- Extreme microcytosis (eg, mean corpuscular volume [MCV] <80 fL), suggestive of thalassemia
- Macrocytosis (MCV >100 fL), suggestive of vitamin B12 or folate deficiency or reticulocytosis due to hemolysis
- Other cytopenias such as thrombocytopenia or neutropenia
- Abnormally high white blood cell (WBC) count or platelet count
- Abnormal RBC or WBC morphologies
- Failure of the anemia to correct with iron supplementation

The details of the evaluation depend on the specific abnormalities found. Of note, macrocytosis due to vitamin B12 or folate deficiency can be masked by concomitant iron deficiency [47]. Thus, absence of macrocytosis should not be considered sufficient to eliminate the possibility of these deficiencies if there are other reasons to suspect them. A general approach to the evaluation of anemia is also presented separately. (See "Approach to the adult with anemia".)

Pregnant women are generally screened for hemoglobinopathy to identify and counsel women whose offspring may be at risk of an inherited hemoglobinopathy. (See "Prenatal screening and testing for hemoglobinopathy".)

## MANAGEMENT

The health of both the mother and the child can be affected by anemia during pregnancy. Thus, identifying, preventing, and treating anemia in pregnancy is likely beneficial, although not established by high-quality studies.

**Prevention of iron deficiency** — We provide supplemental oral iron to all pregnant women to compensate for the increased iron demands during pregnancy and delivery, as outlined in 1998 guidance from the Centers for Disease Control and Prevention (CDC) in the United States, which recommends that all pregnant women begin a 30 mg/day iron supplement at the first prenatal visit [16]. This corresponds approximately to the amount of iron in most iron-containing prenatal vitamins.

For women who are intolerant of the iron in prenatal vitamins, it may be possible to take prenatal vitamins without iron and to supplement with oral iron supplements on an every-other-day basis (typical dose, 60 mg once every other day or 60 mg once daily on Monday, Wednesday, and Friday). The rationale for alternate-day dosing (improved absorption and reduced gastrointestinal adverse effects) is discussed separately. (See "Treatment of iron deficiency anemia in adults", section on 'Dosing and administration (oral iron)'.)

A 55 kg woman requires approximately one gram of additional iron from conception to delivery (figure 1), which includes 300 to 350 mg for the fetus and placenta, 500 mg for the expansion of the maternal red blood cell (RBC) mass, and 250 mg associated with blood loss during labor and

delivery [47]. Supplementation exceeds this one gram requirement because only a small portion of ingested iron is absorbed, and the increase in the portion absorbed does not match the increase in iron requirements [17].

Despite the increase in iron requirements during pregnancy, high-quality evidence that routine iron supplementation improves health outcomes and quality of life has been challenging to obtain. The 2015 review of evidence dating back to 1996 from the United States Preventive Services Task Force (USPSTF) concluded that "there is insufficient evidence that routine prenatal supplementation for iron deficiency anemia improves maternal or infant clinical health outcomes, but supplementation may improve maternal hematologic indices" [25]. A 2015 Cochrane review came to similar conclusions, stating that "supplementation reduces the risk of maternal anaemia and iron deficiency in pregnancy, but the positive effect on other maternal and infant outcomes is less clear" [53]. This lack of high-quality evidence is largely due to the challenges of performing prospective randomized trials in pregnant women as well as the limited outcomes reported for iron supplementation in gravidas or neonates.

**Treatment of iron deficiency** — The standard treatment for uncomplicated iron deficiency (regardless of hemoglobin level) is administration of iron at doses higher than found in prenatal vitamins. The choice between oral and intravenous iron depends on a number of factors, as discussed below. (See 'Oral and intravenous iron formulations' below.)

Antenatal maternal treatment with iron results in an increase in the hemoglobin level in approximately two weeks (the time it takes to create new RBCs in the bone marrow). (See 'Assessing response to treatment' below.)

For women with severe anemia for whom this two-week delay would be expected to result in significant morbidity, transfusion and/or referral to a specialist (eg, hematologist) may be appropriate [4]. We reserve transfusion for those who have significant symptoms associated with severe anemia or those for whom transfusion is indicated for other reasons, such as those mentioned below. (See 'Management of other anemias' below.)

Transfusion is not required in women with mild symptoms of anemia, which may be difficult to distinguish from other symptoms related to the hormonal or anatomic changes of pregnancy. (See "Indications and hemoglobin thresholds for red blood cell transfusion in the adult", section on 'Overview of our approach'.)

**Oral and intravenous iron formulations** — Oral and intravenous iron are both effective for replenishing iron stores. Each route carries different advantages and disadvantages as outlined in the table (table 3). We generally use oral iron for most women with iron deficiency who can tolerate it, and for all women being treated during the first trimester. We give intravenous iron to women who cannot tolerate oral iron; those who have severe anemia, especially later in the

pregnancy; and those for whom oral iron does not effectively increase the hemoglobin and/or ferritin levels. This practice is consistent with a 2019 United Kingdom guideline [4].

Three meta-analyses published in 2018 to 2019 evaluated the benefits and risks of oral versus intravenous iron based on data from randomized trials in pregnant or postpartum women with iron deficiency [54-56]. These analyses found that iron supplementation by either route (oral or intravenous) increased the hemoglobin and ferritin levels; compared with oral iron, intravenous iron was associated with a higher hemoglobin level following therapy (eg, at four weeks or upon admission to the labor and delivery service or at the six-week postpartum check). (See 'Postpartum' below.)

However, the magnitude of the antepartum hemoglobin increase was modest (weighted mean difference [WMD] at admission to labor and delivery, 0.66 g/dL, 95% CI 0.31-1.02) [55]. One of the analyses evaluated maternal and neonatal outcomes and found no significant differences in the rates of maternal blood transfusion or cesarean delivery, but found that intravenous iron was associated with higher neonatal birth weight (WMD 69 grams; 95% CI 12-127 grams) and higher neonatal ferritin levels (WMD, 21 ng/mL; 95% CI 6-37 ng/mL) [55]. All of the analyses found that adverse effects and discontinuation of therapy were less frequent with intravenous iron.

**Oral iron** — For most women with iron deficiency, especially those diagnosed in the first trimester, we treat with oral iron. Oral iron is safe, inexpensive, and readily available. For many women, this is adequate therapy. Ferrous sulfate (FS) is the most commonly prescribed oral formulation. It is inexpensive and, when tolerated, effective. Up to 70 percent of those to whom it is prescribed report significant gastrointestinal perturbation, and two meta-analyses of oral iron therapy in pregnancy report that the incidence of gastrointestinal side effects is unacceptably high [57-59]. Some experts use intravenous iron in the second half of the pregnancy due to concerns that oral iron will not provide sufficient iron to the developing fetus [39,47].

- **Dosing** – Recommended doses of oral iron range from 40 to 200 mg elemental iron per day [4,60]. There has been a trend towards using doses on the lower end of this range as well as alternate day dosing due to recognition that higher and more frequent doses may increase adverse effects without improving iron uptake [4]. We agree with this dose range and often administer 60 mg of elemental iron. Standard oral iron formulations and their elemental iron content are listed in the table (table 4). However, we provide the dose every other day (or, on Monday, Wednesday, and Friday) rather than daily, based on evidence that alternate-day dosing results in improved absorption of oral iron as well as improved tolerability. Compared with more frequent dosing (such as once daily or three times per day), alternate-day dosing improves iron absorption and reduces gastrointestinal adverse effects in non-pregnant women [61]. Absorption may be improved by taking vitamin C concurrently with iron and/or avoiding coffee, tea, and milk at the time the iron supplement is taken. (See "Treatment of iron deficiency anemia in adults", section on 'Dosing and administration (oral iron)'.)

## Oral iron products

| Drug | Examples of United States trade (brand) names | Elemental iron content (mg iron per mg tablet or per mL liquid)* |
|---|---|---|
| **Ferrous fumarate**<br>(Contains 33% elemental iron per mg of mineral salt) | ▪ Tablets | |
| | Various over-the-counter and store-brand products with "iron" in the name | 29.5 mg/90 mg |
| | Ferrimin 150 | 150 mg elemental iron per tablet |
| | Ferretts, Ferrocite, Hemocyte | 106 mg/324 or 325 mg |
| **Ferrous gluconate**<br>(Contains approximately 10 to 14% elemental iron per mg of mineral salt) | ▪ Tablets | |
| | Fergon, Ferrotabs | 27 mg/240 mg |
| | Various over-the-counter and store-brand products with "iron" in the name | 28 mg/256 mg or 38 mg/324 or 325 mg |
| **Ferrous sulfate**<br>(Generally contains 20 to 30% elemental iron per mg of mineral salt but can vary by manufacturer) | ▪ Liquids | Multiple concentrations exist; check packaging closely |
| | BProtected Pedia, Fer-In-Sol, Fer-Iron | 15 mg/1 mL ("drops," "solution") |
| | FeroSul | 44 mg/5 mL ("elixir," "liquid") |
| | Various over-the-counter and store-brand products with "iron" in the name | 60 mg/5 mL ("syrup") |
| | ▪ Tablets | |
| | Feosol original | 65 mg/200 mg |
| | Ferro-Bob, FerrouSul | 65 mg/325 mg |
| **Polysaccharide-iron complex (PIC)**<br>(Also available as PIC plus folic acid and PIC plus folic acid and vitamin B12) | ▪ Liquids | |
| | NovaFerrum | 15 mg/1 mL ("drops") |
| | NovaFerrum 125 | 125 mg/5 mL ("liquid") |
| | ▪ Capsules | |
| | EZFE 200, Ferrex 150, Ferric-X 150, iFerex 150, Myferon 150, NovaFerrum 50, Nu-Iron 150, PIC 200, Poly-Iron 150 | The number in the name is the mg of elemental iron (eg, NovaFerrum 50 contains 50 mg elemental iron per capsule) |

Commonly available products in the United States are shown; other products are available by prescription or over the counter (eg, iron polymaltose [Maltofer]; ferric maltol [Accrufer]). Enteric-coated and extended-release formulations are also available for some products, but we generally do not advise use of these preparations because they are poorly absorbed. Refer to UpToDate and to Lexicomp drug monographs (included with UpToDate) for details of dosing, treatment of iron deficiency anemia, and management of acute iron poisoning.

* Commonly available concentrations are listed, but other concentrations may be available and some brands may have been reformulated. Always refer to the latest available information on specific products.

Graphic 106069 Version 8.0