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REVIEW

Routine Iron Supplementation and Screening for Iron Deficiency Anemia in Pregnancy: A Systematic Review for the U.S. Preventive Services Task Force

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Background: Routine screening and supplementation for iron deficiency anemia (IDA) in asymptomatic, nonanemic pregnant women could improve maternal and infant health outcomes.

Purpose: Update of a 2006 systematic review by the U.S. Preventive Services Task Force on screening and supplementation for IDA in pregnancy.

Data Sources: MEDLINE and the Cochrane Library (1996 to August 2014) and reference lists of relevant systematic reviews to identify studies published since 1996.

Study Selection: English-language trials and controlled observational studies about effectiveness of screening and routine supplementation for IDA in developed countries.

Data Extraction: Data extraction and quality assessment confirmed and dual-rated by a second investigator using prespecified criteria.

Data Synthesis: No study directly compared clinical outcomes or harms of screening or not screening pregnant women for IDA. Twelve supplementation trials were included, and no controlled observational studies met inclusion criteria. On the basis of 11 trials, routine maternal iron supplementation had inconsistent effects on rates of cesarean delivery, small size for gestational age, and low birthweight and no effect on maternal quality of life, gestational age, Apgar scores, preterm birth, or infant mortality. Twelve trials reported improvements in maternal hematologic indices, although not all were statistically significant. Pooled analysis of 4 trials resulted in a statistically significant difference in IDA incidence at term, favoring supplementation (risk ratio, 0.29 [95% CI, 0.17 to 0.49]; I^2 = 0%). Maternal iron supplementation did not affect infant iron status at 6 months. Harms, none of which were serious or had long-term consequences, were inconsistently reported in 10 of the trials, with most finding no difference between groups.

Limitations: Data from trials in countries with limited generalizability to U.S. populations were included. Studies were methodologically heterogeneous, and some were small and underpowered.

Conclusion: There is inconclusive evidence that routine prenatal supplementation for IDA improves maternal or infant clinical health outcomes, but supplementation may improve maternal hematologic indices.

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Iron deficiency is the most common pathologic cause of anemia in pregnancy. Increased risk during pregnancy is due to increased maternal iron needs and demands from the growing fetus and placenta; increased erythrocyte mass; and, in the third trimester, expanded maternal blood volume (1–5). Definitions of iron deficiency anemia (IDA) in pregnant women may be imprecise given pregnancy-associated physiologic changes and variable definitions in population subgroups (1, 2). Physiologic anemia, or dilutional anemia of pregnancy, is common in healthy pregnant women due to blood volume expansion to support the growing fetus and is associated with a modest decrease in hemoglobin levels. Iron deficiency occurs when the level of stored iron becomes depleted. Iron deficiency anemia occurs when iron levels are sufficiently depleted to produce anemia (1, 6). Serum ferritin is useful in diagnosing iron deficiency in pregnant women, who can have an elevated serum transferrin level in the absence of iron deficiency. As an acute-phase reactant, serum ferritin can be elevated in inflammatory conditions and may be of limited usefulness when concentrations decrease late in pregnancy (7).

Overall prevalence of iron deficiency in pregnant women in the United States is near 18%, with anemia in 5% of pregnant women and rates of iron deficiency increasing across trimesters from 6.9% to 14.3% to 28.4% (5). Risk factors for iron deficiency or IDA in pregnant women include an iron-deficient diet, gastrointestinal issues affecting absorption, or a short pregnancy interval (8). Pregnant women with clinically significant iron deficiency or IDA may present with fatigue, weakness, pallor, tachycardia, and shortness of breath (9). Maternal iron requirements average 1000 mg/d (10). Because many pregnant women lack sufficient iron stores, iron supplementation may be included in prenatal care. Primary prevention for average-risk populations includes adequate intake of dietary iron and oral, low-dose (30 mg/d) iron supplements early in pregnancy (11). Suggested prophylaxis for IDA in high-risk populations is 60 to 100 mg of elemental iron daily (12).

The association between iron status and negative outcomes for women and their infants is inconclusive. Although many older observational studies, including uncontrolled and cross-sectional studies, have shown

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an association between various measures of iron status and negative perinatal outcomes, such as low birthweight (13–15), premature birth (13–18), and perinatal death (14), more rigorous trial evidence is inconsistent. Screening for IDA may lead to earlier identification and earlier treatment, which may prevent serious negative health outcomes.

The U.S. Preventive Services Task Force (USPSTF) last reviewed evidence on prenatal screening for IDA in 2006 and recommended routine screening (B recommendation) on the basis of fair-quality evidence (19). There was insufficient evidence (no studies) on the accuracy of screening in asymptomatic pregnant women but fair-quality evidence that treating asymptomatic IDA in pregnancy results in moderate health benefits. Evidence was also insufficient to recommend for or against routine iron supplementation for nonanemic pregnant women (I statement).

This review was commissioned by the USPSTF to update the prior recommendations (19). We examined evidence from U.S.-relevant populations on the effectiveness of routine supplementation and screening for IDA in pregnancy.

METHODS

Methods are described in detail in a technical report (20). On the basis of evidence gaps identified from prior reviews (21, 22), and in consultation with the USPSTF (23), we developed key questions and analytic frameworks for routine supplementation (Appendix Figure 1, available at www.annals.org) and screening (Appendix Figure 2, available at www.annals.org) for IDA during pregnancy. Key questions were as follows.

Supplementation

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

1. What are the benefits of screening asymptomatic pregnant women for iron deficiency anemia 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 for iron deficiency anemia in pregnant women on maternal and infant health outcomes?

4. What are the harms of iron treatment in pregnant women?

5. What is the association between a change in maternal iron status (including changes in ferritin or hemoglobin level) and improvement in newborn and peripartum outcomes in U.S.-relevant populations?

Data Sources

We searched the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and Ovid MEDLINE (1996 to August 2014) (Appendix Table 1, available at www.annals.org). We also searched reference lists of relevant systematic reviews to identify studies published before 1996, the year that the prior reviews concluded.

Study Selection

Abstracts were selected for full-text review if they included asymptomatic pregnant women receiving screening or supplementation for IDA, were relevant to a key question, and met predefined inclusion criteria (20). For the screening framework, key questions focused on the effectiveness of screening compared with not screening in preventing adverse health outcomes and reducing the incidence of complications, as well as the association of improvements in intermediate and clinical health outcomes with harms (including infant harms). Health outcomes included long- or short-term maternal and infant morbidity (including birth outcomes), infant mortality, and maternal quality of life (including postpartum depression) resulting from screening, supplementation, or treatment and related harms. Intermediate outcomes included iron status based on hematologic indices, including ferritin levels. Additional outcomes included the relationship between a change in maternal iron status and maternal and infant health outcomes. We focused on studies using iron supplementation and treatment regimens commonly used in clinical practice in the United States and those conducted in countries with "high" or "very high" human development based on the United Nations Human Development Index (24). We included only English-language articles and excluded studies published as abstracts or without original data. Two reviewers independently evaluated each study to determine inclusion eligibility. We included randomized, controlled trials; nonrandomized, controlled trials; and cohort studies for all key questions. When good- and fair-quality studies were available, poor-quality studies were excluded. The selection of studies is summarized in Figure 1.

Data Abstraction and Quality Rating

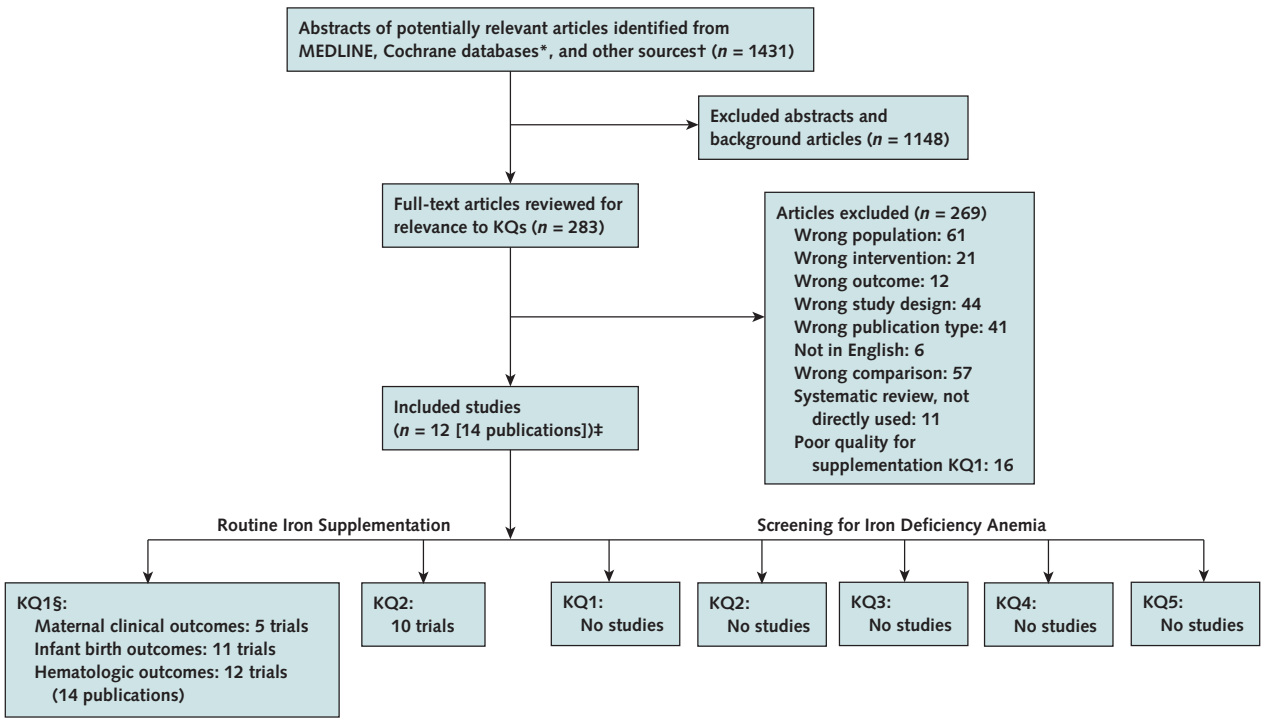
One investigator abstracted details about study design, patient population, setting, screening method, analysis, follow-up, and results. A second investigator reviewed the data abstraction for accuracy. Using predefined criteria developed by the USPSTF (23), 2 investigators rated the quality of studies (good, fair, or poor) (23) and resolved discrepancies by consensus.

Data Synthesis and Analysis

We assessed the aggregate internal validity (quality) of the body of evidence for each key question (good, fair, or poor) by using methods developed by the USPSTF, based on the number, quality, and size of studies; consistency of results among studies; and directness of evidence (23).

Meta-analysis was performed when studies were available that used comparable dosages, durations, and timing of outcome assessment. We conducted meta-analyses using the Mantel–Haenszel random- or fixed-effects models in Review Manager, version 5.2 (Cochrane Collaboration), to calculate risk ratios of the

Figure 1. Summary of evidence search and selection.



KQ = key question.
* Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews.
† Prior reports, reference lists of relevant articles, and systematic reviews.
‡ Some studies are included for >1 KQ.
§ Poor-quality studies were excluded because good- and fair-quality evidence was available.

effects of routine iron supplementation on incidence of preterm delivery, low birthweight, and maternal IDA and iron deficiency at term. Statistical heterogeneity was assessed using the I^2 statistic. Due to 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.

Role of the Funding Source

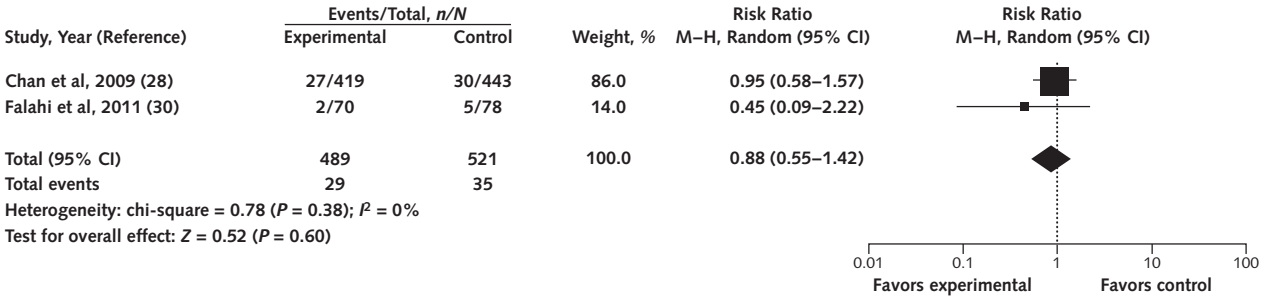
This research was funded by the Agency for Healthcare Research and Quality (AHRQ) under a contract to support the work of the USPSTF. Investigators worked with USPSTF members and AHRQ staff to develop and refine the scope, analytic framework, and key questions; resolve issues arising during the project; and finalize the report. The AHRQ had no role in study selection, quality assessment, synthesis, or development of conclusions. The AHRQ provided project oversight; reviewed the draft report; and distributed the draft for peer review, including to representatives of professional societies and federal agencies. The AHRQ performed a final review of the manuscript to ensure that the analysis met methodological standards. The investigators are solely responsible for the content and the decision to submit the manuscript for publication.

RESULTS

Effectiveness of Routine Iron Supplementation in Pregnancy

We identified a total of 12 good-quality (25–27) and fair-quality (28–36) trials comparing the effects of routine prenatal iron supplementation versus no supplementation (37, 38). Studies were conducted in the United States, Iran, Hong Kong, Australia, and Europe. Sample sizes ranged from 45 to 1164 participants, although only 2 studies had more than 500 (27, 28). Most studies reported that women with significantly low hematologic indices at baseline were excluded from the study and received treatment (25–29, 31–33, 35). Several studies also reported providing treatment if indices dropped too low during the study (25–28, 31, 33). The majority of enrolled women were in their 20s, and most were white or black (or race was not reported). Two of the 3 studies that were conducted in the United States (29, 32) were in women at higher risk for anemia on the basis of reported risk factors (such as eligibility for the Special Supplemental Nutrition Program for Women, Infants, and Children; black race; or 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.

Figure 2. Meta-analysis: preterm delivery.



M–H = Mantel–Haenszel.

The timing of supplementation varied from the first prenatal visit to 20 weeks' gestation and continued until delivery. However, in 2 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 are included in this report (29, 32). Outcomes were measured in the third trimester or at delivery, or studies included a short duration of follow-up 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, was variably reported but ranged from 54% to 98%.

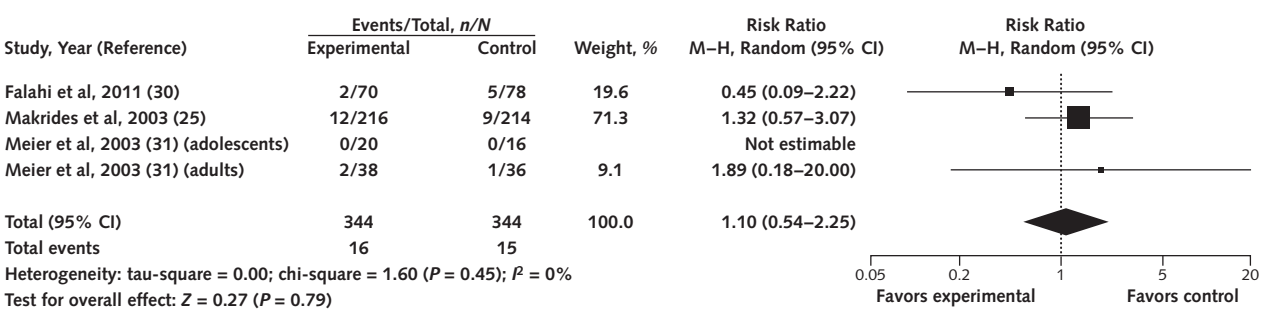
Only 5 of the included studies (in 6 publications) reported power or sample size calculations (25, 27–29, 32, 37). Two studies were powered to detect reductions in the rate of anemia (from 30% to 15% [29] and from 25% to 15% [32]). One of these studies was also powered to detect between-group differences of 0.407 times the SD of birthweight and gestational age (29). One study was powered to detect reductions in rates of IDA (from 11.5% to 3%) and iron deficiency (from 30% to 15%) and an increase in rates of gastrointestinal adverse effects (from 10% to 20%) (25). The sample size of 1 study was calculated to detect a 7% difference in the proportion of infants born small for their gestational age (27), and another study enrolled enough patients to detect an increase in the incidence of gestational diabetes from 10% to 15% (28).

Maternal Clinical Outcomes

Quality of life was reported as a secondary outcome in a good-quality trial (n = 430) that found no clear differences between women receiving iron supplementation versus placebo in any of the 8 Short Form-36 health concepts during pregnancy or after delivery (25).

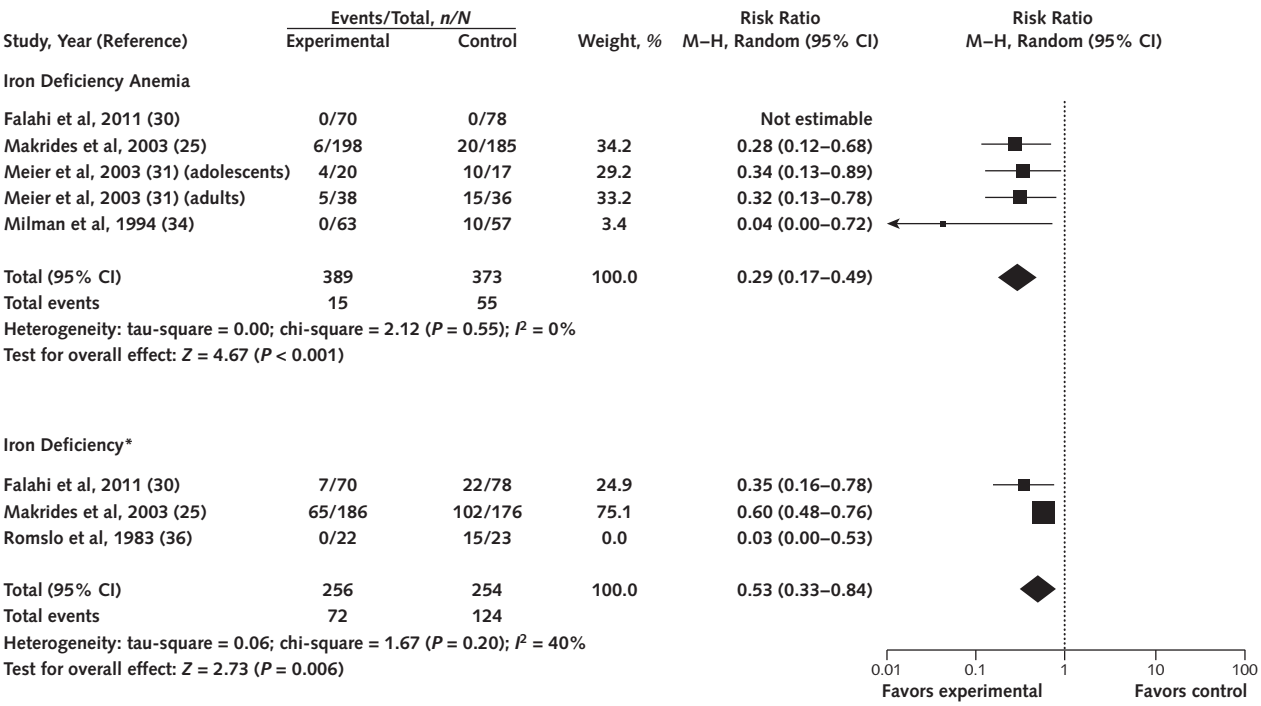
Cesarean delivery may occur for various indications, including elective ones, and has no known causal relationship with IDA. However, it is typically considered a measurable clinical outcome in pregnancy and was reported in 5 trials as an ad hoc event (25, 27, 28, 31, 35). These trials of average-risk women compared groups of pregnant women receiving or not receiving iron supplementation. Reported rates of cesarean delivery ranged from 7.6% to 26% in the supplementation groups and from 9.1% to 33% in the placebo groups (25, 27, 28, 31, 35). One large fair-quality trial (n = 1164) from Hong Kong found a significant reduction in the rate of cesarean delivery for women receiving 60 mg of elemental iron daily versus placebo (25.2% vs. 33.1%; odds ratio, 0.58 [95% CI, 0.37 to 0.89]; P = 0.008) (28). However, findings from 4 smaller fair- and good-quality trials (n = 97 to 727) on the effect of supplementation on rates of cesarean delivery for women receiving 20, 50, or 60 mg of elemental iron supplementation versus placebo were inconclusive (25, 27, 31, 35).

Figure 3. Meta-analysis: low birthweight.



M–H = Mantel–Haenszel.

Figure 4. Meta-analysis: iron deficiency anemia and iron deficiency at term.



* Includes 2 studies that used 20- and 60-mg dosing. Reference 36 was excluded from the analysis because the study used 200-mg dosing. M-H = Mantel–Haenszel.

Infant Clinical Outcomes

A total of 11 good-quality (25, 27) and fair-quality (28–36) trials reported infant birth outcomes, including mortality, preterm delivery, length of gestation, small size for gestational age, birthweight, and Apgar scores (Appendix Table 2, available at www.annals.org).

Four trials (25, 27, 31, 35) of pregnant women at average risk for anemia anecdotally reported no clear effect of prenatal iron supplements on infant mortality, with rates of 0% to 1.9% in the supplementation groups and 0% to 1.7% in the placebo groups, although this was not a prespecified outcome in these studies. One good-quality Iranian trial reported no difference in rates of perinatal mortality for supplementation versus placebo (0.8% vs. 1.7%) (27).

Four fair-quality trials conducted in Hong Kong, the United States, and Iran reported rates of preterm delivery (defined as delivery at <37 weeks) ranging from 3% to 12.8% in the supplementation groups and from 6.8% to 13.9% in the placebo groups (28–30, 32). Consistent with the prior report, these trials found no statistically significant difference between exposure to routine prenatal iron supplementation and rates of preterm delivery compared with placebo. Pooling estimates from 2 studies (28, 30) that provided 60 mg of elemental iron as supplemental dosing also resulted in a nonstatistically significant difference in the incidence of preterm birth in the supplementation groups (risk ratio [RR], 0.88 [CI, 0.55 to 1.42]; I^2 = 0%) compared with placebo (Figure 2).

Six fair-quality trials and 1 good-quality trial reported no effect of maternal iron supplementation on length of gestation, with all studies reporting gestational ages between 38 and 40 weeks for participants in the supplementation and placebo groups (25, 28–32, 36). Two of the studies were conducted in the United States and included women at higher risk for iron deficiency.

Three fair-quality trials and 1 good-quality trial conducted in Hong Kong, the United States, and Iran reported inconsistent findings for infants exposed to prenatal iron supplementation who were small for their gestational age (defined as below the 10th percentile of birthweight for their gestational age), with ranges of 3.6% to 15% for those in the supplementation groups and 7.5% to 17.7% for those in the placebo groups (27–29, 32). 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 infants who were small for their gestational age among women in the supplementation group versus the placebo group (3.6% vs. 7.5% [P = 0.013] [28] and 6.8% vs. 17.7% [P = 0.014] [29]). Another U.S. trial of women at higher risk for iron deficiency reported no difference between the supplementation and placebo groups (10.8% vs. 15.5% [P = 0.22] [32]). One good-quality Iranian trial of women at average risk for anemia found that those not receiving supplementation had significantly fewer infants who were

small for their gestational age (15% vs. 10% [$P = 0.035$]) (27).

Six trials (5 fair-quality and 1 good-quality) conducted in the United States, Iran, Ireland, and Australia that reported the incidence of infants born with low birthweight (defined mostly as <2500 g) found inconsistent results. Incidence of low birthweight ranged from 0% to 9.4% in the supplementation groups and from 0% to 16.7% in the placebo groups (25, 29–32, 35). One U.S. trial of women at higher risk for iron deficiency ($n = 275$) found significantly lower rates of low-birthweight infants in the supplementation group versus the placebo group (4.3% vs. 16.7% [$P = 0.003$]) (29). However, 5 trials, including a separate 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 (25, 30–32, 35). Pooled analysis of 3 comparable studies (25, 30, 31) that used supplementation with 20 to 60 mg of elemental iron resulted in a non–statistically significant relative risk of 1.10 (CI, 0.54 to 2.25; $I^2 = 0\%$) compared with placebo (**Figure 3**).

In 8 trials reporting mean infant birthweight, all infants had birthweight within the normal range, and 5 trials found no difference among participants receiving supplementation versus placebo (25, 30, 33, 34, 36). Three other trials found that women receiving placebo had infants with lower mean birthweight (3247 vs. 3151 g [$P = 0.001$] [28], 3277 vs. 3072 g [$P = 0.010$] [29], and 3325 vs. 3217 g [$P = 0.03$] [32]).

Five trials (4 fair-quality and 1 good-quality) reported Apgar scores at 1, 5, or 10 minutes and found no difference in scores between infants exposed to routine maternal iron supplementation versus placebo (25, 27, 28, 31, 36).

Maternal Intermediate Outcomes

Consistent with the prior reports (21, 22), 12 good- or fair-quality trials reported improvement in maternal hematologic indices with variable doses of iron supplementation versus placebo at various time points and used variable definitions of hematologic indices, although not all improvements were statistically significant (**Appendix Table 3**, available at www.annals.org) (25–36). The clinical significance of these findings is unclear. We report results at term because this was the most consistently reported and, possibly, the most clinically relevant time point. Results for the third trimester and various postpartum time points are detailed in **Appendix Table 3** and in the full report (20).

Six trials reported incidence of IDA (defined as hemoglobin level <110 g/L and serum ferritin level <27 or <44.9 pmol/L), with overall ranges of 0% to 12.7% for women in the supplementation groups and 0% to 29% for those in the placebo groups in the third trimester, at delivery, or after delivery (25, 29–32, 34). One good-quality ($n = 430$) and 1 fair-quality ($n = 120$) trial reported a significantly lower incidence of IDA at term in pregnant women receiving routine iron supplementation versus placebo (3% vs. 11% [RR, 0.28 {CI, 0.12 to 0.68}] [25] and 0% vs. 17.5% [$P = 0.02$] [34]). However, 2 smaller fair-quality trials found no difference between groups, with one reporting incidence of 0% in both groups (30) and the other reporting incidence of 5% versus 29% for adolescents ($P = 0.137$) and 10.5% versus 22.2% for adults ($P = 0.259$) (31). Pooled analysis of 4 comparable trials resulted in a statistically significant difference between groups in incidence of IDA at term, favoring supplementation (RR, 0.29 [CI, 0.17 to 0.49]; $I^2 = 0\%$) (**Figure 4**) (25, 30, 31, 34).

Six trials reported incidence of iron deficiency (defined as serum ferritin level <27, <33.7, or <44.9 pmol/L). Overall ranges were 0% to 56% for women in the supplementation groups and 28% to 85% for those in the placebo groups, with consistent results across measurement time points; however, not all results reached statistical significance (25, 29, 30, 32, 33, 36). At term, 3 trials (2 fair-quality and 1 good-quality) found lower rates of iron deficiency at delivery for women receiving supplementation (9.5% vs. 28.2% [$P < 0.05$] [30], 35% vs. 58% [RR, 0.60 {CI, 0.48 to 0.76}] [25], and 0% vs. 65.2% [$P = 0.02$] [36]). Pooled results of 2 trials with comparable dosing regimens (20 to 60 mg of elemental iron daily) indicated a statistically significant difference in iron deficiency at term that favored supplementation (RR, 0.53 [CI, 0.33 to 0.84]; $P = 0.006$; $I^2 = 40\%$) (**Figure 4**) (25, 30).

Four trials reported incidence of anemia (defined as hemoglobin level <100 or <110 g/L), with overall ranges of 3.7% to 21% for women in the supplementation groups and 4.5% to 27% for those in the placebo groups (25, 29, 32, 33). At term, 1 good-quality trial reported a significantly lower incidence of anemia at delivery for pregnant women receiving routine iron supplementation versus placebo (7% vs. 16%; RR, 0.45 [CI, 0.25 to 0.82]) (25).

Eleven good- or fair-quality trials of women receiving iron supplementation versus placebo reported hemoglobin levels in the third trimester, at delivery, or up to 6 months after delivery, with overall ranges of 114 to 139 g/L for those in the supplementation groups and 113 to 134 g/L for those in the placebo groups (25–32, 34–36). At term, 8 trials found that women receiving supplementation had higher hemoglobin levels at delivery than those receiving placebo, although results were statistically significant in only 6 (25, 26, 28, 31, 34, 35).

Ten trials reported serum ferritin levels in the third trimester, at delivery, or up to 6 months after delivery, with values ranging from 16.6 to 76.4 pmol/L for women receiving supplementation and from 13.5 to 58.4 pmol/L for those receiving placebo (25, 26, 28–32, 34–36). Five trials of women at average risk for anemia found that those receiving supplementation had significantly higher serum ferritin levels at term than those receiving placebo (25, 26, 28, 31, 34).

Table. Summary of Evidence

Outcome, by Key Question	Primary Findings From Prior USPSTF Reviews	Studies Identified for Update	Limitations
Routine iron supplementation in pregnant women			
What are the benefits of routine iron supplementation in pregnant women on maternal and infant health outcomes?			
Maternal clinical outcomes	Limited evidence showing improved clinical outcomes	5 RCTs	Outcomes reported mostly as ad hoc events; variable doses of iron supplements
Infant clinical outcomes			
Mortality	Limited evidence; 1 trial reported fewer infant deaths in the selective supplementation group	4 trials	Outcomes reported mostly as ad hoc events; variable doses of iron supplements
Preterm delivery	Limited evidence showing no effect on pregnancy outcomes	4 RCTs	Variable doses of iron supplements
Length of gestation	Limited evidence showing no effect on pregnancy outcomes	6 RCTs	Variable doses of iron supplements
Small size for gestational age	No studies	4 RCTs	Variable doses of iron supplements
Low birthweight	Limited evidence showing no effect on pregnancy outcomes	6 RCTs	Variable doses of iron supplements
Apgar scores	No studies	5 RCTs	Variable doses of iron supplements
Maternal intermediate outcomes	Iron supplements are effective in improving maternal hematologic indices	12 RCTs for intermediate outcomes	Variable doses of iron supplements
Infant intermediate outcomes	Not assessed	1 follow-up study	No issues
What are the harms of routine iron supplementation in pregnant women?	Reversible GI symptoms associated with iron use	10 RCTs	Outcomes mostly reported as ad hoc events; variable doses of iron supplements
Screening for iron deficiency anemia in pregnant women			
What are the benefits of screening asymptomatic pregnant women for iron deficiency anemia on maternal and infant health outcomes?	No studies	None	NA
What are the harms of screening for iron deficiency anemia in pregnant women?	No studies	None	NA
What are the benefits of treatment for iron deficiency anemia in pregnant women on maternal and infant health outcomes?	Iron supplements are effective in improving maternal hematologic indices, but limited evidence exists showing improved clinical outcomes	None	NA
What are the harms of iron treatment in pregnant women?	Reversible GI symptoms associated with iron use	None	NA
What is the association between a 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 reviewed	None	NA

GI = gastrointestinal; NA = not applicable; RCT = randomized, controlled trial; RR = risk ratio; USPSTF = U.S. Preventive Services Task Force.
* Based on new evidence identified for this update plus previously reviewed evidence.

Table—Continued

Consistency	Applicability	Summary of Findings	Overall Quality*
Consistent	Studies limited to those done in U.S.-relevant countries and populations	1 trial reported no differences in quality of life between pregnant women receiving iron supplementation and those receiving placebo. 5 trials reported rates of cesarean delivery. 1 trial found significantly fewer cesarean deliveries in women receiving iron supplementation, whereas 4 trials of women receiving 20, 50, or 60 mg of elemental iron supplementation versus placebo were inconclusive.	Poor
Consistent	1 trial done in Iran	4 trials reported no clear effect of prenatal iron supplementation on infant mortality.	Poor
Consistent	No issues	4 studies found no association between prenatal iron supplementation and incidence of preterm delivery.	Fair
Consistent	No issues	6 trials reported no effect of maternal iron supplementation on length of gestation. All studies reported gestational ages between 38 and 40 wk for infants in both the supplementation and placebo groups.	Fair
Inconsistent	No issues	4 trials reported inconsistent findings for small size for gestational age.	Fair
Inconsistent	No issues	1 U.S. trial of higher-risk women reported significantly lower rates of low-birthweight (<2500 g) infants exposed to prenatal iron supplementation (4.3% vs. 16.7%; $P = 0.003$). 5 studies, including a separate U.S. trial of higher-risk women, found no effect of prenatal iron supplementation on the rate of low-birthweight infants.	Fair
Consistent	No issues	5 trials found no difference in Apgar scores at 1 and 5 min in infants exposed to prenatal iron supplements versus placebo.	Fair
Consistent	Studies limited to those done in U.S.-relevant countries and populations	12 trials reported improvement in maternal hematologic indices with variable doses of iron supplementation versus placebo but inconsistent associations between iron supplementation and incidence of maternal iron deficiency or anemia. Pooled analysis of 4 comparable trials (20 to 66 mg of iron daily) found a statistically significant between-group difference in incidence of iron deficiency anemia at term, favoring supplementation (RR, 0.29 [95% CI, 0.17 to 0.49]; $I^2 = 0\%$). The clinical significance of these findings is unclear.	Fair
NA	No issues	1 study reported infant hematologic outcomes as a follow-up to the good-quality Australian trial; mothers were randomly allocated to receive 20 mg of elemental iron daily from 20 wk of gestation until delivery. No difference was found in iron status of infants at age 6 mo.	Poor
Inconsistent	No issues	Harms of routine iron supplementation in pregnant women were sparsely and variably reported in 10 trials comparing iron supplementation versus placebo. None of the harms were serious or associated with long-term significance, and there were mostly no significant differences between groups. Reported harms included transient treatment effects (nausea, constipation, and diarrhea). Findings on rates of maternal hypertension were inconsistent. 6 trials found no between-group difference in nonadherence to supplementation versus placebo; 1 trial had lower nonadherence in the supplementation group than in the placebo group.	Poor
NA	NA	NA	NA
NA	NA	NA	NA
NA	NA	NA	NA
NA	NA	NA	NA
NA	NA	NA	NA

Infant Intermediate Outcomes

A 6-month follow-up study to a good-quality Australian trial (25) of 336 infants, in which mothers at 20 weeks' gestation were randomly allocated to receive 20 mg of elemental iron supplementation daily until delivery, was the only study reporting infant hematologic outcomes and found no differences in iron status of children at 6 months.

Harms of Routine Iron Supplementation in Pregnancy

Harms of routine iron supplementation in pregnant women were sparsely and variably reported, often as ad hoc events, in 10 good- or fair-quality trials comparing iron supplementation with placebo. None of the harms were serious or associated with long-term significance, and there were mostly no significant differences between groups (**Appendix Table 4**, available at www.annals.org) (25, 27–33, 35, 36).

Two trials conducted in Australia and the United States reported no differences in various minor gastrointestinal adverse effects between supplementation (60 and 20 mg of elemental iron daily, respectively) and placebo (25, 31). Four studies from Australia, the United States, and Norway reported no significant differences in rates of any adverse event and no differences in adherence or discontinuation of supplementation (25, 29, 31, 33). Harms were measured after at least 1 clinic visit through 36 weeks and included general medication adverse effects, fatigue, or any adverse event. Additional reporting on related maternal harms was limited and inconsistent. There was no relationship between supplementation and maternal hypertension (27, 30) or gestational diabetes (28).

Screening for IDA

No studies met inclusion criteria for any of the key questions on benefits and harms of screening for IDA in pregnancy, benefits and harms of screen-detected treatment, or the association between a change in maternal iron deficiency or IDA status and improvement in newborn and peripartum outcomes in U.S.-relevant populations.

DISCUSSION

A summary of the evidence is presented in the **Table**. Newer evidence identified for this review is consistent with findings from the previous USPSTF reviews (21, 22) and shows that iron supplementation is often effective in improving maternal hematologic indices and may result in a lower incidence of women with iron deficiency and IDA during pregnancy and at delivery. However, evidence is insufficient to demonstrate a substantial effect on clinical outcomes for women and infants. No study directly compared clinical outcomes or harms of screening or not screening pregnant women for IDA.

In this updated review, 12 trials compared the effects of routine prenatal iron supplementation versus no supplementation, and 11 reported various clinical outcomes for women and infants. No controlled observational studies met inclusion criteria. One trial reported no difference in quality of life for pregnant women receiving iron supplementation versus placebo. Trials of prenatal iron supplementation found no clear effect on infant gestational age, Apgar scores, preterm birth, or infant mortality; however, infant mortality was not a prespecified outcome. Findings were inconsistent among studies reporting an effect of maternal iron supplementation on rates of cesarean delivery, small size for gestational age, and low birthweight. Of note, the strength of this evidence was reduced by the small number of trials reporting these outcomes (for example, 5 trials reporting on premature birth, small size for gestational age, and cesarean delivery); the combined lack of power in these studies; and methodological heterogeneity, which prevented pooling of studies and determination of consistency and study quality. As such, meta-analysis was not performed for all outcomes. These findings are similar to those of recent Cochrane reviews that compared daily and intermittent oral iron supplementation or assessed iron treatment during pregnancy in trials conducted mostly in developing countries (11, 39–41). These reviews found overall methodologically poor evidence showing no effect on infant outcomes, including low birthweight and preterm birth.

The strongest evidence supporting a benefit of supplementation on hematologic outcomes was from a good-quality, Australian randomized trial of pregnant women at average risk for anemia (25) that reported improvements in some maternal hematologic parameters. Eleven other good- or fair-quality trials (26–36) supported the evidence that maternal iron supplements may improve hematologic parameters or reduce the incidence of IDA, but the clinical significance of the findings is unclear. One follow-up study of maternal iron supplementation during pregnancy reported no differences in iron status of children at age 6 months (37). No studies reported serious harms resulting from supplementation.

We excluded non–English-language articles, which could have resulted in language bias, although no such studies meeting inclusion criteria at the abstract level were identified. We could not formally assess for publication bias with graphical or statistical methods because of small numbers of pooled studies or inability to pool studies. Although all study locations met criteria for at least high human development on the United Nations Human Development Index (24), some studies included data that may not be generalizable to the United States due to differences in such factors as nutritional status, resources, and health care infrastructure. Study populations included mostly women at average risk for IDA or did not report risk level, except for 2 of the 3 U.S. studies (29, 32) that included women at higher risk for anemia based on reported risk factors (such as eligibility for the Special Supplemental Nutrition Program for Women, Infants, and Children [29, 32] or black race [32]). Results may differ for high-risk populations, especially in the United States. However, 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, thereby limiting the interpretation of trial results.

Better research is needed to identify the long-term clinical health effects of routine iron supplementation during pregnancy in developed countries. Infants exposed to prenatal iron supplementation should continue to be followed to identify unexpected or

emerging long-term benefits or harms from maternal supplementation. Research is needed to understand the clinical significance of the short-term improvement in maternal hematologic outcomes after prenatal iron supplementation and the nuances of supplementation dose and timing, as well as to strengthen conclusions by more consistently examining the effect on clinical maternal and infant outcomes in large, high-quality studies.

In summary, routine iron supplementation during pregnancy may improve maternal hematologic indices and reduce the incidence of iron deficiency and IDA in the short term. However, there is no clear or consistent evidence that prenatal iron supplementation has a beneficial clinical impact on maternal or infant health. In addition, no trials are available on the effect of prenatal screening for IDA on clinical outcomes despite routine screening practices in many high-income countries. Rigorous studies are needed to fully understand the short- and long-term effect of routine iron supplementation and screening during pregnancy on women and infants, including the effects on rates of cesarean delivery, small size for gestational age, and low birthweight. Until then, the evidence on routine iron supplementation and screening in prenatal care will remain unclear at best.

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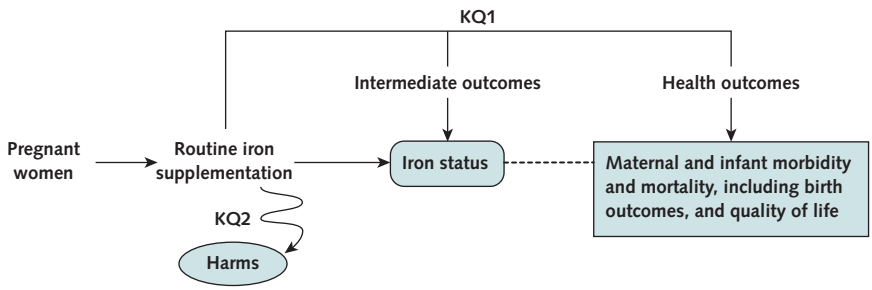
Appendix Figure 1. Analytic framework for routine iron supplementation in pregnant women.

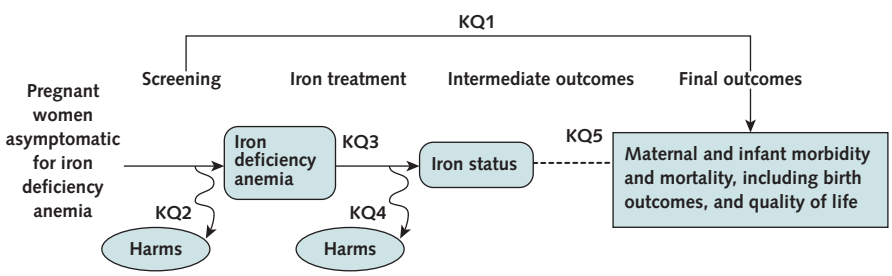


Key Questions

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?

KQ = key question.

Appendix Figure 2. Analytic framework for screening for iron deficiency anemia in pregnant women.



Key Questions

1. What are the benefits of screening asymptomatic pregnant women for iron deficiency anemia 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 for iron deficiency anemia in pregnant women on maternal and infant health outcomes?
4. What are the harms of iron treatment in pregnant women?
5. What is the association between a change in maternal iron status (including changes in ferritin or hemoglobin level) and improvement in newborn and peripartum outcomes in U.S.-relevant populations?

KQ = key question.

Appendix Table 1. Search Strategies

Supplementation KQ1 and KQ2

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 KQ1 and KQ2

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 KQ3 and KQ4

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)

Association KQ5

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 KQs

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

EBM = Evidence-Based Medicine; KQ = key question.

Appendix Table 2. Infant Birth Outcomes*

Study, Year Country *n* Quality	Iron Supplement Dose, Formulation, and Initiation	Risk Factors Reported	Supplementation Versus Control						
			Apgar Score	Preterm Delivery (<37 wk)	Length of Gestation	Small Size for Gestational Age (<10th Percentile of Birthweight for Gestational Age)	Birthweight	Low Birthweight (<2500 g)	Infant Mortality
Barton 1994 (35) Ireland *n*=97 Fair	120 mg elemental iron daily starting at 14 wk of gestation	Race: NR (Ireland) Nulliparous: 45%-47%	–	–	–	–	–	<2700 g: 9.4% vs. 15.9%, *P*=0.34	1.9% vs. 0%, *P*=0.57
Chan 2009 (28) Hong Kong *n*=1164 Fair	60 mg elemental iron daily starting at <16 wk of 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 wk, *P*=0.322	3.6% vs. 7.5%, **P=0.013**	3247.3 vs. 3151.9 g, **P=0.001**	–	–
Cogswell 2003 (29) United States *n*=275 Fair	30 mg elemental iron daily starting at <20 wk of gestation	Race: White 56%-57%, black 24%-26%, Hispanic 16%-17% Parity ≥2: 31% vs. 24% High school education or less: 73%-76% SES: 100% eligible for WIC	–	12.8% vs. 12.5%, *P*=0.944	38.9 vs. 38.3 wk, *P*=0.05	6.8% vs. 17.7%, **P=0.014**	3277 vs. 3072 g, **P=0.010**	4.3% vs. 16.7%, **P=0.003**	–
Eskeland 1997 (33) Norway *n*=90 Fair	27 mg elemental iron daily starting at 20 wk of gestation	Race: NR (Norway) BMI: 22-23 kg/m^2 Parity ≥2: 0%-10% Single: 3%-17% Low education: 3%-10%	–	–	–	–	3690 vs. 3620 vs. 3610 g, *P*=NS†	–	–
Falahi 2011 (30) Iran *n*=148 Fair	60 mg elemental iron daily starting at <20 wk of gestation	Race: NR (Iran) BMI: 24-25 kg/m^2	–	3% vs. 6.8%, *P*=NS	38.9 vs. 38.8 wk, *P*=NS	–	3310 vs. 3270 g, *P*=NS	3% vs. 6.8%, *P*=NS	–
Makrides 2003 (25) Australia *n*=430 Good	20 mg elemental iron daily starting at 20 wk of gestation	Race: White 95%, Aboriginal 0.9%-3.3%, Asian 1.4%-2.3% Multiparous: 52%-53% BMI: 26 kg/m^2 Highest level of education: Year <10: 12%-15%, year 11: 27%- 28%, year 12: 28%-33%, trade certificate or diploma: 5%-8%, tertiary degree: 21%	Score <7 at 5 min: 1.4% vs. 1.5%, *P*=NS	–	39 vs. 39 wk, *P*=NS	–	3406 vs. 3449 g, *P*=NS	5.4% vs. 4.2%, *P*=NS	0.5% (1 case) vs. 0%, *P*=NS (infant born at 22 wk with bilateral intrauterine pneumonia)
Meier 2003 (31) United States *n*=111 Fair	60 mg elemental iron daily starting at first 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 wk, *P*=NS Adults 39.2 vs. 39.5 wk, *P*=NS	–	–	Adolescents 0% vs. 0%, *P*=NS Adults 5.4% vs. 2.9%, *P*=NS	0% vs. 0%, *P*=NS
Milman 1994 (34) Denmark *n*=120 Fair	66 mg elemental iron daily starting at 14-16 wk of gestation	Race: NR (Denmark)	–	–	–	–	3350 vs. 3450 g, *P*=NS (median)	–	–
Romslo 1983 (36) Norway *n*=45 Fair	200 mg elemental iron daily starting within 10 wk of 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 wk, *P*=NR	–	3546 vs. 3510 g, *P*=NR	–	–
Siega-Riz 2006 (32) United States *n*=429 Fair	30 mg elemental iron daily starting at <20 wk of gestation	Race: Black 58%-65%, white 31%-37% 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 wk, *P*=0.43	10.8% vs. 15.5%, *P*=0.22	3325 vs. 3217 g, **P=0.03**	4.8% vs. 9.5%, *P*=0.09	–
Ziaei 2007 (27) Iran *n*=727 Good	50 mg elemental iron daily starting at 20 wk of 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

BMI = body mass index; NR = not reported; NS = not significant; SES = socioeconomic status; WIC = Special Supplemental Nutrition Program for Women, Infants, and Children.
* *P* values in boldface show a significant difference.
† Heme iron supplementation vs. no heme iron supplementation vs. placebo.

Appendix Table 3. Maternal Hematologic Outcomes*

Study, Year Country *n* Quality	Time Point	Iron Supplement Dose, Formulation, and Initiation	Risk Factors Reported	Supplementation Versus Control					
				HB	SF	MCV	Iron Deficiency (SF <12 μg/L)	Anemia (HB <110 g/L)	Iron Deficiency Anemia (HB <110 g/L and SF <12 μg/L)
Third trimester									
Siega-Riz 2006 (32) United States *n*=429 Fair	26-29 wk (end of RCT phase)	30 mg elemental iron daily starting at <20 wk of gestation	Race: Black 58%-65%, white 31%-37% Single: 75% Parity ≥2: 44% vs. 41% SES: 100% eligible for WIC	114 vs. 114 g/L, *P*=0.81	49.4 vs. 45.6 pmol/L, *P*=0.48	–	53% vs. 65%, ***P*=0.08**†	21% vs. 19%, *P*=0.65	10% vs. 15%‡, *P*=0.23
Cogswell 2003 (29) United States *n*=275 Fair	28 wk (end of RCT phase)	30 mg elemental iron daily starting at <20 wk of gestation	Race: White 56%-57%, black 24%-26%, Hispanic 16%-17% Parity ≥2: 31% vs. 24% High school education or less: 73%-76% SES: 100% eligible for WIC	117 vs. 116 g/L, *P*=0.499	16.6 vs. 16.6 pmol/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 (30) Khorramabad City, Iran *n*=148 Fair	28 wk	60 mg elemental iron daily starting at <20 wk of gestation	Race: NR (Iran) BMI: 24-25 kg/m^2	–	–	–	–	–	1.4% vs. 3.8%, ***P*<0.05**
Ziaei 2007 (27) Tehran, Iran *n*=727 Good	Third trimester	50 mg elemental iron daily starting at 20 wk of gestation	Race: NR (Iran) BMI: 24 kg/m^2 Parity: 1.7	138 vs. 125 g/L, ***P*<0.001**	–	–	–	–	–
Barton 1994 (35) Ireland *n*=97 Fair	36 wk	120 mg elemental iron daily starting at 14 wk of gestation	Race: NR (Ireland) Nulliparous: 45%-47%	135 vs. 126 g/L, ***P*=0.043** (adjusted for smoking, *P*=0.25)	73.3 vs. 28.8 pmol/L, ***P*=0.04**	–	–	–	–
Eskeland 1997 (33) Norway *n*=90 Fair	38 wk	27 mg elemental iron daily starting at 20 wk of 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	–	–
At term									
Meier 2003 (31) United States *n*=111 Fair	Delivery, 36-40 wk, stratified by age groups	60 mg elemental iron daily starting at first 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 27.0 vs. 13.9 pmol/L, ***P*=0.010** Adults 29.0 vs. 17.1 pmol/L, ***P*=0.027**	–	–	–	Adolescents 5% vs. 29%, *P*=0.14 Adults 10.5% vs. 22.2%, *P*=0.26
Romslo 1983 (36) Norway *n*=45 Fair	37-40 wk	200 mg elemental iron daily starting within 10 wk of gestation	Race: NR (Norway)	126 vs. 113 g/L, *P*=NR	53.9 vs. 13.5 pmol/L, *P*=NR	–	0% vs. 65.2%, ***P*=0.02**	–	–
Barton 1994 (35) Ireland *n*=97 Fair	40 wk	120 mg elemental iron daily starting at 14 wk of 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 (28) Hong Kong *n*=1164 Fair	Delivery	60 mg elemental iron daily starting at <16 wk of 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**	67.4 vs. 56.0 pmol/L, ***P*<0.003**	–	–	–	–
Falahi 2011 (30) Khorramabad City, Iran *n*=148 Fair	Delivery	60 mg elemental iron daily starting at <20 wk of gestation	Race: NR (Iran) BMI: 24-25 kg/m^2	123 vs. 121 g/L, *P*=NS	63.1 vs. 49.7 pmol/L, *P*=NS	–	9.5% vs. 28.2%, ***P*<0.05**	–	0% vs. 0%, *P*=NS

Appendix Table 3–Continued

Study, Year Country *n* Quality	Time Point	Iron Supplement Dose, Formulation, and Initiation	Risk Factors Reported	Supplementation Versus Control					
				HB	SF	MCV	Iron Deficiency (SF <12 μg/L)	Anemia (HB <110 g/L)	Iron Deficiency Anemia (HB <110 g/L and SF <12 μg/L)
Makrides 2003 (25) Australia *n*=430 Good	Delivery	20 mg elemental iron daily starting at 20 wk of gestation	Race: White 95%, Aboriginal 0.9%-3.3%, Asian 1.4%-2.3% Multiparous: 52%-53% BMI: 26 kg/m^2 Highest level of education: Year <10: 12%-15%, year 11: 27%-28%, year 12: 28%-33%, trade certificate or diploma: 5%-8%, tertiary degree: 21%	127 vs. 120 g/L; **RR, 6.9 (95% CI, 4.4 to 9.3)**	47.2 vs. 31.5 pmol/L; **RR, 7.1 (CI, 4 to 10.2)**	–	35% vs. 58%; **RR, 0.60 (CI, 0.48 to 0.76)**	7% vs. 16%; **RR. 0.45 (CI, 0.25 to 0.82)**	3% vs. 11%; **RR, 0.28 (CI, 0.12 to 0.68)**
Milman 1994 (34) Denmark *n*=120 Fair	Term	66 mg elemental iron daily starting at 14-16 wk of gestation	Race: NR (Denmark)	127 vs. 116 g/L, ***P*<0.0001**	49.4 vs. 31.5 pmol/L, ***P*<0.0001**	–	–	–	0% vs. 17.5%, ***P*=0.03**
Ziaei 2008 (26) Iran (location NR) *n*=205 Good	Delivery	50 mg elemental iron daily starting at 20 wk of gestation	Race: NR (Iran) BMI: 24 kg/m^2 Parity: 1.6-1.7 Educational level: Primary school: 7%-11%, high school: 77%-83%, university: 10%-12%	139 vs. 128 g/L, ***P*<0.0001**	58.9 vs. 42.9 pmol/L, ***P*<0.0001**	–	–	–	–
Postpartum									
Eskeland 1997 (33) Norway *n*=90 Fair	1 wk postpartum	27 mg elemental iron daily starting at 20 wk of 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 (33) Norway *n*=90 Fair	6-10 wk postpartum	27 mg elemental iron daily starting at 20 wk of 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§	–	–
Eskeland 1997 (33) Norway *n*=90 Fair	24 wk postpartum	27 mg elemental iron daily starting at 20 wk of 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§**	–	–
Makrides 2003 (25) Australia *n*=430 Good	6 mo postpartum	20 mg elemental iron daily starting at 20 wk of gestation	Race: White 95%, Aboriginal 0.9%-3.3%, Asian 1.4%-2.3% Multiparous: 52%-53% BMI: 26 kg/m^2 Highest level of education: Year –10: 12%-15%, year 11: 27%-28%, year 12: 28%-33%, trade certificate or diploma: 5%-8%, tertiary degree: 21%	135 vs. 134 g/L; RR, 1.6 (CI, −0.1 to 3.3)	76.4 vs. 58.4 pmol/L; **RR, 7.9 (CI, 3.5 to 12.3)**	–	16% vs. 29%; **RR, 0.57 (CI, 0.38 to 0.84)**	3.7% vs. 4.5%; RR, 0.82 (CI, 0.30 to 2.21)	2.6% vs. 1.7%; RR, 1.55 (CI, 0.38 to 6.40)
Ziaei 2008 (26) Iran (location NR) *n*=205 Good	6 wk postpartum	50 mg elemental iron daily starting at 20 wk of gestation	Race: NR (Iran) BMI: 24 kg/m^2 Parity: 1.6-1.7 Educational level: Primary school: 7%-11%, high school: 77%-83%, university: 10%-12%	133 vs. 126 g/L, ***P*<0.0001**	48.8 vs. 41.6 pmol/L, ***P*<0.0001**	–	–	–	–

BMI = body mass index; HB = hemoglobin; MCV = mean corpuscular volume; NR = not reported; NS = not significant; RCT = randomized, controlled trial; RR = risk ratio; SES = socioeconomic status; SF = serum ferritin; WIC = Special Supplemental Nutrition Program for Women, Infants, and Children.

* *P* values and RRs in boldface show a significant difference.

† Iron deficiency defined as SF <20 μg/L.

‡ Iron deficiency anemia defined as HB <110 g/L and SF <20 μg/L.

§ Heme iron supplementation (A) vs. no heme iron supplementation (B) vs. placebo (C).

Appendix Table 4. Maternal Adverse Events

Study, Year Country *n* Quality	Iron Supplement Dose, Formulation, and Initiation	Risk Factors Reported	Supplementation Versus Control			
			Gestational Diabetes	Pregnancy-Induced Hypertension	GI Events	Other
Barton 1994 (35) Ireland *n*=97 Fair	120 mg elemental iron daily starting at 14 wk of 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 (28) Hong Kong *n*=1164 Fair	60 mg elemental iron daily starting at <16 wk of gestation	Race: NR (Hong Kong) Parity ≥2: 0.50% vs. 0.18% BMI: 20.8 vs. 21.0 kg/m^2	At 28 wk of gestation: 10% vs. 10%; OR, 1.04 (95% CI, 0.7 to 1.53)	–	–	Nonadherence: 46% overall, *P*=NS
Cogswell 2003 (29) United States *n*=275 Fair	30 mg elemental iron daily starting at <20 wk of gestation	Race: White 56%-57%, black 24%-26%, Hispanic 16%-17% Parity ≥2: 31% vs. 24% High school education or less: 73%-76% SES: 100% eligible for WIC	–	–	–	Nonadherence at wk 28: 36.6% vs. 34.8%, *P*=NS Side effects reported at >1 visit from enrollment to wk 28: 24.6% vs. 18.5%, *P*=NS
Eskeland 1997 (33) Norway *n*=90 Fair	27 mg elemental iron daily starting at 20 wk of 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 (30) Iran *n*=148 Fair	60 mg elemental iron daily starting at <20 wk of gestation	Race: NR (Iran) BMI: 24-25 kg/m^2	–	1.4% (1 case) vs. 0%, *P*=NS	–	–
Makrides 2003 (25) Australia *n*=430 Good	20 mg elemental iron daily starting at 20 wk of gestation	Race: White 95%, Aboriginal 0.9%-3.3%, Asian 1.4%-2.3% Multiparous: 52%-53% BMI: 26 kg/m^2 Highest level of education: Year <10: 12%-15%, year 11: 27%-28%, year 12: 28%-33%, trade certificate or diploma: 5%-8%, tertiary degree: 21%	–	–	At 36 wk of gestation: Nausea: 29% vs. 28%; RR. 1.04 (CI, 0.76 to 1.42) Stomach pain: 35% vs. 30%; RR, 1.19 (CI, 0.89 to 1.58) Heartburn: 68% vs. 69%; RR, 0.99 (CI, 0.86 to 1.13) Vomiting: 12% vs. 13%; RR, 0.89 (CI, 0.53 to 1.50) Rash: 7.5% vs. 6.2%; RR, 1.21 (CI, 0.58 to 2.51) Bowel ≤3 times/wk: 4% vs. 1.6%; RR, 2.56 (CI, 0.69 to 9.51)	Nonadherence: 14% vs. 15%, *P*=NS
Meier 2003 (31) United States *n*=111 Fair	60 mg elemental iron daily starting at first prenatal visit	Race: NR (Wisconsin) Private group practice	–	–	Adolescents: Nausea: 53% vs. 65%, *P*=NS Vomiting: 41% vs. 41%, *P*=NS Constipation: 29% vs. 12%, *P*=NS Diarrhea: 13% vs. 17%, *P*=NS Adults: 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: Adolescents: 4.5% vs. 12.6%, *P*=0.320 Adults: 2.2% vs. 16.1%, **P=0.036**
Romslo 1983 (36) Norway *n*=45 Fair	200 mg elemental iron daily starting within 10 wk of 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 (32) United States *n*=429 Fair	30 mg elemental iron daily starting at <20 wk of gestation	Race: Black 58%-65%, white 31%-37% Single: 75% Parity ≥2: 44% vs. 41% SES: 100% eligible for WIC	–	–	–	Nonadherence: 34% vs. 37%, *P*=0.27
Ziaei 2007 (27) Iran *n*=727 Good	50 mg elemental iron daily starting at 20 wk of gestation	Race: NR (Iran) BMI: 24 kg/m^2 Parity: 1.7	–	10 (2.7%) vs. 3 (0.8%), *P*=0.05	–	–

BMI = body mass index; GI = gastrointestinal; NR = not reported; NS = not significant; OR = odds ratio; RR = risk ratio; SES = socioeconomic status; WIC = Special Supplemental Nutrition Program for Women, Infants, and Children.