Assessment and management of anemia during pregnancy

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Anemia is the most common hematologic condition affecting individuals during pregnancy and the puerperium, with the most common causes being iron deficiency and acute blood loss. Clinicians providing prenatal and postpartum care must be vigilant to conduct a thorough assessment and provide evidence-based management as the often under recognized sequela of untreated anemia during this time may lead to maternal and fetal morbidity and mortality. Clinicians should understand the diagnostic tools and treatment options available to appropriately counsel patients through the various types of anemia.

KEY WORDS: anemia, iron deficiency, acute blood loss, hemoglobinopathies

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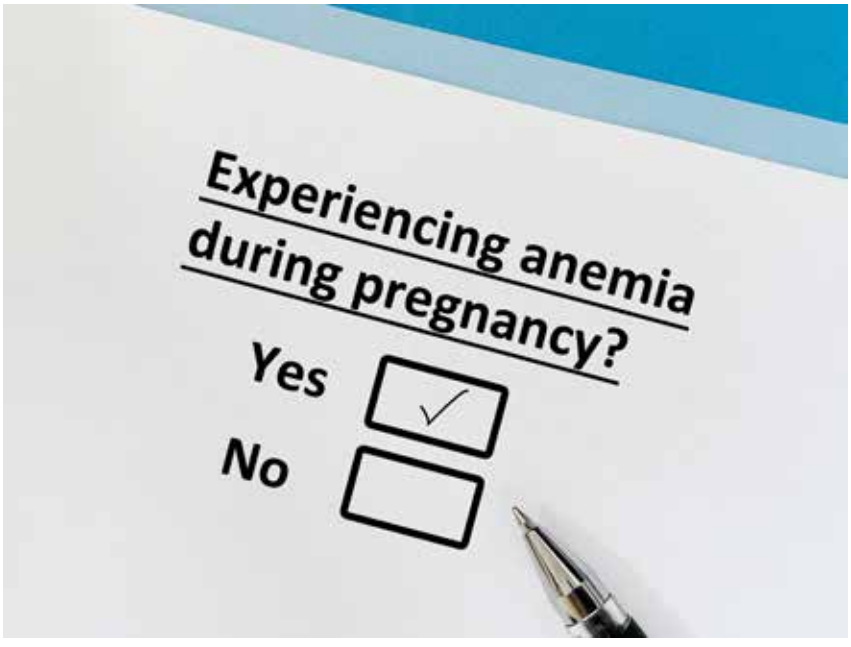

Anemia, recognized as a reduction in hemoglobin or erythrocyte concentration in the blood, is the most common hematologic condition affecting individuals during pregnancy and the puerperium. There is a rising trend in pregnancy-associated anemia in the United States as well as increasing disparity by race, ethnicity, and socioeconomic status. The overall incidence of anemia during pregnancy ranges from 6.9% to 28.7%, with iron deficiency being the most prevalent type. Data are difficult to quantify related to variation in levels of prenatal care across the healthcare continuum, particularly those impacted by various social determinants of health.[1] The best data available are based on pregnant patients who participate in Special Supplemental Nutrition Program for Women, Infants, and Children (WIC). Among WIC participants, approximately 1 in 10 is affected by maternal anemia, although there is significant variation based on race, ethnicity, and geographic location. Anemia among all pregnant patients who participate in WIC is currently classified as a mild public health risk, while anemia among Black pregnant patients overall and in pregnant patients whose hemoglobin was only assessed in the third trimester is classified as a moderate public health risk.[2]

Table 1. Defining anemia by trimester[21]

First trimester	• Hemoglobin < 11 g/dL • Hematocrit < 33%
Second trimester	• Hemoglobin < 10.5 g/dL • Hematocrit < 32%
Third trimester	• Hemoglobin < 11 g/dL • Hematocrit < 33%

Table 2. Anemia characterized by RBC morphology[12]

Microcytic (MCV < 80 fL)	• Iron deficiency anemia
	• Thalassemias
	• Anemia of chronic disease
	• Sideroblastic anemia
	• Anemia associated with:
	  • Copper deficiency
	  • Lead poisoning

Normocytic (MCV 80–100 fL)	• Hemorrhagic anemia
	• Early iron deficiency anemia
	• Anemia of chronic disease
	• Autoimmune hemolytic anemia
	• Hereditary spherocytosis
	• Hemolytic anemia associated with paroxysmal nocturnal hemoglobinuria
	• Anemia associated with:
	  • Bone marrow suppression
	  • Chronic renal insufficiency
	  • Endocrine dysfunction
	  • Hypothyroidism or hypopituitarism

Macrocytic (MCV > 100 fL)	• Folic acid deficiency anemia
	• Drug-induced hemolytic anemia
	• Anemia associated with:
	  • Liver disease
	  • Ethanol abuse
	  • Acute myelodysplastic syndrome
	  • Reticulocytosis

MCV, mean corpuscular volume; RBC, red blood cell.

Severe anemia during pregnancy is associated with an increased risk for both maternal and fetal/infant morbidity and mortality.[2–4] There is an association between severe anemia during pregnancy and preterm birth, low birth weight, small for gestational age, and perinatal mortality.[3,5] Adverse maternal outcomes associated with severe anemia include postpartum hemorrhage, preeclampsia, and transfusion.[3,4,6]

Given the available data on incidence of anemia during pregnancy, the existence of significant disparities, and known maternal and fetal risks related to severe anemia, enhanced evidence-based public health interventions and education are needed.[7,8] This article provides an overview of the etiologies of anemia during pregnancy, reviews essential assessment and management components, and describes strategies for prevention.

Etiology and diagnosis

There is an approximate 40% to 50% increase in plasma volume while erythrocyte mass expands only 15% to 25% with a single gestation pregnancy.[9] This expected physiologic change during pregnancy is reflected in decreased hemoglobin and hematocrit levels. Accompanying fetal growth and placental demands result in a threefold increase in iron requirement in the second and third trimesters.[10] Despite the amenorrhea that accompanies pregnancy and increased iron absorption, most pregnant individuals do not maintain adequate iron stores without supplementation, particularly in the second and third trimesters.[11] The Centers for Disease Control and Prevention (CDC) defines anemia in pregnancy as a hemoglobin or hematocrit value less than the fifth percentile of the distribution of hemoglobin or hematocrit in a health reference population based on the stage of pregnancy (*Table 1*).[2] Anemias are categorized based on whether they are inherited or acquired, underlying cause, and red blood cell (RBC) morphology (*Table 2*).[12]

A systematic approach should be undertaken to appropriately diagnose maternal anemia based on its characteristics—decreased RBC production, increased RBC destruction, and blood loss. Decreased RBC production may result from inadequate nutrition, particularly a deficiency in nutrients such as iron, vitamin B12, or folate. This deficiency may be a result of lack of dietary intake or malabsorption. Bone marrow disorders or suppression, hormone deficiencies, chronic disease, and infection also may lead to decreased RBC production. Hemolysis or increased RBC destruction may be the result of a hemoglobinopathy such as sickle cell anemia or may be induced by medications, infection, trauma, or some systemic diseases. Acute or chronic

blood loss can result in anemia. Anemias also may be classified by RBC size as evidenced by their mean corpuscular volume (MCV). Macrocytic anemias are associated with an MCV greater than 100 fL. A common cause of macrocytic anemia is folate deficiency, with vitamin B12 deficiency another. Reticulocytosis also may cause an increased MCV. Microcytic anemias are associated with an MCV less than 80 fL. The most common cause of microcytic anemia during pregnancy is iron deficiency, while another cause of microcytic anemia is thalassemia. There are a variety of causes for anemias with normal MCV (80 to 100 fL) including chronic disease, bone marrow suppression, early iron deficiency anemia, and acute hemorrhage.[12–14]

As part of the diagnostic process, clinicians should remember that racial disparities exist related to distribution of hemoglobin and hematocrit. Because these etiologies are poorly understood and the use of varied criteria may lead to gaps in care, the same diagnostic criteria should be used for all patients.[15] Factors that may cause a generalized increase in hemoglobin and hematocrit levels should be considered with interpreting test results, such as maternal tobacco use and living at a high altitude.

Initial evaluation

The initial evaluation of all pregnant patients with mild-to-moderate anemia should include a comprehensive medical history (including family history), physical examination, and appropriate laboratory studies—specifically complete blood count (CBC) with differential, vitamin B12 level, and serum iron studies (including iron level and total iron binding capacity [TIBC]), transferrin saturation, and ferritin level). For patients with a family history of inherited anemias or in those patients with abnormal RBC indices, a hemoglobinopathy evaluation with hemoglobin electrophoresis should be considered if not previously performed. In patients without evidence of a cause other than iron deficiency, it is reasonable to begin empiric iron therapy. When adequate iron therapy is provided, reticulocytosis should be observed 7 to 10 days following initiation followed by an increase in hemoglobin and hematocrit levels in subsequent weeks. Failure to respond appropriately to iron therapy should prompt further investigation and may suggest a cause other than iron deficiency: malabsorption (often related to concurrent use of antacids), nonadherence, or chronic blood loss.[12]

Iron deficiency anemia

Risk factors for developing iron deficiency anemia during the reproductive years include lack of iron-rich dietary choices, lack of dietary iron absorption enhancers, dietary choices that impair iron absorption, gastrointestinal complications that impair absorption, pica, heavy menses, short-interval pregnancy, and postpartum hemorrhage. Iron deficiency anemia may be diagnosed based on abnormal values on biochemical test results and increases in hemoglobin concentrations of more than 1 g/dL after iron treatment. The total amount of iron in the body is determined by intake, loss, and storage. When there is adequate iron to meet needs, more than 70% is classified as functional iron. The remainder is storage iron primarily ferritin but also hemosiderin and transport iron or protein transferrin.[16,17]

The spectrum of iron deficiency includes:

- Iron depletion: low levels of stored iron
- Iron deficient erythropoiesis: low levels of both stored and transport iron
- Iron deficiency anemia: low levels of stored, transport, and functional iron[17]

Measurements of serum hemoglobin or hematocrit are the primary screening tests for identifying anemia but are nonspecific for identifying iron deficiency. Laboratory test findings characteristic of iron deficiency anemia are microcytic, hypochromic erythrocytes, and with evidence of depleted iron stores (low plasma iron levels, high TIBC, low serum ferritin levels). Serum ferritin levels have the highest sensitivity and specificity for establishing a diagnosis of iron deficiency anemia with a level less than 30 µg/L confirming the diagnosis.[18]

Macrocytic anemia

Macrocytic anemia can be either megaloblastic or nonmegaloblastic. Causes of megaloblastic anemia include folate and vitamin B12 deficiencies and pernicious anemia, while causes of nonmegaloblastic anemia include alcoholism, liver disease, myelodysplasia, aplastic anemia, hypothyroidism, and increased reticulocyte count. Macrocytic anemia is characterized by an MCV greater than 100 fL, while an MCV greater than 115 fL is almost exclusively seen in patients with folic acid or vitamin B12 deficiencies. The diagnosis may be confirmed by measurement of serum folic acid or vitamin B12 levels. In the US, macrocytic anemia beginning during pregnancy is overwhelmingly caused by folic acid deficiency and is associated with diets lacking fresh leafy vegetables, legumes, and/or animal proteins.[19] During pregnancy, folic acid requirements increase to 400 µg per day. Treatment of pregnancy-induced folic acid deficiency should include a dietary modification and folic acid and iron supplementation. Folic acid 1 g oral

daily typically produces an appropriate response. Macrocytic anemia in pregnancy caused by vitamin B12 (cyanocobalamin) deficiency may be encountered in individuals who have had a partial or total gastric resection or in individuals with Crohn's disease. Women who have had a total gastrectomy require vitamin B12 1,000 µg intramuscularly per month.

Clinical management

All pregnant patients should be screened for anemia during the first trimester and again between 24 and 29 weeks' gestation via CBC. Patients who meet criteria for anemia should receive further evaluation to determine the cause, particularly if iron deficiency is ruled out. The American College of Obstetricians and Gynecologists and the CDC recommend all pregnant patients begin low-dose iron supplementation during the first trimester to decrease the prevalence of maternal anemia at delivery except in the presence of certain genetic disorders such as hemochromatosis.[19] Clinicians might consider the development and implementation of a protocol to standardize anemia screening, diagnosis, treatment, and follow-up that includes support for pregnant patients with fewer resources. In patients with non-iron deficiency anemias, consideration should be given for referral to hematology for diagnosis and targeted therapy.

Blood transfusion is rarely indicated unless the pregnant person exhibits signs of hypovolemia and/or shock secondary to blood loss or a high-risk surgical procedure, such as cesarean hysterectomy on a patient with a placenta accreta spectrum disorder, significant postpartum hemorrhage, or cesarean section with higher-than-normal blood loss. Unfortunately, antepartum complications necessitating blood transfusion are often not predictable.[20] Transfusion for fetal indications should be considered in cases of severe anemia with a maternal hemoglobin less than 6 g/dL as this has been associated with abnormal fetal oxygenation, resulting in non-reassuring fetal heart rate patterns, oligohydramnios, fetal cerebral vasodilation, and intrauterine fetal death.[21]

Iron deficiency during pregnancy is one of the strongest predictors of postpartum anemia. The current recommendation is the continued use of oral iron supplementation, either alone or in combination with folic acid supplementation, for at least 6 to 12 weeks following delivery.[22] Consideration also must be given to the significant and often underrecognized association between anemia and postpartum depression (PPD), even in pregnant patients without a history of mental health disorders. In a systematic review and meta-analysis, eight studies showed a significant increase in risk for PPD following anemia during pregnancy and 10 studies indicated a significantly higher rate of PPD in individuals with postpartum anemia than in nonanemic individuals.[23] Depression during pregnancy and PPD are among the most common complications related to pregnancy with significant public health sequelae.

Table 3. Iron formulations

Preparation	Dosing
Oral	
Ferrous fumarate	106 mg elemental iron per 325 mg tablet
Ferrous gluconate	34 mg elemental iron per 300 mg tablet
Ferrous sulfate	65 mg elemental iron per 325 mg tablet
Ferric maltol	30 mg iron per tablet
IV or IM	
Iron dextran	50 mg elemental iron per mL
IV only	
Ferric gluconate	12.5 mg iron per mL
Iron sucrose	20 mg iron per mL

Dietary education

Primary prevention during pregnancy begins with comprehensive patient education, ideally beginning prior to pregnancy. Current daily dietary iron recommendation during pregnancy is 27 mg, while it is 9 mg for lactating individuals.[22] Dietary education should be provided to all patients with particular attention to those in their reproductive years. Foods that are iron rich include nuts and seeds, dried fruit, tofu, beef, shrimp, turkey, liver, beans, lentils, dark green leafy vegetables, and enriched bread and breakfast cereals. Foods that enhance iron absorption include orange juice, grapefruit, strawberries, cantaloupe, fresh broccoli, and fresh bell peppers.[24] Clinicians should provide information and referrals for those in low socioeconomic status and with health disparities to provide access and resources to healthier, iron-rich foods.

Prenatal iron supplementation

is important as the typical US diet provides insufficient sources for the increased iron requirements during pregnancy. Effectiveness can be enhanced by advising patients on limiting food items that decrease iron absorption, especially within 2 hours of oral iron supplementation, including dairy products, soy products, spinach, coffee, and tea. Clinicians should consider encouraging patients to take all oral iron supplementation with a glass of orange juice to increase absorption. Approximately 4 ounces of orange juice is adequate for this purpose.

Medication management

Various formulations of iron available for use in the US are listed in *Table 3*. Sustained-release and enteric-coated preparations may be less effective despite their design to decrease gastrointestinal complaints. Oral and parenteral iron replacement are both effective for iron store repletion in pregnant patients. Three meta-analyses evaluated the benefits and risks of oral versus parenteral iron for pregnant or postpartum patients with iron deficiency anemia.[25–27] For treatment of iron deficiency anemia during pregnancy, intravenous iron was associated with higher maternal hemoglobin at delivery, fewer medication reactions, greater likelihood of achieving target hemoglobin, and increased hemoglobin level after 4 weeks.[26,27] Postpartum patients receiving intravenous iron had higher hemoglobin concentrations at 6 weeks' postpartum along with fewer gastrointestinal adverse effects.[25] Based on the available evidence, parenteral iron is an option that can be considered for those who cannot tolerate or do not respond to oral iron or for those with severe iron deficiency later in pregnancy.[12]

Conclusion

The prevalence of anemia during pregnancy has continued to increase over time with notable racial, ethnic, and socioeconomic disparities. It is often overlooked and dismissed as clinically insignificant. However, severe maternal and fetal sequelae are often preventable with equitable implementation of public health and clinical strategies. As clinicians providing prenatal and postpartum care, the implementation of recommendations and providing comprehensive patient education related to primary prevention rests with us. ■

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The impact that mentors can have on young professionals in the AANHPI community and specific ethnic backgrounds such as Filipino Americans is manifold. Sociocultural phenomena including the bamboo ceiling and model minority myth may restrict young nursing students or registered nurses from seeing themselves in an APRN or leadership role, in particular in women's health. Mentorship can provide for culturally congruent support to these individuals, further increase the WHNP pipeline, and diversify the women's health community. Conducting more research on mentorship among AANHPI WHNPs is needed for addressing the unique barriers and facilitators in developing effective mentorship, advancing nursing career trajectories, and supporting and building a strong pipeline of advanced practice providers who are knowledgeable in providing equitable care for the AANHPI community and beyond. ■

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