



In an era of high technology precision medicine, many pregnant women are—surprisingly—iron deficient, anemic, and not receiving adequate iron supplementation.

ILLUSTRATION: KIMBERLY MARTENS FOR OBG MANAGEMENT

## Recognize and treat iron deficiency anemia in pregnant women

By measuring ferritin levels and treating with oral and IV iron, obstetricians can close the gap in the care of pregnant women with iron deficiency anemia



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All mammalian life is dependent on a continuous supply of molecular oxygen. Molecular oxygen is carried to cells by non-covalent binding to the iron moiety in the hemoglobin of red blood cells. It is utilized within cells by noncovalent binding to the iron moiety in various microsomal and mitochondrial proteins, including myoglobin and cytochromes. Consequently, to efficiently utilize molecular oxygen all mammalian life is dependent on an adequate supply of iron. Surprisingly, in an era of high technology precision medicine, many pregnant women are iron deficient, anemic, and not receiving adequate iron supplementation.

### Iron deficiency is prevalent in women and pregnant women

Women often become iron deficient because of pregnancy or heavy menstrual bleeding. During pregnancy, maternal iron is provided to supply the

needs of the fetus and placenta. Additional iron is needed to expand maternal red blood cell volume and replace iron lost due to bleeding at delivery. In the National Health and Nutrition Examination Survey (NHANES) of 1988–1994, 11% of women aged 16 to 49 years were iron deficient. By contrast, less than 1% of men aged 16 to 49 years were iron deficient.<sup>1</sup>

In a NHANES study from 1999–2006, risk factors for iron deficiency included multiparity, current pregnancy, and regular menstrual cycles. Use of hormonal contraception reduced the rate of iron deficiency.<sup>2</sup> Using the same data, **the prevalences of iron deficiency during the first, second, and third trimesters of pregnancy were reported to be 7%, 14%, and 30%, respectively.**<sup>3</sup> In addition to pregnancy and menstrual bleeding there are many other medical problems that may contribute to iron deficiency, including *Helicobacter pylori* (*H pylori*) infection, gastritis, celiac disease, and bariatric surgery.

### Iron deficiency anemia may be associated with adverse pregnancy outcomes

In a retrospective study of 75,660 singleton pregnancies, 7,977 women were diagnosed with iron deficiency anemia when they were admitted for delivery. Compared with pregnant women without iron deficiency, the presence of iron deficiency increased the risk of:

- blood transfusion (odds ratio [OR], 5.48; 95% confidence interval [CI], 4.57–6.58)
- preterm delivery (OR, 1.54; 95% CI, 1.36–1.76)
- cesarean delivery (OR, 1.30; 95% CI, 1.13–1.49)
- 5-minute Apgar score <7 (OR, 2.21; 95% CI, 1.84–2.64)
- intensive care unit (ICU) admission (OR, 1.28; 95% CI, 1.20–1.39).<sup>4</sup>

In a systematic review and meta-analysis of 26 studies, maternal anemia (mostly iron deficiency anemia) was associated with a higher risk of

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## Diagnosis of anemia, iron deficiency, and iron deficiency anemia in pregnancy

### Requirements for a diagnosis of anemia in pregnancy

The American College of Obstetricians and Gynecologists recommends obtaining a hemoglobin and hematocrit test at the first prenatal visit and at the beginning of the third trimester of pregnancy.<sup>1</sup>

If the hemoglobin concentration is less than 11 g/dL, or hematocrit is less than 33%, anemia is present.<sup>2,3</sup>

If anemia is diagnosed, additional testing to investigate potential causes of anemia includes hemoglobin electrophoresis and measurement of vitamin B12 and folate levels. Many obstetricians perform hemoglobin electrophoresis on all their pregnant patients as part of the routine prenatal screen.

### Requirements for a diagnosis of iron deficiency in pregnancy

We recommend obtaining a ferritin measurement at the first prenatal visit and at the beginning of the third trimester.

In pregnant women with anemia, iron deficiency is present if the ferritin is less than 40 ng/mL.

If a pregnant woman is not anemic, iron deficiency is present if the ferritin is less than 15 ng/mL.<sup>4</sup>

### Requirements for a diagnosis of iron deficiency anemia

Hemoglobin concentration less than 11 g/dL, or hematocrit less than 33% (diagnosis of anemia).

PLUS

Ferritin less than 40 ng/mL (diagnosis of iron deficiency in an anemic woman)

PLUS

Evaluation for other known major causes of anemia, including blood loss, hemolysis, bone marrow disease, medications that suppress bone marrow function, kidney disease, malignancy, hemoglobinopathy, and vitamin B12 or folate deficiency.

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low birth weight (relative risk [RR], 1.31; 95% CI, 1.13-1.51), preterm birth (RR, 1.63; 95% CI, 1.33-2.01), perinatal mortality (RR, 1.51; 95% CI, 1.30-1.76), and neonatal mortality (RR, 2.72; 95% CI, 1.19-6.25).<sup>5</sup>

In a clinical trial, pregnant women were randomly assigned to receive folic acid alone; folic acid plus iron supplements; or 15 vitamins and minerals, including folic

acid and iron. At delivery, women in the iron-folic acid and the 15 vitamin and minerals groups had higher hemoglobin concentrations than the folic acid monotherapy group. Among 4,697 live births, women in the iron-folic acid group had significantly fewer preterm births (<34 weeks' gestation) than the folic acid group (RR, 0.50; 95% CI, 0.27-0.94;  $P = .031$ ).<sup>6</sup> Data from

additional randomized trials are needed to further clarify the effect of iron supplementation on obstetric outcomes.

## The diagnosis of iron deficiency is optimized by measuring serum ferritin

Serum ferritin measurement is an excellent test of iron deficiency.

**We recommend that all pregnant women have serum ferritin measured at the first prenatal visit and at the beginning of the third trimester to assess maternal iron stores.**

In pregnancy, the Centers for Disease Control and Prevention and the World Health Organization define anemia as a hemoglobin level of less than 11 g/dL or hematocrit less than 33% in the first and third trimesters. If a pregnant woman is *not* anemic, a serum ferritin level less than 15 ng/mL indicates iron deficiency.<sup>7</sup> Some experts believe that in pregnant women who are *not* anemic, a serum ferritin level between 15 and 30 ng/mL may also indicate iron deficiency.<sup>8</sup> If the pregnant woman is anemic and does not have another cause of the anemia, a serum ferritin level less than 40 ng/mL is indicative of iron deficiency.<sup>7</sup>

Ferritin is an acute phase reactant and levels may be falsely elevated due to chronic or acute inflammation, liver disease, renal failure, metabolic syndrome, or malignancy. Some women with iron deficiency due to bariatric surgery or malabsorption also have vitamin B12 and, less commonly, folate deficiency, which can contribute to the development of anemia (see "Diagnosis of anemia, iron deficiency, and iron deficiency anemia in pregnancy.") Clinicians are often advised that a mean corpuscular volume demonstrating microcytosis is the "best

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## Start using alternate-day oral iron dosing, and stop using daily iron dosing

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Recent research reports alternate-day oral iron dosing compared with daily oral iron dosing results in higher absorption of iron.

### Details of the study

A total of 40 iron deficient women (mean serum ferritin level, 14 ng/mL) were randomly assigned to receive a daily dose of 60 mg of elemental iron (325 mg of ferrous sulfate) for 14 days or an alternate-day dose of 60 mg for 28 days. A small amount of radioactive iron was added to the oral medication to assess iron absorption. The primary outcome was fractional and total iron absorption, calculated by measuring radioactive iron in circulating red blood cells 14 days after the final oral iron dose.

Alternate-day iron dosing, compared with daily dosing, resulted in a higher fraction of the iron dose being absorbed (22% vs 16%;  $P = .0013$ ). In addition, alternate-day iron dosing resulted in greater cumulative total iron absorption (175 mg vs 131 mg;  $P = .001$ ). Nausea was reported less frequently by women in the alternate-day dosing group (11%) than in the daily iron dose group (29%).

The investigators concluded that prescribing iron as a single alternate-day dose may be a superior dosing regimen compared with daily dosing.

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test” to assess a patient for iron deficiency. However, reduced iron availability and low ferritin precede microcytosis. Hence microcytosis is a lagging measure and iron deficiency is diagnosed at an earlier stage by ferritin.

### Dietary iron

Iron in food is present in heme (meat, poultry, fish) and non-heme forms (grains, plant food, supplements). Heme iron is better absorbed than non-heme iron. Foods rich in non-heme iron include spinach, lentils, prune juice, dried prunes, and fortified cereals. Absorption of non-heme iron can be increased by vitamin C or vitamin C-rich foods (broccoli, bell peppers, cantaloupe, grapefruit, oranges, strawberries, and tomatoes). Absorption of non-heme iron is reduced by consumption of dairy products, coffee, tea, and chocolate.

### Oral iron treatment

Oral iron is an effective treatment for iron deficiency<sup>9,10</sup> and is inexpensive, safe, and widely available. The CDC recommends that all pregnant women take a 30 mg/day iron supplement, unless they have hemochromatosis.<sup>11</sup> For women with a low ferritin level and anemia, iron supplementation should be increased to 30 to 120 mg daily.<sup>11</sup> Not all prenatal vitamins contain iron; those that do typically contain 17 to 28 mg of elemental iron per dose.

Many pregnant women taking oral iron, especially at doses greater than 30 mg daily, have gastrointestinal side effects, which cause them to discontinue the iron therapy.<sup>12</sup> Taking iron supplementation on an intermittent basis may help to reduce gastrointestinal side effects and improve iron stores.<sup>13</sup>

In the past, a standard approach to the treatment of iron deficiency

anemia was oral ferrous sulfate 325 mg (65 mg elemental iron) spaced in 3 doses each day for a total daily dose of 195 mg elemental iron. However, recent absorption studies concluded that maximal absorption of iron occurs with a dose in the range of 40 to 80 mg of elemental iron daily. Greater doses do not result in more iron absorption and are associated with more side effects.<sup>14,15</sup> (See “Start using alternate-day oral iron dosing, and stop using daily iron dosing.”)

Oral iron should not be taken in close approximation to the consumption of milk, cereals, tea, coffee, eggs, or calcium supplements. The absorption of oral iron is enhanced by the consumption of orange juice or 250 mg of vitamin C. Gastrointestinal side effects include nausea, flatulence, constipation, diarrhea, epigastric distress, and vomiting. If gastrointestinal side effects occur, interventions that might improve tolerability include: reduce the dose of iron or administer intermittently or use a low dose of oral iron, where dosing can be more easily titrated.

We re-check ferritin and hemoglobin levels 2 to 4 weeks after initiation of oral iron therapy and expect to see a hemoglobin rise of 1 g/dL if the therapy is effective.

### Intravenous iron treatment

For women with iron deficiency anemia who cannot tolerate oral iron or in whom oral iron treatment has not resolved their anemia, intravenous (IV) iron treatment may be an optimal approach. Women in the third trimester of pregnancy with iron deficiency anemia have very little time to consume sufficient quantities of oral iron in food and supplements to restore their deficiency and reverse their anemia. Consequently,

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treatment with IV iron may be especially appropriate for women with iron deficiency anemia in the third trimester of pregnancy. Prior gastric surgery, including gastric bypass, results in reduced gastric acid production and causes severe impairment of intestinal absorption of iron. Patients with malabsorption syndromes, including celiac disease, also may have limited absorption of oral iron. These populations of pregnant women may particularly benefit from the use of IV iron. In pregnant women IV iron has fewer gastrointestinal side effects than oral iron.<sup>16</sup>

Many severely iron deficient patients need 1,000 mg of iron to resolve their deficit. In order to avoid giving multiple standard doses

(200 mg per infusion, with 5 infusions over many days), some centers have explored the use of 1 large dose of IV iron (1,000 mg of low molecular weight iron dextran administered over 1 hour) (INFeD, Watson Pharma).<sup>17-19</sup> This is not a regimen that is specifically approved by the US Food and Drug Administration. An alternative regimen is to administer 750 mg of ferrous carboxymaltose (Injectafer, Luitpold Pharmaceuticals) over 15 minutes, which is an FDA-approved regimen.<sup>18</sup> Many hematologists prefer to administer multiple smaller doses of iron. For example, in our practice, pregnant women are commonly treated with IV iron sucrose (300 mg) every 2 weeks for 3 doses. To increase

access of pregnant women to IV iron treatment, obstetricians need to work with hematologists and infusion centers to create collaborative protocols to expeditiously treat women in the third trimester.

There is an epidemic of iron deficiency in pregnant women in the United States. In an era of high technology medicine, it is surprising that iron deficiency remains an unsolved obstetric problem in our country. ☹



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