

PROTOCOL 11

Maternal Anemia

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A comprehensive review of all causes of anemia may be intimidating, and many available algorithms are not high yield when evaluating pregnant women. The protocol presented here provides an algorithm for the initial evaluation of anemia in pregnancy, with treatment algorithms for the most common causes in pregnancy. Women who do not meet one of the definitions provided below are best managed in consultation with a hematologist.

Definition

During a singleton gestation, plasma volume doubles (increasing approximately 1000 mL) and red blood cell (RBC) volume increases by 25% (300 mL), with RBC production lagging slightly behind plasma expansion. This results in a physiological dilutional anemia of pregnancy, which reaches a nadir during the late second to early third trimester (Table 11.1). The Centers for Disease Control and Prevention (CDC) define anemia as a hemoglobin (Hb) below the fifth centile for a healthy, iron-supplemented population. This translates to a threshold of Hb less than 11 g/dL in the first and third trimesters, and less than 10.5 g/dL during the second trimester. Rates of anemia in pregnancy vary widely between different populations and socioeconomic classes.

Consequences

In developed countries, maternal anemia has been associated with increased risk of preterm birth and low-birthweight infants, as well as neonatal and perinatal death. In addition, maternal complications associated

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Table 11.1 Changes in laboratory values in pregnancy

	Nonpregnant women	Pregnant women
Hemoglobin (g/dL)	12–16	11–14
Hematocrit	36–46%	33–44%
RBC count ($\times 10^6/\text{mL}$)	4.8	4.0
MCV (fL)	80–100	=
MCHC	31–36%	=
Reticulocytes ($\times 10^9/\text{L}$)	50–150	=
Ferritin (ng/mL)	>25	>20
RDW (red cell distribution width)	11–15%	=

=, unchanged.

Source: Based on ACOG Practice Bulletin No. 107, 2009.

with anemia include preeclampsia, cesarean delivery, postpartum depression, and an increased likelihood for transfusion either intrapartum or postpartum despite equivalent blood loss. Women with anemia are asymptomatic or describe vague symptoms such as fatigue and palpitations; therefore, screening for anemia during pregnancy is recommended regardless of symptoms.

Diagnostic work-up and treatment

Causes of anemia may be classified by pathophysiology, such as comparing acquired versus inherited causes, or mechanisms of anemia such as decreased RBC production versus increased destruction. In clinical practice, more often the evaluation of maternal anemia starts with the mean corpuscular volume (MCV), based on which anemias are defined as microcytic (less than 80 fL), normocytic (80–100 fL) or macrocytic (greater than 100 fL) (Figure 11.1).

Macrocytic anemia

Figure 11.1 shows the appropriate work-up for the search of causes in the presence of macrocytic anemia. *Vitamin B₁₂ deficiency* is rare, as most healthy individuals have 2–3 years' storage available in the liver. However, vitamin B₁₂ deficiency can be encountered in individuals who have undergone bariatric surgery with partial gastric resection and are noncompliant with recommended vitamin B₁₂ supplementation (350 µg/day sublingually plus 1000 µg IM every three months if needed), in individuals with pernicious anemia (an extremely uncommon autoimmune disease in women of reproductive

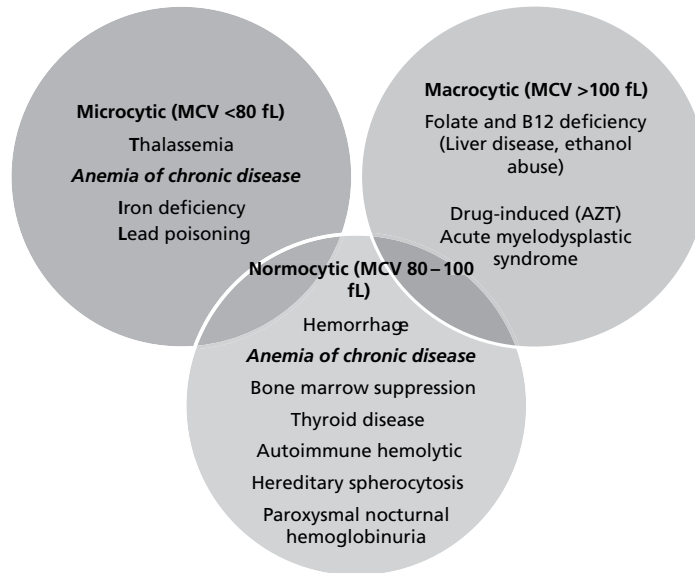


Figure 11.1 Causes of maternal anemia, classified by mean corpuscular volume (MCV).

age which is diagnosed by the presence of serum intrinsic factor antibodies), and in those with malabsorption (e.g., Crohn disease or ileal resection). *Folate deficiency* is less common today given the supplementation of foods with folate and universal folic acid supplementation in pregnancy. Recommended folate requirements are 400 µg/day during pregnancy, with higher doses recommended in the presence of multiple gestations, hemolytic disorders such as sickle cell anemia or thalassemia, and in patients taking antiepileptic drugs (AED) or sulfa drugs (e.g., sulfasalazine). In addition to macrocytic anemia, folate deficiency may also cause thrombocytopenia.

If a diagnosis of folate deficiency is made, or the woman had a prior pregnancy affected by a neural tube defect, the recommended dose of folic acid is 4 mg/day. Anemia due to folate or B₁₂ deficiency should respond briskly, with an elevated reticulocyte count, within 4–7 days of beginning treatment. In the case of macrocytic anemia with normal folate and vitamin B₁₂ levels, a consultation with a hematologist is indicated for bone marrow biopsy.

Normocytic anemia

The recommended laboratory evaluation for normocytic anemia is displayed in Figure 11.2. A high reticulocyte count indicates either hemolysis or blood loss with resultant bone marrow activation. If a normocytic anemia with an elevated reticulocyte count is found, a careful history and evaluation of laboratory studies for hemolysis, such as Coombs test,

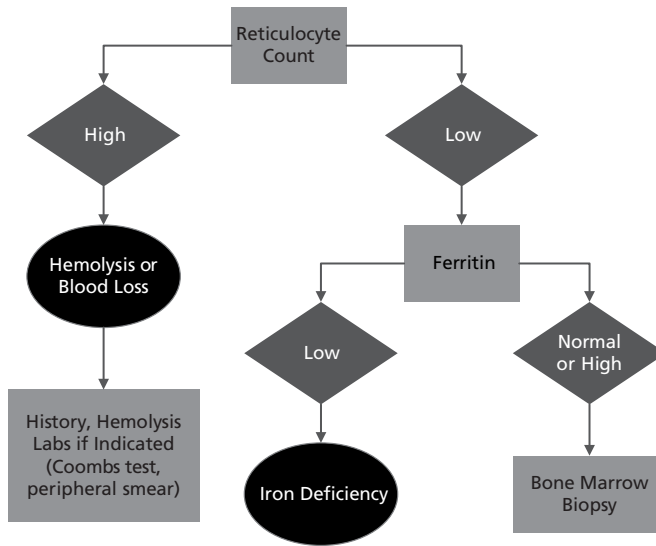


Figure 11.2 Algorithm for evaluation of normocytic anemia.

peripheral smear, and lactate dehydrogenase level, should be undertaken. A normal or low reticulocyte count in the setting of anemia raises concern for iron deficiency (a ferritin level less than 10–15 $\mu\text{g}/\text{dL}$ is diagnostic) or bone marrow suppression/disorders. Low reticulocyte count with normal or high serum ferritin levels can be seen in the presence of hypothyroidism or chronic disorders, such as inflammatory bowel disease, systemic lupus erythematosus, granulomatous infections, malignant neoplasms, and rheumatoid arthritis. Hematology consultation for further assessment is indicated in these circumstances.

Mixed nutritional deficiencies (folate and iron) may lead to normocytic anemia in pregnancy, but routine supplementation makes the probability of such a scenario low. If concern for a mixed nutritional deficiency does arise, the red cell distribution width (RDW), a marker of increased variability in red cell size or anisocytosis, is a useful indicator as an RDW greater than 15% indicates the presence of nutritional deficiencies.

Microcytic anemia

Most cases of microcytic anemia in pregnancy are due to iron deficiency anemia. Evaluation of a ferritin level should be the next step, as shown in Figure 11.3. Serum ferritin is the most sensitive and specific screening test for iron deficiency, with a level less than 10–15 $\mu\text{g}/\text{dL}$ indicating depleted iron stores. If serum ferritin is normal or high, the next step is hemoglobin electrophoresis to evaluate for a thalassemia. Such situations usually warrant consultation with a hematologist for further evaluation and bone marrow biopsy as indicated.

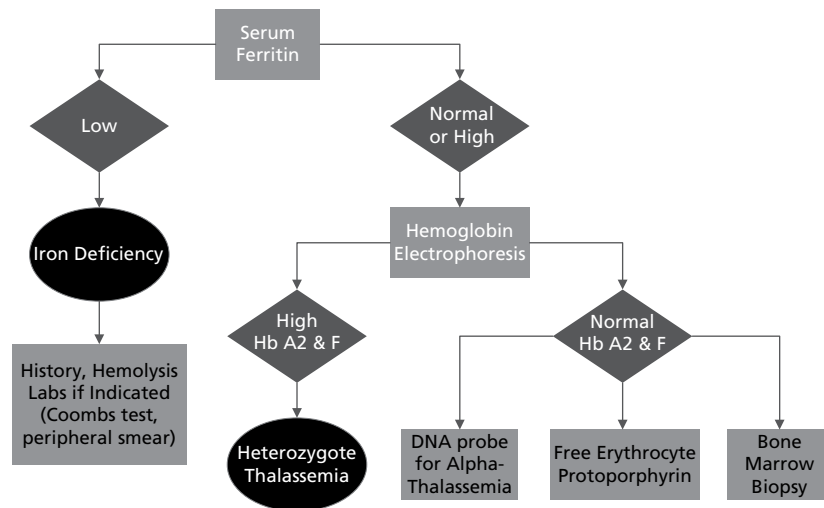


Figure 11.3 Algorithm for evaluation of microcytic anemia.

Iron supplementation in pregnancy

In a typical singleton gestation, maternal iron requirements (including blood volume expansion as well as fetal and placental requirements) average 1 g for the entire pregnancy, with this requirement further increased in the setting of multiple gestations. In a landmark study of healthy, nonanemic, menstruating young women who agreed to bone marrow biopsy, 66% had inadequate iron stores. For the above reasons, and because gastrointestinal side effects of oral iron supplementation (constipation, nausea, and diarrhea) are negligible with doses less than 45–60 mg, supplementation with elemental iron (30 mg/day) is recommended for all pregnant women in the United States, regardless of indices.

Supplementation should be continued until three months postpartum in areas with high prevalence of anemia. A review of randomized clinical trials (most performed in Western countries) showed that routine supplementation in nonanemic women results in higher maternal Hb levels at term and one month postpartum, higher serum ferritin levels, lower rates of anemia at term (RR = 0.26) and of iron deficiency anemia in particular (RR = 0.33), and higher serum ferritin levels in the infants (Peña-Rosas and Viteri 2009). However, no differences are noted in most clinical outcomes, such as preterm birth, preeclampsia, or need for transfusion, birthweight, small for gestational age, perinatal mortality or need for NICU admissions.

Treatment of iron deficiency anemia

Compared to routine supplementation in pregnancy, higher doses of iron are required for the treatment of maternal anemia (up to 200 mg/day). *Oral iron* therapy is most often utilized, with a list of the most commonly

Table 11.2 Oral preparations for therapy of iron deficiency anemia

Type of iron	Elemental iron (mg)	Brand
Ferrous fumarate	64–200	Femiron, Feostat, Ferrets, Fumasorb, Hemocyte, Ircan, Nephro-Fer, Vitron-C
Ferrous sulfate	40–65	Chem-Sol, Fe50, Feosol, Fergensol, Ferinsol, Ferrogradumet, Ferosul, Ferratab, FerraTD, Ferrobob, Ferrospace, Ferrotine, Moliron, Slowfe, Yieronia
Ferrous gluconate	38	Fergon, Ferralet, Simron
Ferric	50–150	Ferrimin, Fe-Tinic, Hytanic, Niferex, Nu-iron

Source: Based on ACOG Practice Bulletin No. 107, 2009.

available formulations given in Table 11.2. Enteric-coated forms should be avoided because they are poorly absorbed; absorption is increased by intake of iron on an empty stomach and with vitamin C or orange juice. Although several trials have been conducted to compare iron formulations, it is not possible to assess the efficacy of the treatments due to the use of different drugs, doses, and routes. Gut absorption decreases with increasing doses of iron; therefore it is best to divide the total daily dose into 2–3 doses.

A relationship exists between dose of oral iron and gastrointestinal side effects, with worsening of symptoms as dose increases, with such side effects leading to discontinuation of therapy in 50% of women. To encourage compliance, it is important to minimize side effects by increasing the dose gradually, with larger doses in the evening, and consideration for the use of an iron sulfate elixir which allows more gradual titration of dose. Stool softeners are often required to prevent constipation. Serum reticulocyte count should be elevated within 7–10 days of treatment initiation, with an improvement in hemoglobin levels less rapid – the hemoglobin deficit should be expected to halve in one month and normalize by 6–8 weeks after initiation of treatment. To replenish iron stores, oral therapy should be continued for three months after the anemia has been corrected.

Intravenous (IV) iron therapy is generally reserved for women who cannot or will not take oral iron preparations. Hemoglobin indices are equivalent after 40 days of treatment in women receiving IV iron therapy compared to those receiving oral therapy, but the rate of rise is more rapid in women receiving IV therapy. Randomized trials have not shown significant differences in need for maternal blood transfusion, neonatal birthweight, or neonatal anemia between the two forms of supplementation, and studies have demonstrated a preference for oral supplementation among most women. Therefore, IV therapy is indicated only in patients with severe

Table 11.3 Intravenous preparations for therapy of iron deficiency anemia

Type of intravenous iron	Commercial names	Dose
Iron dextran LMW	INFeD, Cosmofer	1000 mg/60 min (diluted in 250–1000 mL of normal saline)
Ferric gluconate	Ferlecit	125 mg/30 min (diluted in 100 mL of normal saline)
Iron sucrose	Venofer	200 mg/60 min
Ferric carboxymaltose	Ferinject	100 mg/15 min

Source: Based on ACOG Practice Bulletin No. 107, 2009.

anemia with intolerance to oral therapy or malabsorption. Iron dextran is associated with a greater risk of anaphylaxis and is not recommended in the light of other available formulations with a lower risk of allergic reaction. Intravenous preparations tested in pregnancy or puerperium are shown in Table 11.3.

Erythropoietin is not indicated in the treatment of iron deficiency anemia unless the anemia is caused by chronic renal failure or other serious chronic medical conditions and is expensive with many associated side effects – its use should be reserved for treatment by a hematologist.

Blood transfusion is indicated only for anemia associated with hypovolemia from blood loss or in preparation for a cesarean delivery in the presence of severe anemia.

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