JAMA | US Preventive Services Task Force | EVIDENCE REPORT

# Screening and Supplementation for Iron Deficiency and Iron Deficiency Anemia During Pregnancy

## Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Amy G. Cantor, MD, MPH; Rebecca Holmes, MD, MS; Christina Bougatsos, MPH; Chandler Atchison, MPH; Thomas DeLoughery, MD; Roger Chou, MD

**IMPORTANCE** In 2015 the US Preventive Services Task Force (USPSTF) found insufficient evidence to assess the balance of benefits and harms of routine screening and supplementation for iron deficiency anemia during pregnancy.

**OBJECTIVE** To update the 2015 review on screening for iron deficiency anemia, in addition to iron deficiency during pregnancy, to inform the USPSTF.

**DATA SOURCES** Ovid MEDLINE and Cochrane databases through May 24, 2023; surveillance through May 24, 2024.

**STUDY SELECTION** Randomized clinical trials of iron supplementation, screening effectiveness, treatment, and harms; observational studies of screening.

**DATA EXTRACTION AND SYNTHESIS** Dual review of abstracts, full-text articles, study quality, and data abstraction. Data were pooled using a random-effects model.

**MAIN OUTCOMES AND MEASURES** Maternal and infant clinical outcomes, hematologic indices, and harms.

**RESULTS** Seventeen trials (N = 24 023) on maternal iron supplementation were included. Iron supplementation was associated with decreased risk of maternal iron deficiency anemia at term (4 trials, n = 2230; 8.6% vs 19.8%; relative risk, 0.40 [95% CI, 0.26-0.61]; $I^2$ = 20.5%) and maternal iron deficiency at term (6 trials, n = 2361; 46% vs 70%; relative risk, 0.47 [95% CI, 0.33-0.67]; $I^2$ = 81.9%) compared with placebo or no iron supplement. There were no statistically significant differences in maternal quality of life, rates of gestational diabetes, maternal hemorrhage, hypertensive disorders of pregnancy, cesarean delivery, preterm birth, infant low birth weight, or infants small for gestational age for maternal iron supplementation compared with placebo or no supplementation. Harms of iron supplementation included transient gastrointestinal adverse effects. No studies evaluated the benefits or harms of screening for iron deficiency or iron deficiency anemia during pregnancy. Data on the association between iron status and health outcomes, such as hypertensive disorders of pregnancy and preterm birth, were very limited.

**CONCLUSIONS AND RELEVANCE** Routine prenatal iron supplementation reduces the incidence of iron deficiency and iron deficiency anemia during pregnancy, but evidence on health outcomes is limited or indicates no benefit. No studies addressed screening for iron deficiency or iron deficiency anemia during pregnancy. Research is needed to understand the association between changes in maternal iron status measures and health outcomes.

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**Author Affiliations:** The Pacific Northwest Evidence-based Practice Center, Department of Medical Informatics and Clinical Epidemiology, Oregon Health & Science University, Portland (Cantor, Holmes, Bougatsos, Atchison, Chou); Department of Family Medicine, Oregon Health & Science University, Portland (Cantor); Department of Obstetrics and Gynecology, Oregon Health & Science University, Portland (Cantor); Department of Hematology/Oncology, Knight Cancer Institute, Oregon Health & Science University, Portland (DeLoughery); Department of General Internal Medicine, Oregon Health & Science University, Portland (Chou).

**Corresponding Author:** Amy G. Cantor, MD, MPH, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Mail Code BICC, Portland, OR 97239 (cantor@ohsu.edu).

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Iron deficiency is the most common pathologic cause of anemia during pregnancy, due in part to higher maternal iron needs and physiologic changes during pregnancy.[1-3] In the US, the overall prevalence of iron deficiency in pregnancy is nearly 18%, with a 5% prevalence of iron deficiency anemia,[3] although these may be underestimates due to changing diagnostic cutoffs.[4,5] Disparities in prevalence of iron deficiency anemia and iron deficiency have been reported, with higher prevalence among non-Hispanic Black and Mexican American individuals[3] and those at lower income levels.[6]

Given the high prevalence, screening for iron deficiency and iron deficiency anemia may lead to earlier identification and treatment and routine supplementation could treat underlying iron deficiency and iron deficiency anemia, potentially preventing negative health outcomes. However, evidence on the relationship between iron status and perinatal health outcomes is limited. Although older observational data report associations between various measures of iron status and negative perinatal outcomes in women and infants,[7-10] rigorous trial evidence has been inconsistent.[11-13]

In 2015, the US Preventive Services Task Force (USPSTF) concluded that the evidence was insufficient to assess the balance of benefits and harms of screening for iron deficiency anemia in pregnant women (I statement).[14] There was also inadequate evidence on treatment of iron deficiency anemia during pregnancy owing to lack of generalizability to US clinical settings in treatment studies, due to differential nutritional status or hemoparasite burden.[15] The USPSTF also concluded that the evidence was insufficient to assess the balance of benefits and harms of routine iron supplementation for pregnant women (I statement). This systematic review was conducted to update the 2015 review on this topic[11,16] and inform an updated USPSTF recommendation, with an expanded scope to evaluate the effect of iron supplementation and screening on iron deficiency without anemia.

## Methods

### Scope of the Review

Detailed methods and evidence tables with additional study details are available in the full evidence report.[17] **Figure 1** and **Figure 2** show the analytic frameworks and key questions that guided the review. This review was based on 2 separate analytic frameworks on the effectiveness of routine preventive iron supplementation during pregnancy and the effectiveness of screening for iron deficiency and iron deficiency anemia during pregnancy.

### Data Sources and Searches

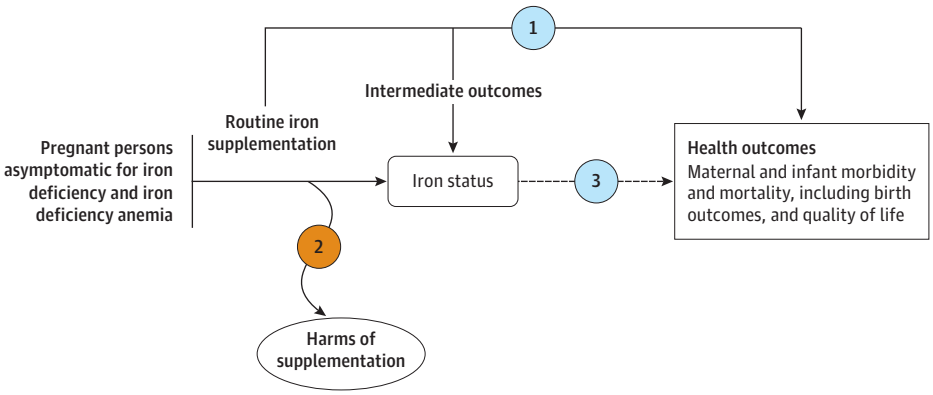
Searches included Ovid MEDLINE, the Cochrane Database of Systematic Reviews, and the Cochrane Central Register of Controlled Trials from June 1, 2014, to May 24, 2023 (for iron deficiency anemia) and from database inception to May 3, 2024 (for iron deficiency without anemia). For iron deficiency anemia, studies from the prior USPSTF review were included. Reference lists of relevant articles supplemented the searches. Surveillance was last conducted on May 24, 2024, and identified no studies eligible for inclusion.

### Study Selection

Two investigators independently reviewed English-language titles, abstracts, and full-text articles for inclusion using predefined criteria (eMethods 1 in the Supplement).

The population included pregnant adolescents and adults asymptomatic for iron deficiency or iron deficiency anemia. For supplementation, the population was those without known iron deficiency or iron deficiency anemia at study entry. For screening, the treated population was those found to have screen-detected iron deficiency or iron deficiency anemia. Studies of nonpregnant indi-

Figure 1. Analytic Framework and Key Questions: Routine Iron Supplementation During Pregnancy

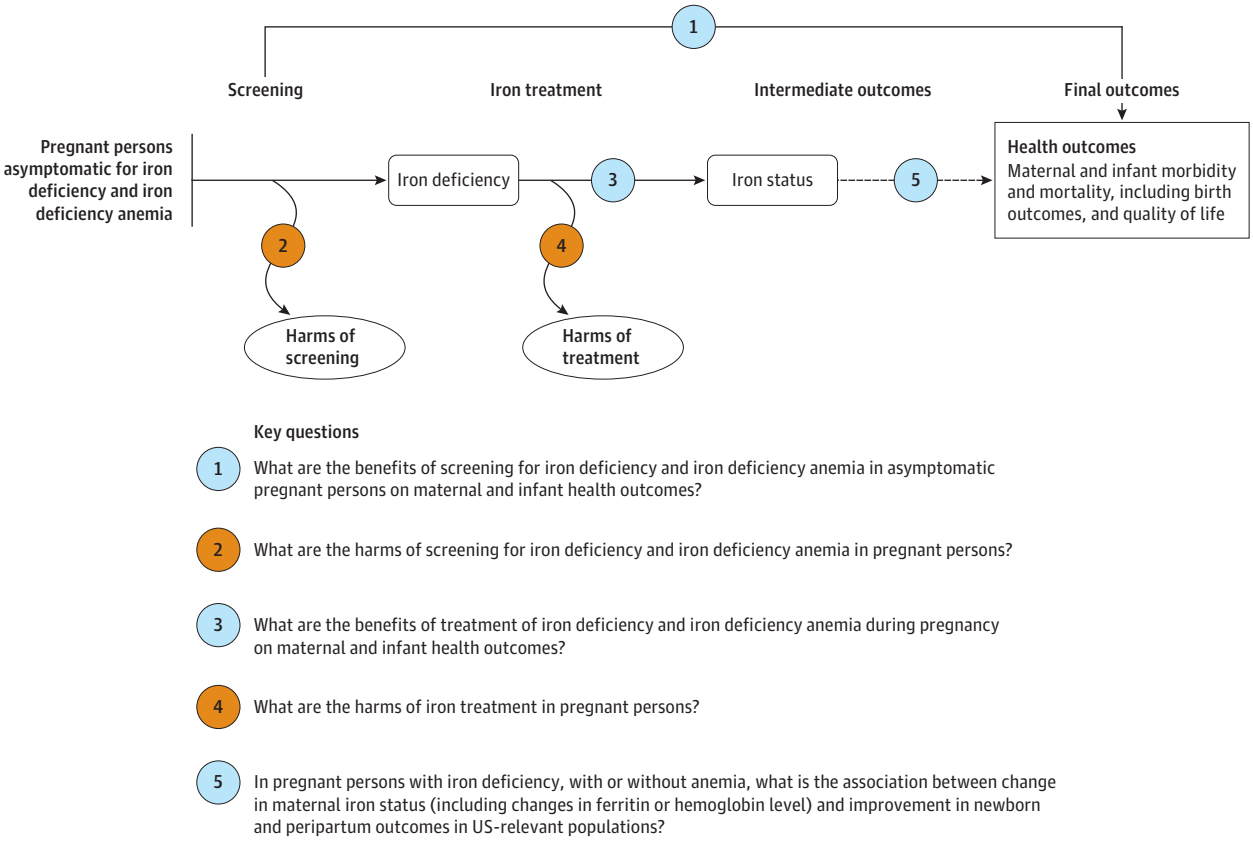



Key questions

1. What are the benefits of routine iron supplementation during pregnancy on maternal and infant health outcomes?
2. What are the harms of routine iron supplementation during pregnancy?
3. In pregnant persons 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 US-relevant populations?

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions (KQs) that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate interventions and outcomes. A dashed line depicts a health outcome that follows an intermediate outcome. For additional information, see the USPSTF Procedure Manual.[18]

Figure 2. Analytic Framework and Key Questions: Screening for Iron Deficiency and Iron Deficiency Anemia During Pregnancy

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viduals and those with known nutritional deficiencies or symptoms of iron deficiency or iron deficiency anemia were excluded. Nongendered terms (eg, person, individual) were used to increase inclusivity except where the data were specified as women or females, and the term "pregnant person" was used to characterize the study population that included pregnant women and other individuals capable of pregnancy.

For supplementation, interventions were oral iron supplementation or iron-fortified foods compared with placebo or no supplementation. Mean baseline gestational age at enrollment was used to estimate timing of dose initiation. Due to the availability of good- and fair-quality randomized clinical trials (RCTs) of supplementation, observational studies were only included for the association questions. Eligible maternal outcomes were health outcomes (eg, mortality, quality of life, preeclampsia, postpartum hemorrhage, postpartum depression, and cesarean delivery rates) and hematologic outcomes (eg, incidence of iron deficiency or iron deficiency anemia, hematologic indices). Infant outcomes were health outcomes (eg, perinatal mortality, respiratory distress, neonatal intensive care unit admission, low birth weight, small for gestational age, and preterm delivery) and hematologic outcomes. Adverse effects included clinical harms, harms leading to discontinuation, and accidental overdose. Timing of maternal outcomes was classified as during pregnancy, at term, and postpartum; infant outcomes were limited to the first year of life.

A question on the association between a change in maternal iron status and changes in health outcomes was included in both the screening (key question [KQ] 5) and supplementation (KQ3) frameworks. To be eligible for inclusion, studies had to examine the association between a change in maternal iron deficiency or iron deficiency anemia resulting from treatment or supplementation and improved health outcomes.

For the screening framework, studies compared screening with no screening or treatment with no treatment for screen-detected iron deficiency or iron deficiency anemia. Eligible interventions were routine blood tests (eg, complete blood cell count) and supplementation with oral or intravenous iron or iron-fortified foods. Eligible study designs included RCTs or controlled observational studies as well as large uncontrolled observational studies on harms. Supplementation outcomes also applied to the screening framework, with additional screening for specific harms such as overdiagnosis, anxiety, and labeling.

Inclusion was restricted to studies conducted in primary care or prenatal settings and in countries categorized in 2020 as high or very high on the United Nations Human Development Index (HDI)[19] to enhance applicability to US primary care/prenatal settings. Trials

from China were included for this update because of reclassification from a medium to a high HDI rating in 2011/2012.[20,21]

### Data Abstraction and Quality Rating

A single investigator abstracted details from each study including study design, patient population, setting, interventions, analysis, follow-up, and results. A second investigator reviewed data for accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor using predefined criteria developed by the USPSTF (eMethods 2 in the Supplement).[18] In accordance with the USPSTF Procedure Manual,[18] poor quality studies were excluded.

### Data Synthesis

Meta-analyses using the DerSimonian-Laird random-effects model (STATA version 14.2 [StataCorp]) were conducted for outcomes and comparisons for which there were multiple studies comparable enough to provide a meaningful combined estimate.[22] Stratified analyses were conducted to assess the potential variation across studies by country HDI rating (defined as very high HDI vs high HDI) and supplementation dosing based on elemental iron dose (defined as high if ≥60 mg and low if <60 mg). Hematologic values were pooled separately at term and third trimester time points; postpartum time points were not pooled due to variable and less frequent reporting. For intermediate outcomes, data were pooled for risk of iron deficiency or iron deficiency anemia, which were considered more informative than changes in individual hematologic indices such as ferritin or hemoglobin level.

Two independent reviewers assessed the aggregate internal validity (quality) for each KQ using methods developed by the USPSTF[18] based on the number, quality, and size of studies; consistency of results between studies; and directness of evidence.[18] Disagreements were resolved through consensus.

## Results

Across all KQs, 18 studies (reported in 28 publications[23-50]) of maternal iron supplementation (17 RCTs [N = 24 023] and 1 observational study[27] [N = 20 690]) were included (**Figure 3**). The observational study evaluated the association between improvement in iron indices and health outcomes and was relevant for both analytic frameworks. No other study addressed KQs on screening for iron deficiency or iron deficiency anemia. Twelve RCTs[23,24,26,28,29,34,36,37,41,43,48,49] addressing iron supplementation were carried forward from the prior USPSTF report.[11] Five RCTs[30,32,40,45,46] and the observational study[27] were added for this update.

### Benefits of Supplementation

**Key Question 1.** What are the benefits of routine iron supplementation during pregnancy on maternal and infant health outcomes?

Sixteen trials (in 26 publications) compared the effects of routine preventive iron supplementation vs no supplementation during pregnancy. Twelve trials (in 14 publications)[23,24,26,28,29,34,36-38,41,43,47-49] were carried forward from the prior review.[11] Four additional trials[25,31-33,35,40,42,44-46] and 2 new secondary publications[39,50] of older trials[34,37] were identified for this update. Three studies were conducted in the US,[26,36,43] 3 in rural China,[32,45,46] and 4 in Iran[29,40,48,49]; the others were conducted in Hong Kong,[24] Australia,[34] or Europe.[23,28,37,41]

Sample sizes ranged from 52 to 12 513 participants (total n = 23 844). Four studies had more than 1000 participants; 3 were added for this update, had the largest sample sizes, and were conducted in rural China (n = 12 513,[32] 3929,[45] and 2371[46]). Most studies included pregnant individuals at average risk for anemia and excluded those with baseline hemoglobin level below 8 g/dL to 11 g/dL, preexisting anemia, or related chronic conditions.[23,24,26,28,32,34,36,40,43,46,48,49] Mean baseline hemoglobin levels ranged from 11.9 g/dL to 14.3 g/dL. Seven studies reported providing treatment if hematologic indices dropped too low in the supplementation group during the course of the study.[24,28,34,36,40,48,49] Studies enrolled participants aged 20 to 30 years; 2 studies also included adolescents.[36,43] In 1 US study, 58% to 65% of participants were Black[43]; in another US study, 16% to 17% of participants were Hispanic, 24% to 25% non-Hispanic Black, and 56% to 57% non-Hispanic White.[43] Both of these studies restricted enrollment to individuals eligible for or participating in Special Supplemental Nutrition Program for Women, Infants, and Children services. Race, ethnicity, and socioeconomic status were not reported in the third US-based study, which was set in private group practice in Wisconsin.[36] No study stratified results according to population characteristics.

In all studies, supplementation was initiated at the first prenatal visit (up to 20 weeks' gestation) and continued through delivery; mean gestational age at enrollment ranged from 11 to 16 weeks in studies that reported this information. In 2 US studies, all participants in the placebo group received supplementation at 26 to 29 weeks' gestation[26,43] Outcomes were measured during the third trimester, at delivery, or included follow-up into the postpartum period (1 day to 6 months postpartum); 1 study included health-related quality of life follow-up to 4 years.[50] Supplement dosing ranged from 20 to 200 mg of elemental iron daily. Intervention groups in most studies received 30 to 60 mg of elemental iron daily; 1 study used 20 mg,[34] and 2 smaller studies used higher doses of 120 mg[23] or 200 mg.[41] Nonadherence, usually based on pill counts, ranged from 4.5% to 68%.[24,26,28,32,34,36,41,43,45,46]

Four studies were rated good quality[32,34,48,49] and 12 studies were rated fair quality[23,24,26,28,29,36,37,40,41,43,45,46] due to unclear randomization and allocation concealment methods; unclear masking of outcome assessors; high or unclear attrition or differential attrition; and inadequate randomization methods.

**Table 1** reports the results of meta-analyses, including analyses stratified by country and dose; forest plots for the primary meta-analyses are provided in eFigures 1-8 in the Supplement.

#### Maternal Clinical Outcomes

Routine iron supplementation was not associated with reduced risk of hypertensive disorders of pregnancy (eg, pregnancy-induced hypertension,[29,32,40] hypertensive disorder, or not defined[23,49]) compared with placebo, although the estimate was imprecise (5 trials; n = 13 610; 4.7% vs 3.1% [all studies pooled, weighted rates]; relative risk [RR], 1.24 [95% CI, 0.75-2.06]; $I^2$ = 48%) (eFigure 1 in the Supplement).[23,29,32,40,49] One trial found that supplementation was not associated with reduced risk of preeclampsia vs placebo but also had an imprecise estimate (3.9% vs 2.7%; RR, 1.45 [95% CI, 0.67-3.16]). Routine iron supplementation and placebo were associated with similar risk of cesarean delivery vs placebo (8 studies; n = 4919; 42.8% vs 41.5%; RR, 1.01 [95% CI, 0.90-1.14];

Figure 3. Literature Search Flow Diagram: Routine Iron Supplementation and Screening for Iron Deficiency and Iron Deficiency Anemia During Pregnancy




[a]The sum of the number of studies per key question (KQ) exceeds the total number of studies because some studies were applicable to multiple KQs.

[b]KQ3 in the routine iron supplementation framework and KQ5 in the screening for iron deficiency and iron deficiency anemia framework are the same KQ and therefore cover the same evidence.

Table 1. Summary of Meta-Analyses

| Outcome | Subgroup | Subgroup definition | No. of trials (No. of participants) | RR (95% CI) and ARD if significant | $I^2$, % |
|---|---|---|---|---|---|
| **Maternal clinical outcomes** | | | | | |
| Hypertensive disorders of pregnancy | All trials | NA | 5 (13 610) | 1.24 (0.75-2.06) | 48.0 |
| | Country (*P* = .64 for interaction) | Ireland (very high HDI) | 1 (97) | 0.83 (0.22-3.13) | NA |
| | | Rural China, Iran (medium to high HDI) | 4 (13 513) | 1.38 (0.74-2.56) | 60.9 |
| | Iron dose (*P* = .64 for interaction) | Low (<60 mg) | 3 (13 365) | 1.35 (0.70-2.61) | 71.6 |
| | | High (≥60 mg) | 2 (245) | 1.02 (0.30-3.47) | 0.0 |
| Cesarean delivery | All trials | NA | 8 (4919) | 1.01 (0.90-1.14) | 42.7 |
| | Country (*P* = .03 for interaction) | US or other applicable countries (very high HDI) | 4 (1562) | 0.85 (0.66-1.11) | 23.8 |
| | | Rural China, Iran (medium to high HDI) | 4 (3357) | 1.07 (1.01-1.14) | 0.0 |
| | Iron dose (*P* = .24 for interaction) | Low (<60 mg) | 4 (2173) | 1.11 (0.99-1.25) | 0.0 |
| | | High (≥60 mg) | 4 (2746) | 0.89 (0.67-1.20) | 67.6 |
| **Maternal hematologic outcomes** | | | | | |
| Iron deficiency anemia, third trimester | All trials | NA | 3 (660) | 0.63 (0.41-0.97)[a]<br>ARD, −4% (−8% to 0.02%)[a] | 0.0 |
| Iron deficiency anemia, at term | All trials | NA | 4 (2230) | 0.40 (0.26-0.61)[a]<br>ARD, −10% (−16% to −3%)[a] | 20.5 |
| | Country (*P* = .36 for interaction) | US or other applicable countries (very high HDI) | 3 (614) | 0.29 (0.15-0.55)[a]<br>ARD, −12% (−19% to −6%)[a] | 0.0 |
| | | Rural China (medium to high HDI) | 1 (1616) | 0.49 (0.38-0.62)[a]<br>ARD, −5% (−16% to 5%)[a] | NA |
| | Iron dose (*P* = .37 for interaction) | Low (<60 mg) | 1 (383) | 0.28 (0.12-0.68)[a]<br>ARD, −8% (−13% to −3%)[a] | NA |
| | | High (≥60 mg) | 3 (1847) | 0.42 (0.24-0.71)[a]<br>ARD, −11% (−19% to −2%)[a] | 21.0 |
| Iron deficiency, third trimester | All trials | NA | 4 (1220) | 0.70 (0.53-0.92)[a]<br>ARD, −17% (−24% to −10%)[a] | 77.4 |
| Iron deficiency, at term | All trials | NA | 6 (2361) | 0.47 (0.33-0.67)[a]<br>ARD, −34% (−46% to −22%)[a] | 81.9 |
| | Country (*P* = .60 for interaction) | US or other applicable countries (very high HDI) | 4 (596) | 0.35 (0.18-0.65)[a]<br>ARD, −44% (−63% to −25%)[a] | 79.3 |
| | | Rural China, Iran (medium to high HDI) | 2 (1765) | 0.57 (0.29-1.13) | 69.5 |
| | Iron dose (*P* = .58 for interaction) | Low (<60 mg) | 2 (431) | 0.57 (0.46-0.69)[a]<br>ARD, −32% (−52% to −11%)[a] | 0.0 |
| | | High (≥60 mg) | 4 (1930) | 0.26 (0.09-0.77)[a]<br>ARD, −36% (−54% to −18%)[a] | 86.0 |
| Anemia, third trimester | All trials | NA | 7 (2148) | 0.71 (0.51-0.97)[a]<br>ARD, −8% (−15% to −0.66%)[a] | 64.2 |
| Anemia, at term | All trials | NA | 4 (2261) | 0.43 (0.26-0.72)[a]<br>ARD, −12% (−15% to −9%)[a] | 43.7 |
| | Country (*P* = .61 for interaction) | US or other applicable countries (very high HDI) | 3 (645) | 0.22 (0.06-0.84)[a]<br>ARD, −12% (−19% to −6%)[a] | 49.3 |
| | | Rural China (medium to high HDI) | 1 (1616) | 0.53 (0.43-0.66)[a]<br>ARD, −12% (−15% to −8%)[a] | NA |
| | Iron dose (*P* = .95 for interaction) | Low (<60 mg) | 1 (393) | 0.45 (0.25-0.82)[a]<br>ARD, −9% (−15% to −2%)[a] | NA |
| | | High (≥60 mg) | 3 (1868) | 0.22 (0.05-1.02) | 61.1 |
| **Infant clinical outcomes** | | | | | |
| Preterm birth | All trials | NA | 5 (16 827) | 0.92 (0.81-1.04) | 0.0 |
| | Country (*P* = .88 for interaction) | Hong Kong (very high HDI) | 1 (862) | 0.95 (0.58-1.57) | NA |
| | | Rural China, Iran (medium to high HDI) | 4 (15 965) | 0.92 (0.81-1.04) | 0.0 |
| | Iron dose (*P* = .41 for interaction) | Low (<60 mg) | 2 (12 614) | 0.95 (0.83-1.10) | 0.0 |
| | | High (≥60 mg) | 3 (4213) | 0.83 (0.65-1.06) | 0.0 |

(continued)

Table 1. Summary of Meta-Analyses (continued)

| Outcome | Subgroup | Subgroup definition | No. of trials (No. of participants) | RR (95% CI) and ARD if significant | $I^2$, % |
|---|---|---|---|---|---|
| Low birth weight | All trials | NA | 6 (15 591) | 0.95 (0.79-1.14) | 0.0 |
| | Country (*P* = .83 for interaction) | US or other applicable countries (very high HDI) | 3 (601) | 1.02 (0.54-1.94) | 0.0 |
| | | Rural China, Iran (medium to high HDI) | 3 (14 990) | 0.95 (0.78-1.15) | 0.0 |
| | Iron dose (*P* = .26 for interaction) | Low (<60 mg) | 2 (12 257) | 1.05 (0.83-1.33) | 0.0 |
| | | High (≥60 mg) | 4 (3334) | 0.82 (0.61-1.10) | 0.0 |
| Small for gestational age | All trials | NA | 4 (5386) | 0.94 (0.67-1.31) | 75.5 |
| | Country (*P* = .21 for interaction) | US or other applicable countries (very high HDI) | 1 (862) | 0.48 (0.26-0.87)[a] ARD, −3.9% (−6.9% to −0.8%)[a] | NA |
| | | Rural China, Iran (medium to high HDI) | 3 (4524) | 1.07 (0.80-1.41) | 66.6 |
| | Iron dose (*P* = .53 for interaction) | Low (<60 mg) | 2 (1509) | 1.10 (0.59-2.05) | 83.3 |
| | | High (≥60 mg) | 2 (3877) | 0.75 (0.35-1.59) | 83.7 |

Abbreviations: ARD, absolute risk difference; HDI, Human Development Index; NA, not applicable; RR, relative risk.

[a] Statistically significant.

$I^2$ = 42.7%) (eFigure 2 in the Supplement).[23,24,34,36,40,46,48,49] Clinical indications for cesarean delivery were not reported in any study. Findings were similar when analyses were stratified by country HDI category and dose.

One trial (n = 430) found no statistically significant differences between routine iron supplementation during pregnancy vs placebo or no supplement on quality of life based on the 36-Item Short Form Health Survey at 36 weeks' gestation or at 6 weeks, 6 months, or 4 years postpartum.[34,50] There were also no statistically significant differences in risk of gestational diabetes (2 trials[24,40]; n = 2124) or risk of maternal hemorrhage (2 trials[23,48]; n = 341), although rates of hemorrhage were low (eTable 1 in the Supplement).

### Maternal Hematologic Outcomes

Sixteen trials (n = 23 844) reported maternal incidence of iron deficiency or iron deficiency anemia (Table 1; eTable 2 [third trimester], eTable 3 [term], and eTable 4 [postpartum] in the Supplement).[23-26,28,29,31-49] Routine iron supplementation during pregnancy was associated with a statistically significant decreased risk of maternal iron deficiency anemia at term (4 trials; n = 2230; 8.6% vs 19.8%; RR, 0.40 [95% CI, 0.26-0.61]; $I^2$ = 20.5%; absolute risk difference [ARD], −9.59% [95% CI, −16.2% to −2.98%]) (eFigure 3 in the Supplement); maternal iron deficiency at term (6 trials; n = 2361; 46% vs 70%; RR, 0.47 [95% CI, 0.33-0.67]; $I^2$ = 81.9%; ARD, −34.25% [95% CI, −46.49% to −22.01%]) (eFigure 4 in the Supplement); and anemia at term (4 trials; n = 2261; 10.9% vs 22.5%; RR, 0.43 [95% CI, 0.26-0.72]; $I^2$ = 43.7%; ARD, −11.73% [95% CI, −14.87% to −8.60%]) (eFigure 5 in the Supplement) compared with placebo or no supplementation. Findings were similar for third-trimester outcomes. For iron deficiency and iron deficiency anemia, stratified analysis by country HDI category and dose resulted in similar findings.

### Infant Clinical Outcomes

Eleven trials (n = 20 435; 3 good quality[32,34,49] and 8 fair quality[23,24,29,36,38,40,41,45]) reported infant birth outcomes including infant mortality, preterm delivery, small size for gestational age, and low birth weight (eTable 5 in the Supplement; summary of meta-analyses in Table 1).

Comparing maternal iron supplementation with placebo, there were no statistically significant differences in risk of preterm birth (5 trials[24,29,32,40,45]; n = 16 827; 5.5% vs 6.0%; RR, 0.92 [95% CI, 0.81-1.04]; $I^2$ = 0.0%) (eFigure 6 in the Supplement); infants small for gestational age (4 trials[24,40,45,49]; n = 5386; 15.3% vs 15.2%; RR, 0.94 [95% CI, 0.67-1.31]; $I^2$ = 75.5%) (eFigure 7 in the Supplement); or infants with low birth weight (6 trials[23,29,32,34,36,45]; n = 15 591; 2.7% vs 2.9%; RR, 0.95 [95% CI, 0.79-1.14]; $I^2$ = 0.0%) (eFigure 8 in the Supplement), although some imprecision in estimates was present. There was no statistically significant interaction between country HDI category or iron dose and effects of supplementation on infant outcomes (Table 1). There was statistical heterogeneity in the pooled estimate for small for gestational age. One small trial from Hong Kong found iron supplementation (60 mg) vs placebo associated with decreased risk of infant small for gestational age (3.6% vs −7.5%; RR, 0.48 [95% CI, 0.26-0.87]),[24] the 3 other trials from high HDI countries showed no statistically significant differences or favored placebo.[40,45,49] Infant mortality rates were not a prespecified outcome in any study, and event rates were low (<1% to 2%).

### Infant Hematologic Outcomes

Two trials (n = 12 943) found no statistically significant differences between routine iron supplementation during pregnancy vs placebo in infant hematologic indices at 6 months or 1 year follow-up.[32,34]

## Harms of Supplementation

**Key Question 2.** What are the harms of routine iron supplementation during pregnancy?

Eleven trials (n = 22 536)[24,26,28,32,34,36,40,41,43,45,46] included for KQ1 and 1 additional trial[30] addressed supplementation harms (eTable 6 in the Supplement). No trial reported any serious adverse events from iron supplementation, and infant harms were not reported in any study. One large (n = 12 513) trial conducted in rural China found elemental iron supplementation (30 mg) beginning in

Table 2. Summary of Evidence: Routine Iron Supplementation During Pregnancy

| Outcome | No. of studies (No. of participants) | Summary of findings by outcome | Consistency/precision, reporting bias | Body of evidence limitations | Overall quality | Strength of evidence | Applicability |
|---|---|---|---|---|---|---|---|
| **KQ1: Benefits of supplementation** | | | | | | | |
| Maternal: quality of life | 1 RCT (n = 430) | No statistically significant differences in quality of life for iron supplementation vs placebo in 1 trial at 36 wk of gestation, and at 6 wk, 6 mo, or 4 y postpartum | Unable to assess consistency (1 trial)<br>Imprecise<br>No reporting bias detected | Single trial<br>Outcome based on SF-36; reported as secondary outcome | Fair | Insufficient | One trial conducted in Australia<br>Applicability limited due to insufficient evidence |
| Maternal: hypertensive disorders of pregnancy | 5 RCTs (n = 14 468) | No statistically significant difference for iron supplementation vs placebo or no iron (5 trials; RR, 1.24 [95% CI, 0.75-2.06]; $I^2$ = 48%)<br>No statistically significant interaction in stratified analyses by country HDI category or supplement dose | Inconsistent<br>Imprecise<br>Some reporting bias detected | Poorly defined outcome definition: 3 studies reported pregnancy-induced hypertension, 1 study reported preeclampsia and PIH, 2 studies reported the category of hypertensive diseases of pregnancy | Fair | Low for no effect of iron supplementation on hypertensive disorders of pregnancy | Studies conducted in Ireland, Iran (3), rural China<br>Stratified analysis by country HDI category or supplement dose did not affect results |
| Maternal: gestational diabetes | 2 RCTs (n = 2214) | Two studies reported no statistically significant differences in rates of gestational diabetes for iron supplementation vs placebo | Consistent<br>Imprecise<br>No reporting bias detected | Diagnostic criteria defined in 1 of 2 studies | Fair | Insufficient | Studies conducted in Hong Kong and Iran; unclear diagnostic criteria |
| Maternal: cesarean delivery | 8 RCTs (n = 6160) | No statistically significant difference for iron supplementation vs placebo or no iron (8 trials; RR, 1.01 [95% CI, 0.90-1.14]; $I^2$ = 42.7%)<br>In 1 trial (n = 1164): Reduced risk of cesarean delivery for 60 mg elemental iron daily vs placebo (25.2% vs 33.1%; OR, 0.58 [95% CI, 0.37-0.89])<br>No statistically significant interaction in stratified analyses by country HDI category or supplement dose | Inconsistent<br>Some imprecision<br>No reporting bias detected | Cesarean delivery may occur for a variety of indications, including elective reasons | Fair | Low for no effect on cesarean delivery | Studies conducted in Ireland, Hong Kong, Australia, US, Iran (3), rural China<br>Cesarean delivery rates were unusually high in 2 studies<br>Stratified analysis by country HDI category or supplement dose did not affect results |
| Maternal: hemorrhage | 2 RCTs (n = 341) | Two studies report no statistically significant difference in rates of maternal hemorrhage | Consistent<br>Imprecise<br>No reporting bias detected | Low event rates in both studies | Fair | Insufficient for maternal hemorrhage | Studies conducted in Ireland and Iran |

(continued)

Table 2. Summary of Evidence: Routine Iron Supplementation During Pregnancy (continued)

| Outcome | No. of studies (No. of participants) | Summary of findings by outcome | Consistency/precision, reporting bias | Body of evidence limitations | Overall quality | Strength of evidence | Applicability |
|---|---|---|---|---|---|---|---|
| Maternal: iron deficiency anemia | 7 RCTs (n = 4045) | Iron supplementation associated with statistically significant reduced risk of iron deficiency anemia vs placebo or no iron:<br>Third trimester: 3 trials; RR, 0.63 (95% CI, 0.41-0.97); $I^2$ = 0%; ARD, −4% (95% CI, −8% to 0%)<br>Term: 4 trials; RR, 0.40 (95% CI, 0.26-0.61); $I^2$ = 20.5%; ARD, −10% (95% CI, −16% to −3%)<br>Statistically significant difference in stratified analyses, at term:<br>By country HDI category: RR, 0.29 (95% CI, 0.15-0.55); $I^2$ = 0.0%; ARD, −12% (95% CI, −19% to −6%) for very high HDI vs RR, 0.49 (95% CI, 0.38-0.62); $I^2$ = NA; ARD, −5% (95% CI, −16% to 5%) for medium to high HDI<br>By supplement dose: RR, 0.28 (95% CI, 0.12-0.68); $I^2$ = NA; ARD, −8% (95% CI, −13% to −3%) for low dose vs RR, 0.42 (95% CI, 0.24-0.71); $I^2$ = 21.0%; ARD, −11% (95% CI, −19% to −2%) for high dose | Consistent<br>Some imprecision<br>No reporting bias detected | Variable doses of iron supplements | Fair | Moderate for reduced risk of iron deficiency anemia during third trimester and at term | Studies conducted in US (3), Iran, Australia, Denmark, rural China; similar results in subgroup analysis by country<br>Clinical significance of differences is uncertain |
| Maternal: iron deficiency | 9 RCTs (n = 16 556) | Iron supplementation associated with statistically significant reduced risk of iron deficiency vs placebo or no iron:<br>Third trimester: 4 trials; RR, 0.70 (95% CI, 0.53-0.92); $I^2$ = 77.4%; ARD, −17% (95% CI, −24% to −10%)<br>Term: 6 trials; RR, 0.47 (95% CI, 0.33-0.67); $I^2$ = 81.9%; ARD, −34% (95% CI, −46% to −22%)<br>Mostly statistically significant differences in stratified analyses, at term:<br>By country HDI category: RR, 0.35 (95% CI, 0.18-0.65); $I^2$ = 79.3%; ARD, −44% (95% CI, −63% to −25%) for very high HDI, although medium to high HDI analysis showed no difference<br>By supplement dose: RR, 0.57 (95% CI, 0.46-0.69); $I^2$ = 0.0%; ARD, −32% (95% CI, −52% to −11%) for low dose vs RR, 0.26 (95% CI, 0.09-0.77); $I^2$ = 86.0%; ARD, −36% (95% CI, −54% to −18%) for high dose | Consistent<br>Some Imprecision<br>No reporting bias detected | Study heterogeneity ($I^2$) was high<br>Variable doses of iron supplements | Fair | Moderate for reduced risk of iron deficiency during third trimester and at term | Studies conducted in US (2), Norway (2), Iran, Australia, rural China (2), Denmark<br>Largest studies in rural China; analysis stratified by country showed similar results for very high HDI countries, but results of the analysis of medium to high HDI countries were no longer statistically significant<br>Clinical significance of differences is uncertain |

(continued)

Table 2. Summary of Evidence: Routine Iron Supplementation During Pregnancy (continued)

| Outcome | No. of studies (No. of participants) | Summary of findings by outcome | Consistency/precision, reporting bias | Body of evidence limitations | Overall quality | Strength of evidence | Applicability |
|---|---|---|---|---|---|---|---|
| Maternal: anemia | 9 RCTs (n = 20 330) | Iron supplementation associated with statistically significant decreased risk of anemia vs placebo or no iron:<br>Third trimester: 7 trials; RR, 0.71 (95% CI, 0.51-0.97); $I^2$ = 64.2%; 3 studies were statistically significant; ARD, −7.97% (95% CI, −15.28% to −0.66%)<br>Term: 4 trials; RR, 0.43 (95% CI, 0.26-0.72); $I^2$ = 43.7%; ARD, −11.73% (95% CI, −14.87 to −8.60%)<br>Mostly statistically significant differences in stratified analyses, at term:<br>By country HDI category: RR, 0.22 (95% CI, 0.06-0.84); $I^2$ = 49.3%; ARD, −12.42% (95% CI, −18.76% to −6.08%) for very high HDI vs RR, 0.53 (95% CI, 0.43-0.66); $I^2$ = NA; ARD, −11.67% (95% CI, −15.48% to −7.87%) for medium to high HDI<br>By supplement dose: RR, 0.45 (95% CI, 0.25-0.82); $I^2$ = NA; ARD, −8.54% (95% CI, −14.76% to −2.33%) for low dose vs RR, 0.22 (95% CI, 0.05-1.02); $I^2$ = 61.1% for high dose<br>Anemia rates ranged from 0% to 45% in the supplementation group and 4.5% to 61% in the placebo group | Inconsistent<br>Imprecise<br>Some reporting bias detected | Type of anemia not defined in most studies | Fair | Low | Studies conducted in US (2), Norway, Australia, rural China (3), Denmark<br>Largest studies conducted in rural China |
| Maternal: hemoglobin | 15 RCTs (n = 20 069) | Findings were inconsistent during the third trimester and postpartum and mostly significant at term, with higher hemoglobin values with supplementation vs placebo<br>Hemoglobin levels ranged from 11.0 to 13.9 g/dL in the supplementation group and 10.5 to 13.4 g/dL in the placebo group | Inconsistent<br>Imprecise<br>No reporting bias detected | Hemoglobin values decrease during pregnancy due to physiologic blood volume expansion and, in isolation, have unclear clinical significance | Fair | Low for increased hemoglobin | Studies conducted in US (3), Iran (5), Hong Kong, Australia, Ireland, Norway, Denmark, rural China (2) |
| Maternal: serum ferritin | 13 RCTs (n = 19 075) | Reported ferritin levels were inconsistent during the third trimester and postpartum and mostly significant at term with higher serum ferritin values with supplementation vs placebo in most studies<br>Serum ferritin levels ranged from 7.4 to 34 µg/L in the supplementation group and 6.0 to 26 µg/L in the placebo group | Inconsistent<br>Imprecise<br>Reporting bias not detected | Ferritin levels are associated with inflammation and, in isolation, have unclear clinical significance | Fair | Low for increased serum ferritin | Studies conducted in US (3), Hong Kong, Iran (3), Australia, Ireland, Norway, Denmark, rural China (2)<br>Clinical significance of these findings remains unclear |
| Infant: mortality | 6 RCTs (n = 17 863) | Five trials reported no statistically significant differences between maternal iron supplementation and infant mortality, while 1 study reported a statistically significant difference in rates of neonatal deaths (1.1% vs 2.0%; RR, 0.53 [95% CI, 0.29-0.97]) | Some inconsistency<br>Imprecise<br>No reporting bias detected | Not a prespecified outcome in any study; event rates were generally low | Fair | Insufficient | Studies conducted in Ireland, rural China (2), Australia, US, Iran |
| Infant: preterm birth | 5 RCTs (n = 18 714) | No statistically significant difference for iron supplementation vs placebo (5 trials; RR, 0.92 [95% CI, 0.81-1.04]; $I^2$ = 0%)<br>No statistically significant difference in stratified analyses by country HDI category or supplement dose | Consistent<br>Precise<br>No reporting bias detected | Reported as a secondary outcome | Fair | Moderate for no effect of iron supplementation on preterm birth | Studies conducted in Hong Kong, Iran (3), rural China (2)<br>Stratified analysis by country HDI category or supplement dose did not affect results |

*(continued)*

Table 2. Summary of Evidence: Routine Iron Supplementation During Pregnancy (continued)

| Outcome | No. of studies (No. of participants) | Summary of findings by outcome | Consistency/precision, reporting bias | Body of evidence limitations | Overall quality | Strength of evidence | Applicability |
|---|---|---|---|---|---|---|---|
| Infant: small for gestational age | 4 RCTs (n = 6803) | No statistically significant difference for iron supplementation vs placebo (4 trials; RR, 0.94 [95% CI, 0.67-1.31]; $I^2$ = 75.5%)<br>No statistically significant difference in stratified analyses by country HDI category or supplement dose, with 1 exception: the 1 very high HDI trial (RR, 0.48 [95% CI, 0.26-0.87]) | Inconsistent<br>Imprecise<br>No reporting bias detected | Reported as a secondary outcome | Fair | Insufficient | Studies conducted in Hong Kong, rural China, Iran |
| Infant: low birth weight | 6 RCTs (n = 17 261) | No statistically significant difference for iron supplementation vs placebo (6 trials; RR, 0.95 [95% CI, 0.79-1.14]; $I^2$ = 0.0%)<br>No statistically significant difference in stratified analyses by country HDI category or supplement dose | Some inconsistency<br>Some imprecision<br>No reporting bias detected | Reported as a secondary outcome | Fair | Moderate for no effect of iron supplementation on LBW | Studies conducted in Ireland, Iran, rural China (2), Australia, US<br>Stratified analysis by country HDI category or supplement dose did not affect results |
| Infant: hematologic outcomes | 2 RCTs (n = 12 943) | Infant hemoglobin and anemia reported at 6 mo and 1 y in 1 trial, and infant hemoglobin level, ferritin level, iron deficiency, and iron deficiency anemia reported in another trial at 6 mo<br>No statistically significant differences reported between groups for any hematologic indices or time points | Consistent<br>Imprecise<br>No reporting bias detected | Changes in infant intermediate outcomes up to 1 y could be multifactorial; only the smaller trial (n = 430) reported iron deficiency and iron deficiency anemia outcomes, and event rates were low | Fair | Insufficient | Studies conducted in rural China and Australia |
| **KQ2: Harms of supplementation** | | | | | | | |
| | 12 RCTs (n = 22 716) | Twelve trials (11 included in KQ1) assessed harms of routine iron supplementation in pregnant women<br>Most reported harms included transient treatment effects such as nausea, constipation, and diarrhea, and all but 1 found no difference in harms; 1 large trial conducted in rural China found a higher rate of gastrointestinal discomfort for those receiving supplementation (3.6% vs 2.3%; RR, 1.59 [95% CI, 1.28-1.97])<br>Nine trials found no statistically significant differences in nonadherence to supplementation vs placebo between groups; however, 1 trial had lower nonadherence in the supplementation group than in the placebo group | Mostly consistent<br>Some imprecision<br>Some reporting bias detected | Outcomes mostly reported as ad hoc events | Fair | Moderate for no major harms and some transient adverse effects of prenatal iron supplementation | Studies conducted in Hong Kong, US (3), Norway, rural China (3), Australia, Iran (2), Norway |
| **KQ3: Association between change in maternal iron status and improvement in newborn and peripartum outcomes** | | | | | | | |
| | 1 Observational study (n = 20 690) | Response to iron therapy was associated with a reduction in the odds of preeclampsia and preterm delivery compared with persons with untreated anemia or those who did not respond to treatment | Unable to assess consistency<br>Imprecise<br>Reporting bias detected | Inconsistent methods for defining anemia; included participants already using iron supplementation; lack of reporting on methods for outcome assessment; unclear documentation of iron deficiency or use of supplementation; unclear classification and reporting of symptoms | Fair | Insufficient | Conducted in US; some participants already using iron supplementation; lack of information on dosing, timing, or duration of treatment |

Abbreviations: ARD, absolute risk difference; HDI, Human Development Index; KQ, key question; LBW, low birth weight; NA, not available; OR, odds ratio; PIH, pregnancy-induced hypertension; RCT, randomized clinical trial; RR, relative risk; SF-36, 36-Item Short Form Health Survey.

Table 3. Summary of Evidence: Screening for Iron Deficiency and Iron Deficiency Anemia During Pregnancy

| No. of studies (No. of participants) | Summary of findings by outcome | Consistency/ precision, reporting bias | Body of evidence limitations | Overall quality | Strength of evidence | Applicability |
|---|---|---|---|---|---|---|
| **KQ1: Benefits of screening** | | | | | | |
| No studies | NA | NA | NA | NA | Insufficient | NA |
| **KQ2: Harms of screening** | | | | | | |
| No studies | NA | NA | NA | NA | Insufficient | NA |
| **KQ3: Benefits of treatment** | | | | | | |
| No studies | NA | NA | NA | NA | Insufficient | NA |
| **KQ4: Harms of treatment** | | | | | | |
| No studies | NA | NA | NA | NA | Insufficient | NA |
| **KQ5: Association between change in maternal iron status and improvement in newborn and peripartum outcomes[a]** | | | | | | |
| 1 Observational study (n = 20 690) | Response to iron therapy was associated with a reduction in the odds of preeclampsia and preterm delivery compared with persons with untreated anemia or those who did not respond to treatment | Unable to assess consistency<br>Imprecise<br>Some reporting bias detected | Inconsistent methods for defining anemia; included participants already using iron supplementation; lack of reporting on methods for outcome assessment; unclear documentation of iron deficiency or use of supplementation; unclear classification and reporting of symptoms | Fair | Insufficient | Conducted in US; some participants already using iron supplementation; lack of information on dosing, timing, or duration of treatment |

Abbreviations: KQ, key question; NA, not applicable.

[a] Same as KQ3 in the supplementation framework.

the second trimester associated with increased risk of gastrointestinal symptoms vs placebo (3.6% vs 2.3%; RR, 1.59 [95% CI, 1.28-1.97]).[32] In contrast, no statistically significant differences in rates of gastrointestinal adverse effects (variably defined) between supplementation and placebo groups were reported in 5 other studies (n = 7053).[30,34,36,45,46]

Nonadherence, a potential marker of intolerability, was similar between supplementation vs placebo in 10 trials (n = 21 397).[24,26,28,32,34,36,41,43,45,46]

### Change in Maternal Iron Status and Improvement in Newborn and Peripartum Outcomes

**Key Question 3.** In pregnant persons 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 US-relevant populations?

One fair-quality, US-based observational study (n = 20 690) added for this update compared the association between response to iron supplementation in pregnant persons with iron deficiency (with or without anemia) and risk of preeclampsia or preterm delivery.[27] Patients in a perinatal database were classified as anemic (n = 7416) or nonanemic (reference group; n = 13 274), with anemic patients further categorized by treatment group (treated or untreated anemic, n = 3402) and, among those treated, response to treatment (refractory anemic, n = 1319; or successfully treated, n = 2695). Dosing, timing, and duration of treatment or iron supplementation was not reported. Most participants identified as Black race (9%-24%) or Hispanic ethnicity (43%-63%). Methodologic limitations included unclear documentation of iron deficiency or use of supplementation and unclear classification and reporting of symptoms.

Successful response to treatment was defined as presenting to labor and delivery with normal hemoglobin level and reporting having taken iron supplementation; this was associated with reduced risk of preterm birth (adjusted odds ratio [OR], 0.59 [95% CI, 0.47-0.72]) and preeclampsia (adjusted OR, 0.75 [95% CI, 0.6-0.91]) vs no anemia. Refractory or untreated anemia was associated with increased risk of preterm birth and preeclampsia (adjusted OR, 1.44 [95% CI, 1.16-1.76] and adjusted OR, 1.45 [95% CI, 1.26-1.67], respectively) vs no anemia. There were no differences between groups in composite neonatal morbidity.

### Screening for Iron Deficiency and Iron Deficiency Anemia During Pregnancy

No studies addressed key questions on the effectiveness of screening on any maternal or infant health outcomes, including benefits or harms. Evidence on the association between change in maternal iron status and improvement in outcomes (KQ3) is addressed in the Supplement.

## Discussion

The findings of this evidence report are summarized in **Table 2** and **Table 3**. Despite the inclusion of data from 5 additional RCTs of supplementation,[30,32,40,45,46] conclusions were consistent with findings from the previous USPSTF review.[11] Specifically, iron supplementation decreases the risk of iron deficiency or iron deficiency anemia during pregnancy and at delivery, without evidence of improvement in maternal or infant clinical outcomes. As in the prior USPSTF review, no studies evaluated the benefits or harms of screening. Expanding the scope to assess the impact of iron supplementation or screening on iron deficiency alone or inclusion of trials from

high HDI index countries (including rural China) did not affect the results.

There were no clear effects of prenatal iron supplementation on maternal clinical outcomes including hypertensive disorders of pregnancy, gestational diabetes, or cesarean delivery, but estimates were imprecise. Results were somewhat inconsistent for cesarean delivery, with 1 fair-quality, large trial[24] finding supplementation associated with reduced risk of cesarean delivery but 8 trials of varying sizes and similar dosing regimens finding no difference. However, effects on cesarean delivery are difficult to interpret due to lack of information on indications (eg, elective or urgent) and the lack of a clear mechanism by which iron deficiency or iron deficiency anemia would affect cesarean delivery. Some observational studies[51-53] not eligible for this review suggest that iron supplementation may increase the risk of gestational diabetes, but results are susceptible to residual confounding. Data on harms were limited, but no serious harms were reported.

Regarding infant health outcomes, iron supplementation was not associated with decreased rates of preterm delivery, low birth weight infants, or infants small for gestational age. Findings regarding infant outcomes were limited by relatively small numbers of trials (eg, 6 trials reporting preterm delivery, 3 trials reporting small for gestational age, and 6 trials for low birth weight) and imprecision. In addition, there was unexplained statistical heterogeneity in the pooled estimate for small for gestational age. There was insufficient evidence to assess the effect of prenatal iron supplementation on infant mortality due low event rates.

As in the prior USPSTF review, maternal iron supplementation, compared with placebo or no supplements, was associated with improved hematologic indices or incidence of iron deficiency or iron deficiency anemia, but the clinical significance of these findings remains unclear. No study evaluated outcomes of screening vs no screening for iron deficiency or iron deficiency anemia in pregnant adults or adolescents. One study of supplementation added to this review provided insufficient evidence to evaluate the association between a change in maternal iron status and clinical outcomes, due to serious methodological limitations.[27]

Studies included in this review focused on pregnant adults and adolescents at average risk for anemia and excluded those with very low hematologic indices at baseline or preexisting anemia or related chronic conditions. Therefore, results of this review may not apply to settings in which pregnant individuals have lower baseline hematologic indices or higher incidence of severe anemia. No study evaluated how outcomes of supplementation varied by population, including those defined by race or ethnicity. Observational studies suggest potential disparities in the incidence of iron deficiency and iron deficiency anemia by socioeconomic status and race or ethnicity, but data are difficult to interpret due to variation in practice guidelines and variability in diagnostic cutoffs by race or ethnicity and may be affected by access to health care services.

### Limitations

This review had several limitations. First, non–English-language articles were excluded, which could result in language bias, although no non–English-language studies that would have met inclusion criteria were identified. Second, publication bias was not formally assessed with graphical or statistical methods[54] because of small numbers of studies and differences in study design, populations, and outcomes assessed. Third, some trials eligible for inclusion because of country categorization as high on the HDI (eg, Hong Kong, rural China; Iran) may have limited generalizability to the US due to differences in nutritional status, diet, resources, infrastructure, or other factors.[19,55,56] However, stratified analyses did not indicate subgroup differences based on HDI category (high vs very high). Fourth, due to anticipated statistical heterogeneity with regard to populations, setting, rates of iron deficiency or iron deficiency anemia, supplementation dose and timing, and other factors, the DerSimonian and Laird random-effects model was used to pool studies, which may result in overly narrow confidence intervals when heterogeneity is present, particularly when the number of studies is small.[22] To evaluate statistical heterogeneity, subgroup analysis was performed to assess the sensitivity of results to variations across study characteristics, including country HDI rating and low and high supplementation dosing based on elemental iron doses. Results did not indicate statistically significant subgroup effects based on these characteristics. However, the utility of stratified analyses was limited by relatively small numbers of trials.

## Conclusions

Routine prenatal iron supplementation reduces the incidence of iron deficiency and iron deficiency anemia during pregnancy, but evidence on health outcomes is limited or indicates no benefit. No studies addressed screening for iron deficiency or iron deficiency anemia during pregnancy. Research is needed to understand the association between changes in maternal iron status measures and health outcomes.

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*Concept and design:* Cantor, Bougatsos, DeLoughery, Chou.
*Acquisition, analysis, or interpretation of data:* All authors.
*Drafting of the manuscript:* Cantor, Holmes, Bougatsos, Atchison, DeLoughery.
*Critical review of the manuscript for important intellectual content:* Cantor, Holmes, DeLoughery, Chou.
*Statistical analysis:* Cantor, Holmes.
*Obtained funding:* Cantor, Bougatsos, Chou.
*Administrative, technical, or material support:* Cantor, Holmes, Bougatsos, Atchison, DeLoughery.
*Supervision:* Cantor, Bougatsos, DeLoughery, Chou.

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**Editorial Disclaimer:** This evidence report is presented as a document in support of the accompanying USPSTF recommendation statement. It did not undergo additional review after submission to *JAMA*.

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