Northwest Perinatal Center

Perinatal Progress

Anemia in Pregnancy

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Anemia is the most common hematologic abnormality addressed by prenatal care providers and it remains an important contributor to maternal morbidity and mortality worldwide. Anemia is also associated with an increased risk of low birth weight, preterm birth, and perinatal mortality.

Prenatal care presents an opportunity for providers to screen for and institute treatment that can improve the health of the mother and fetus in preparation for delivery. About half to two-thirds of women (both non-pregnant and pregnant) have minimal iron stores without actually being anemic—due to menstrual loss and inadequate dietary intake of iron. In addition to often starting with low iron stores, the normal (yet discordant) physiologic changes in pregnancy of 50% increase in plasma volume and 30% increase in red blood cell mass account for this frequent pregnancy complication (1).

A normal hemoglobin level for an adult female is 14.0 +/- 2.0 g/dL. In contrast, the Center for Disease Control (CDC) defines anemia in a pregnant woman as a hemoglobin level less than 11 g/dL in the 1st trimester, less than 10.5 g/dL in the 2nd trimester, and less than 11 g/dL in the 3rd trimester. According to CDC estimates, the prevalence of anemia of pregnancy is 20-50%, with the vast majority of cases (75%) being due to iron deficiency. Other potential causes of anemia include hemoglobinopathies, other nutrient deficiencies (i.e., folate, vitamin B12), hemolysis, acute or chronic blood loss, and anemia of chronic disease, among others (2).

Symptoms

Most women with low iron stores or mild to moderate anemia are asymptomatic, but are identified through routine laboratory screening in early pregnancy or in the 3rd trimester. Symptomatic women typically report increased fatigue, dizziness, and shortness of breath; all of which can overlap with frequently reported discomforts of pregnancy. Pica may also be disclosed upon further questioning.

Identifying and Categorizing Anemia

All pregnant women should be screened for anemia with a complete blood count (CBC) upon entry into prenatal care and again in the 3rd trimester. Additional testing should be considered for symptomatic patients, as well as those being treated for iron-deficiency anemia to verify adequacy of treatment. Once anemia (hemoglobin <11 g/dL) has been identified, the next step is to try to identify the underlying cause by assessing the mean corpuscular volume (MCV), which reflects the size of a typical red blood cell. Anemia can be classified as microcytic (MCV <80), normocytic (MCV of 80-100), or macrocytic (MCV >100). Women with iron-deficiency typically have low or low-normal MCV, but hemoglobinopathies (such as sickle cell and thalassemia syndromes) will also have a low MCV (<80).

Microcytic Anemia

For women with microcytic anemia in early pregnancy, additional studies are warranted to assess iron stores and possible inheritable traits. A detailed history (menstrual history, gestational bleeding, medical illnesses, family history, etc.) may help identify an underlying cause. Measurement of ferritin levels has the highest sensitivity and specificity for diagnosing iron deficiency in anemic patients (3). Levels of less than 20 mcg/dL confirm iron-deficiency anemia (Table 1). Serum iron levels and total iron-binding capacity (TIBC) are complementary tests to assess for iron deficiency; however, they are less sensitive than ferritin levels and add additional cost to an initial evaluation. In some instances of concomitant acute or chronic disease processes, ferritin levels may be normal or elevated (as an acute phase reactant) and follow-up testing of serum iron and TIBC can identify iron deficiency. **In the vast majority of cases, though, serum ferritin levels alone are adequate to identify iron deficiency when suspected.**

For roughly the same cost as serum iron with TIBC, a hemoglobin electrophoresis can be obtained and is recommended in patients in certain ethnic groups (Af-

rican, African-American, Mediterranean, and Southeast Asian) with a low MCV (even without anemia) to screen for sickle cell trait and/or thalassemia traits. Hemoglobin electrophoresis should not be repeated if previously performed. Women with sickle cell trait or suspected thalassemia trait (high risk ethnicity with microcytic anemia and normal iron stores) should be offered genetic counseling and partner testing, given the potential for sickle cell disease or thalassemia major conditions in the offspring.

For women with microcytic anemia in the 3rd trimester who have previously had a normal CBC and red blood cell indices in early pregnancy, it is reasonable to start a therapeutic trial of iron supplementation and repeat the CBC in four to six weeks to assess response. If anemia persists despite patient compliance, then further evaluation of iron stores (as above) should be considered.

Macrocytic Anemia

For women with macrocytic anemia (MCV >100), assessment of serum folate and vitamin B12 levels, in addition to a detailed history, may help elucidate cause. Folic acid deficiency due to dietary insufficiency is the most common cause of macrocytic anemia and MCV is typically >115. This can be corrected with improved nutrition, folic acid 1 mg daily, and iron supplementation. Vitamin B12 deficiency (serum level <160–200 pg/mL) is rare, as most individuals have two to three years of adequate stores in their liver, and may be due to dietary insufficiency or malabsorption (as with pernicious anemia). Macrocytic anemia with normal folic acid levels warrants further evaluation and consultation with MFM or hematology should be considered.

Normocytic Anemia

Women with anemia and a low normal MCV (>80) may have early iron deficiency anemia. This can be confirmed by checking serum ferritin level and/or a therapeutic trial of iron supplementation. Normocytic anemia is the most difficult type in which to identify the underlying cause and several contributing causes may be at play. Failure to respond to iron supplementation warrants further evaluation, and MFM or hematology consultation should be considered.

Treatment of Iron Deficiency Anemia

In the absence of an iron-rich diet or supplementation, most women enter pregnancy with some degree of iron deficiency due to monthly losses from menstruation. There are approximately 2.3 g of total body iron in women. Additional iron stores are required during pregnancy (approximately 1 g) to support the increased red blood cell mass production, the fetus and placenta, and the anticipated blood loss accompanying a vaginal delivery. Only about 10% of dietary iron is absorbed (average diet contains 6 mg/1000 kcal (12-15 mg/day)) and dietary sources alone are typically insufficient to support a healthy pregnancy (4,5).

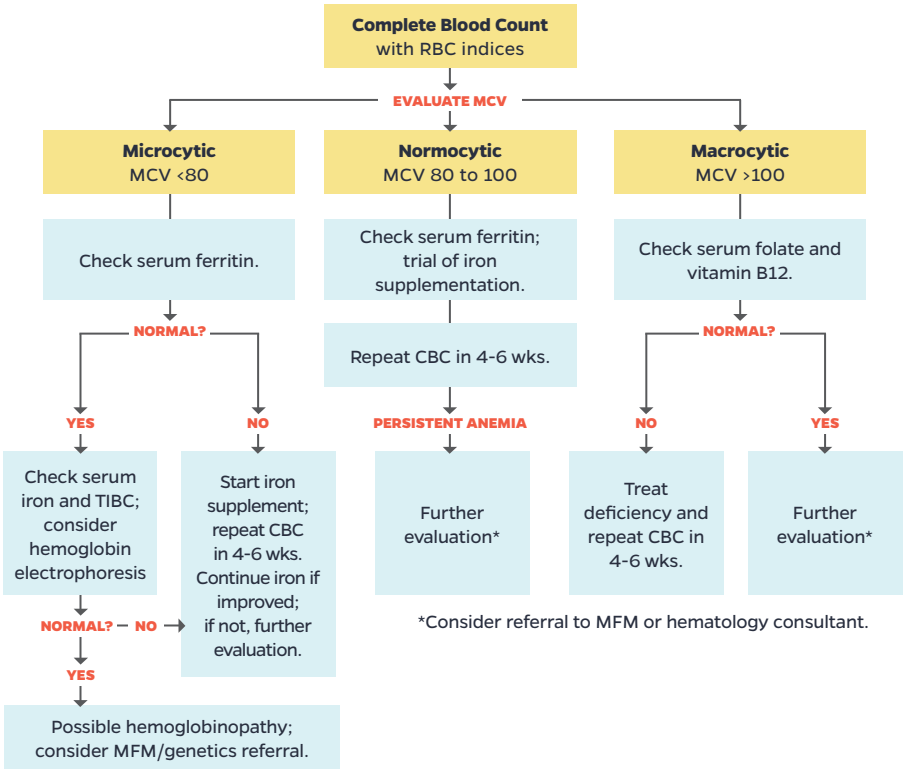
Iron supplementation (30-60 mg elemental iron per day) is recommended in all pregnant women (this is typically present in a prenatal vitamin). Increased iron supplementation (120-200 mg elemental iron/day or higher) is recommended in women with iron deficiency anemia. Ferrous sulfate 325 mg tablets (65 mg elemental iron) are the least expensive option and can be prescribed 2-3 times per day (once daily may be adequate for mild iron deficiency). Administration of ascorbic acid 500 mg (vitamin C) or a glass of orange juice can improve absorption, which is most favorable in a slightly acidic environment. Avoiding antacids and calcium around the time of dosing will also improve absorption. Side effects of nausea, intestinal discomfort and constipation affect about 30 percent of patients and can be ameliorated with food, gradual dose titration and/or stool softeners (6). Other oral iron supplements are available with varying amounts of elemental iron, but note that slow-release formulations or enteric coated iron supplements are poorly absorbed.

Table 1: Normal Values in Pregnancy

Ferritin	>20 mcg/dL
Iron	40-175 mcg/dL
Total Iron Binding Capacity	190-400 mcg/dL
Vitamin B12	190-950 ng/L
Folate	>20 mcg/L

Iron supplementation beyond the recommended daily intake (from diet and prenatal vitamin) in the absence of iron deficiency is of unclear benefit and does not enhance hematopoiesis. Folic acid supplementation (in absence of deficiency) with iron supplementation does not appear to add benefit compared to iron supplement alone (7). Similarly, the addition of intravenous iron replacement to oral iron therapy has not shown significant benefits over placebo in hemoglobin rise, symptoms, or adverse side effects. For patients with acute blood loss anemia, IV iron replacement results in quicker recovery of ferritin levels at two weeks compared to oral iron replacement, but there is no difference in hemoglobin or hematocrit levels at one, two, and six weeks (8).

Identifying, categorizing and treating anemia in pregnancy



In the absence of symptoms, oral iron supplementation is sufficient and less costly for treatment of iron deficiency anemia. In symptomatic patients with severe anemia, blood transfusion should be considered, in addition to iron supplementation. With maternal hemoglobin levels <6 g/dL, adequate fetal oxygenation is compromised, and maternal blood transfusion is warranted for fetal benefit (9). The decision for transfusion and amount to transfuse should be balanced with the severity of the patient's symptoms and clinical status, bearing in mind that the risk for subsequent alloimmunization is related to the number of units received.

Follow-up patient questioning soon after prescription of iron supplementation can address any side effects or other barriers to compliance. Repeat assessment of blood counts by CBC should be performed four to six weeks after initiation of iron supplementation to ensure appropriate response and adequate dosing.

Recommendations

In general

1. Oral iron supplementation is the safest and most cost-effective method for treatment of iron deficiency. Intravenous iron replacement should be rarely used and reserved for patients with malabsorption syndromes or non-compliant patients with severe iron deficiency.
2. Severe anemia (hemoglobin <6 g/dL) is associated with abnormal fetal oxygenation and can result in increased perinatal morbidity and mortality. Maternal blood transfusion should be considered for fetal indications.

First trimester

1. In women with anemia (hemoglobin <11 g/dL), laboratory evaluation for the cause based on the MCV is recommended to guide treatment, as well as repeat assessment of hemoglobin after the start of appropriate therapy. Consider MFM consultation if the cause remains unclear after initial laboratory evaluation.

Our Author

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Dr. Smrtka was raised in Detroit, Michigan and attended Fordham University in New York City for his undergraduate studies. He completed medical school, residency in Obstetrics and Gynecology, and fellowship in Maternal-Fetal Medicine at Duke University in Durham, North Carolina. While there, he served as Administrative Chief Resident and conducted research in bleeding and clotting disorders in pregnancy and obesity in pregnancy. Dr. Smrtka is a member of the Society for Maternal-Fetal Medicine and the American Congress of Obstetricians and Gynecologists. He is board-certified in Obstetrics and Gynecology and in Maternal-Fetal Medicine.

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2. Hemoglobin electrophoresis is recommended (if not previously performed) in women with MCV <80 in certain ethnic groups (African, African-American, Mediterranean, SE Asian) to screen for hemoglobinopathies. Genetic counseling and partner testing should be offered to women with a known or suspected hemoglobinopathy.
3. Supplement with a daily prenatal vitamin containing iron and folic acid, as well as provide education about dietary sources of iron.

Second / Third trimesters

1. Repeat screening for anemia at 26-28 weeks' gestation.
2. In women with previously normal red cell indices that now have suggestion of iron deficiency anemia (low or normal MCV), presumptive treatment of iron deficiency anemia with oral iron supplementation is reasonable. Repeat assessment of hemoglobin levels 4-6 weeks after initiation of iron supplement is recommended.
3. Failure to respond to treatment should be further evaluated. Consider MFM consultation.

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