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SYSTEMATIC REVIEW

Iron supplements in pregnant women with normal iron status: A systematic review and meta-analysis

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Abstract

Introduction: Effects of daily iron supplementation in iron replete pregnancy are unclear. This systematic review aimed to assess benefits and harms of oral iron supplements in pregnant women without anemia and iron deficiency.

Material and methods: We predefined and registered a protocol in PROSPERO (CRD42020186210) and performed the review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. We searched for randomized clinical trials (RCTs) and observational studies comparing daily oral iron supplementation with no iron supplements in non-anemic iron replete pregnant women. Searches were conducted in MEDLINE (by PubMed), EMBASE (by OVID), Cochrane Library, and ClinicalTrials.gov from inception to September 2022 without language restrictions. Two authors independently screened records, extracted data, and assessed risk of bias using the revised Cochrane risk of bias tool (RoB2). One author read full-texts, assessed certainty of evidence by GRADE and conducted meta-analyses using a random-effects model. Primary outcomes included iron deficiency anemia, iron deficiency, hemoglobin >130 g/L, elevated iron status, small for gestational age newborns, low birthweight newborns, preterm birth, and congenital anomalies.

Results: Eight RCTs (2822 women) but no observational studies were eligible for inclusion. Daily oral iron supplementation in pregnancy probably reduces iron deficiency anemia at term (risk ratio [RR]: 0.51, 95% confidence interval [CI]: 0.38–0.70; 4 RCTs, 1670 women; $I^2 = 13\%$; moderate-certainty evidence) and the incidence of low birthweight babies (RR: 0.30, 95% CI: 0.13–0.68; 2 RCTs, 361 infants; $I^2 = 0\%$; moderate-certainty evidence). In addition, it may reduce iron deficiency at term (RR: 0.74, 95% CI: 0.60–0.92; 4 RCTs, 1663 women; $I^2 = 58\%$; low-certainty evidence) and the incidence of small for gestational age babies (RR: 0.39, 95% CI: 0.17–0.86; 1 RCT, 213 infants; I^2 not estimable; low-certainty evidence).

Abbreviations: CI, confidence interval; GRADE, Grades of Recommendation, Assessment, Development and Evaluation framework; Hb, hemoglobin; LBW, low birthweight; RCT, randomized clinical trial; RR, risk ratio; SGA, small for gestational age.

Conclusions: Daily iron supplementation in iron replete non-anemic pregnant women probably reduces the risk of maternal iron deficiency anemia at term and low birthweight.

KEYWORDS
iron, iron deficiency, iron replete, maternal iron deficiency, non-anemic, pregnant, review

1 | INTRODUCTION

Iron status is defined by the amount of stored and mobilizable body iron.[1] During pregnancy iron is crucial for a range of vital functions including oxygen delivery and fetal organogenesis,[2] and iron requirements increase as gestation proceeds.[3] As iron is prioritized for erythropoiesis, iron deficiency anemia is an end-stage result of iron deficiency.[4] While anemia is a key contributor to maternal and offspring morbidity,[5] high hemoglobin (Hb) and iron status have also been associated with higher risks of adverse pregnancy outcomes.[6,7] This has raised questions to whether or not all women should be advised iron supplements in pregnancy, and especially if it is safe for women with normal Hb and iron status. There are various theories about the potential harmful mechanisms of high iron status; for instance, placental oxidative stress, altered maternal gut microbiome, impaired immunity, and excessive erythropoiesis with increased blood viscosity and compromised placental flow.[6]

A Cochrane review has concluded that use of iron supplements in pregnancy reduces the risk of iron deficiency and iron deficiency anemia near term, but also increases the risk of high Hb. No clear beneficial effect on infant and maternal clinical outcomes could be demonstrated.[8] However, a substantial number of women enter pregnancy with normal Hb and iron, but no analyses in the Cochrane review incorporated initial maternal iron status. How the use of iron supplements in non-anemic iron replete pregnant women effect newborn and maternal health therefore remains unclear. The aim of this systematic review was to assess benefits and harms of daily use of oral iron supplements by non-anemic pregnant women with normal iron status.

Key message

Daily iron supplementation in iron replete non-anemic pregnant women probably reduces the risk of maternal iron deficiency anemia and low birthweight. However, its effect on several clinical infant and maternal outcomes remains unclear and warrants further study.

2 | MATERIAL AND METHODS

A study protocol was developed prior to study start and registered in the international prospective register of systematic reviews registry (PROSPERO: CRD42020186210). Patients were not involved in the planning or conduct of this systematic review. Reporting of the review adheres to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[9] The work was paid for by internal funding only.

2.1 | Data sources and searches

With assistance from an information specialist, we searched The Cochrane Library, MEDLINE (by PubMed), and Embase (by Ovid) for observational studies and randomized clinical trials (RCTs) published to September 13, 2022, comparing oral iron supplementation with no iron supplementation in iron replete non-anemic pregnant women. Search terms and detailed search strategies are provided in Table S1. We conducted the first search on August 27, 2020, and a final updated search on September 13, 2022, respectively. The ClinicalTrials.gov registry was searched for both completed and ongoing studies. In addition, we screened reference lists of the included papers as well as of relevant systematic reviews and meta-analyses. We applied no time or language restriction.

2.2 | Selection criteria

We aimed to include RCTs and observational studies that compared oral iron supplementation with iron-free supplements, placebo, or no intervention in non-anemic iron replete pregnant women, determined by Hb and at least one additional indicator of iron status (ferritin, transferrin, transferrin saturation and/or soluble transferrin receptor) measured no more than 20 weeks prior to, or after, conception. We excluded studies published only as abstracts or without original data. A study was included if it used an iron supplement in tablet or capsule formulation containing either iron alone or iron in conjunction with ascorbic- and/or folic acid as experimental intervention and compared it to supplements without iron, placebo, or no treatment. We did not include studies examining food-based interventions, parenteral iron, or studies with regimens where iron was not provided daily. Cointerventions (such as education) were only allowed if both the iron and comparison groups received the same cointerventions.

2.3 | Outcomes

All primary and secondary outcomes are summarized in Table S2.

Maternal primary outcomes included iron deficiency anemia at term (≥37 weeks' gestation); iron deficiency at term; Hb > 130 g/L in pregnancy; elevated iron status in pregnancy. Secondary outcomes for mothers included Hb < 70 g/L in pregnancy (severe anemia), gestational diabetes, pre-eclampsia, gestational hypertension, infections, red blood cell transfusion, postpartum anemia, gastrointestinal side effects, quality of life, and fatigue.

Newborn primary outcomes included small for gestational age (SGA; <10th percentile of weight at birth for gestational age); low birthweight (LBW; <2500 g); preterm birth (before 37 weeks' gestation); and congenital anomalies. Secondary outcomes for newborns included failure to thrive and concentrations of Hb and ferritin in the first 6 months.

For outcomes defined as in pregnancy, we included the information reported closest to term if the incidence was reported at more than one timepoint in a study (eg at both 28- and 37-weeks' gestation). We originally intended to assess iron deficiency anemia in pregnancy both overall and at term, but as the data extracted for these two outcomes ended up being identical, we have chosen to report this as a single outcome: iron deficiency anemia at term.

2.4 | Study selection

One author removed duplicates (RH). Titles and abstracts from database searches were independently screened by two authors (RH and EPFS) using the Rayyan QCRI online software (http://rayyan.qcri.org). Records from the ClinicalTrials.gov registry were likewise independently screened (RH and EPFS). Disagreements were resolved by discussion or, if necessary, a third author was consulted (JBS). Full text versions were obtained for all potentially relevant documents and read by one author (RH), who advised a second and third party (EPFS and JBS) when uncertain about a publication's eligibility. If uncertainty could not be solved by discussion, we tried to contact the author of the study for additional information.

2.5 | Data extraction

Two authors (RH and EPFS) independently extracted information from each included study and recorded data in identical spreadsheets. If a study reported an outcome in more than one publication, data were included only once and extracted from the publication with the most comprehensive data. Disagreements were resolved by discussion or, if necessary, by a third author (JBS). In addition to maternal and infant outcomes and definitions of these (Table S2), we extracted information about study design, eligibility criteria, location, number of participants, baseline Hb, baseline iron status, and allocated treatment (including type, dose, and duration). When needed, we contacted authors and requested clarifying and/or additional information.

2.6 | Assessment of risk of bias and the quality of evidence

Included studies were assessed for risk of bias by two authors (RH and EPFS) independently. We assessed RCTs with the revised Cochrane risk of bias tool (RoB2).[10] We planned to assess observational studies with the risk of bias in non-randomized studies - of interventions (ROBINS-I) tool,[11] but found no observational studies that were eligible for inclusion. Disagreements were resolved by discussion or, if necessary, by a third party (JBS). The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) framework[12] and GRADEpro GDT online software (McMaster University, 2020, Ontario, Canada, https://gradepro.org) was used to rate the certainty of the effect and to generate "Summary of findings" tables. Outcomes were rated and downgraded according to the presence or absence of factors (risk of bias, inconsistency, indirectness, imprecision, publication bias) affecting the quality of the body of studies included in each outcome.

2.7 | Statistical analysis

We analyzed data using Review Manager software (RevMan Version 5.4, The Cochrane Collaboration, 2020). We used a random-effects model as we expected some between-trial differences in study designs (eg participants, intervention). We tested for heterogeneity using the I^2 statistic. Summary risk ratio (RR) with 95% confidence intervals (CIs) were calculated. Analyses were performed by one reviewer (RH) and reviewed by a second and third party (EPFS and JBS). We planned to perform sensitivity analyses based on risk of bias by repeating analyses after excluding studies at high risk. For primary outcomes we planned to conduct subgroup analyses based on daily elemental iron dose (low: ≤30 mg; medium: >30 mg and <60 mg; high: ≥60 mg) and based on gestational age at start of intervention (before/after 20 weeks' gestation).

3 | RESULTS

3.1 | Selection process

We identified 4960 citations through the electronic and manual searches (Figure 1). After excluding duplicate citations, we screened the titles and abstracts of 3142 publications (2696, 198, and 248 identified in the first and updated database searches, respectively) and screened 211 records identified in the ClinicalTrials.gov registry. Eight additional relevant publications were identified from reference lists. Of the 3361 screened records we excluded 3234 as irrelevant and a total of 127 publications were assessed in full text. We tried to contact authors when we believed that additional information could lead to inclusion. However, the majority of the contacted authors either did not respond to our request or replied that they had no current access to data. Among all assessed publications, we found no observational studies eligible for inclusion. Subsequently, eight

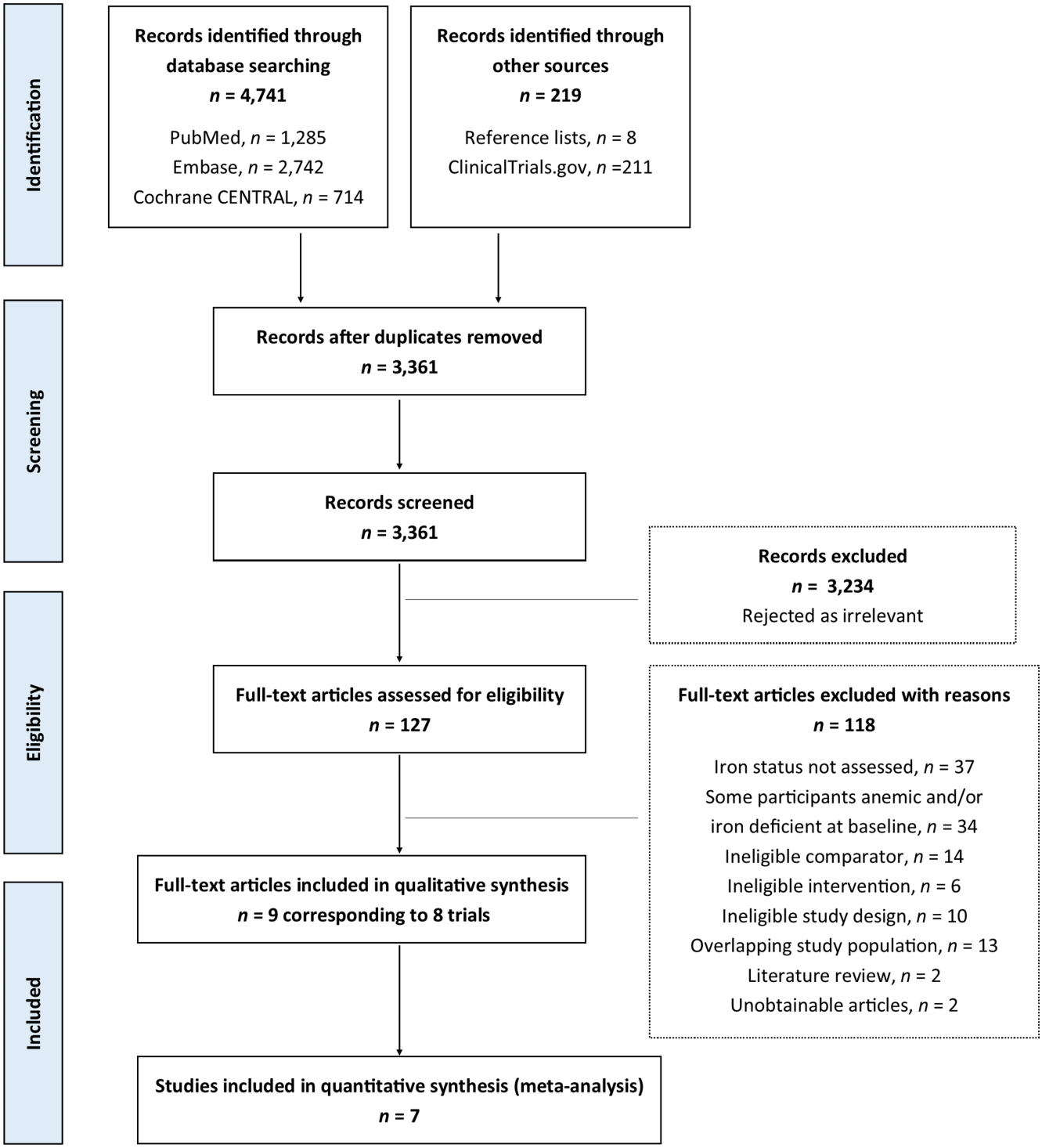

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

unique randomized trials (in nine publications)[13–21] could be included in the systematic review.

3.2 | Characteristics

The eight trials included 2822 participants, of whom 1430 were randomly allocated to receive iron supplements vs 1392 randomly allocated to receive no iron. Characteristics of all included trials are summarized in Table 1. Three trials had been conducted in Iran[17–19,21] and the remaining in Finland,[13] Italy,[14] Sweden,[15] USA[16] and China,[20] respectively. Two trials provided us with additional outcome data[16,20] and another three responded but could not provide us with the requested outcome data.[15,19,21] One of the latter trials[15] did not report any of our predefined primary or secondary outcomes and could therefore not contribute with data to any meta-analyses.

TABLE 1 Characteristics of the included studies.

Trial	Country	Design	Treatment; no of patients I: Iron C: Comparator T: Total	Duration of intervention	Iron intervention	Comparator intervention	Adherence assessment I: Iron C: Comparator	Plan in case of treatment failure	BaselineHb (g/L)[a] I: Iron C: Comparator	Baseline ferritin (ng/mL)[a] I: Iron C: Comparator
Puolakka et al. (1980)[13]	Finland	RCT, non-blinded	I: 16 C: 16 T: 32	Start: 16 weeks' gestation Stop: 1 month postpartum	Ferrous sulfate, 100 mg, twice daily	No treatment	Not described	Not described	I: 119 ± 7 C: 121 ± 6	Geometric mean (±1 SD range): I: 97 (55–171) C: 86 (50–150)
Tura et al. (1989)[14]	Italy	RCT, non-blinded	I: 136 C: 118 T: 254	Start: 12–16 weeks' gestation Stop: 2 months postpartum	Capsules (preparation not specified), 40 mg elemental iron, once daily	No treatment	Participants taking more or less than intended I: 6% C: 9%	Not described	I: 128 ± 8 C: 129 ± 9	I: 63 ± 27 C: 63 ± 38
Tholin et al. (1995)[15]	Sweden	RCT, double-blind	I: 27 C: 21 T: 48	Start: 20 weeks' gestation throughout pregnancy (stop not specified)	Ferrous sulfate, 100 mg elemental iron, once daily	Placebo, not further described, once daily	Not described	Not described	Median (range): I: 128 (111–150) C: 126 (119–142)	Median (range): I: 43 (17–102) C: 42 (23–212)
Cogswell et al.[b,c] (2003)[16]	USA	RCT, double-blind	I: 146 C: 129 T: 275	Start: <20 weeks' gestation throughout pregnancy (stop not specified)	Ferrous sulfate, 30 mg elemental iron, once daily	Placebo, gelatin capsules identical to iron intervention, once daily	Mean dose taken (pill count by investigator) I: 63% C: 65%	Iron supplements and/or medical evaluation	I: 129 ± 9 C: 127 ± 10	Antilog of mean (25th and 75th percentile): I: 45 (30–60) C: 49 (34–77)
Ziaei et al. (2008)[17,18]	Iran	RCT, double-blind	I: 122 C: 122 T: 244	Start: 20 weeks' gestation Stop: delivery	Ferrous sulfate, 50 mg elemental iron, once daily	Placebo, not further described, once daily	Mentioned but not described	Not described	I: 140 ± 6 C: 139 ± 5	I: 28 ± 11 C: 28 ± 10
Falahi et al. (2011)[19]	Iran	RCT, triple-blind	I: 70 C: 78 T: 148	Start: <20 weeks' gestation Stop: delivery	Ferrous sulfate, 60 mg elemental iron, once daily	Placebo, indistinguishable from iron intervention, once daily	Not described	Not described	I: 130 ± 10 C: 131 ± 9	I: 37 ± 21 C: 32 ± 20

(Continues)

TABLE 1 (Continued)

Trial	Country	Design	Treatment; no of patients I: Iron C: Comparator T: Total	Duration of intervention	Iron intervention	Comparator intervention	Adherence assessment I: Iron C: Comparator	Plan in case of treatment failure	BaselineHb (g/L)[a] I: Iron C: Comparator	Baseline ferritin (ng/mL)[a] I: Iron C: Comparator
Zhao et al.[d,e] (2015)[20]	China	RCT, double-blind	I: 881 C: 876 T: 1757	Start: 10–20 weeks' gestation Stop: delivery	Ferrous sulfate, 60 mg elemental iron, once daily, and 0.4 mg folate, once daily	Placebo (starch, dextrin, sucrose, and magnesium stearate), once daily, and 0.4 mg folate, once daily	Mean capsules consumed (self-reported) I: 85% C: 84%	Individualized (up to physicians' clinical judgment)	I: 124 ± 8 C: 123 ± 8	I: 50 ± 45 C: 48 ± 34
Alizadeh & Salehi (2016)[21]	Iran	RCT, double-blind	I: 32 C: 32 T: 64	Start: 16–20 weeks' gestation Stop: delivery	Ferrous sulfate, 50 mg elemental iron, once daily	Placebo, not further described, once daily	Not described	Not described	I: 137 ± 4 C: 136 ± 4	I: 34 ± 14 C: 37 ± 17

Abbreviations: Hb, hemoglobin; RCT, randomized clinical trial.

[a]Reported as mean ± SD and if not available then as specified in table.

[b]Some included data were provided by the author upon request.

[c]At 28 weeks' gestation, the following algorithm was applied: continued initial intervention if non-iron deficient and non-anemic; additional iron supplements if iron deficient (dose depending on severity); excluded and referred for medical evaluation in case of severe anemia or non-iron deficient anemia. Consequently, only 15 iron participants and 15 placebo participants continued with initial intervention whereas most participants received additional iron supplements.

[d]Included data are subgroup data for non-anemic iron replete participants provided by the author upon request (asked for subgroup data for only iron replete non-anemic participants). Hb and ferritin cutoff defined by author.

[e]All women were free to obtain over-the-counter iron-containing supplements. Physicians were blinded to the supplement group and free to use clinical judgment in treating anemic women. Local clinical practice was to prescribe medicinal iron therapy and/or to make dietary recommendations.

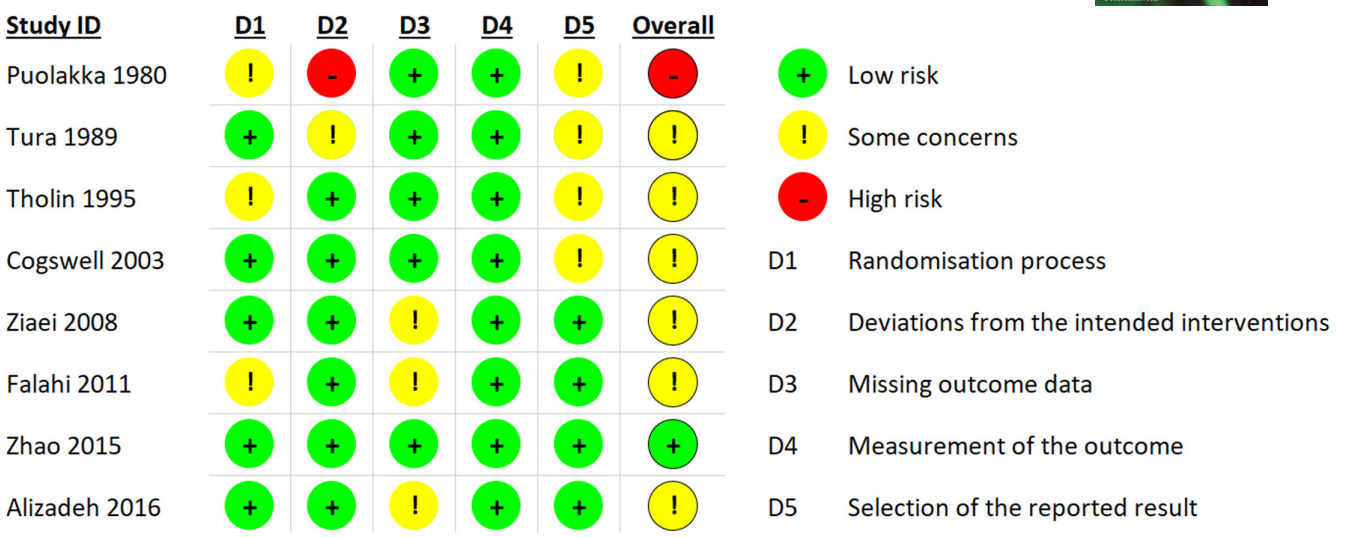

FIGURE 2 Summary of risk of bias for each included trial assessed by the revised Cochrane risk-of-bias tool (RoB2). With this tool, the risk of bias of each included study is judged according to five domains (D1–D5) and overall, as "low risk", "some concerns", or "high risk".

In all the included trials interventions were initiated no later than 20 weeks' gestation. One trial administered treatment twice daily[13] and the remaining once daily. The total daily elemental iron dose ranged from 30 to 200 mg. In one trial, folic acid was given to all participants in addition to iron and placebo treatment,[20] whereas the remaining trials used iron-only interventions. One trial stated that iron supplements were given to almost all participants at some point after 28 weeks' gestation regardless of initial allocation,[16] and another that all participants regardless of initial allocation were allowed to buy over-the-counter iron-containing supplements and that physicians were free to use clinical judgment in treating those who became anemic.[20]

3.3 | Risk of bias and the quality of evidence

Figure 2 illustrates the summarized risk of bias for the included trials. One trial had low risk of bias in all five domains and was also the trial contributing with the most comprehensive data.[20] One non-blinded trial did not evaluate adherence to the allocated intervention[13] and was assessed to be at high risk of bias because it is plausible that participants allocated to no iron could have used iron supplements on their own or their caregiver's initiative. This trial only contributed with data for a single secondary outcome (maternal red blood cell transfusion). The remaining trials had some concerns of risk of bias, most commonly arising from the randomization process, missing outcome data that could not be accounted for, or due to no mention or use of a predefined analysis plan (Figure 2). Certainty of the evidence ranged from very low to moderate. The most common reasons for downgrading quality of the evidence for an outcome included substantial heterogeneity, imprecision, and risk of bias in the trials contributing with data.

Summary of findings including quality of evidence assessments have been summarized for primary and secondary outcomes in Tables 2 and 3, respectively. Forest plots can be seen in Figures S1, S2, S3, S4, S5, S6.

3.4 | Primary outcomes

Four trials reported incidences of maternal iron deficiency anemia at term.[14,16,19,20] Three of the trials[16,19,20] used similar definitions of iron deficiency anemia (Hb < 110 g/L and ferritin <12–15 ng/mL) while the definition in the fourth was different[14] (Hb ≤ 115 g/L and ferritin <40 ng/mL or transferrin saturation <20%). The meta-analysis showed lower risk of iron deficiency anemia at term in favor of oral iron treatment (pooled RR: 0.51, 95% CI: 0.38–0.70; 4 RCTs, 1670 women; $I^2 = 13\%$; moderate-certainty evidence) (Table 2; Figure S1).

Maternal iron deficiency at term was reported in four trials.[14,16,19,20] Three trials used similar definitions of iron deficiency (ferritin <12 ng/mL[16,19] and ferritin <15 ng/mL[20]) while the definition in the fourth was different (Hb > 115 g/L, ferritin <40 ng/mL and/or transferrin saturation <20%).[14] The meta-analysis showed lower risk of iron deficiency at term in favor of oral iron treatment (pooled RR: 0.74, 95% CI: 0.60–0.92; 4 RCTs, 1663 women; $I^2 = 58\%$; low-certainty evidence) (Table 2; Figure S2).

Three trials reported incidences of high Hb (>130 g/L) in pregnancy.[16,20,21] The meta-analysis showed no between group difference (pooled RR: 0.94, 95% CI: 0.09–10.07; 3 RCTs, 1346 women; $I^2 = 83\%$; very low certainty evidence) (Table 2; Figure S3). The estimate from one of the trials (unpublished data provided by the author) was affected by substantial loss to follow up: this trial found a higher incidence of elevated Hb concentration in the placebo group at term (but a similar incidence between groups at 28 weeks). Excluding the trial from the meta-analysis gave the following result: RR: 2.19, 95% CI: 1.64–2.93, I^2 0%; 2 RCTs, 1194 women; moderate-certainty evidence.

TABLE 2 Summary of results: Maternal and infant primary outcomes.

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no oral iron supplements	Risk with oral iron supplements			
Maternal iron deficiency anemia at term (37 weeks' gestation or more)	177 per 1.000	90 per 1.000 (67–124)	RR 0.51 (0.38–0.70)	1670 (4 RCTs)[b]	⨁⨁⨁◯ MODERATE[c]
Maternal iron deficiency at term (37 weeks' gestation or more)	672 per 1.000	497 per 1.000 (403–618)	RR 0.74 (0.60–0.92)	1663 (4 RCTs)[b]	⨁⨁◯◯ LOW[c,d]
Maternal high Hb concentrations during pregnancy (more than 130 g/L)	106 per 1.000	100 per 1.000 (10–1.000)	RR 0.94 (0.09–10.07)	1346 (3 RCTs)[e]	⨁◯◯◯ VERY LOW[c,f,g,h]
Small for gestational age	177 per 1.000	69 per 1.000 (30–152)	RR 0.39 (0.17–0.86)	213 (1 RCT)[i]	⨁⨁◯◯ LOW[j,k]
Low birthweight (less than 2500 g)	121 per 1.000	36 per 1.000 (16–82)	RR 0.30 (0.13–0.68)	361 (2 RCTs)[l]	⨁⨁⨁◯ MODERATE[m]
Preterm birth (before 37 weeks' gestation)	98 per 1.000	88 per 1.000 (46–167)	RR 0.90 (0.47–1.71)	361 (2 RCTs)[l]	⨁⨁◯◯ LOW[g,m]

Note: GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. Maternal elevated iron status and congenital anomalies are not included in the table as no trials reported these outcomes.

Abbreviations: CI, confidence interval; Hb, hemoglobin; RCTs, randomized clinical trials; RR, risk ratio.

[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Tura et al. (1989),[14] Cogswell et al. (2003),[16] Falahi et al. (2011),[19] Zhao et al. (2015).[20]

[c]Several trials contributing data had design limitations.

[d]Moderate/high heterogeneity: $I^2 = 58\%$.

[e]Cogswell et al. (2003),[16] Zhao et al. (2015),[20] Alizadeh & Salehi (2016).[21]

[f]High heterogeneity: $I^2 = 83\%$.

[g]Wide 95% CI.

[h]Cogswell et al.[16] reported higher incidence of elevated Hb concentration at term in the placebo group. However, the incidence of elevated Hb at 28 weeks' gestation was similar between groups, whereas the conflicting estimate from term was affected by substantial loss to follow-up. Excluding the trial from the meta-analysis gave the following result: RR: 2.19, 95% CI: 1.64–2.93, I^2 0%; 2 RCTs, 1194 women; moderate-certainty evidence.

[i]Cogswell et al. (2003).[16]

[j]The trial contributing data had design limitations.

[k]Small sample size.

[l]Cogswell et al. (2003),[16] Falahi et al. (2011).[19]

[m]Both trials contributing data had design limitations.

TABLE 3 Summary of results: maternal and infant secondary outcomes.

Outcomes	Anticipated absolute effects[a] (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE) Comments
	Risk with no oral iron supplements	Risk with oral iron supplements			
Maternal severe anemia during pregnancy (Hb concentration below 70 g/L)	0 per 1.000	0 per 1.000 (0–0)	Not estimable	1407 (4 RCTs)[b]	⨁⨁⨁◯ MODERATE[c]
Gestational hypertension	0 per 1.000	0 per 1.000 (0–0)	RR 3.34 (0.14–80.63)	148 (1 RCT)[d]	⨁◯◯◯ VERY LOW[e,f]
Maternal red blood cell transfusion (intra- and/or postpartum)	63 per 1.000	21 per 1.000 (1–476)	RR 0.33 (0.01–7.62)	32 (1 RCT)[g]	⨁◯◯◯ VERY LOW[e,f]
Maternal postpartum anemia (Hb concentration <110 g/L)	80 per 1.000	33 per 1.000 (10–105)	RR 0.41 (0.13–1.31)	223 (1 RCT)[h]	⨁⨁◯◯ LOW[e,i]

Note: GRADE Working Group grades of evidence. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. The following secondary outcomes are not included in the table as no trials reported them: gestational diabetes, pre-eclampsia, maternal infections, gastrointestinal side effects, maternal quality of life, maternal fatigue, newborn failure to thrive, newborn Hb concentration in the first 6 months, and newborn ferritin concentration in the first 6 months.

Abbreviations: CI, confidence interval; Hb, hemoglobin; RR, risk ratio.

[a]The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Cogswell et al. (2003),[16] Ziaei et al. (2008)[17], Zhao et al. (2015),[20] Alizadeh & Salehi (2016).[21]

[c]Several trials contributing data had design limitations.

[d]Falahi et al. (2011).[19]

[e]The trial had design limitations.

[f]Wide 95% CI, small sample size and few events.

[g]Puolakka et al. (1980).[13]

[h]Tura et al. (1989).[14]

[i]Wide 95% CI and small sample size.

One trial reported incidences of SGA infants, defined by the trialists as <10th percentile of weight at birth for gestational age.[16] The risk of SGA newborns was lower in mothers who received iron (pooled RR: 0.39, 95% CI: 0.17–0.86; 1 RCT, 213 infants; I^2 not estimable; low-certainty evidence) (Table 2).

The incidences of LBW neonates (<2500 g) was reported in two trials.[16,19] The meta-analysis showed lower risk of LBW infants in favor of oral iron treatment (pooled RR: 0.30, 95% CI: 0.13–0.68; 2 RCTs, 361 infants; $I^2 = 0\%$; moderate-certainty evidence) (Table 2; Figure S4).

Two trials reported incidences of infants born preterm (before 37 weeks' gestation).[16,19] The meta-analysis showed no between group difference (pooled RR: 0.90, 95% CI: 0.47–1.71; 2 RCTs, 361 infants; $I^2 = 0\%$; low-certainty evidence) (Table 2; Figure S5).

3.5 | Secondary outcomes

Severe maternal anemia in pregnancy (Hb < 70 g/L) was reported in four trials.[16,18,20,21] Among 727 women treated with daily oral iron supplements and 680 women receiving placebo, there were no events of severe anemia (Table 3; Figure S6).

One trial reported incidences of gestational hypertension.[19] The risk of gestational hypertension was similar across groups (pooled RR: 3.34, 95% CI: 0.14–80.63; 1 RCT, 148 women; I^2 not estimable; very low certainty evidence) (Table 3).

The prevalence of red blood cell transfusion intra- and postpartum was reported in one trial.[13] The risk of transfusion did not differ between groups (pooled RR: 0.33, 95% CI: 0.0–7.62; 1 RCT, 32 women; I^2 not estimable; very low certainty evidence) (Table 3).

One trial reported incidences of postpartum anemia.[14] The risk of postpartum anemia was similar between groups (pooled RR: 0.41, 95% CI: 0.13–1.31; 1 RCT, 223 women; I^2 not estimable; low-certainty evidence) (Table 3).

3.6 | Outcomes not reported

The remaining predefined outcomes for newborns (congenital anomalies, hematological indices, measures for failure of thrive such as physical growth) and mothers (elevated iron status, gestational diabetes, preeclampsia, infections, quality of life, fatigue, gastrointestinal side-effects) were not reported in any trial.

3.7 | Subgroup and sensitivity analysis

The number of trials included in the primary analyses was too small for any subgroup analyses by iron dosing to be meaningful. Subgroup analyses by gestational age at start of intervention was not possible as all trials started intervention no later than at 20 weeks' gestation. It was not possible to perform the planned sensitivity analyses based on risk of bias, as no outcome was reported in ≥ two trials with ≥ one trial at high risk of bias. One trial had a markedly larger sample size[20] and provided significant weight in the meta-analysis of maternal iron deficiency anemia, iron deficiency, high Hb, and severe anemia in pregnancy. When excluding this trial from the analyses (post hoc sensitivity analysis), the effect estimates lost statistical significance, although the trend remained similar (data not shown). An additional post hoc sensitivity analysis was performed for high Hb in pregnancy as described in section 3.2.

4 | DISCUSSION

This systematic review identified eight trials reporting effects of oral iron supplementation in iron replete non-anemic women and highlights that the evidence in this field is sparse. The evidence quality of outcomes ranged from very low to moderate, and most trials had some risk of bias. Several reported outcomes suffered from low numbers of participants as well as design limitations in the trials leading to limited confidence in the pooled effect estimates. Compared to no iron supplements, daily oral iron supplementation in pregnancy probably reduces maternal iron deficiency anemia at term and may reduce maternal iron deficiency at term. Furthermore, daily oral iron supplements in pregnancy may reduce newborn SGA and probably reduces newborn LBW. Among 727 women treated with daily oral iron supplements and 680 women receiving placebo, there were no events of severe anemia. The evidence is very uncertain about the effect of iron supplementation on maternal high Hb. Several outcomes that we aimed to assess showed no between-group difference (i.e., preterm birth, gestational hypertension, maternal red blood cell transfusion, and postpartum anemia) or were not reported in any trials.

As expected, the amount of original research on the topic for our review was sparse and there were inconsistencies between study designs regarding settings, dosing regimens, and outcome measures reported. Although baseline ferritin concentrations indicate that several participants had acceptable iron status, baseline ferritin seem to have varied both within and between trials (Table 1). Most trials allowed baseline ferritin concentrations as low as 10–20 ng/mL,[15–21] which is a substantially lower limit than 70 ng/mL that has been suggested to reflect the amount of body iron required to complete pregnancy without developing iron deficiency.[22,23] As previously mentioned, excessive iron could theoretically do harm by negative influence on oxidative stress, microbiome, immunity, erythropoiesis, and ultimately placental flow.[6] Nevertheless, the studies we included mainly focused on beneficial effects of iron, whereas none reported data for relevant adverse outcomes such as gestational diabetes, preeclampsia, and gastrointestinal side-effects. Regarding the review process, the risk that we oversaw eligible published material is small as we applied no time or language restrictions in the searches and contacted authors for additional information when relevant. However, a more limited number of outcomes with even

more thorough prioritization could have improved the directness and implications of our findings. Furthermore, subgroup analyses on primary outcomes based on dosing was planned but not conducted, as we believe that the number of trials was too small for this to be meaningful.

Whereas physicians internationally agree that iron deficiency anemia in pregnancy should be treated, there is no current consensus as to whether preventive iron supplements should be given to iron replete non-anemic women or not. Subsequently, iron policies for pregnant women vary between nations, and routine iron supplementation is being practiced in several countries, including countries where most women are expected to be iron replete in early pregnancy. As we believe it is important to assess the consequences of iron supplements in those who from a biological perspective probably benefit least, this review focused exclusively on its effect in iron replete non-anemic women. To the best of our knowledge, this has never been the topic of a systematic review before. Two previous reviews including a Cochrane review have stated that iron supplementation in pregnant women result in a lower incidence of iron deficiency and iron deficiency anemia at delivery, but that its effects on clinical maternal and infant outcomes is unclear.[8,24] What distinguishes our and these prior reviews is that we considered initial maternal iron status and focused only on those who started out with normal Hb and iron status. Consistent with the previous reviews, we found that iron supplementation may reduce the risk of iron deficiency anemia (moderate-certainty evidence) and iron deficiency (low-certainty evidence) at term, although the absolute risk of iron deficiency at term was high in both groups: 49.4% in iron supplemented mothers and 67.2% in non-supplemented mothers, respectively, despite 30–60 mg elemental iron daily from ≤20 weeks' gestation. In contrast to the two previous reviews[8,24] we found moderate-quality evidence of reduced risk of LBW infants in iron treated mothers, although this was based on a limited number of infants ($n = 361$) and only two trials.

5 | CONCLUSION

The number of trials exploring benefits and harms of daily oral iron supplements in pregnant iron replete non-anemic women is limited. However, we did find evidence suggesting that iron supplements probably have beneficial effects in means of preventing maternal iron deficiency anemia and newborn LBW. The evidence for the influence of iron supplements on maternal high Hb is uncertain, and if a potential increase has any clinical importance remains unknown. Our finding of no difference in a range of additional obstetric and perinatal outcomes does not suggest that there truly is no difference, but rather that we lack the evidence to tell if there are differences or not. This is further underlined by the fact that several of our predefined outcomes were not reported in any trials. A substantial number of women enter pregnancy with normal Hb and iron status, and therefore, we believe that large-scale, high-quality, blinded RCTs that further explore the effects of iron supplements in pregnancy in these women are warranted.

AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the study. Screening of records, data collection and risk of bias assessments were carried out by RH and EPFS. RH conducted meta-analyses and assessed certainty of the evidence. All authors were involved in the interpretation of the data. RH drafted the manuscript and all authors reviewed and approved the final version.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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