How I treat Anemia in Pregnancy: Iron, Cobalamin and Folate

Maureen M. Achebe, MD, MPH[1] and Anat Gafter-Gvili, MD[2]

[1]Division of Hematology, Brigham and Women's Hospital, Dana-Farber Cancer Institute, Boston, MA.

[2]Institute of Hematology, Davidoff Cancer Center, Medicine A, Rabin Medical Center, Petah-Tikva, and Sackler School of Medicine, Tel-Aviv, Israel.

Corresponding Author:

Maureen M. Achebe, MD MPH

Division of Hematology

Brigham and Women's Hospital

75 Francis Street, Mid-Campus 3

Boston, MA 02115

mokam@bwh.harvard.edu

Phone 617-732-5048

Fax 617-732-5706

Abstract word count - 218

Text word count – 4400

Figure/table count – 3

Reference count - 111

Running Title: How I treat Anemia in Pregnancy

Abstract

Anemia of pregnancy is considered a global health problem, affecting almost 50% of pregnant women. Anemia is an important risk factor for both fetal and maternal morbidity. The purpose of this article is to discuss diagnosis and management of the most frequent causes of anemia in pregnancy: iron, cobalamin and folate deficiencies. This paper considers three clinical cases. Iron deficiency is the most common cause. The laboratory tests that define iron deficiency, the recognition of developmental delays and cognitive abnormalities in iron-deficient neonates and the literature addressing the efficacy and safety of intravenous iron in pregnancy are reviewed. An algorithm is proposed to help the clinician diagnose and treat iron deficiency, recommending oral iron in the first trimester and intravenous iron later in pregnancy. The association of folate deficiency with neural tube defects and the impact of fortification programs are discussed. With increased rates of obesity and bariatric surgery, the 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 and the heightened impact of combined etiologies on the severity of anemia is highlighted. A case of malarial anemia emphasizes the complex relationship between iron deficiency, iron treatment and malaria infection in endemic areas.

Introduction and Epidemiology:

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

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%.[4] 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.[5] 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.[6]

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, and small-for-gestational age (SGA) newborns.[7] Maternal iron deficiency affects iron concentrations in umbilical cord blood.[8] Fetal-neonatal iron deficiency causes

diminished auditory recognition memory in infants, a reflection of its impact on the developing hippocampus.[9] Children born to iron-deficient mothers demonstrate learning and memory impairments that may persist into adulthood.[10] Folic acid deficiency, especially at the time of conception, is strongly correlated with increased neural tube defects (NTDs).[11] Low maternal RBC folate is also associated with low birth weight, and an increased risk for SGA.[12] 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.[13] Maternal risks include fatigue, pallor, tachycardia, poor exercise tolerance and suboptimal work performance.[14] Depleted blood reserves during delivery may increase the need for blood transfusion,[15] preeclampsia,[16] placental abruption,[17] cardiac failure and related death.[18] In this article we present three cases to address how we treat the most common nutritional causes of Anemia of Pregnancy: Iron, cobalamin and folate deficiencies.

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's ileitis, long-standing menorrhagia and a previous preterm delivery due to severe pre-eclampsia. The pulse was 109, blood pressure 145/96 mmHg. CBC revealed leukocytes 10.9×10^9/L; hemoglobin (Hb) 8.8g/dL; hematocrit (Hct) 28.1%; MCV 71fL; platelets 270×10^9/L; RDW 17.1. A month earlier, for a Hb of 8.5g/dL; Hct 26.9% and MCV 76fL, oral iron was started by an obstetrician and caused severe constipation.

Case 2

A 28-year-old G2P1 woman at 29 weeks gestation presented with chronic fatigue, dyspnea and palpitations. Her Hb was 9.1g/dL; Hct 28.0%; MCV 83fL and platelets 192 x 10^9/L. There was a history of conversion of an adjustable gastric band to Roux-en-Y gastric bypass one year before, complicated by persistent nausea. Physical exam 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 one 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/minute), tachypneic (24 breaths/minute) and had splenomegaly. Hb was 5.3g/dL, MCV 80fL, platelets 480 x 10^9/L and white blood cells 18,000/mm^3.

Iron requirements in pregnancy

 In a typical pregnancy, maternal iron requirements include 300-350mg for the fetus and the placenta, 500mg for the expansion of the maternal RBC mass, and 250mg associated with blood loss during labor and delivery.[19] The requirement for iron increases gradually from 0.8mg/d in the first trimester to 7.5mg/d in the third.[20] Yet, the average daily absorption of iron from Western diets is only 1-5mg.[5] 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 30mg/day iron supplement at the first prenatal visit,[2] the

WHO suggests 60mg/day for all pregnant women,[1] while British guidelines do not recommend any routine iron supplementation in pregnancy.[21]

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.

Hemoglobin level

Maternal hemoglobin declines progressively during pregnancy due to hemodilution and may be accentuated by iron deficient erythropoiesis, with a nadir reached at 24-32 weeks gestation.[4,22] 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 35-38, and increases during the month before delivery. The nadir is about 15ng/mL without iron supplementation and 20ng/mL with.[23] Studies correlating the presence or absence of stainable marrow iron with serum ferritin indicate that the 12ng/mL threshold of ferritin is only 25% sensitive for detecting iron deficiency.[24] Instead, a ferritin of 30ng/mL or less has a 92% sensitivity and 98% specificity for diagnosing iron deficiency.[24] Ferritin is a

more sensitive and specific marker for iron deficiency than serum iron, transferrin saturation and erythrocyte protoporphyrin values[25] and is the best test for iron deficiency in pregnancy if low.

In the absence of active co-morbidity, ferritin values greater than 100 ng/mL indicate adequate iron stores and a low likelihood of iron deficiency anemia.[26]

Mean corpuscular volume (MCV)

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.[27] A low MCV, defined as an MCV less than 80fL, is highly sensitive,[26] 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,[28] serum iron is also influenced by recently ingested meals. Therefore no single value is diagnostic of iron deficiency.[29] 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, while pregnancy can raise it, in the absence of iron deficiency.[27]

Plasma transferrin saturation is the ratio of plasma iron to transferrin. A saturation of <15% suggests an inadequate supply of iron,[30] 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.[31] Unlike TIBC and ferritin, sTfR concentrations are not affected by inflammation.[24] A meta-analysis of ten studies of sTfR showed that the assay had a sensitivity of 86% and a specificity of 75%.[32] However, the assay is not standardized and 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.[33] 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.[34] Hepcidin is currently being evaluated as a biomarker in pregnancy.[35]

In summary, hemoglobin, percent transferrin saturation and plasma ferritin are adequate to assess iron status in the majority of pregnant women and the combination of anemia and a ferritin less than 15-30 ng/mL is diagnostic of iron deficiency.[1]

Returning to patient 1: Diagnosis and Management

Additional laboratory data in our 35 year-old patient at 36 weeks gestation included a serum iron of 24 ug/dL, TIBC 623ug/dL and ferritin 6 ug/L (ng/mL), establishing a diagnosis of iron deficiency anemia.

Iron repletion can be achieved with either oral or intravenous (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.[36] In pregnancy, decreased bowel motility caused by elevated progesterone and the enlarging uterus pressing on the rectum, is made worse by oral iron.[37,38]

Recommendations for dosing oral iron vary from 60 – 200mg of elemental iron per day.[2,21] This can be achieved with 325mg tablets (each containing 50-65mg of elemental iron) given once to three times daily. The acid pH of the stomach favors solubility of iron by the conversion of ferric (Fe^{3+}) to ferrous (Fe^{2+}) iron for duodenal uptake. Iron absorption is facilitated by ascorbate (which facilitates Fe^{3+} to Fe^{2+}), amino acids and iron deficiency, and 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,[39] although delayed release compromises absorption. An iron deficient patient absorbs up to 28% of oral iron, if taken without food.[40] The total iron absorbed increases with increasing doses to a maximum of 160mg/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.[41] Two weeks after starting oral iron, a hemoglobin increase of 1 gram or more suggests adequate absorption.[42] Replacement should be continued until iron stores are replenished (generally 2-3 months), and 6 weeks postpartum.

Intravenous 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 hemoglobin response, reducing the need for packed RBC transfusions and improving quality of life chronic heart failure,[43] inflammatory bowel disease,[44] chronic kidney diseases and hemodialysis [45] and cancer related anemia.[46]

Several authors have reported that parenteral iron therapy in pregnancy and postpartum is associated with a more rapid increase in hemoglobin and/or better replenishment of iron stores than is oral therapy, Table 2.[18,47-54] Patient 1 had Crohn's 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 thirteenth week. This is in keeping with recommendations of the European Medicine Agency's Committee of Medicinal Products for Human Use (CHMP).[55] The US FDA does not explicitly restrict the use of IV iron until after the first trimester. Because IV iron has been shown to improve hemoglobin more rapidly than oral iron,[45,51] 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 hemoglobin. Breymann 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). Hemoglobin improvements and newborn outcomes were similar in both groups, but vitality and social functioning were better with IV iron.[53]

 All available IV iron formulations consist of iron-carbohydrate complexes of small spheroidal iron-carbohydrate particles. 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.[56,57] Currently available IV iron formulations are of acceptable safety and equivalent effectiveness in the general population.[58,59] 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[60] and should not be misread as anaphylaxis,[61] and they rarely recur with rechallenge. Empiric use of steroids prior to re-treatment may diminish minor reactions that occur the next day.[62] Patients may also experience self-limited arthralgias, myalgias, and/or headache within a few days of infusion that generally respond to NSAIDs.

 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.[63]

Iron sucrose and sodium ferric gluconate are assigned to FDA pregnancy category B based on safety studies in pregnancy. Both high and low molecular weight iron

dextrans retain a pregnancy category C designation despite evidence suggesting that adverse events ascribed to iron dextran are mostly associated with the high molecular weight (HMW) formulation.[64] 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.[65] An observational study of 189 women treated with low molecular weight (LMW) iron dextran in second and third trimester reported no severe adverse events and only 2% transient infusion reactions.[66] These results corroborated outcomes in other studies showing safety of LMW iron dextran,[67,68] which allows complete replacement of IV iron in a single infusion over 15-60 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 1). In a prospective study Foessler and colleagues treated 65 pregnant women with FCM and reported no serious adverse effects and no change in fetal heart monitoring.[69] 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.[70] 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 two weeks

later (and after the 13th week) 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.[71] 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.[72]

Folate and cobalamin are involved in tetrahydrofolate metabolism, and necessary for DNA synthesis for fetal growth and maternal tissue growth.[73] 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. 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.[74]

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.[75] 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%.[76]

Diagnostic tests:

Most pregnant women with folate or cobalamin deficiency do not exhibit macrocytosis,[74,77] 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.[74]

Serum cobalamin measures cobalamin bound to two circulating binding proteins, haptocorrin and transcobalamin. In non-pregnant patients, serum cobalamin less than 200 pg/ml (<148 pmol/L) are diagnostic of cobalamin deficiency, while levels above 300 are considered normal. Levels in the range of 200-300 pg/ml are borderline, and cobalamin deficiency is possible.[78] Notably, there is no difference in levels of the metabolites homocysteine and methylmalonic acid in pregnant women with subnormal cobalamin levels when compared to pregnant women with normal levels,[79,80] 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.[79,81,82] Holotranscobalamin (biologically-active cobalamin bound to transcobalamin) does not decline in pregnancy and has been suggested as a marker for cobalamin deficiency in pregnancy.[83] Holotranscobalamin is not available for clinical

use. Serum folic acid concentrations less than 2 ng/ml are diagnostic of folic acid deficiency, while levels above 4 ng/ml effectively rule out deficiency. Levels in the range of 2-4 ng/ml are borderline.[84] Serum folate may be affected by recent oral/dietary intake, limiting the value of a single test. While 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 a serum iron of 25 ug/dL; TIBC 395 ug/dL; ferritin 4 ug/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 US and Canada. National-scale public health initiatives requiring fortification of flour with folic acid in the US and Canada have been effective in substantially reducing the prevalence of NTDs.[85] 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.[86] Absent mandatory fortification, the prevalence of NTD in Europe has remained unchanged.

Folate fortification of foods in the US 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 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.[87]

The WHO recommends folate supplementation for pregnant women, 400μg/d from early pregnancy to 3 months postpartum. The U.S. Public Health Service and CDC recommend the same for all women of childbearing age (15-45) to prevent spina bifida and anencephaly.[88]

Most prenatal vitamins contain 1mg of folate, which is more than sufficient to meet the increased needs of pregnancy. A higher supplementation dose, 5 mg/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, pre-gestational diabetes, epilepsy on valproate or carbamezepine).

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.[89]

The WHO and US National Institutes of Health (NIH) recommends a higher daily allowance of cobalamin in pregnant women than in non-pregnant women (2.6 vs 2.4 μg/d)[90,91] to support fetal neurologic development. Growth retardation, general hypotonia and loss of neuromotor skills have been described in infants of mothers with cobalamin deficiency.[92] Furthermore, cobalamin supplementation improves the motor functioning and regurgitation of cobalamin-deficient infants.[93] 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[94] 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 a serum iron of 20 ug/dL, TIBC 600 ug/dL, ferritin 4 ug/L and cobalamin of 113 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/ uL. 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 1000mcg daily for one week. After resolution of parasitemia, ferrous sulfate 200mg and folic acid 5mg 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.[95] The prevalence is higher in primigravidas than in non-pregnant women. *Plasmodium falciparum* is the predominant species. Malaria contracted during pregnancy increases the mother's risk of becoming anemic, infects the fetus (congenital malaria), is associated with low birth weight (LBW) and increased infant mortality.[96]

Malaria prevention reduces neonatal mortality.[97] For pregnant women in areas with medium and high malaria transmission, WHO recommends intermittent preventive treatment during pregnancy (IPTp), with at least three doses of sulfadoxine-pyrimethamine in the second and third trimesters,[98] in conjunction with the use of

insecticide-treated mosquito nets. The patient in case 3 received sulfadoxine-pyrimethamine as recommended.

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

The relationship between iron deficiency and malaria has been a focus of intense study, since the two often co-exist. In vitro, *Plasmodium falciparum* infects erythrocytes from iron-deficient individuals less efficiently than erythrocytes from iron replete humans,[102] 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.[103] In a case control study in Malawi, iron deficiency was less frequent in 112 women with placental malaria than in 110 women without.[104] 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.[105] 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.[106] In the two studies of pregnant women in countries with malaria, there was no difference in placental malaria and parasitaemia between those who received iron to those who did not.

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.[107] The most common indications for blood in sub-Saharan Africa are maternal hemorrhage, trauma, and malaria-associated anemia.[108] In a study of blood transfusion services in Malawi, the mean Hb of transfused patients was 4.8 g/dl, and 17% (18/104) were given to pregnant women.[109]

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 >8g/dL.[110]

The latest transfusion guidelines of the AABB (formerly the American Association of Blood Banks) are based on 12587 patients enrolled in 31 eligible randomized controlled trials in non-obstetric settings. They recommend using a restrictive hemoglobin transfusion threshold of 7 g/dL for hemodynamically stable hospitalized adult patients. The evidence base that supports this approach in obstetrics is limited. Therefore, clinicians should consider the hemoglobin, overall clinical context, patient preferences and alternative therapies when making transfusion decisions for a patient.[111]

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.

References

1.   WHO. Iron deficiency anaemia : assessment, prevention and control : a guide for programme managers. In: Development NfHa ed. Geneva: World Health Organization; 2001.
2.   Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recomm Rep.* 1998;47(RR-3):1-29.
3.   WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vol. Vitamin and Mineral Nutrition Information System. Geneva: World Health Organization; 2011.
4.   Milman N, Byg KE, Agger AO. Hemoglobin and erythrocyte indices during normal pregnancy and postpartum in 206 women with and without iron supplementation. *Acta Obstet Gynecol Scand.* 2000;79(2):89-98.
5.   Lee AI, Okam MM. Anemia in pregnancy. *Hematol Oncol Clin North Am.* 2011;25(2):241-259, vii.
6.   Stevens GA, Finucane MM, De-Regil LM, et al. Global, regional, and national trends in haemoglobin concentration and prevalence of total and severe anaemia in children and pregnant and non-pregnant women for 1995-2011: a systematic analysis of population-representative data. *Lancet Glob Health.* 2013;1(1):e16-25.
7.   Ren A, Wang J, Ye RW, Li S, Liu JM, Li Z. Low first-trimester hemoglobin and low birth weight, preterm birth and small for gestational age newborns. *Int J Gynaecol Obstet.* 2007;98(2):124-128.
8.   de Sa SA, Willner E, Duraes Pereira TA, de Souza VR, Teles Boaventura G, Blondet de Azeredo V. Anemia in Pregnancy: Impact on Weight and in the Development of Anemia in Newborn. *Nutr Hosp.* 2015;32(5):2071-2079.
9.   Geng F, Mai X, Zhan J, et al. Impact of Fetal-Neonatal Iron Deficiency on Recognition Memory at 2 Months of Age. *J Pediatr.* 2015;167(6):1226-1232.
10.   Congdon EL, Westerlund A, Algarin CR, et al. Iron deficiency in infancy is associated with altered neural correlates of recognition memory at 10 years. *J Pediatr.* 2012;160(6):1027-1033.
11.   De-Regil LM, Fernandez-Gaxiola AC, Dowswell T, Pena-Rosas JP. Effects and safety of periconceptional folate supplementation for preventing birth defects. *Cochrane Database Syst Rev.* 2010(10):CD007950.
12.   van Uitert EM, Steegers-Theunissen RP. Influence of maternal folate status on human fetal growth parameters. *Mol Nutr Food Res.* 2013;57(4):582-595.
13.   Rush EC, Katre P, Yajnik CS. Vitamin B12: one carbon metabolism, fetal growth and programming for chronic disease. *Eur J Clin Nutr.* 2014;68(1):2-7.
14.   Routine iron supplementation during pregnancy. Review article. US Preventive Services Task Force. *JAMA.* 1993;270(23):2848-2854.
15.   Breymann C, Honegger C, Holzgreve W, Surbek D. Diagnosis and treatment of iron-deficiency anaemia during pregnancy and postpartum. *Arch Gynecol Obstet.* 2010;282(5):577-580.
16.   Milman N, Agger AO, Nielsen OJ. Iron status markers and serum erythropoietin in 120 mothers and newborn infants. Effect of iron supplementation in normal pregnancy. *Acta Obstet Gynecol Scand.* 1994;73(3):200-204.
17.   Arnold DL, Williams MA, Miller RS, Qiu C, Sorensen TK. Iron deficiency anemia, cigarette smoking and risk of abruptio placentae. *J Obstet Gynaecol Res.* 2009;35(3):446-452.
18.   Reveiz L, Gyte GM, Cuervo LG, Casasbuenas A. Treatments for iron-deficiency anaemia in pregnancy. *Cochrane Database Syst Rev.* 2011(10):CD003094.
19.   Scholl TO. Maternal iron status: relation to fetal growth, length of gestation, and iron endowment of the neonate. *Nutr Rev.* 2011;69 Suppl 1:S23-29.

20.   Bothwell TH. Iron requirements in pregnancy and strategies to meet them. *Am J Clin Nutr*. 2000;72(1 Suppl):257S-264S.

21.   Pavord S, Myers B, Robinson S, et al. UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol*. 2012;156(5):588-600.

22.   Williams MD, Wheby MS. Anemia in pregnancy. *Med Clin North Am*. 1992;76(3):631-647.

23.   Milman N, Agger AO, Nielsen OJ. Iron supplementation during pregnancy. Effect on iron status markers, serum erythropoietin and human placental lactogen. A placebo controlled study in 207 Danish women. *Dan Med Bull*. 1991;38(6):471-476.

24.   Mast AE, Blinder MA, Gronowski AM, Chumley C, Scott MG. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem*. 1998;44(1):45-51.

25.   Romslo I, Haram K, Sagen N, Augensen K. Iron requirement in normal pregnancy as assessed by serum ferritin, serum transferrin saturation and erythrocyte protoporphyrin determinations. *Br J Obstet Gynaecol*. 1983;90(2):101-107.

26.   Guyatt GH, Oxman AD, Ali M, Willan A, McIlroy W, Patterson C. Laboratory diagnosis of iron-deficiency anemia: an overview. *J Gen Intern Med*. 1992;7(2):145-153.

27.   van den Broek NR, Letsky EA, White SA, Shenkin A. Iron status in pregnant women: which measurements are valid? *Br J Haematol*. 1998;103(3):817-824.

28.   Tietz NW, Rinker AD, Morrison SR. When is a serum iron really a serum iron? The status of serum iron measurements. *Clin Chem*. 1994;40(4):546-551.

29.   Auerbach M, Adamson JW. How we diagnose and treat iron deficiency anemia. *Am J Hematol*. 2016;91(1):31-38.

30.   Camaschella C. Iron-deficiency anemia. *N Engl J Med*. 2015;372(19):1832-1843.

31.   Punnonen K, Irjala K, Rajamaki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. *Blood*. 1997;89(3):1052-1057.

32.   Infusino I, Braga F, Dolci A, Panteghini M. Soluble transferrin receptor (sTfR) and sTfR/log ferritin index for the diagnosis of iron-deficiency anemia. A meta-analysis. *Am J Clin Pathol*. 2012;138(5):642-649.

33.   van Santen S, Kroot JJ, Zijderveld G, Wiegerinck ET, Spaanderman ME, Swinkels DW. The iron regulatory hormone hepcidin is decreased in pregnancy: a prospective longitudinal study. *Clin Chem Lab Med*. 2013;51(7):1395-1401.

34.   Koenig MD, Tussing-Humphreys L, Day J, Cadwell B, Nemeth E. Hepcidin and iron homeostasis during pregnancy. *Nutrients*. 2014;6(8):3062-3083.

35.   Bah A, Wegmuller R, Cerami C, et al. A double blind randomised controlled trial comparing standard dose of iron supplementation for pregnant women with two screen-and-treat approaches using hepcidin as a biomarker for ready and safe to receive iron. *BMC Pregnancy Childbirth*. 2016;16(1):157.

36.   Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS One*. 2015;10(2):e0117383.

37.   Beard JL. Effectiveness and strategies of iron supplementation during pregnancy. *Am J Clin Nutr*. 2000;71(5 Suppl):1288S-1294S.

38.   Makrides M, Crowther CA, Gibson RA, Gibson RS, Skeaff CM. Efficacy and tolerability of low-dose iron supplements during pregnancy: a randomized controlled trial. *Am J Clin Nutr*. 2003;78(1):145-153.

39.   Milman N, Paszkowski T, Cetin I, Castelo-Branco C. Supplementation during pregnancy: beliefs and science. *Gynecol Endocrinol*. 2016:1-8.

40.   Cook JD, Reddy MB. Efficacy of weekly compared with daily iron supplementation. *Am J Clin Nutr*. 1995;62(1):117-120.

41.   Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood*. 2015;126(17):1981-1989.

42.   Okam MM, Koch TA, Tran MH. Iron deficiency anemia treatment response to oral iron therapy: a pooled analysis of five randomized controlled trials. *Haematologica*. 2016;101(1):e6-7.

43.   Avni T, Leibovici L, Gafter-Gvili A. Iron supplementation for the treatment of chronic heart failure and iron deficiency: systematic review and meta-analysis. *Eur J Heart Fail*. 2012;14(4):423-429.

44.   Avni T, Bieber A, Steinmetz T, Leibovici L, Gafter-Gvili A. Treatment of anemia in inflammatory bowel disease--systematic review and meta-analysis. *PLoS One*. 2013;8(12):e75540.

45.   Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A. Intravenous Versus Oral Iron Supplementation for the Treatment of Anemia in CKD: An Updated Systematic Review and Meta-analysis. *Am J Kidney Dis*. 2016.

46.   Gafter-Gvili A, Rozen-Zvi B, Vidal L, et al. Intravenous iron supplementation for the treatment of chemotherapy-induced anaemia - systematic review and meta-analysis of randomised controlled trials. *Acta Oncol*. 2013;52(1):18-29.

47.   Froessler B, Cocchiaro C, Saadat-Gilani K, Hodyl N, Dekker G. Intravenous iron sucrose versus oral iron ferrous sulfate for antenatal and postpartum iron deficiency anemia: a randomized trial. *J Matern Fetal Neonatal Med*. 2013;26(7):654-659.

48.   Kochhar PK, Kaundal A, Ghosh P. Intravenous iron sucrose versus oral iron in treatment of iron deficiency anemia in pregnancy: a randomized clinical trial. *J Obstet Gynaecol Res*. 2013;39(2):504-510.

49.   Neeru S, Nair NS, Rai L. Iron sucrose versus oral iron therapy in pregnancy anemia. *Indian J Community Med*. 2012;37(4):214-218.

50.   Bencaiova G, von Mandach U, Zimmermann R. Iron prophylaxis in pregnancy: intravenous route versus oral route. *Eur J Obstet Gynecol Reprod Biol*. 2009;144(2):135-139.

51.   Al RA, Unlubilgin E, Kandemir O, Yalvac S, Cakir L, Haberal A. Intravenous versus oral iron for treatment of anemia in pregnancy: a randomized trial. *Obstet Gynecol*. 2005;106(6):1335-1340.

52.   Bayoumeu F, Subiran-Buisset C, Baka NE, Legagneur H, Monnier-Barbarino P, Laxenaire MC. Iron therapy in iron deficiency anemia in pregnancy: intravenous route versus oral route. *Am J Obstet Gynecol*. 2002;186(3):518-522.

53.   Breymann C, Milman N, Mezzacasa A, Bernard R, Dudenhausen J, investigators F-A. Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: an international, open-label, randomized controlled trial (FER-ASAP). *J Perinat Med*. 2016.

54.   Breymann C, Gliga F, Bejenariu C, Strizhova N. Comparative efficacy and safety of intravenous ferric carboxymaltose in the treatment of postpartum iron deficiency anemia. *Int J Gynaecol Obstet*. 2008;101(1):67-73.

55.   New Recommendations to Manage Risk of Allergic Reactions With Intravenous Iron-Containing Medicines. Vol. EMA/377372/2013: European Medicine Agency; 2013.

56.   Danielson BG. Structure, chemistry, and pharmacokinetics of intravenous iron agents. *J Am Soc Nephrol*. 2004;15 Suppl 2:S93-98.

57.   Auerbach M, Coyne D, Ballard H. Intravenous iron: from anathema to standard of care. *Am J Hematol*. 2008;83(7):580-588.

58.   Okam MM, Mandell E, Hevelone N, Wentz R, Ross A, Abel GA. Comparative rates of adverse events with different formulations of intravenous iron. *Am J Hematol*. 2012;87(11):E123-124.

59.	Bircher AJ, Auerbach M. Hypersensitivity from intravenous iron products. *Immunol Allergy Clin North Am*. 2014;34(3):707-723, x-xi.
60.	Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anaemia. *Lancet*. 2007;369(9572):1502-1504.
61.	Aronoff GR. Safety of intravenous iron in clinical practice: implications for anemia management protocols. *J Am Soc Nephrol*. 2004;15 Suppl 2:S99-106.
62.	Auerbach M, Chaudhry M, Goldman H, Ballard H. Value of methylprednisolone in prevention of the arthralgia-myalgia syndrome associated with the total dose infusion of iron dextran: a double blind randomized trial. *J Lab Clin Med*. 1998;131(3):257-260.
63.	Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. *Mayo Clin Proc*. 2015;90(1):12-23.
64.	Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. *Nephrol Dial Transplant*. 2006;21(2):378-382.
65.	McCarthy JT, Regnier CE, Loebertmann CL, Bergstralh EJ. Adverse events in chronic hemodialysis patients receiving intravenous iron dextran--a comparison of two products. *Am J Nephrol*. 2000;20(6):455-462.
66.	Wong L, Smith S, Gilstrop M, et al. Safety and efficacy of rapid (1,000 mg in 1 hr) intravenous iron dextran for treatment of maternal iron deficient anemia of pregnancy. *Am J Hematol*. 2016;91(6):590-593.
67.	Ayub R, Tariq N, Adil MM, Iqbal M, Junaid A, Jaferry T. Efficacy and safety of total dose infusion of low molecular weight iron dextran in the treatment of iron deficiency anemia during pregnancy. *J Coll Physicians Surg Pak*. 2008;18(7):424-427.
68.	Myers B, Myers O, Moore J. Comparative efficacy and safety of intravenous ferric carboxymaltose (Ferinject) and iron(III) hydroxide dextran (Cosmofer) in pregnancy. *Obstet Med*. 2012;5(3):105-107.
69.	Froessler B, Collingwood J, Hodyl NA, Dekker G. Intravenous ferric carboxymaltose for anaemia in pregnancy. *BMC Pregnancy Childbirth*. 2014;14:115.
70.	Christoph P, Schuller C, Studer H, Irion O, De Tejada BM, Surbek D. Intravenous iron treatment in pregnancy: comparison of high-dose ferric carboxymaltose vs. iron sucrose. *J Perinat Med*. 2012;40(5):469-474.
71.	Sifakis S, Pharmakides G. Anemia in pregnancy. *Ann N Y Acad Sci*. 2000;900:125-136.
72.	Ackurt F, Wetherilt H, Loker M, Hacibekiroglu M. Biochemical assessment of nutritional status in pre- and post-natal Turkish women and outcome of pregnancy. *Eur J Clin Nutr*. 1995;49(8):613-622.
73.	Grieger JA, Clifton VL. A review of the impact of dietary intakes in human pregnancy on infant birthweight. *Nutrients*. 2015;7(1):153-178.
74.	Frenkel EP, Yardley DA. Clinical and laboratory features and sequelae of deficiency of folic acid (folate) and vitamin B12 (cobalamin) in pregnancy and gynecology. *Hematol Oncol Clin North Am*. 2000;14(5):1079-1100, viii.
75.	Maggard MA, Yermilov I, Li Z, et al. Pregnancy and fertility following bariatric surgery: a systematic review. *JAMA*. 2008;300(19):2286-2296.
76.	Toh SY, Zarshenas N, Jorgensen J. Prevalence of nutrient deficiencies in bariatric patients. *Nutrition*. 2009;25(11-12):1150-1156.
77.	Karaoglu L, Pehlivan E, Egri M, et al. The prevalence of nutritional anemia in pregnancy in an east Anatolian province, Turkey. *BMC Public Health*. 2010;10:329.
78.	Matchar DB, McCrory DC, Millington DS, Feussner JR. Performance of the serum cobalamin assay for diagnosis of cobalamin deficiency. *Am J Med Sci*. 1994;308(5):276-283.
79.	Pardo J, Peled Y, Bar J, et al. Evaluation of low serum vitamin B(12) in the non-anaemic pregnant patient. *Hum Reprod*. 2000;15(1):224-226.

80.   Metz J, McGrath K, Bennett M, Hyland K, Bottiglieri T. Biochemical indices of vitamin B12 nutrition in pregnant patients with subnormal serum vitamin B12 levels. *Am J Hematol*. 1995;48(4):251-255.

81.   Ball EW, Giles C. Folic Acid and Vitamin B12 Levels in Pregnancy and Their Relation to Megaloblastic Anaemia. *J Clin Pathol*. 1964;17:165-174.

82.   Pardo J, Gindes L, Orvieto R. Cobalamin (vitamin B12) metabolism during pregnancy. *Int J Gynaecol Obstet*. 2004;84(1):77-78.

83.   Morkbak AL, Hvas AM, Milman N, Nexo E. Holotranscobalamin remains unchanged during pregnancy. Longitudinal changes of cobalamins and their binding proteins during pregnancy and postpartum. *Haematologica*. 2007;92(12):1711-1712.

84.   Galloway M, Rushworth L. Red cell or serum folate? Results from the National Pathology Alliance benchmarking review. *J Clin Pathol*. 2003;56(12):924-926.

85.   De Wals P, Tairou F, Van Allen MI, et al. Reduction in neural-tube defects after folic acid fortification in Canada. *N Engl J Med*. 2007;357(2):135-142.

86.   Khoshnood B, Loane M, de Walle H, et al. Long term trends in prevalence of neural tube defects in Europe: population based study. *BMJ*. 2015;351:h5949.

87.   Green R, Miller JW. Folate deficiency beyond megaloblastic anemia: hyperhomocysteinemia and other manifestations of dysfunctional folate status. *Semin Hematol*. 1999;36(1):47-64.

88.   Force USPST. Folic acid for the prevention of neural tube defects: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2009;150(9):626-631.

89.   Mead NC, Sakkatos P, Sakellaropoulos GC, Adonakis GL, Alexandrides TK, Kalfarentzos F. Pregnancy outcomes and nutritional indices after 3 types of bariatric surgery performed at a single institution. *Surg Obes Relat Dis*. 2014;10(6):1166-1173.

90.   World Health Organization FaAOotUN. Vitamin and mineral requirements in human nutrition. In: Organization WH ed; 2004:341.

91.   National Institutes of Health OoDS. Vitamin B12 Fact Sheet for Consumers: U.S. Department of Health and Human Services.

92.   Bicakci Z. Growth retardation, general hypotonia, and loss of acquired neuromotor skills in the infants of mothers with cobalamin deficiency and the possible role of succinyl-CoA and glycine in the pathogenesis. *Medicine (Baltimore)*. 2015;94(9):e584.

93.   Torsvik I, Ueland PM, Markestad T, Bjorke-Monsen AL. Cobalamin supplementation improves motor development and regurgitations in infants: results from a randomized intervention study. *Am J Clin Nutr*. 2013;98(5):1233-1240.

94.   Sharabi A, Cohen E, Sulkes J, Garty M. Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route. *Br J Clin Pharmacol*. 2003;56(6):635-638.

95.   Holtz TH, Kachur SP, Roberts JM, et al. Use of antenatal care services and intermittent preventive treatment for malaria among pregnant women in Blantyre District, Malawi. *Trop Med Int Health*. 2004;9(1):77-82.

96.   Helitzer-Allen DL, McFarland DA, Wirima JJ, Macheso AP. Malaria chemoprophylaxis compliance in pregnant women: a cost-effectiveness analysis of alternative interventions. *Soc Sci Med*. 1993;36(4):403-407.

97.   Menendez C, Bardaji A, Sigauque B, et al. Malaria prevention with IPTp during pregnancy reduces neonatal mortality. *PLoS One*. 2010;5(2):e9438.

98.   World Health Organization; Global Malaria Program. Updated WHO Policy Recommendation (October 2012): Intermittent Preventive Treatment of Malaria in Pregnancy Using Sulfadoxine-Pyrimethamine (IPTp-SP). Geneva, Switzerland: World Health Organization; 2012.

99.   Greenwood BM. The epidemiology of malaria. *Ann Trop Med Parasitol*. 1997;91(7):763-769.

100.   Menendez C, Fleming AF, Alonso PL. Malaria-related anaemia. *Parasitol Today*. 2000;16(11):469-476.
101.   Boele van Hensbroek M, Calis JC, Phiri KS, et al. Pathophysiological mechanisms of severe anaemia in Malawian children. *PLoS One*. 2010;5(9):e12589.
102.   Clark MA, Goheen MM, Fulford A, et al. Host iron status and iron supplementation mediate susceptibility to erythrocytic stage Plasmodium falciparum. *Nat Commun*. 2014;5:4446.
103.   Kabyemela ER, Fried M, Kurtis JD, Mutabingwa TK, Duffy PE. Decreased susceptibility to Plasmodium falciparum infection in pregnant women with iron deficiency. *J Infect Dis*. 2008;198(2):163-166.
104.   Senga EL, Harper G, Koshy G, Kazembe PN, Brabin BJ. Reduced risk for placental malaria in iron deficient women. *Malar J*. 2011;10:47.
105.   Neuberger A, Okebe J, Yahav D, Paul M. Oral iron supplements for children in malaria-endemic areas. *Cochrane Database Syst Rev*. 2016;2:CD006589.
106.   Cross JH, Bradbury RS, Fulford AJ, et al. Oral iron acutely elevates bacterial growth in human serum. *Sci Rep*. 2015;5:16670.
107.   Akinola OI, Fabamwo AO, Tayo AO, Rabiu KA, Oshodi YA, Onyekwere CA. Evaluation of blood reservation and use for caesarean sections in a tertiary maternity unit in south western Nigeria. *BMC Pregnancy Childbirth*. 2010;10:57.
108.   Pitman JP, Wilkinson R, Liu Y, et al. Blood component use in a sub-Saharan African country: results of a 4-year evaluation of diagnoses associated with transfusion orders in Namibia. *Transfus Med Rev*. 2015;29(1):45-51.
109.   Bugge HF, Karlsen NC, Oydna E, et al. A study of blood transfusion services at a district hospital in Malawi. *Vox Sang*. 2013;104(1):37-45.
110.   Sentilhes L, Vayssiere C, Deneux-Tharaux C, et al. Postpartum hemorrhage: guidelines for clinical practice from the French College of Gynaecologists and Obstetricians (CNGOF): in collaboration with the French Society of Anesthesiology and Intensive Care (SFAR). *Eur J Obstet Gynecol Reprod Biol*. 2016;198:12-21.
111.   Carson JL, Guyatt G, Heddle NM, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. *JAMA*. 2016;316(19):2025-2035.

Table 1: Examples of Trials of IV iron formulations and dosing in pregnancy

Study ID	Design	Iron formulation	Participants	Dosing
Iron Sucrose				
Froessler 2013	RCT	IS vs oral	271 anemic women, 148 late pregnancy	400 mg of IS divided into two 200 mg infusions of 30 minutes duration, given a minimum of 24 hours apart
Kochhar 2013	RCT	IS vs oral	100 pregnant patients, week 24-34	IS divided doses of 200mg on alternate days
Dhanani 2012	RCT	IS vs IM iron iron sorbitol citric acid	60 pregnant, weeks 12-32	IS 200 mg, over 30 minutes, each infusion (to a total according to a formula of total iron deficit)
Neeru 2012	RCT	IS vs oral	89 pregnant patients, weeks36-14	IS 200 mg each infusion (to a total according to a formula of total iron deficit)
Christoph 2012	retrospective observational comparative	IS vs FCM	206 pregnant women after 13 weeks	IS 400 mg iron per week in two infusions, 48 h apart, FCM most patients 1000 mg
Bencaiova 2009	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)
Al 2005	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 minutes, total dose was administered over 5

28

				days and maximum daily dose administered was 400, usually every other day
Bayoumeu 2002	RCT	IS vs oral	Week 24-28	IS administered according to a formula*

Low-molecular-weight iron dextran

Wong 2016	retrospective observational study	LMWID	189 second and third trimester pregnant women	single infusion of 1000mg, 1 hour
Ayub 2008	Nonrandomized prospective trial	LMWID	100 pregnant women after 12 weeks	Single infusion, amount given according to calculated iron deficit

Ferric carboxymaltose

Breymann 2016 (FER-ASAP)	RCT	FCM vs. oral iron (ferrous sulphate)	252 pregnant women their second or third trimester (gestational weeks 16–33)	1000mg-1500 mg, according to weight and Hb level: Weight<66kg, Hb 8-9: 3×500 mg iron within 2 weeks of baseline Weight<66kg, Hb 9-10.5/11: 2×500 mg iron within 2 weeks of baseline Weight >66 kg, Hb 8-9: 1×1000 mg iron, followed by 1×500 mg iron 1 week later Weight >66 kg, , Hb 9-10.5/11: 1×1000 mg iron
Froessler 2014	Prospective	FCM	65 pregnant, second	

	observational		and third trimester	FCM 15mg/kg
Pels 2015	retrospective observational	FCM	64 pregnant women	FCM 1000mg in a single infusion of 15 minutes weekly. Most received only one dose.
Myers 2012[†]	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
Schneider J 2015	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

Abbreviations:

FCM= ferric carboxymaltose; Hb= hemoglobin;IM=intramuscular; IS = iron sucrose; LMWID= Low-molecular-weight iron dextran; RCT= randomized controlled trials

*Iron formula deficit: Weight × (Target hemoglobin – Actual hemoglobin) × 0.24 + 500 mg

[†]Myers shows safety of FCM and LMWID in pregnancy

Table 2: Intravenous Iron preparations

Generic name	Iron Sucrose	Sodium Ferric gluconate	Low-molecular-weight iron dextran	Ferumoxytol	Ferric carboxymaltose	Iron Isomaltoside
Trade (brand) name	Venofer	Ferrlecit	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	Low-molecular-weight iron dextran	Polyglucose sorbitol carboxymethylether	Carboxymaltose	Isomaltoside
Concentration of elemental iron	20mg/mL	12.5 mg/mL	50mg/mL	30 mg/mL	50mg/mL	100 mg/mL
Total dose infusion (TDI)	No	No	Yes	No	Yes	Yes

Test dose required	No	No	Yes	No	No	No
Recommended Max Dose	Multiple doses of 200mg-300mg	Multiple doses of 125mg-187.5mg	Multiple doses of 100mg or single infusion of 1000mg	Two infusions of 510mg given 3-8 days apart or a single dose of 1020mg	Two doses of 750mg, given 7 or more days apart (weight <50 kg) Two doses of 15mg/kg (or 1000mg) given 7 or more days apart if weight >50kg	a single infusion, at a dose of 20 mg/kg (or 1000mg) or up to 3 doses of 500mg given over 7 days
Infusion Time	over a period of at least 15 minutes	One hour	One hour	15 minutes	15 minutes	15 minutes
Pregnancy Category	B	B	C	C	C	Not listed

Abbreviations:

FCM= ferric carboxymaltose; Hb= hemoglobin; IDA = iron deficiency anemia; IM=intramuscular; IS = iron sucrose; LMWID= Low-molecular-weight iron dextran; RCT= randomized controlled trials
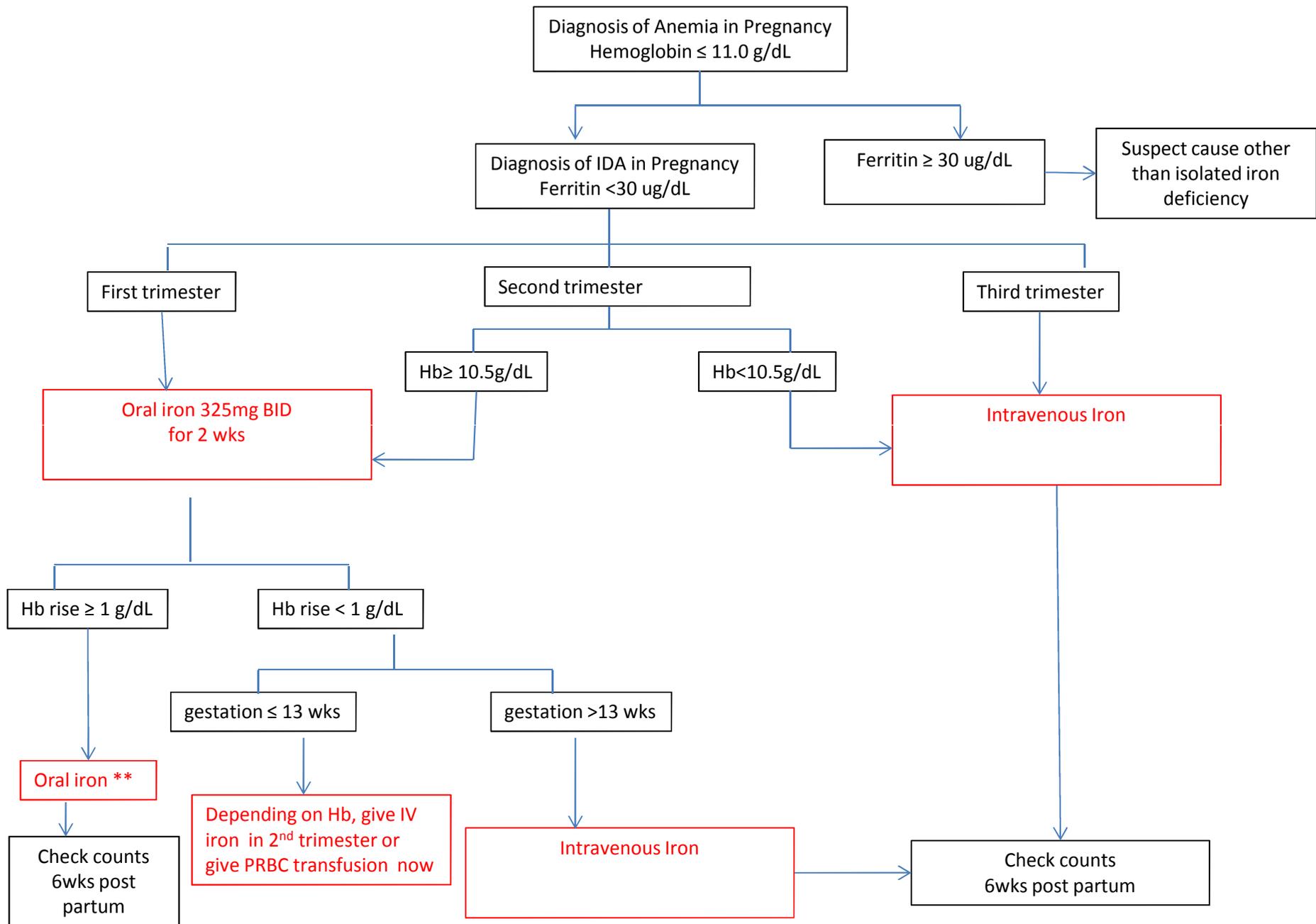
FDA Pregnancy Categories: **B**. Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women; **C**. animal reproductive studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks

Figure Legend

Figure 1: Algorithm of Suggested Approach to Diagnoses and Managment of Iron Deficiency Anemia in Pregnancy.

Hb: hemoglobin

** 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).

```
                          ┌─────────────────────────────┐
                          │ Diagnosis of Anemia in Pregnancy │
                          │   Hemoglobin ≤ 11.0 g/dL    │
                          └─────────────────────────────┘
```

Diagnosis of Anemia in Pregnancy
Hemoglobin ≤ 11.0 g/dL

Diagnosis of IDA in Pregnancy
Ferritin <30 ug/dL

Ferritin ≥ 30 ug/dL

Suspect cause other than isolated iron deficiency

First trimester

Second trimester

Third trimester

Hb≥ 10.5g/dL

Hb<10.5g/dL

Oral iron 325mg BID for 2 wks

Intravenous Iron

Hb rise ≥ 1 g/dL

Hb rise < 1 g/dL

gestation ≤ 13 wks

gestation >13 wks

Oral iron **

Depending on Hb, give IV iron in 2nd trimester or give PRBC transfusion now

Intravenous Iron

Check counts 6wks post partum

Check counts 6wks post partum

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

Maureen M. Achebe and Anat Gafter-Gvili

Information about reproducing this article in parts or in its entirety may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests

Information about ordering reprints may be found online at:
http://www.bloodjournal.org/site/misc/rights.xhtml#reprints

Information about subscriptions and ASH membership may be found online at:
http://www.bloodjournal.org/site/subscriptions/index.xhtml