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Committee on Practice Bulletins—Obstetrics. This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Obstetrics with the assistance of Maureen Malee, PhD, MD.

INTERIM UPDATE: The content in this Practice Bulletin has been updated as highlighted (or removed as necessary) to reflect limited, focused changes to provide additional information regarding screening for anemia, intravenous iron supplementation, and the use of cell salvage.

Anemia in Pregnancy

Anemia, the most common hematologic abnormality, is a reduction in the concentration of erythrocytes or hemoglobin in blood. The two most common causes of anemia in pregnancy and the puerperium are iron deficiency and acute blood loss. Iron requirements increase during pregnancy, and a failure to maintain sufficient levels of iron may result in adverse maternal–fetal consequences. The purpose of this document is to provide a brief overview of the causes of anemia in pregnancy, review iron requirements, and provide recommendations for screening and clinical management of anemia during pregnancy.

Background

Classification

The definition of *anemia* recommended by the Centers for Disease Control and Prevention (CDC) is a hemoglobin or hematocrit value less than the fifth percentile of the distribution of hemoglobin or hematocrit in a healthy reference population based on the stage of pregnancy. Classification derived from an iron-supplemented population lists the following levels as anemic: hemoglobin (g/dL) and hematocrit (percentage) levels below 11 g/dL and 33%, respectively, in the first trimester; 10.5 g/dL and 32%, respectively, in the second trimester; and 11 g/dL and 33%, respectively, in the third trimester (1).

Anemias may be categorized by whether they are inherited or acquired, underlying causative mechanism, or red blood cell morphology (Boxes 1–3). A mechanistic approach categorizes anemias caused by decreased red blood cell production, increased red blood cell destruction, and blood loss. Decreased production may result from a lack of nutrients, such as iron, vitamin B_{12}, or folate. This lack may be a result of dietary deficiency, malabsorption, or bleeding. Bone marrow disorders or suppression, hormone deficiencies, and chronic disease or infection also may lead to decreased production. Hemolytic anemias are associated with increased destruction.

Anemias also may be classified by cell size. In contemporary practice, this typically is done by an automated cell counter. Macrocytic anemias are associated with a mean corpuscular volume (MCV) greater than 100 fL. Reticulocytosis also may cause an increased MCV. A common cause of macrocytic anemia is folate deficiency. Microcytic anemias are associated with an MCV less than 80 fL. The most common cause of microcytic anemia is iron deficiency. Another common cause of microcytic anemia in certain ethnic groups is hemoglobinopathy (2).

Anemia in Pregnancy

Pregnancy is associated with physiologic changes that may complicate the diagnosis of hematologic disorders. There is an increased iron requirement during pregnancy because plasma volume expands by 40–50%, and erythrocyte mass expands by 15–25% during a singleton gestation (3). The greater expansion in plasma typically is

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Box 1. Anemia Classification

Acquired

- Deficiency anemia (eg, iron, vitamin B_{12}, folate)
- Hemorrhagic anemia
- Anemia of chronic disease
- Acquired hemolytic anemia
- Aplastic anemia

Inherited

- Thalassemias
- Sickle cell anemia
- Hemoglobinopathies (other than sickle cell anemia)
- Inherited hemolytic anemias

reflected by decreases in hemoglobin and hematocrit levels.

The total amount of iron in the body is determined by intake, loss, and storage (4). There are approximately 2.3 g of total body iron in women. Additional iron stores during pregnancy (approximately 1 g) support this increased red blood cell mass, the fetus and placenta, and the anticipated blood loss accompanying a vaginal delivery. When there is adequate iron to meet needs, more than 70% is classified as functional iron, and the remainder as storage iron. Of the functional iron, more than 80% is found in the red blood cell mass as hemoglobin, with the remainder in myoglobin and in respiratory enzymes.

Box 2. Anemias Characterized by Mechanism

Decreased red blood cell production

- Iron deficiency anemia
- Anemia associated with vitamin B_{12} deficiency
- Folic acid deficiency anemia
- Anemia associated with bone marrow disorders
- Anemia associated with bone marrow suppression
- Anemia associated with low levels of erythropoietin
- Anemia associated with hypothyroidism

Increased red blood cell destruction

- Inherited hemolytic anemias
  - Sickle cell anemia
  - Thalassemia major
  - Hereditary spherocytosis
- Acquired hemolytic anemias
  - Autoimmune hemolytic anemia
  - Hemolytic anemia associated with thrombotic thrombocytopenic purpura
  - Hemolytic anemia associated with hemolytic uremic syndrome
  - Hemolytic anemia associated with malaria
- Hemorrhagic anemia

Iron Deficiency Anemia

Iron deficiency can be defined as abnormal values on biochemical test results, increases in hemoglobin concentrations of more than 1 g/dL after iron treatment, or absent bone marrow iron stores as determined by a bone marrow iron smear (1). The spectrum of iron deficiency ranges from iron depletion, when stored iron is low, to iron deficient erythropoiesis, when both stored and transport iron are low, to iron deficiency anemia, when stored, transport, and functional iron are low (1).

Measurements of serum hemoglobin concentration or hematocrit are the primary screening tests for identifying anemia but are nonspecific for identifying iron deficiency. Normal iron indices are listed in Table 1. Laboratory test results characteristic of iron deficiency anemia are a microcytic, hypochromic anemia with evidence of depleted iron stores, low plasma iron levels, high total iron-binding capacity, low serum ferritin levels, and increased levels of free erythrocyte protoporphyrin.

Measurement of serum ferritin levels has the highest sensitivity and specificity for diagnosing iron deficiency in anemic patients (5, 6). Levels of less than 30 micrograms/L confirm iron deficiency anemia (6). The CDC recommends screening for iron deficiency anemia in pregnant women and implementing universal iron supplementation to meet the iron requirements of pregnancy except in the presence of certain genetic disorders, such as hemochromatosis (1, 7). The rationale is that treatment maintains maternal iron stores and may be beneficial for neonatal iron stores. The typical diet confers 15 mg of elemental iron per day. The recommended daily dietary allowance of ferrous iron during pregnancy is 27 mg and in lactation it is 9 mg, which is present in most prenatal vitamins (7). Available iron supplements are listed in Table 2. Perinatal iron supplementation is important because the typical American diet and endogenous stores are insufficient sources for the increased iron requirements during pregnancy. Sustained-release or enteric-coated preparations dissolve poorly and may be less effective.

Prevalence, Etiologies, and Risk Factors

Limited data are available to estimate the current prevalence of iron deficiency anemia in pregnant individuals in the United States (8). A national study of anemia in pregnancy in the United States found a prevalence of 21.55 per 1,000 women when *anemia* was defined as a hemoglobin concentration less than 10 g/dL (9). The

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prevalence of anemia in pregnancy in non-Hispanic Black women (35.38 per 1,000 women) was two times higher than that of non-Hispanic White women (18.02 per 1,000 women) (9). Teenaged mothers had the highest prevalence of anemia in pregnancy of all races (9). An assessment of iron status in pregnant individuals in the United States using data from the National Health and Nutrition Examination Survey (known as NHANES) from 1999 to 2006 found that iron deficiency prevalence increased significantly with each trimester (mean ± standard error, 6.9% ± 2.2%, 14.3% ± 2.1%, and 29.5% ± 2.7% in the first, second, and third trimesters, respectively) and was higher in Mexican American pregnant women, non-Hispanic Black pregnant women, and women with parity greater than 2 (10).

Box 3. Anemias Classified by Mean Corpuscular Volume

Microcytic (MCV less than 80 fL)

- Iron deficiency anemia
- Thalassemias
- Anemia of chronic disease
- Sideroblastic anemia
- Anemia associated with copper deficiency
- Anemia associated with lead poisoning

Normocytic (MCV 80–100 fL)

- Hemorrhagic anemia
- Early iron deficiency anemia
- Anemia of chronic disease
- Anemia associated with bone marrow suppression
- Anemia associated with chronic renal insufficiency
- Anemia associated with endocrine dysfunction
- Autoimmune hemolytic anemia
- Anemia associated with hypothyroidism or hypopituitarism
- Hereditary spherocytosis
- Hemolytic anemia associated with paroxysmal nocturnal hemoglobinuria

Macrocytic (MCV greater than 100 fL)

- Folic acid deficiency anemia
- Anemia associated with vitamin B_{12} deficiency
- Drug-induced hemolytic anemia (eg, zidovudine)
- Anemia associated with reticulocytosis
- Anemia associated with liver disease
- Anemia associated with ethanol abuse
- Anemia associated with acute myelodysplastic syndrome

Abbreviation: MCV, mean corpuscular volume.

In reproductive-aged women, risk factors for iron deficiency anemia include a diet poor in iron-rich foods, such as clams, oysters, liver, beef, shrimp, turkey, enriched breakfast cereals, beans, and lentils; a diet poor in iron absorption enhancers, such as orange juice, grapefruit, strawberries, broccoli, and peppers; a diet rich in foods that diminish iron absorption, such as dairy products, soy products, spinach, coffee, and tea; pica (eating nonfood substances such as clay or laundry starch); gastrointestinal disease affecting absorption; heavy menses; short interpregnancy interval; and blood loss at delivery exceeding that of an uncomplicated vaginal delivery.

Iron deficiency anemia during pregnancy has been associated with an increased risk of low birth weight, preterm delivery, and perinatal mortality and should be treated with iron supplementation in addition to prenatal vitamins (11, 12). In addition, there may be an association between maternal iron deficiency anemia and postpartum depression, with poor results in mental and psychomotor performance testing in offspring (13–16).

Macrocytic Anemia

Macrocytic anemia may be megaloblastic or nonmegaloblastic. Causes of megaloblastic anemia include folate and vitamin B_{12} deficiency and pernicious anemia. Causes of nonmegaloblastic anemia include alcoholism, liver disease, myelodysplasia, aplastic anemia, hypothyroidism, and an increased reticulocyte count. Macrocytic anemia is characterized by an MCV greater than 100 fL. Levels greater than 115 fL are almost exclusively seen in patients with folic acid or vitamin B_{12} deficiencies. The diagnosis may be confirmed by measurement of serum folic acid or vitamin B_{12} levels. Measurement of red cell folate also has been proposed (17). In the United States, macrocytic anemia beginning during pregnancy is overwhelmingly caused by folic acid deficiency. It is associated with diets lacking fresh leafy vegetables, legumes, or animal proteins. During pregnancy, folic acid requirements increase from 50 micrograms to 400 micrograms per day. Treatment of pregnancy-induced folic acid deficiency should include a nutritious diet and folic acid and iron supplementation. Treatment with 1 mg of folic acid, administered orally, each day typically produces an appropriate response. Macrocytic anemia in pregnancy caused by vitamin B_{12} (cyanocobalamin) deficiency may be encountered in women who have had a partial or total gastric resection or in women with Crohn disease. Women who have had a total gastrectomy require 1,000 micrograms of vitamin B_{12}, intramuscularly, at monthly intervals.

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Table 1. Normal Iron Indices in Pregnancy

Test	Normal Value
Plasma iron level	40–175 micrograms/dL
Plasma total iron-binding capacity	216–400 micrograms/dL
Transferrin saturation	16–60%
Serum ferritin level	More than 30 micrograms/L
Free erythrocyte protoporphyrin level	Less than 3 micrograms/g

Clinical Considerations and Recommendations

▶ ***Who should be screened for anemia during pregnancy?***

All pregnant women should be screened for anemia with a complete blood count in the first trimester and again at 24 0/7–28 6/7 weeks of gestation. Patients who meet criteria for anemia based on hematocrit levels less than 33% in the first and third trimesters and less than 32% in the second trimester should be evaluated to determine the cause. If iron deficiency is ruled out, other etiologies should be investigated. Those with iron deficiency anemia should be treated with supplemental iron, in addition to prenatal vitamins.

There are disparities in the distribution of hematocrit and hemoglobin by race. The National Academy of Medicine (formerly known as the Institute of Medicine) historically recommended a change in the threshold for diagnosis of anemia based on race for this reason (18). However, since the etiology of these disparities is unknown and using a different standard may result in a failure to identify and treat people at risk for adverse pregnancy outcomes related to anemia, the same criteria should be used for all populations. A secondary analysis of pregnant people with an antepartum hemoglobin of less than 11 who delivered at a single institution found that in the setting of a differential threshold for iron supplementation, Black women were at significant increased odds of delivery admission anemia in comparison with non-Black women with the same antepartum hemoglobin, which may perpetuate disparities in maternal and neonatal outcomes (19).

Living at a high altitude and tobacco use cause a generalized increase in hematocrit and hemoglobin levels, and consideration of these factors may be appropriate when interpreting test results (1).

▶ ***How should asymptomatic pregnant women with mild to moderate anemia be evaluated?***

The initial evaluation of pregnant women with mild to moderate anemia may include a medical history, physical examination, and measurements of the complete blood count, red blood cell indices, serum iron levels, and ferritin levels. Examination of a peripheral smear is helpful for the diagnosis of hemolytic or parasitic disease. Depending on the personal and family history and the red blood cell indices, evaluation for hemoglobinopathies with hemoglobin analysis and genetic testing may be indicated. Using biochemical tests, *iron deficiency anemia* is defined by results of abnormal values for levels of serum ferritin, transferrin saturation, and levels of free erythrocyte protoporphyrin, along with

Table 2. Iron Supplements

Preparation	Dose
Ferrous fumarate	106 mg elemental iron per 325 mg tablet
Ferrous sulfate	65 mg elemental iron per 325 mg tablet
Ferrous gluconate	34 mg elemental iron per 300 mg tablet
Iron dextran	50 mg elemental iron per milliliter, intramuscularly or intravenously
Ferric gluconate	12.5 mg iron per milliliter, intravenously only
Iron sucrose	20 mg iron per milliliter, intravenously only

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low hemoglobin or hematocrit levels (Table 1 and Table 3). In practice, the diagnosis of mild to moderate iron deficiency anemia is often presumptive. In patients without evidence of causes of anemia other than iron deficiency, it may be reasonable to empirically initiate iron therapy without first obtaining iron test results. When pregnant women with moderate iron deficiency anemia are given adequate iron therapy, reticulocytosis may be observed 7–10 days after iron therapy, followed by an increase in hemoglobin and hematocrit levels in subsequent weeks. Failure to respond to iron therapy should prompt further investigation and may suggest an incorrect diagnosis, coexisting disease, malabsorption (sometimes caused by the use of enteric-coated tablets or concomitant use of antacids), nonadherence, or blood loss.

▶ *Are there benefits of iron supplementation for patients who are not anemic?*

The recommended daily dietary allowance of iron during pregnancy is 27 mg. Low-dose supplementation of iron during pregnancy improves maternal hematologic parameters, reduces the likelihood of iron deficiency at term, and is not associated with harms (20). The CDC recommends that all pregnant patients begin low-dose iron supplementation at the first prenatal visit (1). The U.S. Preventive Services Task Force concluded that there was inadequate evidence to recommend for or against routine iron supplementation in pregnancy to improve maternal or neonatal outcomes and identified this as a critical gap in the evidence (8). In particular, it is unclear whether iron supplementation in well-nourished pregnant women who are not anemic affects perinatal outcomes. There is little evidence that iron supplementation results in morbidity beyond gastrointestinal symptoms, except in patients with hemochromatosis or certain other genetic disorders. Low-dose iron supplementation is recommended starting in the first trimester to decrease the prevalence of maternal anemia at delivery (20).

▶ *When should transfusion be considered in the antepartum or preoperative patient?*

Transfusions of red cells seldom are indicated unless hypovolemia from blood loss coexists or an operative delivery must be performed on a patient with anemia. The need for transfusion in women with antepartum complications can be predicted in only 24% of those who ultimately require blood products (21). The most common diagnoses associated with transfusion include trauma caused by instrumented delivery, uterine atony, placenta previa, retained products of conception, placental abruption, and coagulopathy (eg, the syndrome of hemolysis, elevated liver enzymes, and low platelet count [HELLP]). The presence of these diagnoses in a patient with anemia should prompt consideration of transfusion, particularly in the presence of unstable vital signs (21).

Severe anemia with maternal hemoglobin levels less than 6 g/dL has been associated with abnormal fetal oxygenation, resulting in nonreassuring fetal heart rate patterns, reduced amniotic fluid volume, fetal cerebral vasodilatation, and fetal death (22, 23). Thus, maternal transfusion should be considered for fetal indications in cases of severe anemia.

▶ *When should parenteral iron be used in pregnant patients? Is there a role for erythropoietin?*

Oral and parenteral iron are both effective for repletion of iron stores. Three meta-analyses evaluated the benefits and risks of oral versus parenteral iron for pregnant or postpartum women with iron deficiency anemia (24–26). For treatment of iron deficiency anemia in pregnancy, intravenous iron was associated with higher maternal hemoglobin at delivery (weighted mean difference, 0.66 g/dL; 95% CI, 0.31–1.02 g/dL) and fewer medication reactions (relative risk, 0.34; 95% CI, 0.20–0.57) in one review (26) and greater likelihood of achieving target hemoglobin (pooled odds ratio [OR], 2.66; 95% CI, 1.71–4.15), increased hemoglobin level after

Table 3. Biochemical Tests for Diagnosis of Anemia

Test	Results Indicating Iron Deficiency Anemia	Results Indicating Thalassemia	Results Indicating Anemia of Chronic Disease
Iron level	Decreased level	Normal	Decreased level
Total iron-binding capacity	Increased capacity	Normal	Decreased capacity
Ferritin level	Decreased level	Normal	Increased level
Iron/Total iron-binding capacity	Less than 18%	Normal	More than 18%

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4 weeks (pooled weighted mean difference, 0.84 g/dL; 95% CI, 0.59–1.09 g/dL), and decreased adverse reactions (pooled OR, 0.35; 95% CI, 0.18–0.67) in another (25). In the postpartum period, women receiving intravenous iron had higher hemoglobin concentrations at 6 weeks postpartum (mean difference, 0.9 g/dL; 95% CI, 0.4–1.3 g/dL) and fewer gastrointestinal adverse effects (24). Based on the available evidence regarding efficacy and side effect profile for use in pregnancy after the first trimester and postpartum, parenteral iron may be considered for those who cannot tolerate or do not respond to oral iron or for those with severe iron deficiency later in pregnancy.

Few studies have examined the role of erythropoietin in pregnant patients with anemia. In a randomized, controlled trial that examined the time to reach the targeted hemoglobin value and changes in efficacy measurements, including reticulocyte count and hematocrit levels, the use of both parenteral iron and parenteral iron plus erythropoietin improved measured parameters. However, the use of adjuvant erythropoietin alone was associated with a significantly shorter time to the targeted hemoglobin level and improved indices (reticulocyte count, hematocrit levels) in less than 2 weeks after treatment was initiated. No differences in maternal–fetal safety parameters were reported (27). In contrast, a randomized trial of women with postpartum anemia showed no additional benefit of the use of erythropoietin and iron versus iron alone (28).

▶ *Is there a role for autologous transfusion?*

Case reports suggest a role for autologous transfusion in patients with diagnoses placing them at high risk of symptomatic blood loss, such as placenta previa. Suggested criteria for consideration of autologous donation include a hematocrit level greater than 32% at 32 weeks of gestation (29). However, autologous transfusions rarely are performed, and the inability to predict the eventual need for transfusion has led to the conclusion that they are not cost-effective (30).

Intraoperative blood salvage, or cell salvage, has been associated with decreased need for transfusion in nonobstetric settings, including trauma, orthopedic, cardiac, and vascular surgery (31, 32). Use of intraoperative cell salvage in obstetrics has been shown to be feasible, safe, and potentially effective in reducing the need for transfusion, particularly in women at increased risk for significant blood loss at the time of delivery (33–36). In situations such as placenta previa or placenta accreta in which significant blood loss is anticipated, having this tool available may reduce the need for transfusion or reduce the volume of transfusion (37). Intraoperative cell salvage also may be acceptable to some people who are Jehovah's Witnesses and will not accept blood transfusion, depending on the technique used (38).

Summary of Recommendations

The following conclusion is based on good and consistent scientific evidence (Level A):

- Low-dose iron supplementation is recommended starting in the first trimester to decrease the prevalence of maternal anemia at delivery.

The following recommendation and conclusions are based on limited or inconsistent scientific data (Level B):

- Iron deficiency anemia during pregnancy has been associated with an increased risk of low birth weight, preterm delivery, and perinatal mortality and should be treated with iron supplementation in addition to prenatal vitamins.
- Severe anemia with maternal hemoglobin levels less than 6 g/dL has been associated with abnormal fetal oxygenation, resulting in nonreassuring fetal heart rate patterns, reduced amniotic fluid volume, fetal cerebral vasodilatation, and fetal death. Thus, maternal transfusion should be considered for fetal indications in cases of severe anemia.
- Based on the available evidence regarding efficacy and side effect profile for use in pregnancy after the first trimester and postpartum, parenteral iron may be considered for those who cannot tolerate or do not respond to oral iron or for those with severe iron deficiency later in pregnancy.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- All pregnant women should be screened for anemia with a complete blood count in the first trimester and again at 24 0/7–28 6/7 weeks of gestation. Patients who meet criteria for anemia based on hematocrit levels less than 33% in the first and third trimesters and less than 32% in the second trimester should be evaluated to determine the cause. If iron deficiency is ruled out, other etiologies should be investigated.
- Failure to respond to iron therapy should prompt further investigation and may suggest an incorrect diagnosis, coexisting disease, malabsorption (sometimes caused by the use of enteric-coated tablets or concomitant use of antacids), nonadherence, or blood loss.

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The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and September 2007. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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