Optimize detection and treatment of iron deficiency in pregnancy

We are in the midst of a nationwide severe blood product shortage, necessitating that we optimize maternal red blood cell status prior to birth. Measure ferritin and hemoglobin levels at the first prenatal visit and again at 24 to 28 weeks' gestation to optimize the early detection and treatment of iron deficiency, thereby reducing the prevalence of anemia at term.

Nawal Nour, MD, MPH, and Robert L. Barbieri, MD

During pregnancy, anemia and iron deficiency are prevalent because the fetus depletes maternal iron stores. Iron deficiency and iron deficiency anemia are not synonymous. Effective screening for iron deficiency in the first trimester of pregnancy requires the measurement of a sensitive and specific biomarker of iron deficiency, such as ferritin. Limiting the measurement of ferritin to the subset of patients with anemia will result in missing many cases of iron deficiency. By the time iron deficiency causes anemia, a severe deficiency is present. Detecting iron deficiency in pregnancy and promptly treating the deficiency will reduce the number of women with anemia in the third trimester and at birth.

Dr. Nawal is Chair, Department of Obstetrics and Gynecology and Founding Director, African Women's Health Center, Brigham and Women's Hospital, and Kate Macy Ladd Professorship, Harvard Medical School, Boston, Massachusetts.

Dr. Barbieri is Chair Emeritus, Department of Obstetrics and Gynecology, and Chief of Obstetrics, Brigham and Women's Hospital, and Kate Macy Ladd Distinguished Professor of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School.

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Diagnosis of anemia

Anemia in pregnancy is diagnosed by a hemoglobin level and hematocrit concentration below 11 g/dL and 33%, respectively, in the first and third trimesters and below 10.5 g/dL and 32%, respectively, in the second trimester.[1] The prevalence of anemia in the first, second, and third trimesters is approximately 3%, 2%, and 11%, respectively.[2] At a hemoglobin concentration <11 g/dL, severe maternal morbidity rises significantly.[3] The laboratory evaluation of pregnant women with anemia may require assessment of iron stores, measurement of folate and cobalamin (vitamin B12), and hemoglobin electrophoresis, if indicated.

Diagnosis of iron deficiency

Iron deficiency anemia is diagnosed by a ferritin level below 30 ng/mL.[4,5] Normal iron stores and iron insufficiency are indicated by ferritin levels 45 to 150 ng/mL and 30 to 44 ng/mL, respectively.[4,5] Ferritin is an acute phase reactant, and patients with inflammation or chronic illnesses may have iron deficiency and a normal ferritin level. For these patients, a transferrin saturation (TSAT) <16% would support a diagnosis of iron deficiency.[6] TSAT is calculated from measurement of serum iron and total iron binding capacity. TSAT saturation may be elevated by iron supplements, which increase serum iron. If measurement of TSAT is necessary, interference with the measurement accuracy can be minimized by not taking an iron supplement on the day of testing.

Iron deficiency is present in approximately 50% of pregnant women.[7,8] The greatest prevalence of iron deficiency in pregnancy is observed in non-Hispanic Black females, followed by Hispanic females. Non-Hispanic White females had the lowest prevalence of iron deficiency.[2]

Fetal needs for iron often cause the depletion of maternal iron stores. Many pregnant women who have a normal ferritin level in the first trimester will develop iron deficiency in the third trimester, even with the

usual recommended daily oral iron supplementation. We recommend measuring ferritin and hemoglobin at the first prenatal visit and again between 24 and 28 weeks' gestation.

Impact of maternal anemia on maternal and newborn health

Iron plays a critical role in maternal health and fetal development independent of its role in red blood cell formation. Many proteins critical to maternal health and fetal development contain iron, including hemoglobin, myoglobin, cytochromes, ribonucleotide reductase, peroxidases, lipoxygenases, and cyclooxygenases. In the fetus, iron plays an important role in myelination of nerves, dendrite arborization, and synthesis of monoamine neurotransmitters.[9]

Many studies report that maternal anemia is associated with severe maternal morbidity and adverse newborn outcomes. The current literature must be interpreted with caution because socioeconomic factors influence iron stores. Iron deficiency and anemia is more common among economically and socially disadvantaged populations.[10-12] It is possible that repleting iron stores, alone, without addressing social determinants of health, including food and housing insecurity, may be insufficient to improve maternal and newborn health.

Maternal anemia is a risk factor for severe maternal morbidity and adverse newborn outcomes.[3,13-18] In a study of 515,270 live births in British Columbia between 2004 and 2016, maternal anemia was diagnosed in 12.8% of mothers.[15] Maternal morbidity at birth was increased among patients with mild anemia (hemoglobin concentration of 9 to 10.9 g/dL), including higher rates of intrapartum transfusion (adjusted odds ratio [OR], 2.45; 95% confidence interval [CI], 1.74-3.45), cesarean birth (aOR, 1.17; 95% CI, 1.14-1.19), and chorioamnionitis (aOR, 1.35; 95% CI, 1.27-1.44). Newborn morbidity was also increased among newborns of mothers with mild anemia (hemoglobin concentrations of 9 to 10.9 g/dL), including birth before 37 weeks' gestation (aOR, 1.09; 95% CI, 1.05-1.12), birth before 32 weeks' gestation (aOR, 1.30; 95% CI, 1.21-1.39), admission to the intensive care unit (aOR, 1.21; 95% CI, 1.17-1.25), and respiratory distress syndrome (aOR, 1.35; 95% CI, 1.24-1.46).[15] Adverse maternal and newborn outcomes were more prevalent among mothers with moderate (hemoglobin concentrations of 7 to 8.9 g/dL) or severe anemia (hemoglobin concentrations of <7 g/dL), compared with mild anemia. For example, compared with mothers with no anemia, mothers with moderate anemia had an increased risk of birth <37 weeks (aOR, 2.26) and birth <32 weeks (aOR, 3.95).[15]

In a study of 166,566 US pregnant patients, 6.1% were diagnosed with anemia.[18] Patients with anemia were more likely to have antepartum thrombosis, preeclampsia, eclampsia, a cesarean birth, postpartum hemorrhage, a blood transfusion, and postpartum thrombosis.[18] In this study, the newborns of mothers with anemia were more likely to have a diagnosis of antenatal or intrapartum fetal distress, a 5-minute Apgar score <7, and an admission to the neonatal intensive care unit.

Maternal anemia and neurodevelopmental disorders in children

Some experts, but not all, believe that iron deficiency during pregnancy may adversely impact fetal neurodevelopment and result in childhood behavior issues. All experts agree that more research is needed to understand if maternal anemia causes mental health issues in newborns. In one meta-analysis, among 20 studies of the association of maternal iron deficiency and newborn neurodevelopment, approximately half the studies reported that low maternal ferritin levels were associated with lower childhood performance on standardized tests of cognitive, motor, verbal, and memory function.[19] Another systematic review concluded that the evidence linking maternal iron deficiency and child neurodevelopment is equivocal.[20]

In a study of 532,232 nonadoptive children born in Sweden from 1987 to 2010, maternal anemia was associated with an increased risk of autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and intellectual disability (ID).[21] In Sweden maternal hemoglobin concentration is measured at 10, 25, and 37 weeks of gestation, permitting comparisons of anemia diagnosed early and late in pregnancy with neurodevelopmental outcomes. **The association between anemia and neurodevelopmental disorders was greatest if anemia was diagnosed within the first 30 weeks of pregnancy.** Compared with mothers without anemia, maternal anemia diagnosed within the first 30 weeks of pregnancy was associated with higher childhood rates of ASD (4.9% vs 3.5%), ADHD (9.3% vs 7.1%), and ID (3.1% vs 1.3%).[21] The differences persisted in analyses that controlled for socioeconomic, maternal, and pregnancy-related factors. In a matched sibling comparison, the diagnosis of maternal anemia within the first 30 weeks of gestation was associated with an

CONTINUED ON PAGE 12

CONTINUED FROM PAGE 10

increased risk of ASD (OR, 2.25; 95% CI, 1.24-4.11) and ID (OR, 2.59; 95% CI, 1.08-6.22) but not ADHD.[21] Other studies have also reported a relationship between maternal anemia and intellectual disability.[22,23]

Measurement of hemoglobin will identify anemia, but hemoglobin measurement is not sufficiently sensitive to identify most cases of iron deficiency. Measuring ferritin can help to identify cases of iron deficiency before the onset of anemia, permitting early treatment of the nutrient deficiency. In pregnancy, iron deficiency is the prelude to developing anemia. Waiting until anemia occurs to diagnose and treat iron deficiency is suboptimal and may miss a critical window of fetal development that is dependent on maternal iron stores. During pregnancy, ferritin levels decrease as much as 80% between the first and third trimesters, as the fetus utilizes maternal iron stores for its growth.[24] We recommend the measurement of ferritin and hemoglobin at the first prenatal visit and again at 24 to 28 weeks' gestation to optimize early detection and treatment of iron deficiency and reduce the frequency of anemia prior to birth. ●

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