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Routine Iron Supplementation and Screening for Iron Deficiency Anemia in Pregnant Women: A Systematic Review to Update the U.S. Preventive Services Task Force Recommendation

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Structured Abstract

Background: In 2006, the U.S. Preventive Services Task Force (USPSTF) recommended routine screening for iron deficiency anemia in asymptomatic, pregnant women but found insufficient evidence to recommend for or against routine iron supplementation for nonanemic pregnant women.

Purpose: To systematically update the prior USPSTF reviews on screening and supplementation for iron deficiency anemia in pregnancy.

Data Sources: We searched Cochrane and Ovid MEDLINE® databases (1996 to August 2014) and reviewed the reference lists of relevant systematic reviews to identify studies published prior to 1996.

Study Selection: We included randomized, controlled trials and controlled observational studies of supplementation, screening, and related treatment on maternal and infant clinical outcomes; prevalence of iron deficiency anemia and iron deficiency; hematological indexes and ferritin levels; and harms.

Data Extraction: One investigator abstracted details about each article's study design, patient population, setting, screening method, treatment regimen, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF to rate the quality of each study. Discrepancies were resolved through a consensus process.

Results: Eleven trials of routine maternal iron supplementation reported various clinical outcomes for women and infants. One study reported no differences in maternal quality of life. There was inconsistency among studies reporting an effect of maternal iron supplementation on rates of Cesarean delivery and infant outcomes, including small for gestational age and low birthweight. Studies reported no effect of maternal iron supplementation on infant gestational age, Apgar scores, preterm birth, and infant mortality. Twelve trials reported some improvement in maternal hematological indexes with variable doses of iron supplementation versus placebo at various timepoints, although not all were statistically significant. Pooled analysis of four trials reporting a lower incidence of iron deficiency anemia at term (two statistically significant and two with no difference) resulted in a statistically significant difference between groups favoring supplementation. One followup study reported no difference in infant iron status at 6 months. No study directly compared clinical outcomes between pregnant women screened and not screened for iron deficiency anemia. Evidence on the effects of prenatal iron therapy on long-term maternal or infant clinical outcomes remains sparse or unavailable.

Limitations: Non–English-language articles were excluded. Studies conducted in developing countries were excluded, but some data from trials in countries with limited generalizability to U.S. populations were included. Studies were methodologically heterogeneous and possibly underpowered.

Conclusions: Evidence supports the effectiveness of routine iron supplementation during pregnancy for improving maternal hematological indexes, but the clinical significance for both pregnant women and infants remains unclear. No studies addressed the benefits or harms of screening for iron deficiency anemia during pregnancy. More research is needed to understand the clinical effects of routine screening for and treatment of iron deficiency anemia during pregnancy.

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Chapter 1. Introduction

Purpose and Previous U.S. Preventive Services Task Force Recommendation

This report was commissioned by the U.S. Preventive Services Task Force (USPSTF) in order to update its 2006 recommendation on screening and supplementation for iron deficiency anemia in pregnancy.[1]

The USPSTF previously recommended routine screening for iron deficiency anemia in asymptomatic, pregnant women (B recommendation). This recommendation was based on fair evidence that the benefits of routine screening for iron deficiency anemia in asymptomatic, pregnant women outweigh the potential harms. The USPSTF found insufficient evidence (no studies) that specifically addressed the accuracy of screening tests in asymptomatic, pregnant women but found fair evidence that treating asymptomatic, pregnant women for iron deficiency anemia results in moderate benefits in health outcomes.[1]

The USPSTF also previously concluded that the evidence was insufficient to recommend for or against routine iron supplementation for nonanemic pregnant women (I statement). This recommendation was based on poor evidence that iron supplementation may improve health outcomes in nonanemic pregnant women. In addition, the USPSTF found no validated risk-assessment tools to use as guidance for identifying individuals who would benefit from iron supplementation. Therefore, the USPSTF concluded that there was insufficient evidence to determine the balance between the benefits and harms of routine iron supplementation for nonanemic pregnant women.[1]

Condition Definition

Iron is required in the production of hemoglobin, an essential protein found in red blood cells that transports oxygen throughout the body from the respiratory organs and returns carbon dioxide. Over time, iron is stored in the body for use in hemoglobin production. Iron deficiency occurs when the level of stored iron becomes depleted. Iron deficiency anemia occurs when iron levels are sufficiently depleted to produce anemia, characterized by hypochromic and microcytic red blood cells.[2,3]

Defining iron deficiency anemia in pregnant women is imprecise given pregnancy-associated changes in plasma volume and red cell mass, normal differences in hemoglobin concentrations, and ethnic variation. Physiological anemia of pregnancy is observed in healthy pregnant women and occurs as the result of greater expansion of plasma volume relative to the increase in hemoglobin mass and erythrocyte volume associated with pregnancy. This normal physiological change is responsible for a modest decrease in hemoglobin levels and is often referred to as dilutional anemia of pregnancy. The Centers for Disease Control and Prevention (CDC)[4] and the World Health Organization[5] define iron deficiency anemia in pregnancy as iron deficiency

(serum ferritin <12 µg/L) with a hemoglobin level of less than 11g/dL (or <110 g/L) and a hematocrit level of less than 33 percent. However, since hemoglobin and hematocrit levels are typically lower in black adults, the Institute of Medicine (IOM) recommends lowering the hemoglobin cutoff level by 0.8 g/dL in this population.[6]

Iron deficiency is the most common pathological cause of anemia in pregnancy. Total iron loss associated with pregnancy and lactation is about 1,000 mg. Iron is necessary for both fetal and placental development and to expand the maternal red cell mass. Iron is commonly prescribed as part of a prenatal multivitamin or as a separate supplement because it is assumed most women do not have adequate iron stores to handle the demands of pregnancy.

Evidence of test sensitivity and specificity for iron deficiency anemia in pregnant women is not available. Therefore, anemia alone (hemoglobin level <11 g/dL) is not an ideal screening parameter for iron deficiency anemia. In most clinical settings, the simplest and most cost-effective measurement is a complete blood count (CBC), which includes measurements of hemoglobin, hematocrit, mean corpuscular volume, and red blood cell distribution width (a measure of variability in red cell size).

Serum ferritin may be useful in diagnosing iron deficiency in pregnant women, who often have elevated serum transferrin in the absence of iron deficiency. In one study of pregnant women,[7] serum ferritin was found to be a good indicator of reduced iron stores, with a sensitivity of 90 percent and specificity of 85 percent when used as a screening tool for iron deficiency. Ferritin is an acute phase reactant and can be elevated because of inflammatory states, including liver disease, infection, and malignancy. A patient with iron deficiency and inflammation may have a falsely normal ferritin concentration. Serum ferritin may be of limited usefulness when concentrations decrease during late pregnancy, despite the presence of bone marrow iron.[5]

Prevalence and Risk Factors

All pregnant women are at higher risk for iron deficiency than nonpregnant women because of increased iron needs during pregnancy as a result of the growth of the fetus and placenta, increased red cell mass, and the expansion of maternal blood volume, especially as the pregnancy progresses into the third trimester.[3,6,8-10] Analysis of National Health and Nutrition Examination Survey (NHANES) epidemiological data from 1999 to 2006 found an overall prevalence of iron deficiency in pregnancy near 18 percent, with 5 percent of pregnant women found to be anemic; prevalence of iron deficiency increased from 6.9 to 14.3 to 28.4 percent across the three trimesters.[10] Older NHANES data from 1999 to 2000 found a prevalence of iron deficiency anemia in pregnancy of 2 to 3 percent.[11] From 2000 to 2004, one report found rates of iron deficiency anemia of 1.8 percent in a low-income minority U.S. population in the first trimester, 8.2 percent in the second trimester, and 27.4 percent in the third trimester.[9] Additional estimates of iron deficiency anemia in pregnant women are not readily available.

The most commonly cited risk factors for iron deficiency anemia or iron deficiency in pregnant women include eating a diet poor in iron-rich foods (e.g., vegan diet), having gastrointestinal issues that affect absorption, or having a short interval between pregnancies.[12] In addition, 1999

to 2006 NHANES data found a higher prevalence of iron deficiency anemia among non-Hispanic black (30%) and Mexican American (24%) women than white women (14%).[10] In one study, parity of two or more was associated with increased prevalence of iron deficiency (28%) compared with parity of zero (12%) or one (17%);[10] however, no associations were found in women with lower educational levels or family income, which are mentioned as risk factors in other sources.[6,9] For example, a study of women through 6 months postpartum found that 10 percent of those with an income with a poverty index ratio less than 130 percent (the level used to determine Federal aid status) had iron deficiency anemia compared with 2 percent of women whose incomes were above this threshold.[13] Iron deficiency anemia in pregnancy can persist into the postpartum period, with an estimated prevalence of 4 percent.[14] Finally, one study and one NHANES analysis found correlations between higher body mass index and decreased iron levels in pregnant women.[15,16]

Burden of Disease/Illness

Pregnant women with iron deficiency anemia or iron deficiency may experience clinical symptoms of fatigue, weakness, pallor, tachycardia, and shortness of breath.[17]

In pregnant women, the association between iron status and negative outcomes for both women and their infants is inconclusive. Numerous older observational studies have shown various measures of iron status, including iron deficiency anemia, to be associated with serious negative infant outcomes, including low birthweight,[18-20] premature birth,[18-23] and perinatal death.[19] Notably, a literature review found that maternal anemia diagnosed at entry to prenatal care is associated with an increased risk for preterm delivery but anemia diagnosed during the third trimester is not associated with these negative outcomes, postulating that "this lack of association during the third trimester occurs because of third-trimester hemodilution, which makes it difficult to distinguish between gravidas with iron-deficiency anemia and those who experienced a good prognostic sign—an expanded plasma volume."[24] Alternatively, Cochrane reviews of up to 49 trials conducted in mostly developing countries that compared daily oral iron versus intermittent oral iron supplementation or assessed iron treatment during pregnancy found overall methodologically poor evidence showing no effect on infant outcomes, including low birthweight, delayed development, preterm birth, infection, and postpartum hemorrhage.[25-28] In the current review, we examined trial and controlled observational study evidence from countries similar to the United States that assessed the effects of routine supplementation, screening, and screening-related treatment on maternal and infant outcomes.

Rationale for Screening/Screening Strategies

Screening for iron deficiency anemia in asymptomatic, pregnant women may lead to earlier identification and therefore earlier treatment, which has the potential to prevent serious negative health outcomes. Strategies for screening can include either routine screening or targeted screening based on established risk factors, risk-assessment instruments, or diagnostic tests. Routine screening in pregnant women may occur when they present for prenatal care.

Current Clinical Practice

Supplementation

Primary prevention of iron deficiency during pregnancy includes adequate dietary iron intake and iron supplementation. This may include starting an oral low-dose (e.g., 30 mg/day) iron supplement at the beginning of pregnancy or integrating iron-rich foods and foods that enhance iron absorption. Prophylaxis for iron deficiency anemia in high-risk populations may be accomplished with higher doses of supplementation (e.g., 60 to 100 mg elemental iron per day).

Treatment

Treatment of iron deficiency in pregnancy is the same as that in nonpregnant, postpartum, premenopausal, and postmenopausal women. Pregnant women with iron deficiency anemia are generally treated with additional iron in combination with prenatal vitamins and dietary counseling. The dosage of elemental iron required to treat iron deficiency anemia in adults is 120 mg per day for 3 months.[5] Therapy should continue for 3 months after the anemia is corrected to allow iron stores to become replenished.[29] There are no standard recommendations for followup after initiating therapy for iron deficiency anemia; however, one suggested course is to perform a CBC every 3 months for 1 year.[30]

Iron is available orally as ferrous fumarate, ferrous sulfate, or ferrous gluconate. Each iron salt provides different amounts of elemental iron (e.g., ferrous sulfate has 20% elemental iron per mg while ferrous fumarate has 33%). Dosing for adults with iron deficiency anemia is divided into two to four doses per day, depending on the elemental iron content of the dose (**Table 1**). While there is no evidence of a difference in efficacy between the salt forms, there are many different formulations on the market whose specific characteristics may affect the efficacy and tolerability profile of the product. For example, it has been suggested that some slow-release formulations release iron too far down the gastrointestinal tract for optimal absorption.

Adverse events are typically limited to gastrointestinal tract symptoms that limit the ability or willingness of patients to adhere to the regimen. It is estimated that 10 to 20 percent of patients may report nausea, constipation, epigastric distress, and/or vomiting while taking oral iron, and the cause is thought to be directly related to the dose of elemental iron. The absorption of iron is inhibited by food (up to a 40% decrease)[5] and antacids, and is enhance by a more acidic environment. Therefore, experts usually recommend avoiding dosing with meals or within 2 hours of taking antacids and taking the dose with orange juice or ascorbic acid to maximize absorption. However, for patients who experience gastrointestinal adverse effects that affect adherence to the regimen, slowly increasing the dose over several days, reducing the amount of elemental iron taken per dose or daily, or taking the iron with food may improve symptoms. These measures will likely mean that a longer duration of therapy is required. Urine and stool may be darker in color when taking iron, and liquid formulations can cause temporary gray staining of the teeth and gums. Iron can cause important interactions with several drugs and can be fatal in overdose in children.

Indications for the use of injectable iron are the same for pregnant women as for nonpregnant women, and there are concerns about adverse effects, including allergic reactions, and cost. Intravenous iron is generally used only to replenish iron stores in selected patients who have not tolerated a trial of oral iron therapy or those with severe iron deficiency.[31]

Recommendations of Other Groups

Screening

The American Congress of Obstetricians and Gynecologists,[12] the U.S. Department of Veterans Affairs/Department of Defense (VA/DoD),[32] the CDC,[3] and the American Academy of Family Physicians[33] recommend that all pregnant women be screened for anemia at some point during pregnancy. The VA/DoD recommends screening during the first prenatal visit and recommends against routine repeat screening in asymptomatic, pregnant women. The IOM recommends screening for anemia in high-risk pregnant women during each trimester and at 4 to 6 weeks postpartum.[6] The Canadian Task Force on Preventive Health Care does not have a current recommendation for this topic.

Routine Supplementation

While the CDC[3] and the World Health Organization[34] recommend universal iron supplementation in pregnant women, the VA/DoD states that there is insufficient evidence to recommend for or against universal supplementation.[32] The IOM,[6] American Congress of Obstetricians and Gynecologists,[12] and American Academy of Family Physicians[33] recommend screening and treatment as necessary in lieu of routine supplementation. The Canadian Task Force on Preventive Health Care does not have a current recommendation for this topic.

Contextual Questions

Contextual Question 1. How Well Do Risk-Assessment Tools Identify Pregnant Women at Increased Risk for Iron Deficiency Anemia?

There is limited evidence available that evaluates risk-prediction tools to identify pregnant women at increased risk for iron deficiency anemia. We identified one study conducted in the United States in a population of primarily black urban pregnant women (n=141) that developed a risk-prediction tool to identify those at increased risk for iron deficiency anemia.[35] The study used a number of formulas with various hematological indexes (i.e., red blood cell counts, mean corpuscular volume, and hemoglobin) to create a scoring system to predict risk. Anemia was measured using a CBC and serum ferritin was the gold standard. Points were awarded based on specific CBC measures (hemoglobin level and red blood cell distribution width) and gestational age. The study found that a risk score of 2 or greater was the best predictor of iron deficiency anemia, correctly identifying 74 percent of women with iron deficiency anemia (sensitivity, 45%; specificity, 88%; positive likelihood ratio, 1.1). However, the area under the receiving

operator characteristic curve was only 0.66 (95% confidence interval [CI], 0.6 to 0.7), indicating overall poor predictive value. The authors suggest that more data must be collected to validate this model, in addition to validating results in more diverse populations.

We did not identify any other studies that evaluated risk-assessment tools to identify pregnant women with iron deficiency anemia.

Contextual Question 2. What Is the Yield (Number of New Diagnoses) of Repeat (Periodic) Screening in Asymptomatic, Pregnant Women, and at What Timing Intervals?

We did not identify any studies that addressed repeat screening or the timing of screening.

Chapter 2. Methods

Key Questions and Analytic Frameworks

Using methods developed by the USPSTF,[36] and in consultation with the USPSTF, we determined the scope and Key Questions for this review[37,38] and created analytic frameworks with the Key Questions and the patient population, interventions, and outcomes reviewed. The target population was asymptomatic, pregnant women. The Key Questions are presented as two separate analytic frameworks: one for routine supplementation (**Figure 1**) and one for screening (**Figure 2**).

Routine Iron Supplementation in Pregnant Women

1. What are the benefits of routine iron supplementation in pregnant women on maternal and infant health outcomes?
2. What are the harms of routine iron supplementation in pregnant women?

Screening for Iron Deficiency Anemia in Pregnant Women

1. What are the benefits of screening for iron deficiency anemia in asymptomatic, pregnant women on maternal and infant health outcomes?
2. What are the harms of screening for iron deficiency anemia in pregnant women?
3. What are the benefits of treatment of iron deficiency anemia in pregnant women on maternal and infant health outcomes?
4. What are the harms of iron treatment in pregnant women?
5. In pregnant women with iron deficiency, with or without anemia, what is the association between change in maternal iron status (including changes in ferritin or hemoglobin level) and improvement in newborn and peripartum outcomes in U.S.-relevant populations?

We also addressed two Contextual Questions requested by the USPSTF to help inform the report. Contextual Questions address background areas deemed important by the USPSTF for informing its recommendations. Contextual Questions are not reviewed using systematic review methodology but rather by summarizing the evidence from key informative studies.

Contextual Questions

1. How well do risk-assessment tools identify pregnant women at increased risk for iron deficiency anemia?
2. What is the yield (number of new diagnoses) of repeat (periodic) screening in asymptomatic, pregnant women, and at what timing intervals?

For the screening framework, Key Question 1 focuses on direct evidence on the effectiveness of screening for iron deficiency anemia in asymptomatic, pregnant women compared with no

screening. Such direct evidence on the effectiveness of screening interventions may be limited. Therefore, the remainder of the analytic framework (Key Questions 2 through 5) evaluates the chain of indirect evidence needed to link screening with improvement in important health outcomes. Links in the chain of indirect evidence include the accuracy of screening in identifying pregnant women with iron deficiency anemia, the effectiveness of interventions in treating identified iron deficiency anemia and reducing the incidence of complications, the association between improvements in intermediate outcomes and clinical health outcomes, and harms (including infant harms) associated with screening and treatments. Implicit in the indirect chain of evidence is that, to understand the benefits and harms of screening, it is necessary but not sufficient to show that pregnant women with iron deficiency anemia can be identified; it is also necessary to show that there are effective treatments for those identified. Not all of the indirect links are included in this update, as some of the links (e.g., test accuracy) are considered to already be established.

A separate report covers outcomes for children ages 6 to 24 months directly receiving iron supplementation.[39]

Search Strategies

We searched the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Ovid MEDLINE® (1996 to August 2014) for relevant studies and systematic reviews. Because of the variation in scope between this report and the prior USPSTF reports, we also searched the reference lists of relevant systematic reviews to identify studies published prior to 1996. Search strategies are available in **Appendix A1**.

Study Selection

At least two reviewers independently evaluated each study to determine inclusion eligibility. We selected studies on the basis of inclusion and exclusion criteria developed for each Key Question (**Appendix A2**).

Articles were selected for full review if they were about iron deficiency anemia in pregnant women, were relevant to a Key Question, and met the predefined inclusion criteria. We restricted inclusion to English-language articles and excluded studies published only as abstracts. Studies of nonhuman subjects were also excluded, and studies had to report original data. For supplementation Key Questions 1 and 2 and screening Key Questions 1 through 4, we focused on studies that used iron supplementation and treatment regimens commonly used in clinical practice in the United States and excluded studies conducted in resource-poor populations, including nutritionally-deficient populations in developing countries. We included studies conducted in countries listed as having “high” or “very high” human development, using the United Nations International Human Development Index as a guide.[40] For Key Question 5, we also searched for studies conducted in any country and using any intervention that was feasible and/or approved by the Food and Drug Administration that otherwise met our inclusion criteria. Women needed to have iron deficiency (with or without anemia) for inclusion in Key Question

5. Maternal clinical outcomes included Cesarean delivery, postpartum depression, or other clinical outcomes; harms included discontinuation of iron and other harms related to screening, supplementation, or treatment. Maternal intermediate outcomes included incidence of iron deficiency anemia, iron deficiency, and anemia, as well as hematological indexes and ferritin levels. Infant clinical outcomes included birth outcomes (birthweight and size, preterm delivery, gestational age, perinatal mortality) and infant intermediate outcomes included hematological indexes and ferritin levels. We included randomized, controlled trials; nonrandomized controlled clinical trials; and cohort studies for all Key Questions. Association studies were included for Key Question 5. If good- or fair-quality studies were available, evidence from poor-quality studies was excluded.[41] However, if evidence was lacking and only poor-quality studies met inclusion criteria, they were included. **Appendix A3** shows the results of our literature search and selection process, and **Appendix A4** lists excluded studies pulled at the full-text level, with reasons for exclusion.

Data Abstraction and Quality Rating

One investigator abstracted details about each article's study design, patient population, setting, screening method, treatment regimen, analysis, followup, and results. A second investigator reviewed data abstraction for accuracy. Two investigators independently applied criteria developed by the USPSTF[36] to rate the quality of each study as good, fair, or poor (**Appendix A5**). Discrepancies were resolved through consensus. When otherwise not reported and where possible, we calculated relative risks (RRs) and 95 percent CIs or p-values.

Data Synthesis

We assessed the aggregate internal validity (quality) of the body of evidence for each Key Question (good, fair, or poor) using methods developed by the USPSTF, based on the number, quality, and size of studies; consistency of results among studies; and directness of evidence.[36]

We conducted meta-analyses to calculate risk ratios of the effects of routine iron supplementation on incidence of preterm delivery, low birthweight, iron deficiency anemia at term, and iron deficiency at term using the Mantel-Haenszel random- or fixed-effects models with RevMan software (The Cochrane Collaboration, Copenhagen, Denmark). Statistical heterogeneity was assessed using the I^2 statistic. Because of methodological shortcomings in the studies and differences across studies in design, interventions (timing and dosing), patient populations, and other factors, meta-analysis was not attempted for all outcome measures.

External Review

The draft report was reviewed by content experts (**Appendix A6**), USPSTF members, Agency for Healthcare Research and Quality Project Officers, and collaborative partners, and was revised prior to finalization.

Chapter 3. Results

Routine Iron Supplementation in Pregnant Women

Key Question 1. What Are the Benefits of Routine Iron Supplementation in Pregnant Women on Maternal and Infant Health Outcomes?

Summary

Eleven trials of routine iron supplementation in pregnant women reported clinical outcomes for women and infants. One trial reported no differences in quality of life between women receiving iron supplementation and those receiving placebo.[42] Five trials of maternal iron supplementation reported inconsistent findings for rates of Cesarean delivery[42-46] and having an infant born small for gestational age (three studies)[44,47,48] or with low birthweight (six studies).[42,43,45,47-49] Evidence from these studies demonstrates that exposure to maternal iron supplementation does not affect infant gestational age, Apgar scores, preterm birth, or infant mortality. Studies were methodologically heterogeneous and possibly underpowered.

Twelve good- or fair-quality trials reported some improvement in maternal hematological indexes with variable doses and duration of iron supplementation versus placebo measured at different timepoints during pregnancy, although half of the studies had findings that were not statistically significant. Four of these trials reported a lower incidence of maternal iron deficiency anemia at term with variable supplemental dosing (20 to 66 mg iron daily). While two reported statistically significant differences and two did not, pooling these findings resulted in a statistically significant difference between groups favoring supplementation (four trials; 4% (15/389) vs. 15% (55/373); RR, 0.29 (95% CI, 0.17 to 0.49); I^2=0%).[42,45,49,50] The results are from the same trials mentioned above that reported clinical outcomes. The clinical significance of these hematological findings remains unclear.

The prior USPSTF reviews[37,38] found that iron supplementation is effective in improving hematological indexes in anemic pregnant women but found limited evidence to demonstrate improved clinical outcomes for the mother, fetus, or newborn.

Evidence

We identified 12 trials (in 14 publications) of good[42,46,51,54] and fair quality[43-45,47-50,52,53,55] that compared the effects of routine iron supplementation versus no supplementation in pregnant women (**Tables 2** and **3**; **Appendixes B1** and **B2**). Three studies were conducted in the United States, three in Iran, and the others in Hong Kong, Australia, or Europe. Sample sizes ranged from 45 to 1,164 participants, although only two studies had more than 500 participants. Most studies reported that women with seriously low hematological indexes at baseline were excluded from the study and received treatment.[42-48,51,52] Several studies also reported providing treatment if indexes dropped too low during the course of the study.[42,44-46,51,52] The majority of enrolled

women were in their 20s (one study included adolescents[45]), and participants were mostly white or black or race was not reported. Two of the three studies conducted in the United States[47,48] were of women at higher risk for anemia based on reported risk factors (e.g., 100% eligible for the Special Supplemental Nutrition Program for Women, Infants, and Children, >50% black race, 24% to 44% with parity >2). All other included studies were of women at average risk for anemia; however, risk factors were not always reported, and no studies stratified results by risk groups.

The timing of supplementation varied from the first prenatal visit up to 20 weeks' gestation and continued until delivery. However, in two of the studies conducted in the United States, participants in the placebo group were reassigned to supplementation at 26 to 29 weeks' gestation (therefore, results up to that time period are included in this report).[47,48] Outcomes were measured during the third trimester, at delivery, or included a short duration of followup into the postpartum period. Supplement dosing ranged from 20 to 200 mg of elemental iron daily. Adherence, usually based on pill counts or an equation involving pill counts, ranged from 54 to 98 percent and mostly did not differ between groups in the seven studies that reported it; however, adherence data were not available for all included participants.[42,44,45,47,48,52,53]

Five studies (in six publications) reported power or sample size calculations.[42,44,46-48,54] Two studies were powered to detect a reduction in the rate of anemia—one from 30 to 15 percent (Δ, 15%)[47] and the other from 25 to 15 percent (Δ, 10%).[48] One of these studies was also powered to detect between-group differences of 0.407 times the standard deviation of birthweight and gestational age.[47] One study was powered to detect reductions in the rates of iron deficiency anemia (from 11.5% to 3%; Δ, 8.5%) and iron deficiency (from 30% to 15%; Δ, 15%), as well as an increase in the rate of gastrointestinal adverse effects (from 10% to 20%; Δ, 10%).[42] The sample size of one study was calculated to detect a 7-percent difference in the proportion of infants born small for gestational age,[46] and another study enrolled enough patients to detect an increase from 10 to 15 percent (Δ, 5%) in the incidence of gestational diabetes.[44]

Given the heterogeneity of supplementation dosing, duration, timing of initiation, and timing of followup in these studies, we pooled results for selected outcomes. We excluded 16 poor-quality studies[56-71] for this Key Question because of the availability of good- and fair-quality trials. The poor-quality studies suffered from high loss to followup, small sample sizes, and other methodological flaws, including poor reporting of statistical methods.

Clinical Outcomes—Maternal

One good-quality Australian trial (n=430) reported quality of life as a secondary outcome and found no differences between women receiving iron supplementation and those receiving placebo in any of the eight Short-Form 36 health concepts (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and general mental health) at 36 weeks' gestation, 6 weeks postpartum, or 6 months postpartum (specific data only displayed in a figure in the article).[42]

Although Cesarean delivery may occur for a variety of indications, including elective reasons, and there is no known causal relationship between iron deficiency anemia and Cesarean delivery,

it is typically considered a clinical outcome in pregnancy and was reported in five trials as an ad hoc event.[42-46] These trials of women likely at average risk for anemia compared pregnant women receiving iron supplementation with those not receiving supplementation; Cesarean delivery rates ranged from 7.6 to 26 percent in the supplementation group and 9.1 to 33 percent in the placebo group.[42-46] One large (n=1,164) fair-quality trial conducted in Hong Kong found a significant reduction in the rate of Cesarean delivery in women receiving 60 mg elemental iron daily versus placebo (25.2% vs. 33.1%; odds ratio, 0.58 [95% CI, 0.37 to 0.89]; p=0.008).[44] However, four smaller fair- and good-quality trials conducted in Australia (n=430), the United States (n=111), Ireland (N=97), and Iran (n=727) demonstrated no effect on Cesarean delivery rates in women receiving supplementation (20 to 120 mg elemental iron) versus placebo (23.6% vs. 22.0%;[42] 16% vs. 19%;[45] 7.6% vs. 9.1%;[43] and 26% vs. 23%,[46] respectively).

No other maternal clinical outcomes were reported.

Clinical Outcomes—Infant

Eleven trials of good[42,46] and fair quality[43-45,47-50,52,53] reported infant birth outcomes, including infant mortality, preterm delivery, length of gestation, small for gestational age, birthweight, and Apgar scores (**Table 2**). Details are described below.

Infant mortality. Four trials[42,43,45,46] anecdotally reported no effect of prenatal iron supplements on infant mortality, with rates ranging from 0 to 1.9 percent in the supplementation group and 0 to 1.7 percent in the placebo group, although this was not a prespecified outcome in these studies. All trials were of pregnant women at average risk for anemia. One good-quality Iranian trial reported a perinatal mortality rate of 0.8 percent (3/370) in the supplementation group and 1.7 percent (6/357) in the placebo group (p-value reported as nonsignificant).[46] A good-quality Australian trial reported one case of an infant born at 22 weeks with bilateral intrauterine pneumonia in the supplementation group,[42] a fair-quality Irish trial reported one unexplained death at 37 weeks' gestation in the supplementation group,[43] and a U.S. trial reported no infant deaths.[45]

Preterm delivery. Four fair-quality trials conducted in Hong Kong, the United States, and Iran reported rates of preterm delivery (defined as delivery before 37 weeks), ranging from 3 to 12.8 percent in the supplementation group and 6.8 to 13.9 percent in the placebo group.[44,47-49] As with the prior USPSTF report, these trials found no difference in rates of preterm delivery between women exposed to routine prenatal iron supplementation versus placebo (6.4% vs. 6.8%; p=0.85;[44] 3% vs. 6.8%; p=not significant [NS];[49] 12.8% vs. 12.5%; p=0.944;[47] and 7.5% vs. 13.9%; p=0.05[48]). Note that the two trials conducted in the United States (last two results listed) were of women at increased risk for iron deficiency.

Pooled estimates from two studies[44,49] with similar supplemental dosing (60 mg elemental iron) demonstrate a nonsignificant reduction in the incidence of preterm birth in the supplementation groups (RR, 0.88 [95% CI, 0.55 to 1.42]; I^2=0%) (**Appendix C1**).

Length of gestation. Six fair-quality trials and one good-quality trial conducted in Hong Kong, Norway, the United States (three trials), Iran, and Australia reported no effect of maternal iron

supplementation on length of gestation, with all studies reporting normal gestational ages of between 38 and 40 weeks for both supplementation and placebo groups.[42,44,45,47-49,53] The two studies conducted in the United States included women at higher risk for iron deficiency.

Small for gestational age. Four trials (three fair-quality, one good-quality) conducted in Hong Kong, the United States, and Iran reported inconsistent findings for infants exposed to prenatal iron supplementation who were small for gestational age (defined as <10th percentile of birthweight for gestational age), ranging from 3.6 to 15 percent in the supplementation group and 7.5 to 17.7 percent in the placebo group.[44,46-48] A trial conducted in Hong Kong of women at average risk for anemia and a trial conducted in the United States of women at higher risk for iron deficiency reported fewer small for gestational age infants in the supplementation group versus placebo (3.6% vs. 7.5%; p=0.013;[44] and 6.8% vs. 17.7%; p=0.014[47]). Another trial conducted in the United States of women at higher risk for iron deficiency reported no difference between supplementation and placebo groups for small for gestational age infants (10.8% vs. 15.5%; p=0.22[48]). One good-quality Iranian trial of women at average risk for anemia found that women *not* receiving supplementation had significantly fewer small for gestational age infants (15% vs. 10%; p=0.035).[46]

The reason for the inconsistencies in these findings is unclear. Attempting to pool the results of these studies leads to a high degree of statistical heterogeneity (I^2=58%). This heterogeneity can be attributed to two studies that found an increased risk with supplementation and had different dosing (50 and 60 mg elemental iron) than the studies that found a reduced incidence of small for gestational age infants with supplementation (30 mg elemental iron).[47,48] Removing these two studies from the analysis eliminates the heterogeneity (I^2=0%). It is unclear what additional factors may have led to this discrepancy.

Low birthweight. Six trials (five fair-quality, one good-quality) conducted in the United States, Iran, Ireland, and Australia reported the incidence of infants born with low birthweight (mostly defined as <2,500 g) and found inconsistent results, ranging from 0 to 9.4 percent in the supplementation group and 0 to 16.7 percent in the placebo group.[42,43,45,47-49] One trial of women at higher risk for iron deficiency conducted in the United States (n=275) found significantly lower rates of low-birthweight infants in the supplementation versus placebo group (4.3% vs. 16.7%; p=0.003).[47] However, five trials, including a different U.S. trial of women at higher risk for iron deficiency, found no effect of prenatal iron supplementation on the rate of low-birthweight infants.[42,43,45,48,49]

Pooled analysis of three comparable studies[42,45,49] (supplementing with 20 to 60 mg elemental iron) resulted in a nonstatistically significant RR of 1.10 (95% CI, 0.54 to 2.25; I^2=0%) favoring placebo (**Appendix C2**).

Birthweight. Eight trials (seven fair-quality, one good-quality) conducted in Iran, Australia, Norway, Denmark, Hong Kong, and the United States reported mean infant birthweight, with weights all within the normal range; however, some differences were found between groups.[42,44,47-50,52,53] Evidence on infants born with low birthweight is described separately above. Five trials found no difference in mean infant birthweight between women in the supplementation and placebo groups.[42,49,50,52,53] Three other trials, including two U.S. trials conducted in higher-risk

women, found that women in the placebo group had lower mean birthweight infants than women in the supplementation group, although all were still within the normal range (3,247 vs. 3,151 g; p=0.001;[44] 3,277 vs. 3,072 g; p=0.010;[47] and 3,325 vs. 3,217 g; p=0.03[48]).

Apgar scores. Five trials (four fair-quality, one good-quality) conducted in Hong Kong, Australia, Norway, the United States, and Iran reported Apgar scores at 1 minute, 5 minutes, or 10 minutes and found no significant difference between infants exposed to routine maternal iron supplementation versus placebo.[42,44-46,53]

Intermediate Outcomes—Maternal

Twelve good- or fair-quality trials reported maternal intermediate outcomes, including hematological parameters and incidence of iron deficiency anemia, iron deficiency, and anemia (**Table 3**).[42-53] Supplement doses varied across studies, ranging from 20 to 120 mg, and indexes were measured at different timepoints, including second trimester, third trimester, term, and postpartum. Findings on intermediate outcomes are largely consistent with the prior USPSTF reports.[37,38] Details are described below.

Iron deficiency anemia. Six trials reported incidence of iron deficiency anemia (defined as hemoglobin <110 g/L and serum ferritin <12 or 20 µg/L), ranging from 0 to 12.7 percent in the supplementation group and 0 to 29 percent in the placebo group during the third trimester, at delivery, or postpartum.[42,45,47-50]

Three trials found lower incidence of iron deficiency anemia during the third trimester in women receiving iron supplementation (30 to 60 mg elemental iron daily) compared with those taking placebo. Only one of these trials, conducted in Iran (n=148), found the difference to be statistically significant (1.4% vs. 3.8%; p<0.05).[49] Two trials conducted in the United States in women at potentially higher risk for iron deficiency anemia (due to enrollment of higher proportions of minority women with higher rates of parity [≥2], lower incomes, and lower educational levels) ended the controlled portion of the study at approximately 28 weeks' gestation and found no significant difference between groups (12.7% vs. 20.9%; p=0.123;[47] and 10% vs. 15%; p=0.23[48]). Incident rates for women in both the control and supplementation groups were some of the highest of all the studies reporting this outcome, reflecting the higher risk level of the women enrolled.

One good-quality Australian trial (n=430) and a fair-quality trial from Denmark (n=120) reported a significantly lower incidence of iron deficiency anemia at delivery in pregnant women receiving routine iron supplementation (20 and 66 mg elemental iron daily) versus placebo (3% vs. 11%; RR, 0.28 [95% CI, 0.12 to 0.68];[42] and 0% vs. 17.5%; p=0.02[50]), yet two smaller fair-quality trials (both <150 participants) conducted in Iran and the United States found no difference between groups (0% in both groups;[49] 5% vs. 29%; p=0.137 for adolescents and 10.5% vs. 22.2%; p=0.259 for adults[45]). Incidence in the control group in the U.S. study was quite high, although the study did not indicate that the women and adolescents enrolled were at higher risk. Pooling the findings of these trials (in five populations) resulted in a statistically significant difference between groups favoring supplementation (20 to 66 mg iron daily) (four trials; RR, 0.29 [95% CI, 0.17 to 0.49]; I^2=0%) (**Appendix C3**).[42,45,49,50]

The good-quality Australian trial found no significant difference between groups at 6 months postpartum (2.6% vs. 1.7%; RR, 1.55 [95% CI, 0.38 to 6.40]).[42]

Iron deficiency. Six trials reported incidence of iron deficiency (defined as serum ferritin <12, 15, or 20 µg/L), ranging from 0 to 56 percent in the supplementation group and 28 to 85 percent in the placebo group, with consistent results across measurement timepoints; however, not all results reached statistical significance.[42,47-49,52,53]

Two fair-quality trials in the United States of women at higher risk for iron deficiency that replaced the placebo portion with supplementation at approximately 28 weeks' gestation found lower rates of iron deficiency in the supplementation groups (53% vs. 65%; p=0.08;[48] and 56.4% vs. 65.1%; p=0.214[47]). Incidence was 8.7 to 12 percent lower (absolute differences) in the supplementation groups but did not reach statistical significance in either study. One fair-quality Norwegian trial compared heme iron versus nonheme iron supplements versus placebo (three arms) and found lower rates for both supplementation groups at 38 weeks (29% vs. 52% vs. 85%; p<0.001 and p<0.05) compared with placebo.[52] However, the rate of iron deficiency in the control group (85%) was extremely high in a population that was not noted to be at high risk. It is not clear how applicable these data are to average or high-risk populations in the United States.

Three trials (two fair-quality, one good-quality) found lower rates of iron deficiency at delivery in the supplementation group (9.5% vs. 28.2%; p<0.05;[49] 35% vs. 58%; RR, 0.60 [95% CI, 0.48 to 0.76];[42] and 0% vs. 65.2%; p=0.02[53]). Pooled results of the two trials with comparable dosing regimens (20 to 60 mg elemental iron daily) indicated a statistically significant difference in iron deficiency at term in favor of supplementation (two trials; RR, 0.53 [95% CI, 0.33 to 0.84]; p=0.006; I^2=40%) (**Appendix C4**).[42,49]

A good-quality trial reported lower rates of iron deficiency at 6 months postpartum among supplemented pregnant women compared with placebo (16% vs. 29%; RR, 0.57 [95% CI, 0.38 to 0.84]).[42] The trial comparing heme iron versus nonheme iron versus placebo (three arms) found that the heme-iron supplemented group had significantly lower rates of iron deficiency than the placebo group at both 6 to 10 weeks postpartum (8% vs. 52%; p<0.01) and 24 weeks postpartum (4% vs. 51%; p<0.001).[52] However, the nonheme-iron supplemented group (the typical iron supplement in the United States) was not significantly different from placebo at 6 to 10 weeks postpartum (27% vs. 52%; p=NS), although the absolute difference between groups was quite large. The difference in incidence of iron deficiency was significant at 24 weeks postpartum (17% vs. 51%; p<0.05). As noted above, this study had high control group rates of iron deficiency relative to prevalence in pregnant women in the United States.

Anemia. Four trials reported incidence of anemia (defined as hemoglobin <100 or 110 g/L), ranging from 3.7 to 21 percent in the supplementation group and 4.5 to 27 percent in the placebo group.[42,47,48,52]

Two fair-quality trials conducted in the United States of women at higher risk for iron deficiency found no difference between groups during the third trimester (19.8% vs. 26.7%; p=0.25;[47] and 21% vs. 19%; p=0.65[48]).

One good-quality Australian trial reported a significantly lower incidence of anemia at delivery in pregnant women receiving routine iron supplementation versus placebo (7% vs. 16%; RR, 0.45 [95% CI, 0.25 to 0.82]).[42]

This same Australian trial did not find a difference in rates of anemia at 6 months postpartum (3.7% vs. 4.5%; RR, 0.82 [95% CI, 0.30 to 2.21]).[42]

Hemoglobin. Eleven good- or fair-quality trials of women receiving iron supplementation versus placebo reported hemoglobin levels during the third trimester, at delivery, or up to 6 months postpartum, ranging from 114 to 139 g/L in the supplementation group and 113 to 134 g/L in the placebo group.[42-51,53]

One good-quality trial conducted in Iran (n=727) and one fair-quality trial in Ireland reported higher third-trimester hemoglobin levels with supplementation (50 and 120 mg elemental iron daily, respectively) compared with placebo (138 vs. 125 g/L; p<0.001;[46] and 135 vs. 126 g/L; p=0.04[43]). Two fair-quality trials of higher-risk women, both conducted in the United States (n=275 and 429), found no difference between groups (117 vs. 116 g/L; p=0.499;[47] and 114 vs. 114 g/L; p=0.81[48]). Overall hemoglobin levels in the U.S. trials were lower, perhaps due to their higher risk status.

Eight trials, with sample sizes ranging from 45 to 1,164 participants, conducted in Australia, Hong Kong, Iran, Norway, Ireland, Denmark, and the United States, found that women in the supplementation group had higher hemoglobin levels at delivery than those receiving placebo, although not all differences were significant. Statistically significant differences were found in five trials of adult women at average risk for anemia receiving 20 to 120 mg elemental iron daily (127 vs. 120 g/L; RR, 6.9 [95% CI, 4.4 to 9.3];[42] 122 vs. 118 g/L; p<0.001;[44] 139 vs. 128 g/L; p<0.0001;[51] 137 vs. 120 g/L; p<0.001;[43] and 127 vs. 116 g/L; p<0.0001[50]) and a subgroup of adolescents from another trial receiving 60 mg elemental iron daily (122 vs. 115 g/dL; p=0.024).[45] Two fair-quality trials conducted in the United States and Iran found no statistical difference between groups of adult women receiving 60 mg elemental iron daily (123 vs. 121 g/L; p=NS;[49] and 121 vs. 117 g/L; p=0.135[45]). Although the absolute differences in these two studies (both had <150 participants) were small, they were in the same direction, and the studies may have lacked adequate sample sizes to demonstrate statistical differences. One small (n=45) trial conducted in Norway did not report a p-value but also found higher hemoglobin values in the supplementation group (126 vs. 113 g/L).[53]

A good-quality Iranian trial found higher hemoglobin levels at 6 weeks postpartum in women receiving iron supplementation (50 mg elemental iron) versus placebo (133 vs. 126 g/L; p<0.0001),[51] but the good-quality Australian trial did not find a difference at 6 months postpartum in women receiving 20 mg elemental iron compared with placebo (135 vs. 134 g/L; RR, 1.6 [95% CI, −0.1 to 3.3]).[42]

Serum ferritin. Ten trials reported serum ferritin levels during the third trimester, at delivery, or up to 6 months postpartum, ranging from 7.4 to 34 µg/L in the supplementation group and 6.0 to 26 µg/L in the placebo group.[42-45,47-51,53]

Two fair-quality trials of women at higher risk for iron deficiency conducted in the United States found no difference between third-trimester serum ferritin levels with supplementation (30 mg elemental iron daily) versus placebo (7.4 vs. 7.4 µg/L; p=0.985;[47] and 22.0 vs. 20.3 µg/L; p=0.48[48]). However, one trial of 120 mg elemental iron daily conducted in Ireland found lower serum ferritin levels in the placebo group (32.6 vs. 12.8 µg/L; p=0.04).[43]

Five trials of women at average risk for anemia (two good-quality, three fair-quality) conducted in Hong Kong, Australia, Denmark, the United States, and Iran found that women receiving supplementation (20 to 66 mg elemental iron) had significantly higher serum ferritin levels at delivery than those receiving placebo (30.3 vs. 24.9 µg/L; p<0.003;[44] 21 vs. 14 µg/L; RR, 7.1 [95% CI, 4 to 10.2];[42] 12.0 vs. 6.2 µg/L; p=0.010 for adolescents and 12.9 vs. 7.6 µg/L; p=0.027 for adults;[45] 26.2 vs. 19.1 µg/L; p<0.0001;[51] and 22 vs. 14 µg/L; p<0.0001[50]). An additional small (n=45) trial conducted in Norway had results in the same direction (24.0 vs. 6.0 µg/L), but p-values were not reported.[53] However, one small fair-quality Iranian trial found no difference in serum ferritin levels between groups at delivery (28.1 vs. 22.1 µg/L; p=NS[49]).

Two good-quality trials of women at average risk for anemia, one in Iran and one in Australia, also reported ferritin levels at 6 weeks and 6 months postpartum, and both found significantly higher serum ferritin levels in women receiving supplementation (20 to 50 mg elemental iron daily) versus placebo (21.7 vs. 18.5 µg/L; p<0.0001;[51] and 34 vs. 26 µg/L; RR, 7.9 [95% CI, 3.5 to 12.3,[42] respectively).

Intermediate Outcomes—Infant

A 6-month followup study of the good-quality Australian trial[42] of 336 infants whose mothers were randomly allocated to receive 20 mg of elemental iron supplementation daily starting at 20 weeks' gestation and continuing until delivery was the only study to report followup infant hematological outcomes; it found no differences in iron status in children at 6 months (iron deficiency anemia, 0% vs. 0%; p=NS; iron deficiency, 6% vs. 4%; p=0.27; hemoglobin, 121 vs. 119 g/L; p=0.10; and serum ferritin, 32.5 vs. 30.8 µg/L; p=0.48) (**Appendix B1**).[54]

Key Question 2. What Are the Harms of Routine Iron Supplementation in Pregnant Women?

Summary

Ten good- and fair-quality trials included for Key Question 2 assessed harms of routine iron supplementation in pregnant women, although none of the harms were serious or associated with long-term significance, and there were mostly no significant differences between groups.[42-49,52,53] Most reported harms included transient treatment effects such as nausea, constipation, and diarrhea. Findings on rates of maternal hypertension were inconsistent.

The prior USPSTF report[38] included one unblinded fair-quality trial comparing reported adverse effects of routine supplementation with selective supplementation (not placebo).

Evidence

Harms were sparsely and variably reported, often as an ad hoc event, in 10 trials that compared iron supplementation with placebo in Australia, Iran, Hong Kong, Ireland, the United States, and Norway (these studies were also included in Key Question 1) (**Table 4**; **Appendixes B1** and **B2**). Two were rated good-quality[42,46] and eight were fair-quality.[43-45,47-49,52,53] Details are reported below.

Gastrointestinal adverse effects. Two trials conducted in Australia and the United States reported no difference in various minor gastrointestinal adverse effects between supplementation (60 and 20 mg elemental iron daily, respectively) and placebo groups.[42,45]

Any adverse events. Of four studies reporting rates of any adverse event, none reported significant differences between groups, including a good-quality Australian study (n=430) that measured harms at 36 weeks' gestation,[42] a U.S. study of pregnant adolescents and adults that measured adverse events at 24 to 28 weeks' gestation,[45] another U.S. study of women at higher risk for iron deficiency that reported any adverse event at more than one visit from enrollment to week 28,[47] and a Norwegian study that measured fatigue and other adverse events at 28 and 36 weeks' gestation.[52] One additional Norwegian trial (n=54) reported that none of the women reported discomfort that could be attributed to the medication.[53]

Hypertension. The sparse findings on maternal hypertension were inconsistent. One good-quality Iranian trial (n=205) found a lower rate of hypertension diagnoses during pregnancy in women *not* in the supplementation group (2.7% vs. 0.8%; p=0.05).[46] A fair-quality Iranian trial (n=148) reported a single case of hypertension during pregnancy in the supplementation group and none in the control group (1.4% vs. 0%; p=NS).[49] An Irish trial (N=97) reported no differences between groups in hypertensive disorder (7.5% for supplementation vs. 9.0% for placebo; p=0.78).[43]

Diabetes. One Hong Kong study found that iron supplementation beginning at less than 16 weeks' gestation did not increase risk for gestational diabetes.[44]

Nonadherence. While evidence is lacking on discontinuation due to adverse effects, adherence/nonadherence was used as a proxy measure. Nonadherence in adult women was lower with iron supplementation compared with placebo, but nonadherence in adolescents did not reach statistical significance compared with placebo in one small (n=111) trial conducted in the United States (2.2% vs. 16.1%; p=0.036; and 4.5% vs. 12.6%; p=0.320[45]). Six other trials found no difference in nonadherence to supplementation versus placebo,[42,44,47,48,52,53] ranging from 2 to 46 percent; however, most studies reported that these data were not available for all included participants.

Accidental overdose. No studies reported on accidental overdose.

Screening for Iron Deficiency Anemia in Pregnant Women

Key Question 1. What Are the Benefits of Screening for Iron Deficiency Anemia in Asymptomatic, Pregnant Women on Maternal and Infant Health Outcomes?

No randomized trial or observational study compared clinical outcomes between pregnant women who were screened or not screened for iron deficiency anemia.

Key Question 2. What Are the Harms of Screening for Iron Deficiency Anemia in Pregnant Women?

No randomized trial or observational study compared harms between pregnant women who were screened or not screened for iron deficiency anemia.

Key Question 3. What Are the Benefits of Treatment of Iron Deficiency Anemia in Pregnant Women on Maternal and Infant Health Outcomes?

No good- or fair-quality randomized trial or observational study meeting inclusion criteria compared clinical outcomes between pregnant women who were treated or not treated for iron deficiency anemia.

An older poor-quality observational study (n=103) from 1969 examined the effects of iron treatment (two oral formulations and intravenous iron compared with placebo) of anemia in pregnant women[72] (iron deficiency was not a criterion for enrollment). Laboratory values were reported by treatment group, but these groups were not analyzed using statistical methods. Women with low hemoglobin values at the first prenatal visit were treated and followed through 36 weeks' gestation. Although there was a significant increase in hemoglobin levels during the first month of therapy for all groups receiving iron therapy compared with the placebo group, there was no significant difference between treatment groups in hemoglobin or serum iron values at 36 weeks.

Key Question 4. What Are the Harms of Iron Treatment in Pregnant Women?

No randomized good- or fair-quality trial or observational study meeting inclusion criteria compared harms between pregnant women who were treated or not treated for iron deficiency anemia.

The same poor-quality study (n=103) from 1969 discussed in Key Question 3 reported adverse effects of iron treatment (two oral formulations and intravenous iron) of anemia in pregnant women compared with placebo.[72] Adverse events were reported at the end of 1 month of therapy, and results were not analyzed with statistical methods. Nausea, vomiting, and abdominal

cramping were reported by slightly more patients in the oral iron groups. Constipation was similar between groups receiving placebo and iron gluconate, but slightly lower with ferrous sulfate. No patient experienced adverse effects severe enough to withdraw from therapy.

Key Question 5. In Pregnant Women With Iron Deficiency, With or Without Anemia, What Is the Association Between Change in Maternal Iron Status (Including Changes in Ferritin or Hemoglobin Level) and Improvement in Newborn and Peripartum Outcomes in U.S.-Relevant Populations?

No good- or fair-quality study meeting inclusion criteria compared the association between change in maternal iron status and clinical outcomes in pregnant women with iron deficiency, with or without anemia. We also found no studies that met inclusion criteria and were conducted in developing countries.

One older poor-quality observational study with a randomized component[73] (n=203) evaluated the effect of iron supplementation and treatment in women in France. Twenty women (9.8%) were immigrants from Mediterranean countries, Africa, and the Far East with notably different dietary habits. Iron status was evaluated at 6 months' gestation, and 48 women with hemoglobin levels less than 11g/dL were given iron treatment (105 mg elemental iron), while the remaining nonanemic women were randomized to either supplementation (105 mg elemental iron) or placebo. At delivery, data were available for only 59 percent (120/203) of women, with slightly lower percentages of women in the randomized groups providing data at delivery. Iron as treatment or supplementation resulted in increases in maternal hematological indexes (hemoglobin and ferritin). Baseline serum ferritin levels were 19, 20, and 21 µg/L in women in the anemic, nonanemic supplementation, and nonanemic placebo groups, respectively, and corresponding baseline hemoglobin levels were 10.4, 11.7, and 11.9 g/dL. At delivery, serum ferritin levels were improved similarly in women receiving iron (33 and 34 µg/L) but not in the placebo group (20 µg/L). Hemoglobin values improved in all groups, but more in the iron-treated groups. Mean change in hemoglobin levels was 2.4 g/dL in the anemic group, 1.8 g/dL in the nonanemic group, and 0.9 g/dL in the placebo group. In addition, while iron supplementation resulted in an increase in these maternal hematological indexes, no significant differences in ferritin levels were observed in the newborns across the groups.

With respect to clinical outcomes, the study reported no differences between the three groups for perinatal outcomes, including complications at delivery, length of gestation, birthweight, or Apgar scores (details not reported). No other clinical outcomes were reported.

Chapter 4. Discussion

Summary of Review Findings

The evidence reviewed in this update is summarized in **Table 5**. Newer evidence identified for this review was consistent with findings from the previous USPSTF reviews,[37,38] which demonstrated that iron supplementation is often effective in improving maternal hematological indexes and that supplementation may result in a lower incidence of iron deficiency anemia and iron deficiency during pregnancy and at delivery but has limited effect for improving clinical outcomes for the mother, fetus, or infant.

This update includes 11 trials that reported various clinical outcomes of iron supplementation trials in women and infants. One trial reported no differences in quality of life between pregnant women receiving iron supplementation and those receiving placebo. Trials of prenatal iron supplementation found no clear effect on gestational age, infant Apgar score, preterm birth, or infant mortality; however, infant mortality was not a prespecified outcome. Findings were inconsistent among studies that reported an effect of maternal iron supplementation on rates of Cesarean delivery, infants born small for gestational age, and infants with low birthweight. It is important to note that the strength of this evidence is reduced by the small number of trials reporting these outcomes (five trials reporting on premature birth, small for gestational age, and Cesarean delivery) and the possibility that the current studies lack adequate sample size to identify important differences.

The strongest evidence supporting the benefit of supplementation on hematological outcomes was from a good-quality randomized Australian trial of pregnant women at average risk for anemia[42] that reported improvements in some maternal hematological parameters. Eleven other good- or fair-quality trials[43-53] supported the evidence that maternal iron supplementation may improve hematological parameters or reduce the incidence of iron deficiency anemia, but the clinical significance of these findings remains unclear. One followup study of maternal iron supplementation during pregnancy reported no differences in child iron status at age 6 months.[54] No studies reported serious harms or accidental overdose as a result of supplementation.

No trial evaluated screening or harms of screening for iron deficiency anemia in pregnant women. One older study evaluated the effectiveness and harms of treatment of iron deficiency anemia on intermediate outcomes during pregnancy but was of poor quality. One older poor-quality study reported that change in maternal iron status improved maternal hematological indexes but did not affect perinatal outcomes; therefore, evidence on the relationship between improvement in maternal iron status and maternal or infant clinical outcomes remains sparse.

Other published reviews in this topic area include a 2013 systematic review and meta-analysis that included trials and observational studies that did not meet our inclusion criteria because of the country in which it was conducted, quality, and high statistical heterogeneity, even when analysis was limited to high-quality trials (I^2=97%).[74] Therefore, analysis of these results has limited applicability to our review.

Limitations

We excluded non–English-language articles, which could result in language bias, although we identified none that would have met inclusion criteria. We could not formally assess for publication bias with graphical or statistical methods because of the small number of studies and differences in study design, populations, and outcomes assessed. We included some trials from countries that may not be directly generalizable to the United States because of differences in nutritional status, resources, infrastructure, and other factors (Hong Kong, Iran); however, all were rated as at least "high" on the United Nations Human Development Index.[40]

Emerging Issues

The incidence of iron deficiency anemia in the United States has remained essentially unchanged over the past decades, and screening and supplementation in asymptomatic, pregnant women are common. There are very few new studies or emerging issues at this time. However, further elucidating the possible influence of iron supplementation on Cesarean delivery rates could be an area of interest in the United States.

Relevance for Priority Populations

We did not identify any studies that identified specific issues or risk factors or that reported subgroup data for priority populations, including racial or ethnic minorities. However, two of the included iron supplementation trials conducted in the United States primarily included women eligible for the Special Supplemental Nutrition Program for Women, Infants, and Children[47,48] or a population that was more than 50 percent black.[48] While one of these studies found a significantly higher percentage of small for gestational age (6.8% vs. 17.7%; p=0.014) and low birthweight infants (4.3% vs. 16.7%; p=0.003) in the placebo groups, the other study[48] found no differences between groups in clinical outcomes. Regarding iron levels, no differences between groups at the third trimester timepoint reached statistical significance. Both of these studies ended the placebo phase of the trial at 28 weeks' gestation, after which all women in the study received routine iron supplementation, therefore limiting the interpretation of trial results.

Future Research

Research is needed to identify the long-term effects of iron supplementation during pregnancy. Infants exposed to prenatal iron supplementation should continue to be followed to help identify unexpected or emerging long-term benefits or harms from maternal supplementation. Research is also needed to understand the clinical significance of the short-term improvement in maternal hematological outcomes following prenatal iron supplementation. The influence of supplementation dose and timing could also be better studied. Additional trials with sufficient sample sizes would strengthen conclusions regarding infant and maternal harms of iron supplementation during pregnancy.

Conclusions

In summary, the use of iron supplementation during pregnancy appears to be effective at improving maternal hematological indexes and may reduce the incidence of iron deficiency anemia and iron deficiency in the short term, although the definition of these conditions during pregnancy is imprecise. Routine supplementation is not associated with significant short-term maternal harms, but there is no clear benefit on infant birth outcomes, including Apgar score, preterm birth, or infant mortality. More research is needed to fully understand the short- and long-term clinical effects of routine iron supplementation during pregnancy in women and infants, including the effects on rates of Cesarean delivery, small for gestational age infants, and low birthweight infants. There is no new evidence on the use of prenatal screening for iron deficiency anemia. More research is needed to establish the effects of treatment of pregnant women with iron deficiency anemia on maternal and infant clinical outcomes, as well as the association between improvements in iron status measures and clinical outcomes.

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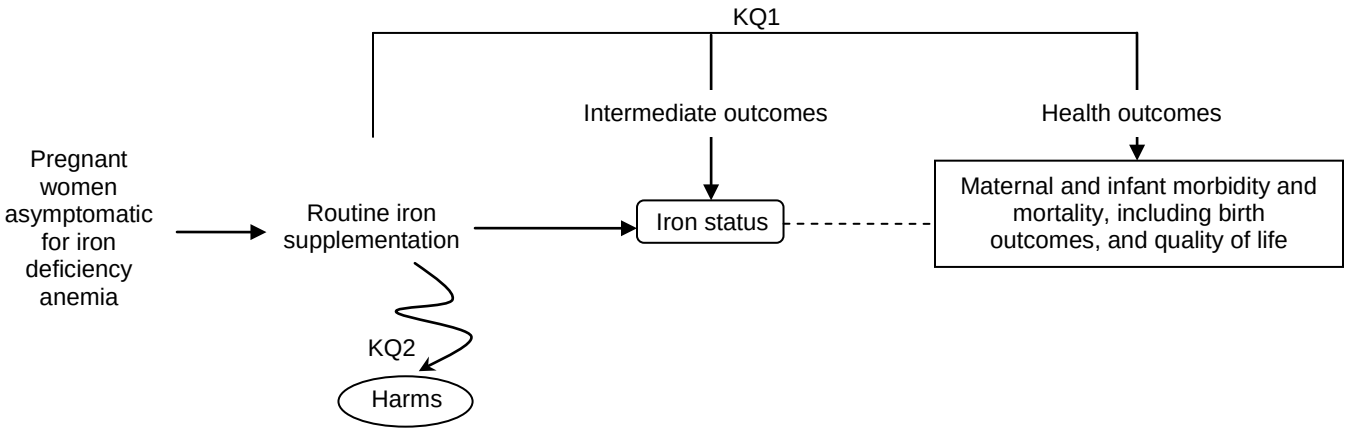
Figure 1. Analytic Framework for Routine Iron Supplementation in Pregnant Women

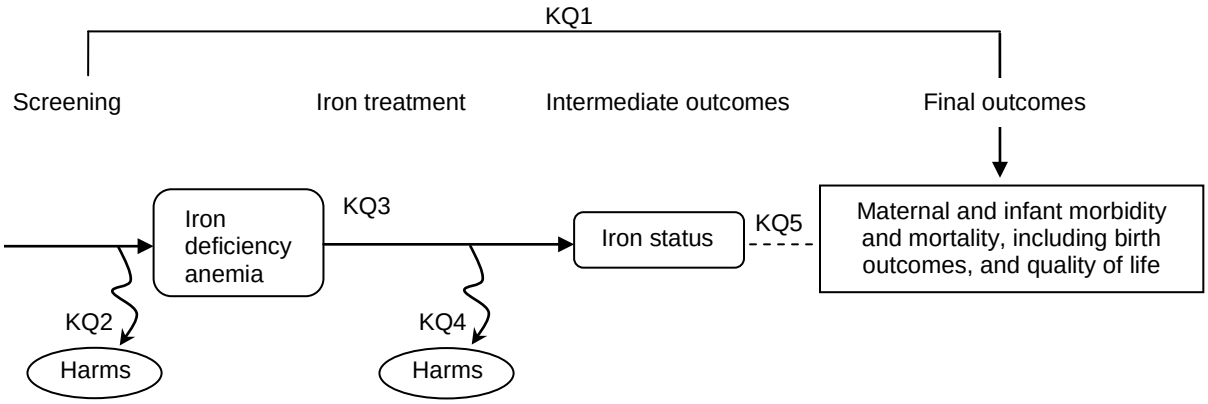


Abbreviation: KQ=key question.

Key Questions

1. What are the benefits of routine iron supplementation in pregnant women on maternal and infant health outcomes?
2. What are the harms of routine iron supplementation in pregnant women?

Figure 2. Analytic Framework for Screening for Iron Deficiency Anemia in Pregnant Women



Abbreviation: KQ=key question.

Key Questions

1. What are the benefits of screening for iron deficiency anemia in asymptomatic pregnant women on maternal and infant health outcomes?
2. What are the harms of screening for iron deficiency anemia in pregnant women?
3. What are the benefits of treatment of iron deficiency anemia in pregnant women on maternal and infant health outcomes?
4. What are the harms of iron treatment in pregnant women?
5. In pregnant women with iron deficiency anemia, with or without anemia, what is the association between change in maternal iron status (including changes in ferritin or hemoglobin level) and improvement in newborn and peripartum outcomes in U.S.-relevant populations?

Contextual Questions (not systematically reviewed)

1. How well does risk assessment identify pregnant women who are at increased risk for iron deficiency anemia?
2. What is the yield (number of new diagnoses) of repeat (periodic) screening in asymptomatic pregnant women, and at what timing intervals?

Table 1. Iron Formulations Available for Supplementation or Treatment

Ferrous Fumarate	Ferrous Gluconate	Ferrous Sulfate
Capsule		
Controlled release (Span-FF®): 325 mg [106 mg]	Soft gelatin (Simron®): 86 mg [10 mg]	Exsiccated (Fer-In-Sol®): 190 mg [60 mg]
		Ferospace®: 250 mg [50 mg]
Tablets		
Tablet: 325 mg [106 mg]	Tablet: 300 mg [34 mg]; 325 mg [38 mg]	Tablet: 324 mg [65 mg]
Femiron®: 63 mg [20 mg]	Fergon®, Ferralet®: 320 mg [37 mg]	Exsiccated (Feosol®): 200 mg [65 mg]
Fumerin®: 195 mg [64 mg]		Feratab®: 300 mg [60 mg]
Fumasorb®, Ircon®: 200 mg [66 mg]		Mol-Iron®: 195 mg [39 mg]
Hemocyte®: 324 mg [106 mg]		
Nephro-Fer™: 350 mg [115 mg]		
Chewable Feostat®: 100 mg [33 mg]		
Extended-release tablets or capsules		
Tablet (Ferro-Sequels®): 150 mg [50 mg] with docusate sodium 100 mg	Tablet (Ferralet® Slow Release): 320 mg [37 mg]	Tablet (Fero-Gradumet®): 525 mg [105 mg]
		Exsiccated, timed release (Slow FE®): 160 mg [50 mg]
		Capsule: exsiccated, timed release (Feosol®): 159 mg [50 mg]
		Capsule: exsiccated, timed release (Ferralyn®, Lanacaps®, Ferra-TD®): 250 mg [50 mg]
Oral liquids		
Drops (Feostat®): 45 mg/0.6 mL [15 mg/0.6 mL]	Elixir (Fergon®): 300 mg/5 mL [34 mg/5 mL]	Drops (Fer-In-Sol®): 75 mg/0.6 mL [15 mg/0.6 mL]
Suspension, oral (Feostat®): 100 mg/5 mL [33 mg/5 mL]		Drops (Fer-Iron®): 125 mg/mL [25 mg/mL]
		Elixir (Feosol®): 220 mg/5 mL [44 mg/5 mL]
		Syrup (Fer-In-Sol®): 90 mg/5 mL [18 mg/5 mL]

Note: Values in brackets indicate elemental iron content.

Table 2. Infant Birth Outcomes

Study, Year Country N Quality	Iron Supplement Dose and Formulation, Initiation	Risk Factors Reported	Supplementation vs. Control						
			Apgar Score	Preterm Delivery[a]	Length of Gestation	Small for Gestational Age[b]	Birthweight	Low Birthweight[c]	Infant Mortality
Barton 1994[43] Ireland N=97 Fair	120 mg elemental iron daily starting at 14 weeks' gestation	Race: NR (Ireland) Nulliparous: 45%–47%						<2,700 g: 9.4% vs. 15.9%; p=0.34	1.9% vs. 0%; p=0.57
Chan 2009[44] Hong Kong N=1,164 Fair	60 mg elemental iron daily starting at <16 weeks' gestation	Race: NR (Hong Kong) Parity ≥2: 0.50% vs. 0.18% BMI: 20.8 vs. 21.0 kg/m^2	Score at 1 min: 8.8 vs. 8.8; p=NS Score at 5 min: 9.8 vs. 9.7; p=NS	6.4% vs. 6.8%; p=0.85	39 vs. 39 weeks; p=0.322	3.6% vs. 7.5%; **p=0.013**	3,247.3 vs. 3,151.9 g; **p=0.001**		
Cogswell 2003[47] U.S. N=275 Fair	30 mg elemental iron daily starting at <20 weeks' gestation	Race: 56%–57% white, 24%–26% black, 16–17% Hispanic Parity ≥2: 31% vs. 24% ≤High school education: 73%–76% SES: 100% eligible for WIC		12.8% vs. 12.5%; p=0.944	38.9 vs. 38.3 weeks; p=0.05	6.8% vs. 17.7%; **p=0.014**	3,277 vs. 3,072 g; **p=0.010**	4.3% vs. 16.7%; **p=0.003**	
Eskeland 1997[52] Norway N=90 Fair	27 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Norway) BMI: 22–23 kg/m^2 Parity ≥2: 0%–10% Single: 3%–17% Low education: 3%–10%					3,690 vs. 3,620 vs. 3,610 g; p=NS[d]		
Falahi 2011[49] Iran N=148 Fair	60 mg elemental iron daily starting at <20 weeks' gestation	Race: NR (Iran) BMI: 24–25 kg/m^2		3% vs. 6.8%; p=NS	38.9 vs. 38.8 weeks; p=NS		3,310 vs. 3,270 g; p=NS	3% vs. 6.8%; p=NS	
Makrides 2003[42] Australia N=430 Good	20 mg elemental iron daily starting at 20 weeks' gestation	Race: 95% white, 0.9%–3.3% Aboriginal, 1.4%–2.3% Asian Multiparous: 52%–53% BMI: 26 kg/m^2 Highest level of education: 12%–15% year <10, 27%–28% year 11, 28%–33% year 12, 5%–8% trade certificate or diploma, 21% tertiary degree	Score <7 at 5 min: 1.4% vs. 1.5%; p=NS		39 vs. 39 weeks; p=NS		3,406 vs. 3,449 g; p=NS	5.4% vs. 4.2%; p=NS	0.5% (1 case) vs. 0%; p=NS (infant born at 22 weeks with bilateral intrauterine pneumonia)
Meier 2003[45] U.S. N=111 Fair	60 mg elemental iron daily starting at 1st prenatal visit	Race: NR (Wisconsin) Private group practice	Score <7 at 1 min: Adolescents: 30% vs. 25%; p=NS Adults: 29.7% vs. 16.7%; p=NS		Adolescents: 39.9 vs. 39.8 weeks; p=NS Adults: 39.2 vs. 39.5 weeks; p=NS			Adolescents: 0% vs. 0%; p=NS Adults: 5.4% vs. 2.9%; p=NS	0% vs. 0%; p=NS

Table 2. Infant Birth Outcomes

Study, Year Country N Quality	Iron Supplement Dose and Formulation, Initiation	Risk Factors Reported	Supplementation vs. Control						
			Apgar Score	Preterm Delivery[a]	Length of Gestation	Small for Gestational Age[b]	Birthweight	Low Birthweight[c]	Infant Mortality
Milman 1994[50] Denmark N=120 Fair	66 mg elemental iron daily starting at 14–16 weeks' gestation	Race: NR (Denmark)					3,350 vs. 3,450 g; p>0.5 (median)		
Romslo 1983[53] Norway N=45 Fair	200 mg elemental iron daily starting within 10 weeks' gestation	Race: NR (Norway)	1-min score: 8.7 vs. 8.8; p=NR 5-min score: 9.0 vs. 9.0; p=NR		39.9 vs. 39.5 weeks; p=NR		3,546 vs. 3,510 g; p=NR		
Siega-Riz 2006[48] U.S. N=429 Fair	30 mg elemental iron daily starting at <20 weeks' gestation	Race: 58%–65% black, 31%–37% white Single: 75% Parity ≥2: 44% vs. 41% SES: 100% eligible for WIC		7.5% vs. 13.9%; p=0.05	39.1 vs. 39.0 weeks; p=0.43	10.8% vs. 15.5%; p=0.22	3,325 vs. 3,217 g; **p=0.03**	4.8% vs. 9.5%; p=0.09	
Ziaei 2007[46] Iran N=727 Good	50 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Iran) BMI: 24 kg/m^2 Parity: 1.7	Score at 10 min: 9.9 vs. 9.8; p=NS			15% vs. 10%; **p=0.035**			0.8% vs. 1.7%; p=NS

[a] <37 weeks' gestation.
[b] <10th percentile of birthweight for gestational age.
[c] <2,500 g.
[d] Heme-iron supplemented group vs. nonheme-iron supplemented group vs. placebo group.

Note: Bolded p-values show a significant difference.

Abbreviations: BMI=body mass index; NR=not reported; NS=not significant; SES=socioeconomic status; WIC= Special Supplemental Nutrition Program for Women, Infants, and Children.

Table 3. Maternal Hematological Outcomes

Study, Year Country N, Quality	Timepoint	Iron Supplement Dose, Formulation, Initiation	Risk Factors Reported	Supplementation vs. Control					
				Hemoglobin	Serum Ferritin	MCV	Iron Deficiency[a]	Anemia[b]	Iron Deficiency Anemia[c]
3rd trimester									
Siega-Riz 2006[48] U.S. N=429 Fair	26–29 weeks (end of RCT phase)	30 mg elemental iron daily starting at <20 weeks' gestation	Race: 58%–65% black, 31%–37% white Single: 75% Parity ≥2: 44% vs. 41% SES: 100% eligible for WIC	114 vs. 114 g/L; p=0.81	22.0 vs. 20.3 µg/L; p=0.48		53% vs. 65%; p=0.08[d]	21% vs. 19%; p=0.65	10% vs. 15%[e]; p=0.23
Cogswell 2003[47] U.S. N=275 Fair	28 weeks (end of RCT phase)	30 mg elemental iron daily starting at <20 weeks' gestation	Race: 56%–57% white, 24%–26% black, 16%–17% Hispanic Parity ≥2: 31% vs. 24% ≤High school education: 73%–76% SES: 100% eligible for WIC	117 vs. 116 g/L; p=0.499	7.4 vs. 7.4 µg/L; p=0.985	90.8 vs. 90.3 fL; p=0.443	56.4% vs. 65.1%; p=0.214	19.8% vs. 26.7%; p=0.251	12.7% vs. 20.9%; p=0.123
Falahi 2011[49] Khorramabad City, Iran N=148 Fair	28 weeks	60 mg elemental iron daily starting at <20 weeks' gestation	Race: NR (Iran) BMI: 24–25 kg/m^2						1.4% vs. 3.8%; **p<0.05**
Ziaei 2007[46] Tehran, Iran N=727 Good	3rd trimester	50 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Iran) BMI: 24 kg/m^2 Parity: 1.7	138 vs. 125 g/L; **p<0.001**					
Barton 1994[43] Ireland N=97 Fair	36 weeks	120 mg elemental iron daily starting at 14 weeks' gestation	Race: NR (Ireland) Nulliparous: 45%–47%	135 vs. 126 g/L; **p=0.043** (adjusted for smoking, p=0.25)	32.6 vs. 12.8 µg/L; **p=0.04**				
Eskeland 1997[52] Norway N=90 Fair	38 weeks	27 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Norway) BMI: 22–23 kg/m^2 Parity ≥2: 0%–10% Single: 3%–17% Low education: 3%–10%				29% vs. 52% vs. 85%; **p<0.001** for A vs. C and **p<0.05** for B vs. C[e]		
At term									
Meier 2003[45] U.S. N=111 Fair	Delivery, 36–40 weeks, stratified by age group	60 mg elemental iron daily starting at 1st prenatal visit	Race: NR (Wisconsin) Private group practice	Adolescents: 122 vs. 115 g/L; **p=0.024** Adults: 121 vs. 117 g/L; p=0.135	Adolescents: 12.0 vs. 6.2 µg/L; **p=0.010** Adults: 12.9 vs. 7.6 µg/L; **p=0.027**				Adolescents: 5% vs. 29%; p=0.14 Adults: 10.5% vs. 22.2%; p=0.26

Table 3. Maternal Hematological Outcomes

Study, Year Country N, Quality	Timepoint	Iron Supplement Dose, Formulation, Initiation	Risk Factors Reported	Supplementation vs. Control					
				Hemoglobin	Serum Ferritin	MCV	Iron Deficiency[a]	Anemia[b]	Iron Deficiency Anemia[c]
Romslo 1983[53] Norway N=45 Fair	37–40 weeks	200 mg elemental iron daily starting within 10 weeks' gestation	Race: NR (Norway)	126 vs. 113 g/L; p=NR	24.0 vs. 6.0 µg/L; p=NR		0% vs. 65.2%; **p=0.02**		
Barton 1994[43] Ireland N=97 Fair	40 weeks	120 mg elemental iron daily starting at 14 weeks' gestation	Race: NR (Ireland) Nulliparous: 45%–47%	137 vs. 120 g/L; **p<0.001**				"No patients were withdrawn from the study due to anemia"	
Chan 2009[44] Hong Kong N=1,164 Fair	Delivery	60 mg elemental iron daily starting at <16 weeks' gestation	Race: NR (Hong Kong) Parity ≥2: 0.50 vs. 0.18% BMI: 20.8 vs. 21.0 kg/m^2	122 vs. 118 g/L; **p<0.001**	30.0 vs. 24.9 µg/L; **p<0.003**				
Falahi 2011[49] Khorramabad City, Iran N=148 Fair	Delivery	60 mg elemental iron daily starting at <20 weeks' gestation	Race: NR (Iran) BMI: 24–25 kg/m^2	123 vs. 121 g/L; p=NS	28.1 vs. 22.1 µg/L; p=NS		9.5% vs. 28.2%; **p<0.05**		0% vs. 0%; p=NS
Makrides 2003[42] Australia N=430 Good	Delivery	20 mg elemental iron daily starting at 20 weeks' gestation	Race: 95% white, 0.9%–3.3% Aboriginal, 1.4%–2.3% Asian Multiparous: 52%–53% BMI: 26 kg/m^2 Highest level of education: 12%–15% year <10, 27%–28% year 11, 28%–33% year 12, 5%–8% trade certificate or diploma, 21% tertiary degree	127 vs. 120 g/L; **RR, 6.9 (95% CI, 4.4 to 9.3)**	21 vs. 14 µg/L; **RR, 7.1 (95% CI, 4 to 10.2)**		35% vs. 58%; **RR, 0.60 (95% CI, 0.48 to 0.76)**	7% vs. 16%; **RR, 0.45 (95% CI, 0.25 to 0.82)**	3% vs. 11%; **RR, 0.28 (95% CI, 0.12 to 0.68)**
Milman 1994[50] Denmark N=120 Fair	Term	66 mg elemental iron daily starting at 14–16 weeks' gestation	Race: NR (Denmark)	127 vs. 116 g/L; **p<0.0001**	22 vs. 14 µg/L; **p<0.0001**				0% vs. 17.5%; **p=0.03**
Ziaei 2008[51] Iran (location NR) N=205 Good	Delivery	50 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Iran) BMI: 24 kg/m^2 Parity: 1.6–1.7 Educational level: 7%–11% primary school, 77%–83% high school, 10%–12% university	139 vs. 128 g/L; **p<0.0001**	26.2 vs. 19.1 µg/L; **p<0.0001**				

Table 3. Maternal Hematological Outcomes

Study, Year Country N, Quality	Timepoint	Iron Supplement Dose, Formulation, Initiation	Risk Factors Reported	Supplementation vs. Control					
				Hemoglobin	Serum Ferritin	MCV	Iron Deficiency[a]	Anemia[b]	Iron Deficiency Anemia[c]
Postpartum									
Eskeland 1997[52] Norway N=90 Fair	1 week post-partum	27 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Norway) BMI: 22–23 kg/m^2 Parity ≥2: 0%–10% Single: 3%–17% Low education: 3%–10%					11.5% vs. 20.7%; p=0.25	
Eskeland 1997[52] Norway N=90 Fair	6-10 weeks post-partum	27 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Norway) BMI: 22–23 kg/m^2 Parity ≥2: 0%–10% Single: 3%–17% Low education: 3%–10%				8% vs. 27% vs. 52%; **p<0.01 for A vs. C;** p=NS for others[f]		
Eskeland 1997[52] Norway N=90 Fair	24 weeks post-partum	27 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Norway) BMI: 22–23 kg/m^2 Parity ≥2: 0%–10% Single: 3%–17% Low education: 3%–10%				4% vs. 17% vs. 51%; **p<0.001 for A vs. C and p<0.05 for B vs. C**[f]		
Makrides 2003[42] Australia N=430 Good	6 months post-partum	20 mg elemental iron daily starting at 20 weeks' gestation	Race: 95% white, 0.9%–3.3% Aboriginal, 1.4%–2.3% Asian Multiparous: 52%–53% BMI: 26 kg/m^2 Highest level of education: 12%–15% year <10, 27%–28% year 11, 28%–33% year 12, 5%–8% trade certificate or diploma, 21% tertiary degree	135 vs. 134 g/L; RR, 1.6 (95% CI, −0.1 to 3.3)	34 vs. 26 µg/L; **RR, 7.9 (95% CI, 3.5 to 12.3)**		16% vs. 29%; **RR, 0.57 (95% CI, 0.38 to 0.84)**	3.7% vs. 4.5%; RR, 0.82 (95% CI, 0.30 to 2.21)	2.6% vs. 1.7%; RR, 1.55 (95% CI, 0.38 to 6.40)
Ziaei 2008[51] Iran (location NR) N=205 Good	6 weeks post-partum	50 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Iran) BMI: 24 kg/m^2 Parity: 1.6–1.7 Educational level: 7%–11% primary school, 77%–83% high school, 10%–12% university	133 vs. 126 g/L; **p<0.0001**	21.7 vs. 18.5 µg/L; **p<0.0001**				

[a] Serum ferritin <12 µg/L.
[b] Hemoglobin <110 g/L.
[c] Hemoglobin <110 g/L and serum ferritin <12 µg/L.
[d] Serum ferritin <20 µg/L.
[e] Hemoglobin <110 g/L and serum ferritin <20 µg/L.
[f] Heme-iron supplemented group (A) vs. nonheme-iron supplemented group (B) vs. placebo group (C).
Note: Bolded p-values and relative risks show a significant difference.
Abbreviations: BMI=body mass index; CI=confidence interval; MCV=mean corpuscular volume; NR=not reported; NS=not significant; RCT=randomized, controlled trial; RR=relative risk; SES=socioeconomic status; WIC= Special Supplemental Nutrition Program for Women, Infants, and Children.

Table 4. Maternal Adverse Events

Study, Year Country N Quality	Iron Supplement Dose and Formulation, Initiation	Risk Factors Reported	Supplementation vs. Control			
			Gestational Diabetes	Pregnancy-Induced Hypertension	Gastrointestinal Events	Other
Barton 1994[43] Ireland N=97 Fair	120 mg elemental iron daily starting at 14 weeks' gestation	Race: NR (Ireland) Nulliparous: 45%–47%		Hypertensive disorder: 7.5% vs. 9.0%; p=0.78		Antepartum hemorrhage: 5.7% vs. 4.5%; p=0.81
Chan 2009[44] Hong Kong N=1,164 Fair	60 mg elemental iron daily starting at <16 weeks' gestation	Race: NR (Hong Kong) Parity ≥2: 0.50 vs. 0.18% BMI: 20.8 vs. 21.0 kg/m^2	At 28 weeks' gestation: 10% vs. 10%; OR, 1.04 (95% CI, 0.7 to 1.53)			Nonadherence: 46% overall; p=NS
Cogswell 2003[47] U.S. N=275 Fair	30 mg elemental iron daily starting at <20 weeks' gestation	Race: 56%–57% white, 24%–26% black, 16%–17% Hispanic Parity ≥2: 31% vs. 24% ≤ High school education: 73%–76% SES: 100% eligible for WIC				Nonadherence at week 28: 36.6% vs. 34.8%; p=NS Side effects reported at >1 visit from enrollment to week 28: 24.6% vs. 18.5%; p=NS
Eskeland 1997[52] Norway N=90 Fair	27 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Norway) BMI: 22–23 kg/m^2 Parity ≥2: 0%–10% Single: 3%–17% Low education: 3%–10%				No difference in fatigue or other side effects; p=NS Nonadherence: 19% (combined 2 iron groups) vs. 18%; p=NS
Falahi 2011[49] Iran N=148 Fair	60 mg elemental iron daily starting at <20 weeks' gestation	Race: NR (Iran) BMI: 24–25 kg/m^2		1.4% (1 case) vs. 0%; p=NS		
Makrides 2003[42] Australia N=430 Good	20 mg elemental iron daily starting at 20 weeks' gestation	Race: 95% white, 0.9%–3.3% Aboriginal, 1.4%–2.3% Asian Multiparous: 52%–53% BMI: 26 kg/m^2 Highest level of education: 12%–15% year <10, 27%–28% year 11, 28%–33% year 12, 5%–8% trade certificate or diploma, 21% tertiary degree			<u>At 36 weeks' gestation:</u> Nausea: 29% vs. 28%; RR, 1.04 (95% CI, 0.76 to 1.42) Stomach pain: 35% vs. 30%; RR, 1.19 (95% CI, 0.89 to 1.58) Heartburn: 68% vs. 69%; RR, 0.99 (95% CI, 0.86 to 1.13) Vomiting: 12% vs. 13%; RR, 0.89 (95% CI, 0.53 to 1.50) Rash: 7.5% vs. 6.2%; RR, 1.21 (95% CI, 0.58 to 2.51) Bowel movement ≤3 times/week: 4% vs. 1.6%; RR, 2.56 (95% CI, 0.69 to 9.51)	Nonadherence: 14% vs. 15%; p=NS

Table 4. Maternal Adverse Events

Study, Year Country N Quality	Iron Supplement Dose and Formulation, Initiation	Risk Factors Reported	Supplementation vs. Control			
			Gestational Diabetes	Pregnancy-Induced Hypertension	Gastrointestinal Events	Other
Meier 2003[45] U.S. N=111 Fair	60 mg elemental iron daily starting at 1st prenatal visit	Race: NR (Wisconsin) Private group practice			<u>Adolescents:</u> Nausea: 53% vs. 65%; p=NS Vomiting: 41% vs. 41%; p=NS Constipation: 29% vs. 12%; p=NS Diarrhea: 13% vs. 17%; p=NS <u>Adults:</u> Nausea: 63% vs. 53%; p=NS Vomiting: 35% vs. 21%; p=NS Constipation: 24% vs. 28%; p=NS Diarrhea: 14% vs. 24%; p=NS	<u>Adolescents:</u> Nonadherence: 4.5% vs. 12.6%; p=0.320 <u>Adults:</u> Nonadherence: 2.2% vs. 16.1%; **p=0.036**
Romslo 1983[53] Norway N=45 Fair	200 mg elemental iron daily starting within 10 weeks' gestation	Race: NR (Norway)			"None of the women complained of discomfort that could be attributed to the medication"	Nonadherence: 45% overall; p=NS
Siega-Riz 2006[48] U.S. N=429 Fair	30 mg elemental iron daily starting at <20 weeks' gestation	Race: 58%–65% black, 31%–37% white Single: 75% Parity ≥2: 44% vs. 41% SES: 100% eligible for WIC				Nonadherence: 34% vs. 37%; p=0.27
Ziaei 2007[46] Iran N=727 Good	50 mg elemental iron daily starting at 20 weeks' gestation	Race: NR (Iran) BMI: 24 kg/m^2 Parity: 1.7		10 (2.7%) vs. 3 (0.8%); p=0.05		

Note: Bolded p-value shows a significant difference.

Abbreviations: BMI=body mass index; CI=confidence interval; NR=not reported; NS=not significant; OR=odds ratio; RR=relative risk; SES=socioeconomic status; WIC= Special Supplemental Nutrition Program for Women, Infants, and Children.

Table 5. Summary of Evidence

Routine Iron Supplementation in Pregnant Women

Main Findings From Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
Key Question 1. What are the benefits of routine iron supplementation in pregnant women on maternal and infant health outcomes?						
Clinical outcomes, maternal						
Limited evidence exists demonstrating improved clinical outcomes	5 RCTs	Outcomes mostly reported as ad hoc events; variable doses of iron supplements	Mostly consistent	Studies limited to those conducted in U.S.-applicable countries and populations	1 trial reported no differences in quality of life between iron-supplemented pregnant women and those receiving placebo. 5 trials reported rates of Cesarean delivery, with 4 finding no difference in rates between supplemented women and placebo. 1 trial found significantly fewer Cesarean deliveries in women receiving iron supplementation.	Poor
Clinical outcomes, infant						
Infant mortality						
Limited evidence; 1 trial reported fewer infant deaths in the selective supplementation group	4 trials	Outcomes mostly reported as ad hoc events; variable doses of iron supplements	Consistent	1 trial conducted in Iran	4 trials reported no association between maternal iron supplementation and infant mortality.	Poor
Preterm delivery						
Limited evidence shows no effect on pregnancy outcomes	4 RCTs	Variable doses of iron supplements	Consistent	No issues	4 studies found no association between prenatal iron supplementation and the incidence of preterm delivery.	Fair
Length of gestation						
Limited evidence shows no effect on pregnancy outcomes	6 RCTs	Variable doses of iron supplements	Consistent	No issues	6 trials reported no association between length of gestation and iron supplementation. All studies reported normal gestational ages of between 38 and 40 weeks for both supplemented and placebo groups.	Fair
Small for gestational age						
No studies	4 RCTs	Variable doses of iron supplements	Inconsistent	No issues	4 trials reported inconsistent findings for infants who were small for gestational age. 1 study reported no difference between supplementation and placebo groups, 2 trials reported fewer small for gestational age infants among the supplementation group, and 1 trial found that women not receiving supplementation had fewer small for gestational age infants.	Fair
Low birthweight						
Limited evidence shows no effect on pregnancy outcomes	6 RCTs	Variable doses of iron supplements	Some inconsistency	No issues	1 study reported a significant reduction in the rate of low birthweight (<2,500 g) among infants exposed to prenatal iron supplementation (4.3% vs. 16.7%; p=0.003). 5 studies found no association.	Fair

Table 5. Summary of Evidence

Main Findings From Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
Apgar score						
No studies	5 RCTs	Variable doses of iron supplements	Consistent	No issues	4 studies found no association in Apgar scores at 1 and 5 minutes in infants exposed to prenatal iron supplements vs. placebo.	Fair
Intermediate outcomes, maternal						
Iron supplements are effective in improving maternal hematological indexes	12 RCTs for intermediate outcomes	Variable doses of iron supplements	Mostly consistent	Studies limited to those conducted in U.S.-applicable countries and populations	12 trials reported mostly improvement in maternal hematological indexes with variable doses of iron supplementation vs. placebo, but inconsistent associations between iron supplements and the incidence of maternal iron deficiency or anemia. Pooled analysis of 4 trials reporting a lower incidence of iron deficiency anemia at term (2 statistically significant and 2 with no difference) resulted in a statistically significant difference between groups favoring supplementation (20–66 mg iron daily) (4 trials; RR, 0.29 [95% CI, 0.17 to 0.49]; I^2=0%). The clinical significance of these findings remains unclear.	Fair
Intermediate outcomes, infant						
Infant iron outcomes not assessed	1 followup study	No issues	Not applicable	No issues	A followup study to the good-quality Australian trial, in which mothers were randomly allocated to receive 20 mg of elemental iron supplementation daily starting at 20 weeks' gestation until delivery, reported child hematological outcomes and found no differences in iron status of children at age 6 months.	Poor
Key Question 2. What are the harms of routine iron supplementation in pregnant women?						
Reversible gastrointestinal symptoms associated with iron use	10 RCTs	Outcomes mostly reported as ad hoc events; variable doses of iron supplements	Some inconsistency	No issues	10 trials included in Key Question 1 assessed variable harms of routine iron supplementation in pregnant women, although none of the harms were serious or associated with long-term significance, and there were mostly no significant differences between groups. Most reported harms included transient treatment effects, such as nausea, constipation, and diarrhea. Findings on rates of maternal hypertension were inconsistent. 6 trials found no difference in nonadherence to supplementation vs. placebo between groups; however, 1 trial had lower nonadherence in the supplementation group than the placebo group.	Poor

Table 5. Summary of Evidence

Screening for Iron Deficiency Anemia in Pregnant Women

Main Findings From Prior USPSTF Reviews	Number and Type of Studies Identified for Update	Limitations	Consistency	Applicability	Summary of Findings	Overall Quality[a]
Key Question 1. What are the benefits of screening for iron deficiency anemia in asymptomatic pregnant women on maternal and infant health outcomes?						
No studies	No studies	No studies	No studies	No studies	No studies	No studies
Key Question 2. What are the harms of screening for iron deficiency anemia in pregnant women?						
No studies	No studies	No studies	No studies	No studies	No studies	No studies
Key Question 3. What are benefits of treatment of iron deficiency anemia in pregnant women on maternal and infant health outcomes?						
Iron supplements are effective in improving maternal hematological indexes but limited evidence exists demonstrating improved clinical outcomes	No studies	No studies	No studies	No studies	No studies	No studies
Key Question 4. What are the harms of iron treatment in pregnant women?						
Reversible gastrointestinal symptoms associated with iron use	No studies	No studies	No studies	No studies	No studies	No studies
Key Question 5. In pregnant women with iron deficiency, with or without anemia, what is the association between change in maternal iron status (including changes in ferritin or hemoglobin level) and improvement in newborn and peripartum outcomes in U.S.-relevant populations?						
Not previously reviewed	No studies	No studies	No studies	No studies	No studies	No studies

[a] "Overall quality" is based on new evidence identified for this update plus previously reviewed evidence.

Abbreviations: CI=confidence interval; RCT=randomized controlled trial; RR=relative risk.

Appendix A1. Search Strategies

Supplementation: Key Questions 1 and 2

Database: Ovid MEDLINE(R) without Revisions
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4 or/1-3
5 pc.fs.
6 Dietary Supplements/
7 Iron/
8 6 and 7
9 (iron adj2 supplemen$).mp.
10 Iron, Dietary/ad
11 or/8-10
12 4 and 5
13 4 and 11
14 12 or 13
15 limit 14 to humans
16 limit 15 to english language
17 limit 15 to abstracts
18 exp Pregnancy/
19 pregnan$.mp.
20 18 or 19
21 17 and 20

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4 or/1-3
5 pc.fs.
6 Dietary Supplements/
7 Iron/
8 6 and 7
9 (iron adj2 supplemen$).mp.
10 Iron, Dietary
11 or/8-10
12 4 and 5
13 4 and 11
14 12 or 13
15 exp Pregnancy/
16 pregnan$.mp.
17 15 or 16
18 14 and 17

Screening: Key Questions 1 and 2

Database: Ovid MEDLINE(R) without Revisions
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4 or/1-3
5 exp Mass Screening/
6 screen$.mp.
7 5 or 6

8 4 and 7
9 Pregnancy/
10 pregnan$.mp.
11 9 or 10
12 8 and 11
13 limit 8 to ("all adult (19 plus years)" or "adolescent (13 to 18 years)")
14 12 or 13
15 limit 14 to humans
16 limit 15 to english language
17 limit 15 to abstracts
18 16 or 17

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4 or/1-3
5 exp Mass Screening/
6 screen$.mp.
7 5 or 6
8 4 and 7
9 Pregnancy/
10 pregnan$.mp.
11 9 or 10
12 8 and 11

Treatment: Key Questions 3 and 4

Database: Ovid MEDLINE(R) without Revisions
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4 or/1-3
5 (de or dt or th).fs.
6 Iron/ or Iron, Dietary/
7 4 and (5 or 6)
8 exp Pregnancy/
9 pregnan$.mp.
10 7 and (8 or 9)
11 limit 10 to (english language and humans)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 exp Anemia, Iron-Deficiency/
2 "iron deficiency anemia".mp.
3 ("ida" or ("iron deficiency" adj2 "anemia")).mp.
4 or/1-3
5 (de or dt or th).fs.
6 Iron/ or Iron, Dietary
7 4 and (5 or 6)
8 exp Pregnancy/
9 pregnan$.mp.
10 7 and (8 or 9)

Appendix A1. Search Strategies

Association: Key Question 5

Database: Ovid MEDLINE(R) without Revisions
1 Iron/
2 Iron, Dietary/
3 Anemia, Iron-Deficiency/
4 1 or 2
5 4 and (anemia or anemic or deficiency or deficient).mp.
6 3 or 5
7 Treatment Outcome/
8 6 and 7
9 6 and association.mp.
10 8 or 9
11 limit 10 to humans
12 limit 11 to english language

Systematic Reviews: All Key Questions

Database: EBM Reviews - Cochrane Database of Systematic Reviews
1 iron deficiency anemia.mp.
2 ("iron deficiency" adj2 anemia).mp.
3 1 or 2

Iron Deficiency Without Anemia

Database: Ovid MEDLINE(R) without Revisions
1 Iron/df [Deficiency]
2 Pregnancy Complications, Hematologic/ or Pregnancy
3 1 and 2
4 limit 3 to humans

Database: EBM Reviews - Cochrane Central Register of Controlled Trials
1 Iron/df [Deficiency]
2 Pregnancy Complications, Hematologic/ or Pregnancy/
3 1 and 2

Appendix A2. Inclusion and Exclusion Criteria

Routine Iron Supplementation in Pregnant Women

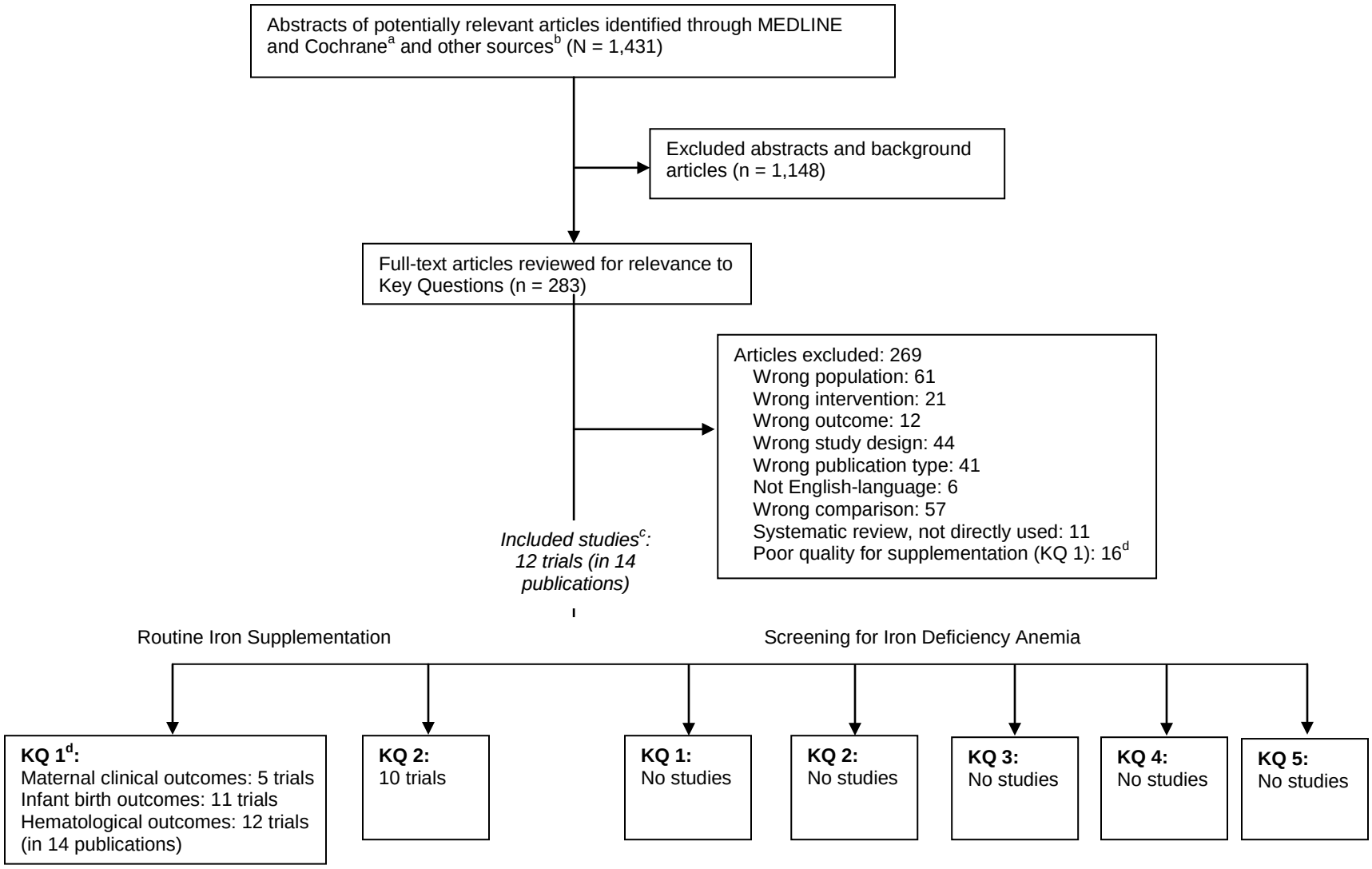
	Include	Exclude
Populations	Pregnant adolescents and women and their infants	Severely malnourished populations not representative of those in the United States
Interventions	Oral iron supplementation, iron-fortified foods	Injectable forms of iron
Comparators	No supplementation	
Outcomes	**KQ 1:** Maternal outcomes (Cesarean delivery rates, postpartum depression, incidence of iron deficiency anemia and iron deficiency, hematological indexes and ferritin levels) and infant outcomes (low birthweight, preterm delivery, perinatal mortality, hematological indexes and ferritin levels) **KQ 2:** More serious harms; discontinuations; accidental overdose	
Settings	Primary care relevant	
Timing	**KQ 1:** Long term **KQ 2:** Short or long term	
Study Designs	**KQ 1:** Randomized, controlled trials; controlled cohort studies and other controlled observational studies **KQ 2:** Studies from KQ 1 and large uncontrolled observational studies	**KQ 1:** Uncontrolled studies

Screening for Iron Deficiency Anemia in Pregnant Women

	Include	Exclude
Populations	**KQs 1, 2:** Pregnant adolescents and women and their infants asymptomatic for iron deficiency anemia **KQs 3, 4:** Pregnant adolescents and women with iron deficiency anemia and their infants **KQ 5:** Pregnant women with iron deficiency, with or without anemia and their infants	• Severely malnourished populations not representative of those in the United States • Those symptomatic for iron deficiency anemia
Interventions	**KQs 1, 2:** Screening for iron deficiency anemia **KQs 3, 4:** Oral iron supplementation, iron-fortified foods	Injectable forms of iron
Comparators	**KQs 1, 2:** No screening for iron deficiency anemia **KQs 3, 4:** No treatment **KQ 5:** Change in maternal iron deficiency and/or iron deficiency anemia status	
Outcomes	**KQs 1, 3, 5:** Maternal outcomes (Cesarean delivery rates, postpartum depression) and infant outcomes (low birthweight, preterm delivery, perinatal mortality, hematological indexes and ferritin levels) **KQ 2:** Overdiagnosis, anxiety, labeling **KQ 3:** Incidence of iron deficiency anemia and iron deficiency; hematological indexes and ferritin levels **KQ 4:** More serious harms; discontinuations and overtreatment	
Settings	Primary care relevant	
Timing	**KQs 1, 3:** Long term **KQs 2, 4, 5:** Short or long term	
Study Designs	**KQs 1, 3:** Randomized, controlled trials; controlled cohort studies and other controlled observational studies **KQs 2, 4:** Studies included from other KQs and large uncontrolled observational studies **KQ 5:** Association studies	**KQs 1, 3:** Uncontrolled studies

Abbreviation: KQ=key question.

Appendix A3. Literature Flow Diagram



[a] Cochrane databases include the Cochrane Central Register of Controlled Trials and the Cochrane Database of Systematic Reviews.
[b] Other sources include prior reports, reference lists of relevant articles, and systematic reviews.
[c] Some studies are included for more than one Key Question.
[d] Excluded poor-quality studies for this Key Question because of availability of good- and fair-quality evidence.

Appendix A4. Excluded Studies

Wrong Population

Adetifa I, Okomo U. Iron supplementation for reducing morbidity and mortality in children with HIV. *Cochrane Database Syst Rev*. 2009;(1):19160298. PMID: 19160298.

Agarwal DK, Agarwal KN, Satya K, et al. Weight gain during pregnancy--a key factor in perinatal and infant mortality. *Indian Pediatr*. 1998;35(8):733-43. PMID: 10216567.

Agarwal KN, Agarwal DK, Mishra KP. Impact of anaemia prophylaxis in pregnancy on maternal haemoglobin, serum ferritin & birth weight. *Indian J Med Res*. 1991;94:277-80. PMID: 1959958.

Aikawa R, Jimba M, Nguen KC, et al. Prenatal iron supplementation in rural Vietnam. *Eur J Clin Nutr*. 2008;62(8):946-52. PMID: 17522600.

Arbuckle TE, Sherman GJ. Comparison of the risk factors for pre-term delivery and intrauterine growth retardation. *Paediatr Perinat Epidemiol*. 1989;3(2):115-29. PMID: 2786628.

Aukett MA, Parks YA, Scott PH, et al. Treatment with iron increases weight gain and psychomotor development. *Arch Dis Child*. 1986;61(9):849-57. PMID: 2429622.

Bokhari F, Derbyshire E, Li W, et al. A study to establish whether food-based approaches can improve serum iron levels in child-bearing aged women. *J Hum Nutr Diet*. 2012;25(1):95-100. PMID: 21749488.

Bondevik GT, Lie RT, Ulstein M, et al. Maternal hematological status and risk of low birth weight and preterm delivery in Nepal. *Acta Obstet Gynecol Scand*. 2001;80(5):402-8. PMID: 11328215.

Borch-Iohnsen B, Sandstad B, Asberg A. Iron status among 3005 women aged 20-55 years in central Norway: the Nord-Trøndelag Health Study (the HUNT study). *Scand J Clin Lab Invest*. 2005;65(1):45-54. PMID: 15859026.

Britto MT. Using evidence-based techniques to modify anemia screening practice. *Am J Manag Care*. 1997;3(10):1507-9. PMID: 10178457.

Cavalli-Sforza T, Berger J, Smitasiri S, et al. Weekly iron-folic acid supplementation of women of reproductive age: impact overview, lessons learned, expansion plans, and contributions toward achievement of the millennium development goals. *Nutr Rev*. 2005;63(12 Pt 2):S152-8. PMID: 16466092.

Chang SC, O'Brien KO, Nathanson MS, et al. Hemoglobin concentrations influence birth outcomes in pregnant African-American adolescents. *J Nutr*. 2003;133(7):2348-55. PMID: 12840205.

Charoenlarp P, Dhanamitta S, Kaewvichit R, et al. A WHO collaborative study on iron supplementation in Burma and in Thailand. *Am J Clin Nutr*. 1988;47(2):280-97. PMID: 2963533.

Choudhury N, Aimone A, Hyder SM, et al. Relative efficacy of micronutrient powders versus iron-folic acid tablets in controlling anemia in women in the second trimester of pregnancy. *Food Nutr Bull*. 2012;33(2):142-9. PMID: 22908696.

Christian P, Murray-Kolb LE, Khatry SK, et al. Prenatal micronutrient supplementation and intellectual and motor function in early school-aged children in Nepal. *JAMA*. 2010;304(24):2716-23. PMID: 21177506.

Christian P, Stewart CP, LeClerq SC, et al. Antenatal and postnatal iron supplementation and childhood mortality in rural Nepal: a prospective follow-up in a randomized, controlled community trial. *Am J Epidemiol*. 2009;170(9):1127-36. PMID: 19778983.

Conde-Agudelo A, Belizan JM, Diaz-Rossello JL. Epidemiology of fetal death in Latin America. *Acta Obstet Gynecol Scand*. 2000;79(5):371-8. PMID: 10830764.

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Criteria for Assessing Internal Validity of Individual Studies

The USPSTF Methods Workgroup developed a set of criteria by which the internal validity of individual studies could be evaluated. The USPSTF accepted the criteria that relate to internal validity, and the associated definitions of quality categories, at its September 1999 meeting.

This appendix describes the criteria relating to internal validity and the procedures that topic teams follow for all updates and new assessments in making these judgments.

All topic teams use initial "filters" to select studies for review that deal most directly with the question at issue and that are applicable to the population at issue. Thus, studies of any design that use outdated technology or that use technology that is not feasible for primary care practice may be filtered out before the abstraction stage, depending on the topic and the decisions of the topic team. The teams justify such exclusion decisions if there could be reasonable disagreement about this step. The criteria below are meant for those studies that pass this initial filter.

Presented below are a set of minimal criteria for each study design and then a general definition of three categories: "good," "fair," and "poor," based on those criteria. These specifications are not meant to be rigid rules but rather are intended to be general guidelines, and individual exceptions, when explicitly explained and justified, can be made. In general, a "good" study is one that meets all criteria well. A "fair" study is one that does not meet (or it is not clear that it meets) at least one criterion but has no known "fatal flaw." "Poor" studies have at least one fatal flaw.

RCTs and Cohort Studies

Criteria:

- Initial assembly of comparable groups:
  - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
  - For cohort studies: Consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to follow-up or overall high loss to follow-up
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Analysis: Adjustment for potential confounders for cohort studies, or intention to treat analysis for RCTs

Definition of ratings based on above criteria:

Good: Meets all criteria; comparable groups are assembled initially and maintained throughout the study (follow-up ≥80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention

to treat analysis is used.

Fair: Studies will be graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.

Poor: Studies will be graded "poor" if any of the following fatal flaws exists: groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Case-Control Studies

Criteria:
- Accurate ascertainment of cases
- Nonbiased selection of cases/controls with exclusion criteria applied equally to both
- Response rate
- Diagnostic testing procedures applied equally to each group
- Measurement of exposure accurate and applied equally to each group
- Appropriate attention to potential confounding variables

Definition of ratings based on criteria above:
Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate ≥80%; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables

Fair: Recent, relevant, without major apparent selection or diagnostic workup bias but with response rate <80 %or attention to some but not all important confounding variables

Poor: Major selection or diagnostic workup biases, response rates <50%, or inattention to confounding variables

Systematic Reviews

Criteria:
- Comprehensiveness of sources considered/search strategy used
- Standard appraisal of included studies
- Validity of conclusions
- Recency and relevance are especially important

Definition of ratings from above criteria:
Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions

Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies

Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

Source: U.S. Preventive Services Task Force Procedure Manual. Available at: http://www.uspreventiveservicestaskforce.org/Page/Name/procedure-manual

Appendix A6. Reviewers of the Draft Report

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Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Pregnant Women

Author, Year	Study Design	Setting Country	Interventions (N)	Study Duration Mean Followup	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Barton 1994[43]	RCT	Maternity hospital Ireland	A. 120 mg elemental iron daily starting at 14 weeks' gestation (n=53) B. Placebo (n=44)	12 weeks' gestation through delivery	Race: NR (Ireland) Nulliparous: 47% vs. 45% Smoking: 47% vs. 31%; p>0.05 Mean hemoglobin: 143 vs. 144 g/L Mean ferritin: 47.53 vs. 43.93 µg/L	Women with a singleton pregnancy and hemoglobin ≥14 g/dL	Recent blood transfusion, chronic respiratory disease, chronic hypertension, renal disease, diabetes mellitus, history of a hematological disorder, or alcohol dependence
Chan 2009[44]	RCT	Single center Hong Kong	A: 60 mg daily iron supplement (ferrous sulfate) <16 weeks' gestation until delivery (n=565) B: Placebo (n=599)	April 2005 to March 2007 women followed through delivery	A vs. B Mean age: 31.3 vs. 31.3 years Race: NR (Hong Kong) Mean hemoglobin: 12.5 vs. 12.6 g/dL Mean ferritin: 182.0 vs. 196.9 pmol/L BMI: 20.8 vs. 21.0 kg/m^2 Parity >2: 0.50% vs. 0.18% Family history of diabetes: 24% vs. 23% SES: NR	1,164 women with singleton pregnancy at <16 weeks' gestation with hemoglobin level of 8–14 g/dL and no pre-existing diabetes or hemoglobinopathy	>16 weeks' gestation, gestational diabetes, history of diabetes, or hemoglobin <8 or >14 g/dL
Cogswell 2003[47]	RCT	Prenatal clinic Ohio	Week 20–27: A. 30 mg ferrous sulfate (n=146) B. Placebo (n=129) Week 28: Reassigned to either 30 mg (n=54), 60 mg (n=118), placebo (n=15), or medical intervention (n=9) based on iron measures; unknown reassessed iron measures (n=79) Week 38: Again reassigned based on iron measures (details NR)	Weeks 20–27 for RCT, but followed up through delivery after intervention reassignment at weeks 28 and 38	A vs. B Age: 24.3 vs. 24.5 years Race: 56% vs. 57% white, 24% vs. 26% black, 16% vs. 17% Hispanic Smokers: 40% vs. 36% Gestational age at entry: 11 vs. 11 weeks Mean hemoglobin: 129 vs. 127 g/L Mean ferritin: 45 vs. 49 µg/L; p=0.0168 MCV: 89 vs. 89 fL Erythrocyte protoporphyrin: 54 vs. 56 µg/dL Prepregnancy weight: 72.5 vs. 77.9 kg; p=0.049 SES: 100% enrolled in WIC Parity ≥2: 31% vs. 24%	Legally competent, nonimprisoned pregnant women at <20 weeks of gestation, enrolled in Cleveland WIC June 1995 to September 1998	NR

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Pregnant Women

Author, Year	Study Design	Setting Country	Interventions (N)	Study Duration Mean Followup	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Eskeland 1997[52]	RCT	Single center Norway	A. 3 tablets containing 1.2 mg heme iron and 8 mg iron fumerate per tablet, plus 1 placebo tablet (n=31) B. 1 tablet containing 27 mg iron fumerate, plus 3 placebo tablets (n=30) C. 4 placebo tablets (n=29) Timing: 20th week of gestation through delivery	<13 weeks through 6 months postpartum	A vs. B vs. C Mean age: 28 vs. 26 vs. 28 years Race: NR (Norway) BMI: 23 vs. 22 vs. 23 kg/m^2 Parity ≥2: 10% vs. 0% vs. 10% Single: 3% vs. 17% vs. 3% Low education: 3% vs. 7% vs. 10%	Healthy women at <13 weeks of gestation	Uncertain gestational age, hemoglobin <110 or >148 g/L, chronic disease or pregnancy complications, multiple pregnancy, liver enzymes out of normal range, or practical difficulties such as planned on moving during study period
Falahi 2011[49]	RCT	Prenatal clinic Khorramabad City, Iran	A. Ferrous sulfate 60 mg elemental iron (n=70) B. Placebo (n=78)	<20 weeks through delivery	A vs. B Age: 24.6 vs. 23.1 years; p=0.02 Race: NR (Iran) BMI: 24.8 vs. 24.4 kg/m^2 Gestational age at study entry: 12.2 vs. 11.9 weeks	Nonanemic pregnant women with gestational age <20 weeks, primigravidae, age between 20 and 35 years, BMI >25 and <30 kg/m^2, hemoglobin >100 g/L, and serum ferritin >20 µg/L	Diabetes mellitus, coronary heart disease, thalassemia, renal disease, respiratory disease, use of supplementary multivitamins or minerals, drug use, special diet. Anemic or iron deficient women were referred for medical evaluation and treatment
Makrides 2003[42] Followup study: Zhou 2007[54]	RCT	Australia	A: 20 mg daily iron supplement (ferrous sulfate) starting at 20 weeks' gestation until delivery (n=216) B: Placebo (n=214)	December 1997 to April 1999 Followup through 6 months postpartum	A vs. B Age: 28.5 vs. 28 years Race: 95.4% vs. 95.3% white, 0.9% vs. 3.3% Aboriginal, 2.3% vs. 1.4% Asian, 1.4% vs. 0.0% other Maternal smoking: 19% vs. 20% Multiparous: 52% vs. 53% BMI: 26 vs. 26 kg/m^2 Highest level of education: 12% vs. 15% year ≤10, 27% vs. 28% year 11, 33% vs. 28% year 12, 5% or 8% trade certificate or diploma, 21% vs. 21% tertiary degree Baseline rate of IDA in population: 11.5%	Attending antenatal clinics at the Women & Children's hospital in Adelaide	Preexisting anemia, thalassemia, history of drug or alcohol abuse, already taking vitamin and mineral preparations containing iron

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Pregnant Women

Author, Year	Study Design	Setting Country	Interventions (N)	Study Duration Mean Followup	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Meier 2003[45]	RCT	Prenatal clinic Wisconsin	A. Iron supplementation 60 mg elemental iron + 1 mg folic acid (n=58, including 20 adolescents) B. Placebo + 1 mg folic acid (n=53, including 17 adolescents) If iron deficiency anemia occurred at 2nd trimester, 180 mg elemental iron was initiated (3 women in iron group and 9 women in placebo group)	1st prenatal visit through delivery	A vs. B *Adolescents:* Age: 18.2 vs. 17.7 years Race: NR Gestational age: 14.1 vs. 12.1 weeks Serum ferritin: 31.1 vs. 34.0 ng/mL Hemoglobin: 12.6 vs. 13.1 g/dL *Adults:* Age 25.2 vs. 28.8 years Gestational age: 10.6 vs. 12.3 weeks Serum ferritin: 39.3 vs. 37.0 ng/mL Mean hemoglobin: 13.0 vs. 12.9 g/dL	Pregnant adolescents and adults age ≥15 years seeking prenatal care at a private group practice	Patients with iron deficiency anemia at 1st prenatal visit
Milman, 1994[50] Followup to Milman, 1991[55]	RCT	Denmark	A: 66 mg elemental iron daily starting at 14–16 weeks' gestation (n=63) B: Placebo (n=57)	14–16 weeks' gestation through birth	Groups were comparable with respect to age, height, weight, parity, and pregnancy duration (data not shown) A vs. B Mean hemoglobin: 122 vs. 119 g/L Mean ferritin: 45 vs. 40 µg/L	Healthy women with a normal single pregnancy, 14–16 weeks' gestation, and an uncomplicated delivery	Uterine bleeding, placenta previa, abruptio placentae, preeclampsia, excessive smoking (<9 cigarettes/day)
Romslo 1983[53]	RCT	Prenatal clinic Norway	A. 200 mg elemental iron daily starting within 10 weeks' gestation (n=22) B. Placebo (n=23)	Within 10 weeks' gestation through birth	A vs. B Age: 27.8 vs. 26.7 years Nonpregnant weight: 125 vs. 131 lb Race: NR (Norway)	Healthy women with a normal pregnancy ending in an uncomplicated delivery of a single, normal infant at between 37 and 42 weeks' gestation	NR

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Pregnant Women

Author, Year	Study Design	Setting Country	Interventions (N)	Study Duration Mean Followup	Baseline Demographics	Eligibility Criteria	Exclusion Criteria
Siega-Riz 2006[48]	RCT	Prenatal clinic North Carolina	A. Prenatal supplementation with 30 mg iron ferrous sulfate (n=218) B. Prenatal supplementation without iron until 26–29 weeks' gestation (n=211)	1st prenatal visit through 26–29 weeks' gestation; followed through delivery	A vs. B Age 19–24 years: 73% vs. 71% Race: 65% vs. 58% black, 31% vs. 37% white Single marital status: 75% vs. 75% High school education or less: 76% vs. 73% Previous live births: 68% vs. 66% Gestational age at study entry: 12.3 vs. 12.4 weeks Mean hemoglobin: 124 vs. 124 g/L Mean ferritin: 83.1 vs. 84.2 µg/L Parity ≥2: 44% vs. 41% SES: 100% eligible for WIC	Pregnant women at <20 weeks' gestation, hemoglobin ≥110 g/L and serum ferritin ≥40 µg/L, spoke English, had not taken supplements that contained iron in the last month, singleton pregnancy, receiving prenatal care during 1997–1999 at Wake County Human Services clinic and therefore eligible for WIC	NR
Ziaei 2007[46]	RCT	Tehran, Iran	A: 1 150mg tablet ferrous sulfate daily starting at 20 weeks' gestation through end of pregnancy (n=370) B: Placebo (n=357)	Early stage of the 2nd trimester through 6 weeks postpartum	A vs. B Age: 25.7 vs. 25.7 years Race: NR (Iran) BMI: 23.6 vs. 23.8 kg/m^2 Mean hemoglobin: 13.98 vs. 14.01 g/dL Parity: 1.7	Pregnant women in early stage of 2nd trimester with hemoglobin >13.2 g/dL and BMI of 19.8–26 kg/m^2, single pregnancy, age 17–35 years, nonsmoking, no diseases related to polycythemia (such as asthma or chronic hypertesion), and no history of threatened abortion in this pregnancy	Smoking, disease related to polycythemia; asthma, chronic hypertension; history of threatened abortion in present pregnancy
Ziaei 2008[51]	RCT	Iran (location NR)	A: 1 150mg tablet ferrous sulfate daily starting at 20 weeks' gestation through end of pregnancy (n=122) B: Placebo (n=122)	March 2005 to August 2006 Followup through 6 weeks postpartum	A vs. B Age: 26.9 vs. 25.7 years Race: NR (Iran) BMI: 24.11 vs. 23.69 kg/m^2 Mean hemoglobin: 13.99 vs. 13.94 g/dL Parity: 1.6 vs. 1.7 Educational level: 11% vs. 7% primary school, 77% vs. 83% high school, 12% vs. 10% university Occupation: 92% vs. 90% housewife, 8% vs. 10% employed	All women ages 17–35 years receiving care at a prenatal clinic in Iran with a hemoglobin concentration ≥13.2 g/dL and serum ferritin >15 µg/L between 13 and 18 weeks' gestation; BMI of 19.8–26 kg/m^2; singleton pregnancy	Smoking, disease related to polycythemia; asthma, chronic hypertension; history of threatened abortion in present pregnancy

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Pregnant Women

Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Withdrawals Loss to Followup	Adjusted Variables for Statistical Analysis	Intermediate Outcome Results	Clinical Health Outcome Results	Adverse Events	Quality Rating	Funding Source
Barton 1994[43]	Screened: NR Eligible: Approximately 500 Enrolled: 97 Analyzed: varied per outcome and timepoint (hemoglobin at week 36: 89% vs. 91%; week 40: 57% vs. 40%; ferritin at week 36: 81% vs. 77%)	Adjusted for smoking	A vs. B *Maternal outcomes at 36 weeks* Mean hemoglobin: 135 vs. 126 g/L; p=0.043 (adjusted for smoking, p=0.25) Mean ferritin: 32.6 vs. 12.8 µg/L; p=0.04 *Maternal outcomes at 40 weeks* Mean hemoglobin: 137 vs. 120 g/L; p<0.001 Anemia: "No patients were withdrawn from the study due to anemia"	A vs. B *Infant outcomes* Low birthweight <2,700 g: 9.4% (5/53) vs. 15.9% (7/44); p=0.34 Perinatal death: 1.9% (1/53) vs. 0% (0/44); p=0.57 *Maternal outcomes* Cesarean delivery: 7.6% (4/53) vs. 9.1% (4/44); p=0.78	A vs. B Hypertension disorder: 7.5% (4/53) vs. 9.0% (4/44); p=0.78 Antepartum hemorrhage: 5.7% (3/53) vs. 4.5% (2/44); p=0.81	Fair	NR
Chan 2009[44]	Screened: 1,400 Eligible: 1,164 Enrolled: 1,164 Analyzed: 1,164 A vs. B Returned questionnaires: 54% (306/565) vs. 56% (335/599)	NR	A vs. B *Maternal outcomes at delivery* Mean hemoglobin: 12.2 vs. 11.8 g/L; p<0.001 Mean ferritin: 67.5 vs. 55.9 pmol/L; p<0.003	A vs. B *Delivery method* Vaginal: 63.5% (290/456) vs. 56.0% (262/468); p=0.021 Cesarean: 25.2% (115/456) vs. 33.1% (155/468); p=0.008 *Neonatal outcomes* Mean gestational age at delivery: 38.8 vs. 38.7 weeks; p=0.322 Preterm delivery: 6.4% (27/419) vs. 6.8% (30/443); p=0.85 Apgar score at 1 min: 8.8 vs. 8.8; p=NS Apgar score at 5 min: 9.8 vs. 9.7; p=NS SGA: 3.58% (15/419) vs. 7.45% (33/443); p=0.013 Birthweight for term infants: 3,247.3 vs. 3,151.9 g; p=0.001	A vs. B Gestational diabetes: 10% (56/565) vs. 10% (60/599); OR, 1.04 95% (95% CI, 0.7 to 1.53) Nonadherence: 46% overall; p=NS	Fair	Research Grant Council, Hong Kong

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Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Withdrawals Loss to Followup	Adjusted Variables for Statistical Analysis	Intermediate Outcome Results	Clinical Health Outcome Results	Adverse Events	Quality Rating	Funding Source
Cogswell 2003[47]	Screened: NR Eligible: NR Enrolled: 513 Analyzed: 275 (238 excluded because required supplementation or treatment) Loss to followup/missing data: 29% iron status outcomes, 23% birth weight outcomes	Prepregnancy weight and initial ferritin	A vs. B *Maternal outcomes* Week 28 (RCT phase): Mean hemoglobin: 117 vs. 116 g/L; p=0.499 Mean ferritin: 7.4 vs. 7.4 µg/L; p=0.985 MCV: 90.8 vs. 90.3 fL; p=0.443 Erythrocyte protoprophyrin: 59.3 vs. 62.9 µg/dL; p=0.140 Anemia (hemoglobin <110 g/L): 19.8% vs. 26.7%; p=0.251 Absent iron stores (serum ferritin <12 µg/L): 56.4% vs. 65.1%; p=0.214 Iron deficiency anemia (hemoglobin <110 g/L + serum ferritin <12 µg/L): 12.7% vs. 20.9%; p=0.123 After adjustment for prepregnancy weight and initial ferritin: Absent iron stores: 14.3 percentage points lower for those on supplements; p=0.031 Iron deficiency anemia: 10 percentage points lower for those on supplements; p=0.062	*Infant outcomes, non-RCT phase, segregated by initial assignment* Birthweight: 3,277 vs. 3,072 g; p=0.010 Gestational age at delivery: 38.9 vs. 38.3 weeks; p=0.049 Low birthweight: 4.3% vs. 16.7%; p=0.003 Preterm delivery: 12.8% vs. 12.5%; p=0.944 Preterm delivery with low birthweight: 2.6% vs. 10.4%; p=0.017 Term delivery with low birthweight: 1.7% vs. 6.3%; p=0.083 SGA: 6.8% vs. 17.7%; p=0.014 Birth length: 49.7 vs. 49.3 cm; p=0.464	Side effects reported at >1 visit from enrollment to week 28: 24.6% vs. 18.5% Nonadherence at week 28: 36.6% vs. 34.8%; p=NS	Fair	U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, and National Institutes of Health grant

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Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Withdrawals Loss to Followup	Adjusted Variables for Statistical Analysis	Intermediate Outcome Results	Clinical Health Outcome Results	Adverse Events	Quality Rating	Funding Source
Eskeland 1997[52]	Screened: NR Eligible: 120 Enrolled: 90 Analyzed: 71 A vs. B vs. C Withdrawal: 22.6% (7/31) vs. 20% (6/30) vs. 20.7% (6/29)	NR	A vs. B vs. C *Maternal outcomes* Anemia (hemoglobin <100 g/L) at 1 week postpartum: 9.7% (3/31) vs. 13.3% (4/30) vs. 20.7% (6/29) Iron deficiency, week 38: 29% vs. 52% vs. 85%; p<0.001 for A vs. C and p<0.05 for B vs. C Iron deficiency, 6–10 weeks postpartum: 8% vs. 27% vs. 52%; p<0.01 for A vs. C Iron deficiency, 24 weeks postpartum: 4% vs. 17% vs. 51%; p<0.001 for A vs. C and p<0.05 for B vs. C Median hemoglobin was significantly lower in placebo than intervention groups from 28 weeks to end of pregnancy (data reported in a figure)	A vs. B *Infant outcomes* Birthweight: 3,690 vs. 3,620 vs. 3,610 g	No difference in fatigue or other side effects; p=NS Nonadherence: 19% (combined 2 iron groups) vs. 18%; p=NS	Fair	NR
Falahi 2011[49]	Screened: NR Eligible: NR Enrolled: NR Analyzed: 148 Withdrawals: NR Loss to followup: NR	Adjusted for age	A vs. B *Maternal outcomes* At delivery: Hemoglobin: 123.2 vs. 120.9 g/L Ferritin: 28.1 vs. 22.1 µg/L Iron deficiency (serum ferritin <12 µg/L): 9.5% vs. 28.2%; p<0.05 Iron deficiency anemia (hemoglobin <110 g/L and serum ferritin <12 µg/L): 0% vs. 0%	A vs. B *Infant outcomes* Birthweight: 3.31 vs. 3.27 kg Birth length: 49.1 vs. 49.3 cm Low birthweight (<2,500 g): 3% vs. 6.8% Preterm delivery (<37 weeks): 3% (2/70) vs. 6.8% (5/78) Gestational age at delivery: 38.9 vs. 38.8 weeks	A vs. B Pregnancy-induced hypertension: 1.4% (1/70) vs. 0% (0/78)	Fair	NR

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Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Withdrawals Loss to Followup	Adjusted Variables for Statistical Analysis	Intermediate Outcome Results	Clinical Health Outcome Results	Adverse Events	Quality Rating	Funding Source
Makrides 2003[42] Followup study: Zhou 2007[54]	Screened: NR Eligible: 498 Enrolled: 430 Analyzed: 386 Withdrawals: 32 Lost: 0	NR	A vs. B *Maternal status at 28 weeks' gestation* Hemoglobin: 120 vs. 116 g/L; RR, 3.4 (95% CI, 1.7 to 2.3) *Maternal status at delivery, ferritin* Hemoglobin: 127 vs. 120 g/L; RR, 6.9 (95% CI, 4.4 to 9.3) Ferritin: 21 vs. 14 µg/L; RR, 7.1 (95% CI, 4 to 10.2) Iron deficiency: 35% (65/186) vs. 58% (102/176); RR, 0.60 (95% CI, 0.48 to 0.76) Anemia: 7% (14/200) vs. 16% (30/193); RR, 0.45 (95% CI, 0.25 to 0.82) Iron deficiency anemia: 3% (6/198) vs. 11% (20/185); RR, 0.28 (95% CI, 0.12 to 0.68) *Maternal status at 6 months postpartum* Hemoglobin: 135 vs. 134 g/L; RR, 1.6 (95% CI, −0.1 to 3.3) Ferritin: 34 vs. 26; RR, 7.9 (95% CI, 3.5 to 12.3) Iron deficiency: 16% (31/190) vs. 29% (51/177); RR, 0.57 (95% CI, 0.38 to 0.84) Anemia: 3.7% (7/189) vs. 4.5% (8/177); RR, 0.82 (95% CI, 0.30 to 2.21) IDA: 2.6% (5/190) vs. 1.7% (3/177); RR, 1.55 (95% CI, 0.38 to 6.40) *Child outcomes at 6 months postpartum* Hemoglobin: 121 vs. 119 g/L; p=0.10 Ferritin: 32.5 vs. 30.8 µg/L; p=0.48 Iron deficiency: 6% (11/170) vs. 4% (6/159); p=0.27 Iron deficiency anemia: 0% vs. 0%; p=NS	A vs. B *Pregnancy outcomes* Gestational age at birth: 39.4 vs. 39.2 weeks; p=NS Birthweight: 3,406 vs. 3,449 g; p=NS Apgar score <7 at 5 min: 1.4% vs. 1.9%; p=NS Low birthweight: 5.4% (12/216) vs. 4.2% (9/214); p=NS Birth length: 49.9 vs. 50.0 cm; p=NS Neonatal death: 0.5% (1 case) vs. 0%; p=NS *Maternal outcomes* SF-36: No differences between women receiving iron and placebo in any of the 8 health concepts (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and general mental health) at 36 weeks' gestation, 6 weeks postpartum, or 6 months postpartum (specific data only displayed in a figure) Cesarean delivery: 23.6% vs. 22.0%	A vs. B 36 weeks' gestation Nausea: 29% (58/200) vs. 28% (54/193); RR, 1.04 (95% CI, 0.76 to 1.42) Stomach pain: 35% (70/200) vs. 30% (57/193); RR, 1.19 (95% CI, 0.89 to 1.58) Heartburn: 68% (136/200) vs. 69% (133/193); RR, 0.99 (95% CI, 0.86 to 1.13) Vomiting: 12% (24/200) vs. 13% (26/193); RR, 0.89 (95% CI, 0.53 to 1.50) Rash: 7.5% (15/200) vs. 6.2% (12/193); RR, 1.21 (95% CI, 0.58 to 2.51) Bowel movement ≤3 times/week: 4% (8/200) vs. 1.6% (3/192); RR, 2.56 (95% CI, 0.69 to 9.51) Nonadherence: 14% vs. 15%; p=NS	Good	Channel 7 Children's Research Foundation, Women & Children's Hospital Perinatal Pathology Fund, Gunn & Gunn Medical Research Foundation

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Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Withdrawals Loss to Followup	Adjusted Variables for Statistical Analysis	Intermediate Outcome Results	Clinical Health Outcome Results	Adverse Events	Quality Rating	Funding Source
Meier 2003[45]	Screened: NR Eligible: NR Enrolled: 144 Analyzed: 111 Withdrawals and loss to followup: 30% (33/111, 20 of which had inadequate data or failed to comply with medication requirements)	NR	A vs. B *Maternal outcomes, weeks 36–40* Adolescents: Median serum ferritin: 12.0 vs. 6.2 ng/mL; p=0.010 Median hemoglobin: 12.2 vs. 11.5 g/dL; p=0.024 Iron deficiency anemia (serum ferritin <12 ng/mL + hemoglobin <11 g/dL): 5% (1/20) vs. 29.4% (5/17); p=0.137 Adults: Median serum ferritin: 12.9 vs. 7.6 ng/mL; p=0.027 Median hemoglobin: 12.1 vs. 11.7 g/dL; p=0.135 Iron deficiency anemia (serum ferritin <12 ng/mL + hemoglobin <11 g/dL): 10.5% (4/38) vs. 22.2% (8/36); p=0.259 *Maternal outcomes, throughout study* Adolescents: Iron deficiency anemia (serum ferritin <12 ng/mL + hemoglobin <11 g/dL): 20% (4/20) vs. 59% (10/17); p=0.021 Severe iron deficiency anemia (hemoglobin <10.0 g/dL): 0% (0/20) vs. 11.8% (2/17) Adults: Iron deficiency anemia (serum ferritin <12 ng/mL + hemoglobin <11 g/dL): 13% (5/38) vs. 42% (15/36); p=0.008 Severe iron deficiency anemia (hemoglobin <10.0 g/dL): 2.6% (1/38) vs. 8.3% (3/36)	A vs. B *Infant outcomes* Adolescent mothers: Apgar score <7 at 1 min: 30% (6/20) vs. 25% (4/16); p=NS Mean length: 50.0 vs. 51.6 cm; p=NS Mean gestational age: 39.9 vs. 39.8 weeks; p=NS Birthweight <2,500 g: 0% vs. 0%; p=NS Cesarean delivery: 20% (4/20) vs. 6.2% (1/16); p=NS Adult mothers: Apgar score <7 at 1 min: 29.7% (11/38) vs. 16.7% (6/36); p=NS Mean length: 52.4 vs. 51.8 cm; p=NS Mean gestational age: 39.2 vs. 39.5 weeks; p=NS Birthweight <2,500 g: 5.4% (2/38) vs. 2.9% (1/36); p=NS Cesarean delivery: 14.3% (5/38) vs. 25% (9/36); p=NS Combined Cesarean delivery: 16% vs. 19%; p=NS Infant death: 0% vs. 0%; p=NS	A vs. B *Maternal outcomes* Adolescent mothers: Nausea: 53% vs. 65%; p=NS Vomiting: 41% vs. 41%; p=NS Constipation: 29% vs. 12%; p=NS Diarrhea: 13% vs. 17%; p=NS Adult mothers: Nausea: 63% vs. 53%; p=NS Vomiting: 35% vs. 21%; p=NS Constipation: 24% vs. 28%; p=NS Diarrhea: 14% vs. 24%; p=NS *Nonadherence* Adolescent mothers: 4.5% vs. 12.6%; p=0.320 Adult mothers: 2.2% vs. 16.1%; p=0.036	Fair	National Institutes of Health, Marshfield Medical Research Foundation, Mead-Johnson Nutritional Division, and Hybritech, Inc.

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Pregnant Women

Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Withdrawals Loss to Followup	Adjusted Variables for Statistical Analysis	Intermediate Outcome Results	Clinical Health Outcome Results	Adverse Events	Quality Rating	Funding Source
Milman, 1994[50] Followup to Milman, 1991[55]	Eligible: 35 Enrolled:120 Excluded: 15 Analyzed:120 Lost: NR	NR	A vs. B *Maternal outcomes at term* Mean hemoglobin: 127 vs. 116 g/L; p<0.0001 Mean ferritin: 22 vs. 14 µg/L; p<0.0001 Iron deficiency anemia: 0% vs. 17.5%; p=0.03	A vs. B *Infant outcomes* Median birthweight: 3,350 vs. 3,450 g; p>0.5	NR	Fair	Sundhedspulgjen and Fonden grants
Romslo 1983[53]	Screened: NR Eligible: NR Enrolled: 52 Analyzed: 43 Withdrawals reported: 7	NR	A vs. B *Maternal outcomes at 37–40 weeks* Mean hemoglobin: 126 vs. 113 g/L; p=NR Mean ferritin: 24.0 vs. 6.0 µg/L; p=NR Iron deficiency: 0% (0/22) vs. 65.2% (15/23); p=0.02	A vs. B *Infant outcomes* Gestation: 39.9 vs. 39.5 weeks; p=NR Birthweight: 3,546 vs. 3,510 g; p=NR Apgar score at 1 min: 8.7 vs. 8.8; p=NR Apgar score at 5 min: 9.0 vs. 9.0; p=NR	A vs. B Nonadherence: 45% overall; p=NS "None of the women complained of discomfort that could be attributed to the medication"	Fair	NR
Siega-Riz 2006[48]	Screened: NR Eligible: NR Enrolled: 867 Analyzed: 429 A vs. B Withdrawals and loss to followup varied by outcome: hemoglobin and anemia outcomes, 27% vs. 26%; ferritin, iron depletion, iron deficiency anemia outcomes, 51% vs. 53%; birthweight and low birthweight, 24% vs. 20%; gestational age at delivery and preterm delivery, 21% vs. 18%; SGA, 28% vs. 27%	NR	A vs. B *Maternal outcomes at 26–29 weeks* Mean hemoglobin: 114 vs. 114 g/L; p=0.81 Mean ferritin: 22.0 vs. 20.3 µg/L; p=0.48 Anemia (hemoglobin <110 g/L): 21% vs. 19%; p=0.65 Iron depletion (serum ferritin <20 µg/L): 53% vs. 65%; p=0.08 Iron deficiency anemia (hemoglobin <110 g/L + serum ferritin <20 µg/L): 10% vs. 15%; p=0.23	A vs. B *Infant outcomes* Mean birthweight: 3,325 vs. 3,217 g; p=0.03 Low birthweight (<2,500 g): 4.8% vs. 9.5%; p=0.09 Mean gestational age at delivery: 39.1 vs. 39.0 weeks; p=0.43 Preterm delivery (<37 weeks): 7.5% vs. 13.9%; p=0.05 SGA (<10th percentile): 10.8% vs. 15.5%; p=0.22	A vs. B Nonadherence: 34% vs. 37%; p=0.27	Fair	Association of Schools of Public Health, Centers for Disease Control and Prevention, National Institute of Child Health and Human Development grant to the Carolina Population Center

Appendix B1. Evidence Table of Trials of Routine Iron Supplementation in Pregnant Women

Author, Year	Number Screened Number Eligible Number Enrolled Number Analyzed Withdrawals Loss to Followup	Adjusted Variables for Statistical Analysis	Intermediate Outcome Results	Clinical Health Outcome Results	Adverse Events	Quality Rating	Funding Source
Ziaei 2007[46]	Screened: 7,429 Eligible: 750 Enrolled: 727 Analyzed: 727 Lost: 21	NR	A vs. B Mean hemoglobin (3rd trimester): 13.75 vs. 12.45 g/dL; p<0.001	A vs. B *Pregnancy outcomes* Cesarean delivery: 25.9% (96/371) vs. 23% (82/356); p=NS *Infant outcomes* Apgar score at 10 min: 9.9 vs. 9.8; p=NS SGA: 15% (57/370) vs. 10% (36/357); p=0.035 Perinatal mortality: 0.8% vs. 1.7%; p=NS	A vs. B Hypertension disorder: 10 (2.7%) vs. 3 (0.8%); p=0.05	Good	NR
Ziaei 2008[51]	Screened: NR Eligible: 244 Enrolled: 234 Analyzed: 205 Withdrawals: 29 Lost: 9	NR	A vs. B *Maternal outcomes* Hemoglobin at delivery: 13.88 vs. 12.78; p<0.0001 Ferritin level at delivery: 26.18 vs. 19.08; p<0.0001 Hemoglobin at 6 weeks postpartum: 13.33 vs. 12.6; p<0.0001 Ferritin level at 6 weeks postpartum: 21.66 vs. 18.46; p<0.0001	NR	NR	Good	NR

Abbreviations: BMI=body mass index; MCV=mean corpuscular volume; NR=not reported; NS=not significant; RCT=randomized, controlled trial; SGA=small for gestational age; WIC= Special Supplemental Nutrition Program for Women, Infants, and Children.

Appendix B2. Quality Assessment of Trials of Routine Iron Supplementation in Pregnant Women

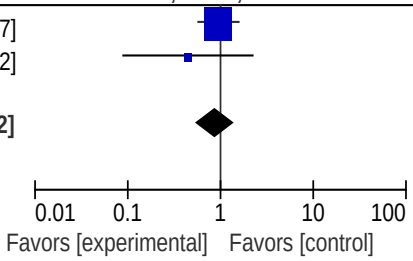
Author, Year	Randomization Adequate?	Allocation Concealment Adequate?	Groups Similar at Baseline?	Eligibility Criteria Specified?	Outcome Assessors Masked?	Care Provider Masked?	Patient Masked?	Attrition and Withdrawals Reported?	Loss to Followup Differential or High?	Subjects Analyzed in the Groups in Which They Were Randomized?	Quality Rating
Barton 1994[43]	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	No	Unclear	Unclear	Fair
Chan 2009[44]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Fair
Cogswell 2003[47]	Yes	Yes	Yes; except for weight and ferritin, which were adjusted for in analysis	Yes	Unclear; yes for laboratory measurements	Unclear	Yes	Yes	No; 23%–29% for various outcomes	Yes	Fair
Eskeland 1997[52]	Unclear	Unclear	Yes	Yes	Unclear	Yes; except hemoglobin	Yes	Yes	No	Yes	Fair
Falahi 2011[49]	Unclear	Unclear	Yes; except for age, which was adjusted for in analysis	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Fair
Makrides 2003[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Meier 2003[45]	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No; 30%	Yes	Fair
Milman 1994[50]	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	Yes	No	Unclear	Fair
Romslo 1983[53]	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	No	Unclear	Fair
Siega-Riz 2006[48]	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No; 18%–53% for various outcomes	Yes	Fair
Ziaei 2007[46]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good
Ziaei 2008[51]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Good

Appendix C1. Meta-Analysis: Preterm Delivery

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Chan 2009	27	419	30	443	86.0%	0.95 [0.58, 1.57]
Falahi 2011	2	70	5	78	14.0%	0.45 [0.09, 2.22]
Total (95% CI)		**489**		**521**	**100.0%**	**0.88 [0.55, 1.42]**
Total events	29		35			

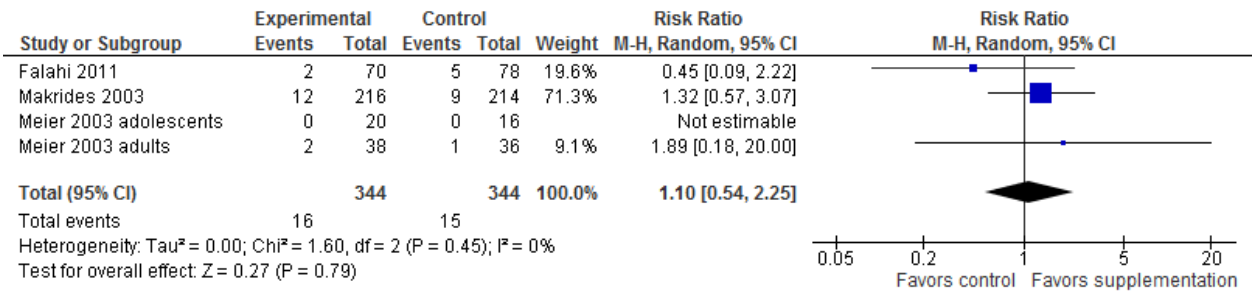
Heterogeneity: Chi² = 0.78, df = 1 (P = 0.38); I² = 0%

Test for overall effect: Z = 0.52 (P = 0.60)



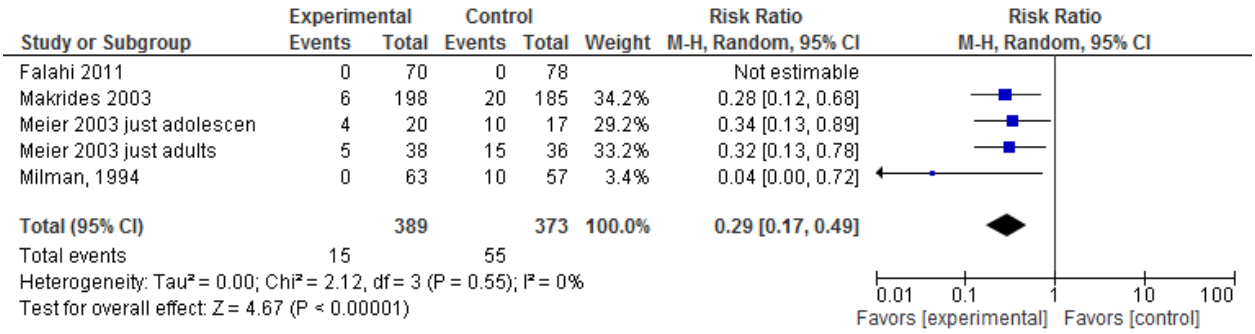
Abbreviations: CI=confidence interval; M-H=Mantzel-Haenzel.

Appendix C2. Meta-Analysis: Low Birthweight



Abbreviations: CI=confidence interval; M-H=Mantzel-Haenzel.

Appendix C3. Meta-Analysis: Iron Deficiency Anemia at Term

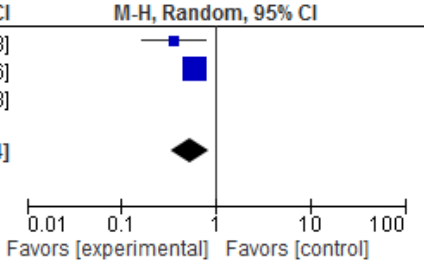


Abbreviations: CI=confidence interval; M-H=Mantzel-Haenzel.

Appendix C4. Meta-Analysis: Iron Deficiency at Term

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Falahi 2011	7	70	22	78	24.9%	0.35 [0.16, 0.78]
Makrides 2003	65	186	102	176	75.1%	0.60 [0.48, 0.76]
Romslo, 1983	0	22	15	23	0.0%	0.03 [0.00, 0.53]
Total (95% CI)		**256**		**254**	**100.0%**	**0.53 [0.33, 0.84]**
Total events	72		124			

Heterogeneity: Tau² = 0.06; Chi² = 1.67, df = 1 (P = 0.20); I² = 40%
Test for overall effect: Z = 2.73 (P = 0.006)



Note: Meta-analysis includes 2 studies with dosages of 20 and 60 mg (Romslo study with dosage of 200 mg excluded).

Abbreviations: CI=confidence interval; M-H=Mantzel-Haenzel.