vs IM iron sorbitol citric acid	60 pregnant, weeks 12-32	IS 200 mg, over 30 min, each infusion (to a total according to a formula of total iron deficit)
49	RCT	IS vs oral	89 pregnant patients, weeks 14-36	IS 200 mg each infusion (to a total according to a formula of total iron deficit)
70	Retrospective observational comparative	IS vs FCM	206 pregnant women after 13 wk	IS 400 mg iron per week in 2 infusions, 48 h apart, FCM most patients 1000 mg
50	RCT	IS vs oral	260 pregnant, weeks 21-37	IS 200 mg, either a total of 2 doses (first week 21-24, second week 28-32) or 3 doses (third week 35-37)
51	RCT	IS vs oral	106 women in third trimester	IS in each infusion, the maximum total dose administered was 200 mg infused in 20-30 min, total dose was administered over 5 d and maximum daily dose administered was 400, usually every other day
52	RCT	IS vs oral	Week 24-28	IS administered according to a formula*
<b>LMWID</b>				
66	Retrospective observational study	LMWID	189 s and third-trimester pregnant women	Single infusion of 1000 mg, 1 h
67	Nonrandomized prospective trial	LMWID	100 pregnant women after 12 wk	Single infusion, amount given according to calculated iron deficit
<b>FCM</b>				
53 (FER-ASAP)	RCT	FCM vs oral iron (ferrous sulfate)	252 pregnant women their second or third trimester (gestational weeks 16-33)	1000-1500 mg, according to weight and Hb level: Weight <66 kg, Hb 8-9: 3 × 500 mg iron within 2 wk of baseline; Weight <66 kg, Hb 9-10.5/11: 2 × 500 mg iron within 2 wk of baseline; Weight >66 kg, Hb 8-9: 1 × 1000 mg iron, followed by 1 × 500 mg iron 1 wk later; Weight >66 kg, Hb 9-10.5/11: 1 × 1000 mg iron
69	Prospective observational	FCM	65 pregnant, second and third trimester	FCM 15 mg/kg
114	Retrospective observational	FCM	64 pregnant women	FCM 1000 mg in a single infusion of 15 min weekly. Most received only 1 dose.
68†	Retrospective observational comparative	FCM vs LMWID	92 pregnant women	FCM in doses of up to a maximum of 1000 mg. LMWID maximum of 1000 mg
115	Open-label pilot study	FCM	19 women in the third trimester of pregnancy with restless legs syndrome	500 or 700 mg of FCM was administered over 20 min

IM, intramuscular; IS, iron sucrose; LMWID, LMW iron dextran; RCT, randomized controlled trial.

\*Iron formula deficit:  $\text{weight} \times (\text{target Hb} - \text{actual Hb}) \times 0.24 + 500 \text{ mg}$ .

†Myers shows safety of FCM and LMWID in pregnancy.

for an assessment of response and to determine the need for IV iron. Tables 1 and 2 show the characteristics and dosing schedules of IV iron formulations with safety in pregnancy.

## Folic acid and vitamin B12 (cobalamin) deficiency

Prior to nationwide mandatory folate fortification programs, folate deficiency was the second most common cause of anemia during pregnancy.<sup>71</sup> The prevalence of folate deficiency in pregnancy varies from 1% to 50%, and is higher in economically deprived regions of the

world. Numerous studies illustrate that the prevalence of both folic acid and cobalamin deficiency increase with advancing gestation.<sup>72</sup>

Folate and cobalamin are involved in tetrahydrofolate metabolism, and are necessary for DNA synthesis for fetal growth and maternal tissue growth.<sup>73</sup> Dietary folate is absorbed in the jejunum. Poor nutrition, intestinal malabsorption, and increased requirements for fetal growth may contribute to folate deficiency. Cobalamin is present in animal protein and absorbed in the terminal ileum. R-protein (haptocorrin), secreted by salivary glands, binds cobalamin in the stomach and transports cobalamin to the duodenum where pancreatic proteases degrade the R-protein. Cobalamin is then released and binds to intrinsic factor released from gastric parietal cells. The cobalamin-intrinsic factor complex subsequently binds to receptors on ileal

enterocytes. Atrophic gastritis, proton pump inhibitors, and malabsorption all increase the risk of cobalamin deficiency.<sup>74</sup>

Bariatric surgery in the United States increased by 800% between 1998 and 2005, with women accounting for 83% of procedures in the 18- to 45-year age group.<sup>75</sup> In a retrospective study, anemia was detected in 17% of patients undergoing bariatric surgery, low ferritin in 15%, low cobalamin in 11%, and low RBC folate in 12%.<sup>76</sup>

## Diagnostic tests

Most pregnant women with folate or cobalamin deficiency do not exhibit macrocytosis,<sup>74,77</sup> which may be masked by iron deficiency or by an underlying minor thalassemic phenotype. Furthermore, 2% to 5% of pregnant women with normocytic anemia have mild megaloblastic changes in the bone marrow that resolve with folic acid supplementation.<sup>74</sup>

Serum cobalamin measures cobalamin bound to 2 circulating binding proteins, haptocorrin and transcobalamin. In nonpregnant patients, serum cobalamin <200 pg/mL (<148 pmol/L) is diagnostic of cobalamin deficiency, whereas levels above 300 are considered normal. Levels in the range of 200 to 300 pg/mL are borderline, and cobalamin deficiency is possible.<sup>78</sup> Notably, there is no difference in levels of the metabolites homocysteine and methylmalonic acid in pregnant women with subnormal cobalamin levels when compared with pregnant women with normal levels,<sup>79,80</sup> suggesting that low cobalamin in pregnancy may not reflect true tissue deficiency. A “physiologic” decline in cobalamin is seen in up to 20% of pregnant women that is indistinguishable from frank deficiency using routine laboratory studies.<sup>79,81,82</sup> Holotranscobalamin (biologically active cobalamin bound to transcobalamin) does not decline in pregnancy and has been suggested as a marker for cobalamin deficiency in pregnancy.<sup>83</sup> Holotranscobalamin is not available for clinical use. Serum folic acid concentrations <2 ng/mL are diagnostic of folic acid deficiency, whereas levels above 4 ng/mL effectively rule out deficiency. Levels in the range of 2 to 4 ng/mL are borderline.<sup>84</sup> Serum folate may be affected by recent oral/dietary intake, limiting the value of a single test. Although RBC folate is not so influenced, serum folate is more readily available and, in most instances, RBC folate measurement could be reserved for patients with borderline low serum values.

## Returning to patient 2: diagnosis and management

Further blood work in case 2 showed: serum iron, 25 µg/dL; TIBC, 395 µg/dL; ferritin, 4 µg/dL; folate, 21.5 ng/mL; and cobalamin, 113 pg/mL, confirming combined cobalamin and iron deficiency.

## Management of folate deficiency

Because of the significant consequences of folate deficiency on neural tube development, folate supplementation is a standard component of antenatal care in the United States and Canada. National-scale public health initiatives requiring fortification of flour with folic acid in the United States and Canada have been effective in substantially reducing the prevalence of NTDs.<sup>85</sup> By contrast, Khoshnood et al, in an observational study of 11 353 cases of NTD in ~12.5 million births in

19 countries in Europe, showed no change in prevalence of NTDs between 1991 and 2011, despite longstanding recommendations promoting folic acid supplementation and the existence of voluntary folic acid fortification.<sup>86</sup> Absent mandatory fortification, the prevalence of NTD in Europe has remained unchanged.

Folate fortification of foods in the United States is recommended because the neural tube closes around day 26 of gestation, a time when most women do not yet know they are pregnant. The C677T single nucleotide polymorphism (SNP) of MTHFR confers higher risk of NTD and such mothers have higher folate requirements. Yet, the SNP may confer greater protection against development of anemia and perhaps even maternal survival. This might explain the high allele frequency of this polymorphism in some populations through selective pressure.<sup>87</sup>

The WHO recommends folate supplementation for pregnant women, 400 µg per day from early pregnancy to 3 months postpartum. The US Public Health Service and CDC recommend the same for all women of childbearing age (15-45 years of age) to prevent spina bifida and anencephaly.<sup>88</sup>

Most prenatal vitamins contain 1 mg of folate, which is more than sufficient to meet the increased needs of pregnancy. A higher supplementation dose, 5 mg per day, is recommended in women who have increased demands for folate (multiple pregnancies, hemolytic disorders, folate metabolism disorders) and in women who are at an increased risk of NTDs (personal or family history of NTD, pregestational diabetes, epilepsy on valproate or carbamazepine).

## Cobalamin deficiency

Owing to the relatively large amounts of cobalamin that are stored in the human body, cobalamin deficiency in pregnancy is far less common than folate deficiency. However, with more pregnant women having undergone bariatric surgery, the risk of cobalamin deficiency is increased. Mead et al examined 113 women with a history of gastric bypass surgery delivering 150 babies and showed low cobalamin in over 10% of patients after biliopancreatic diversion, Roux-en-Y gastric bypass, or sleeve gastrectomy.<sup>89</sup>

The WHO and US National Institutes of Health (NIH) recommend a higher daily allowance of cobalamin in pregnant women than in nonpregnant women (2.6 vs 2.4 µg per day)<sup>90,91</sup> to support fetal neurologic development. Growth retardation, general hypotonia, and loss of neuromotor skills have been described in infants of mothers with cobalamin deficiency.<sup>92</sup> Furthermore, cobalamin supplementation improves the motor functioning and regurgitation of cobalamin-deficient infants.<sup>93</sup> Notably, hematologic abnormalities caused by cobalamin deficiency may respond to folate supplementation, leaving other consequences of cobalamin deficiency unchecked. Therefore, prompt recognition of cobalamin deficiency and rapid treatment are of great significance.

Patient 2 was at risk of cobalamin (and iron) deficiency as a result of her bariatric procedures. She received intramuscular cobalamin 1000 mcg every 4 weeks, through pregnancy and the puerperium, with recommendation for lifelong replacement therapy. Our practice is to treat all pregnant women with laboratory data suggestive of cobalamin deficiency, irrespective of the cause.

Treatment of cobalamin deficiency in pregnancy is similar to that outside of pregnancy and can be achieved through oral or parenteral replacement. When oral vitamin cobalamin 1000 mcg daily is used, serum levels should be monitored to ensure adequate repletion. For patients who have had bariatric surgery, or other conditions that might

interfere with intestinal absorption, sublingual cobalamin is an alternative to oral,<sup>94</sup> and in patients with neurological features attributable to cobalamin deficiency, parenteral treatment is preferred.

### Returning to patient 3: diagnosis and management

Additional results in the 27-year-old febrile Nigerian patient included: serum iron, 20  $\mu\text{g/dL}$ ; TIBC, 600  $\mu\text{g/dL}$ ; ferritin, 4  $\mu\text{g/L}$ ; and cobalamin, 113  $\text{pg/mL}$ . Malaria parasites were seen on blood smear. HIV, hepatitis B and C were negative. Lactate dehydrogenase and bilirubin were normal. Absolute reticulocyte count was 20 000/ $\mu\text{L}$ . A diagnosis of anemia due to combined iron deficiency, cobalamin deficiency, and malaria was established. Malaria treatment was given. She received 6 units of packed RBCs and intramuscular hydroxycobalamin 1000 mcg daily for 1 week. After resolution of parasitemia, ferrous sulfate 200 mg and folic acid 5 mg daily were given.

Malaria poses a significant threat to pregnant women's health. Each year, 23 million women conceive in malaria-endemic zones in Africa.<sup>95</sup> The prevalence is higher in primigravidas than in nonpregnant women. *Plasmodium falciparum* is the predominant species. Malaria contracted during pregnancy increases the mother's risk of becoming anemic, infects the fetus (congenital malaria), and is associated with LBW and increased infant mortality.<sup>96</sup>

Malaria prevention reduces neonatal mortality.<sup>97</sup> For pregnant women in areas with medium and high malaria transmission, WHO recommends intermittent preventive treatment during pregnancy, with at least 3 doses of sulphadoxine-pyrimethamine in the second and third trimesters,<sup>98</sup> in conjunction with the use of insecticide-treated mosquito nets. The patient in case 3 received sulphadoxine-pyrimethamine as recommended.

Severe anemia is seen in areas of very high malarial transmission and is most common in young children and pregnant women.<sup>99</sup> The prevalence of malarial anemia in endemic areas of Africa is 60% to 80% in pregnant women.<sup>100</sup> The pathogenesis includes direct destruction of parasitized and nonparasitized RBCs (extravascular and intravascular hemolysis), splenic and hepatic sequestration of RBCs, bone marrow suppression, and dyserythropoiesis.<sup>101</sup>

The relationship between iron deficiency and malaria has been a focus of intense study because the 2 often coexist. In vitro, *P falciparum* infects erythrocytes from iron-deficient individuals less efficiently than erythrocytes from iron-replete humans,<sup>102</sup> a result supported by clinical studies. A cross-sectional study of 445 Tanzanian pregnant women reported that iron deficiency decreased the risk of placental malaria.<sup>103</sup> In a case control study in Malawi, iron deficiency was less frequent in 112 women with placental malaria than in 110 women without.<sup>104</sup> In a 2016 Cochrane systematic review of 35 randomized controlled trials assessing iron supplementation in children living in areas with hyperendemic or holoendemic malaria transmission, iron did not cause an excess of clinical malaria.<sup>105</sup> This review did not include pregnant women. Provision of supplemental iron to pregnant women in malaria-endemic areas has been controversial due to concerns that iron therapy may exacerbate infections. Oral iron has been shown ex vivo to promote bacterial growth.<sup>106</sup> In the 2 studies of pregnant women in countries with malaria, there was no difference in placental malaria and parasitemia between those who received iron to those who did not.<sup>107</sup>

The third case illustrates the complexity of anemia in pregnancy in areas with malaria.

### RBC transfusions in pregnancy

Patient 3 received blood. Alongside preventive measures, rapid access to safe blood products is critical to reducing anemia-related mortality in women in developing countries.<sup>108</sup> The most common indications for blood in sub-Saharan Africa are maternal hemorrhage, trauma, and malaria-associated anemia.<sup>109</sup> In a study of blood transfusion services in Malawi, the mean Hb of transfused patients was 4.8  $\text{g/dL}$ , and 17% (18 of 104) were given to pregnant women.<sup>110</sup>

Guidelines for the management of postpartum hemorrhage have been published by a number of obstetric societies. The most recent French guidelines recommend transfusion in the setting of postpartum hemorrhage in order to maintain a Hb concentration  $>8 \text{ g/dL}$ .<sup>111</sup>

The latest transfusion guidelines of the AABB (formerly the American Association of Blood Banks) are based on 12 587 patients enrolled in 31 eligible randomized controlled trials in nonobstetric settings. They recommend using a restrictive Hb transfusion threshold of 7  $\text{g/dL}$  for hemodynamically stable hospitalized adult patients. The evidence base that supports this approach in obstetrics is limited. Therefore, clinicians should consider the Hb, overall clinical context, patient preferences, and alternative therapies when making transfusion decisions for a patient.<sup>112</sup>

### Conclusion

Anemia in pregnancy is a significant global health problem. Symptoms mimic those of normal pregnancy therefore active surveillance is required for early diagnosis. Effective treatment improves maternal health and prevents deleterious effects on the child.

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### Authorship

Contribution: M.M.A. and A.G.-G. wrote and revised portions of the manuscript and reviewed the manuscript.

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