Efficacy of daily versus intermittent oral iron supplementation for prevention of anaemia among pregnant women: a systematic review and meta-analysis

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Summary

Background The World Health Organization recommends daily oral supplementation of iron for prevention of maternal anaemia. However, the adverse effects due to daily supplementation leads to poor compliance among pregnant women. Also, the mucosal block theory suggests that intermittent oral iron may be more efficient than daily iron with respect to optimum absorption. Our meta-analysis reviewed the existing clinical studies for the efficacy of daily versus intermittent oral iron supplementation.

Methods In this systematic review and meta-analysis [PROSPERO ID:CRD42024498180], we searched PubMed, Google Scholar, Scopus, Science Direct and Cochrane database for studies published from 1st January 1970 to 31st December, 2023. Studies comparing daily and intermittent iron supplementation in pregnant women were included. The median intermittent iron dose was 120 mg/day and daily iron dose was 60 mg/day. The primary outcome was endpoint haemoglobin levels after iron supplementation. The data was analysed using the 'meta' and 'metafor' packages in RStudio using random effects model. The heterogeneity, publication bias, risk of bias and certainty of evidence were assessed using I2 statistics, funnel plots, Cochrane Risk of Bias 2 (ROB2) tool, and the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach respectively.

Findings Of 4615 search results, 26 studies (n = 4365 participants) were included in this meta-analysis. There was no significant difference (p = 0.18) between the endpoint mean haemoglobin levels of the daily versus intermittent oral iron groups (standardized mean difference (SMD): 0.51, 95% CI: −0.23 to 1.24, I^2 = 97%, low certainty evidence) irrespective of baseline anaemic status. However, the endpoint ferritin levels were significantly higher in the daily supplementation group (SMD: 0.85, 95% CI: 0.15–1.54, p = 0.02, I^2 = 97%, low certainty evidence). The adjusted odds ratio for nausea, (adjusted odds ratio (OR) 3.56, 95% CI: 2.23–5.69, p < 0.001, I^2 = 9%, moderate certainty evidence), diarrhoea (adjusted OR 5.40, 95% CI: 1.90–15.33, p = 0.002, I^2 = 0%, low certainty evidence) and constipation (adjusted OR 1.95, 95% CI: 1.21–3.14, p = 0.006, I^2 = 0%, moderate certainty evidence) was significantly higher in daily oral iron supplementation group.

Interpretation Intermittent oral iron supplementation with a median dose of 120 mg/day demonstrates comparable efficacy to daily oral iron supplementation median dose of 60 mg/day in increasing haemoglobin levels among pregnant women with a significant reduction in adverse events.

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Research in context

Evidence before this study

A Cochrane review published in 2015, suggested that the intermittent regimens yielded similar maternal and infant outcomes to daily supplementation and with fewer side effects. However, due to the low certainty of evidence, the study suggested intermittent oral iron supplementation only for non-anaemic pregnant women. Current World Health Organization (WHO) guidelines (2023) recommend 30 mg–60 mg of daily oral elemental iron and 400 μg of folic acid for the prevention of maternal anaemia and newborn complications. In countries with an anaemia prevalence of less than 20% intermittent oral iron supplementation of 120 mg once a week is recommended when daily iron is not acceptable due to side effects. These guidelines are based on the recommendation of Cochrane Review 2015.

Added value of this study

Recent articles published after the Cochrane review in 2015 were included in our systematic review and meta-analysis. The findings of our meta-analysis indicate that the efficacy of intermittent supplementation is similar to daily iron supplementation. Importantly, this regimen notably reduced the side effects due to daily supplementation. Thus, intermittent supplementation with median dose of 120 mg/day could be recommended for pregnant women with severe side effects.

Implications of all the available evidence

We recommend intermittent oral iron supplementation for individuals who cannot adhere to the daily regime due to adverse events. However, the complexity of iron deficiency and overload warrants further well-designed randomized controlled trials with larger sample sizes to optimize IFA supplementation regimes and improve maternal and neonatal health outcomes while minimizing adverse effects and enhancing compliance.

Introduction

Iron deficiency anaemia (IDA) represents a pressing global public health concern, primarily impacting vulnerable demographics such as children and pregnant women. Anaemia during pregnancy poses significant public health and economic challenges.[1] Globally, approximately 32 million pregnant women suffer from iron deficiency anaemia, with 56% of cases occurring in developing nations. Pregnant women require supplemental iron and folic acid to fulfil both their nutritional requirements and those of the developing foetus. Inadequate intake of these essential nutrients during pregnancy can detrimentally affect maternal health, pregnancy outcomes, and foetal development. The repercussions of anaemia during pregnancy encompass a spectrum of serious adverse effects for both the mother and infant, including low birth weight, increased rates of caesarean section, postpartum haemorrhage necessitating blood transfusion, preterm birth, and neonatal anaemia. Consequently, the prevention of anaemia in pregnancy holds paramount importance in mitigating maternal and infant morbidity and mortality. Empirical evidence underscores the efficacy of iron supplementation in reducing the risk of IDA among pregnant women.

WHO recommends 30 mg–60 mg of daily oral elemental iron and 400 μg of folic acid for the prevention of maternal anaemia and newborn complications. Daily oral iron supplementation for pregnant women is a cost-effective intervention recommended in both public health and clinical settings.[2] However, despite widespread iron supplementation initiatives over the past four decades, the prevalence of anaemia among pregnant women remains largely unchanged. Various potential factors and barriers may impede the success of iron supplementation programs. Firstly, existing healthcare systems in developing countries often distribute iron supplements to pregnant women ineffectively, leading to low utilization of services and poor compliance. Additionally, the daily consumption of iron supplements frequently results in adverse side effects such as nausea, constipation, or gastritis, further exacerbating compliance issues among pregnant women. Moreover, adherence to this supplementation remains problematic. National survey data from 46 countries spanning 2003–2009 reveal that nearly 25–50% of expectant mothers did not receive IFA during pregnancy.[3] This might stem from underlying issues such as inadequate pill distribution, distressing side effects leading to poor compliance among women, or safety concerns surrounding routine iron supplement usage in regions where anaemia is not a prevailing public health issue or among non-anaemic women.

To enhance the effectiveness of iron supplementation programs, intermittent iron supplementation has emerged as a promising alternative. The mucosal block theory suggests that loading the mucosa with iron during the first dose may inhibit the absorption of

subsequent doses. By reducing the frequency of dosing to once or twice a week to match mucosal turnover, each iron tablet may be better absorbed, necessitating a lower overall iron dose. While animal studies support this hypothesis, human studies utilizing radiolabelled iron have shown only minimal reductions in absorption following previous iron administration.[4] Recently it has been observed that iron supplementation induces an increase in serum hepcidin that persists for 24 h, decreasing iron absorption from supplements given later on the same or the next day. Hepcidin, the master regulator of systemic iron homeostasis is primarily synthesized in the liver and released into the bloodstream. Its production increases in response to high iron levels and inflammation, while decreasing when erythropoiesis occurs. This hormone regulates systemic iron levels by interacting with ferroportin, a protein responsible for exporting iron from cells.[5] The rise in serum hepcidin level was significantly linked to reduced absorption from the second iron dose administered 24 h after the initial dose. It was noted that oral iron at doses of 60 mg or higher, when given at least 48 h apart, demonstrated a higher fractional absorption.[6] A study by Stoffel et al. found that taking 60 mg iron supplements every other day led to 34% higher iron absorption compared to taking them daily.[7] In another study, a decline in iron absorption 48 h after the last administered dose was not observed, contrary to the postulation of a mucosal block lasting up to five or six days.[8] The evidence suggests that, oral iron supplementation on alternate days leads to increased absorption of iron.[9] Reducing the frequency of supplementation has been proposed as a means to mitigate transient iron overload and could potentially alleviate adverse effects like nausea and epigastric pain by diminishing the daily iron content in the gastrointestinal tract.

A Cochrane review by Reveiz et al. examining various doses and routes of iron supplementation among pregnant women with anaemia found that while daily oral iron improved haematological parameters, it was associated with more gastrointestinal side effects compared to intramuscular or intravenous regimens. Although the latter was superior in improving haematological parameters, they also carried a higher risk of severe adverse effects such as venous thrombosis and allergic reactions.[10] Another subsequent Cochrane review by Peña-Rosas (2015) encompassed 21 trials involving 5490 women, including studies on iron supplementation alone, iron and folic acid, and iron with multivitamin supplements published up to July 2015.[11] The findings suggested that intermittent regimens yielded similar maternal and infant outcomes to daily supplementation but were associated with fewer side effects. While the quality of evidence was deemed low or very low, the study concluded that intermittent oral iron supplementation could be a viable alternative to daily supplementation for non-anaemic pregnant women receiving adequate antenatal care. However, the review included only four randomized controlled trials (RCTs) involving 676 antenatal women to assess maternal anaemia at term, with very low certainty. Moreover, it did not evaluate markers of maternal iron deficiency at term. Additionally, research explored the effects of various vitamin and mineral supplementation, with or without iron, including vitamin A, zinc supplementation, vitamin C supplementation, multiple vitamin and mineral supplements during pregnancy, and point-of-use fortification with micronutrient powders for pregnant women.[12–16] Consequently, there is a pressing need to incorporate more recent studies from the past decade to establish more robust evidence regarding the efficacy of daily versus intermittent oral iron supplementation among pregnant women for anaemia prevention and to generate pertinent evidence. Thus, the present review aims to provide an updated summary of existing RCTs to date assessing the effectiveness and safety of daily oral iron and/or iron plus folic acid supplementation during pregnancy for preventing anaemia and improving iron status.

Methods

Protocol registration and reporting

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 guidelines for this systematic review and meta-analysis.[17] The review protocol was registered in the International Prospective Register of Systematic Reviews, PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=498180, Registration Number: CRD42024498180, accessed on 15th February, 2024).

Procedures

Search strategy and selection criteria

This systematic review and meta-analysis included articles which evaluated the effect of iron supplementation in pregnant women. Electronic databases including PubMed, Google Scholar, Scopus, ScienceDirect and Cochrane database were searched using a combination of search terms including, 'pregnancy', 'oral iron', 'anaemia', 'haemoglobin' and their synonyms. The detailed search strategy for all the databases is included in Supplementary Appendix I. All published articles from 1st January 1970 to 31st December 2023 were included. Studies were eligible if they included pregnant women of any gestation who received iron supplementation, either daily or intermittently, and collected data on the baseline and/or post-treatment haemoglobin levels and adverse events were included. Conference Abstracts and thesis were also considered for inclusion if the necessary data was available. Case Reports, Reviews and Cross-sectional studies were excluded. Additionally, studies with full text in non-English language were also excluded.

Eligible studies in the English language were included in the analysis. Randomized Controlled Trials with randomisation either at individual or cluster level were included. Cross-over trials or any observational study designs (for example, cohort or case–control studies) were not included in the meta-analysis, but we have considered such evidence in the discussion where relevant. Studies which included pregnant women with pregnancy related complications (multiple pregnancies, abortion, eclampsia, etc.) or diagnosed health issues (thyroid disorder, autoimmune illness, chronic illnesses, infections like HIV, tuberculosis, etc) were not considered. Oral supplements of iron, or iron + folic acid, or iron + folic acid + vitamins were considered as interventions in the included studies. Oral iron supplementation refers to the intake of iron compounds directly to the oral cavity in tablet form. For this review, intermittent oral supplementation was defined as the provision of iron supplements one, two or three times a week on non-consecutive days.

Data extraction

The titles and abstracts of the articles obtained using the search strategy were uploaded to the online Rayyan software for screening.[18] Two reviewers (AB & SA) independently screened for eligibility by initial evaluation of abstracts. The full texts of all the eligible articles were downloaded and further screened for final inclusion in the meta-analysis. Any kind of conflicts for study inclusion were resolved by discussion and consensus was reached with the help of a third reviewer (NK). For multiple articles citing the same patient data, only one of the key papers was chosen and other articles were used for any supplementary data extraction if required. In the case of studies where more than two arms were present, each arm of intermittent dose was noted separately in comparison to the daily supplementation. Also, one study had separate data for anaemic and non-anaemic pregnant women and hence the data was considered twice with data recorded for each population separately.

SA performed data extraction from the final selection of articles using a standardized data format. Information related to the title of the paper, first author, year of publication, study design, country of the study population, type of publication, sample size, week of gestation, type of population (anaemic or non-anaemic), study duration, dose of iron supplement, frequency of dose, any other supplements, mean and standard deviation (SD) of baseline and post-treatment levels of haemoglobin and ferritin are recorded wherever available. Additionally, the frequency of side effects, if available, was also included in the data extraction sheet. All data extraction was checked by a second reviewer (NK or AB). The primary outcome measure of the study was a rise in haemoglobin levels. The secondary outcomes included the change in ferritin levels and side effects due to iron supplementation.

Outcomes

The following outcome measures were evaluated in the studies.

a) Baseline and endpoint haemoglobin levels in pregnant women on oral iron supplementation.
b) Serum ferritin levels in pregnant women on oral iron supplementation.
c) Adverse events of oral iron supplementation.

Statistics

The analysis of extracted data was performed in RStudio version 2023.06.2 + 561 using the 'meta' and 'metafor' packages. The software packages were used to estimate effect sizes using the random effects model, generate forest plots, funnel plots, and perform subgroup and meta-regression analysis. The difference between the haemoglobin levels among pregnant women on daily iron supplementation versus intermittent oral iron supplementation was calculated as SMD with a 95% confidence level using the random effects model, using inverse variance method with hedge's g correction. The Restricted maximum-likelihood estimator was used for tau^2 calculation. For the side effects outcome, adjusted OR was used as a summary measure/estimate. The OR and 95% CI were calculated using the Mantel-Haenszel method. The heterogeneity of the study was estimated using the I^2 statistic and the publication bias was assessed using funnel plots. We performed a sensitivity analysis for endpoint haemoglobin levels in daily versus intermittent supplementation, irrespective of baseline anaemia status, after excluding studies with a high risk of bias. We conducted subgroup analysis on the primary outcomes based on the anaemia and non-anaemic pregnant women. Pregnant women were considered as anaemic when mean Hb < 11 g/dL in the first or third trimester, or mean Hb < 10.5 g/dL in the second trimester.

The quality of the studies was assessed independently by SA and AB using the revised Cochrane ROB2 tool.[19] Disagreements in the assessment of quality were resolved by the third reviewer (NK). The level of certainty of evidence for the important study outcomes was assessed using GRADE approach with the help of the GRADEpro GDT online software.[20,21] A Summary of Evidence was generated for each outcome based on the five important factors that affect the quality of the study, i.e., risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Ethics approval

Not applicable since this is a systematic review and meta-analysis of publicly available data.

Role of funding source

There was no funding for this study.

Results

Selection process

A total of 4615 articles were identified from PubMed, Scopus, Google Scholar, ScienceDirect, and Cochrane database using a search strategy. Using the web-based Rayyan tool, 1544 duplicates were removed and 3071 articles were screened by two independent reviewers. After evaluation of the abstracts, 2991 articles which were not fulfilling the inclusion criteria were excluded. Eighty eligible articles were further checked for full-text availability, out of which only 74 full-texts could be retrieved. On further screening of the full-text, 26 articles were found to be eligible and included in this systematic review and meta-analysis (Fig. 1).

Study characteristics

The 26 studies included 4365 participants, of whom 2095 were randomly allocated to daily iron supplementation and 2270 participants were allocated the intermittent oral iron supplementation.[22–47] A summary of study characteristics of all the included studies is presented in Table 1. The majority of the studies were from India (n = 6), followed by Indonesia (n = 5) and Iran (n = 4). The participants were followed up from 3 weeks to 20 weeks of supplementation. In one study, Hb levels were also measured after 6 months postpartum. The time of enrolment and frequency of iron supplementation varied among the studies. Almost all the studies enrolled women in the second trimester, with 8 studies allowing enrolment in both second and third trimester.

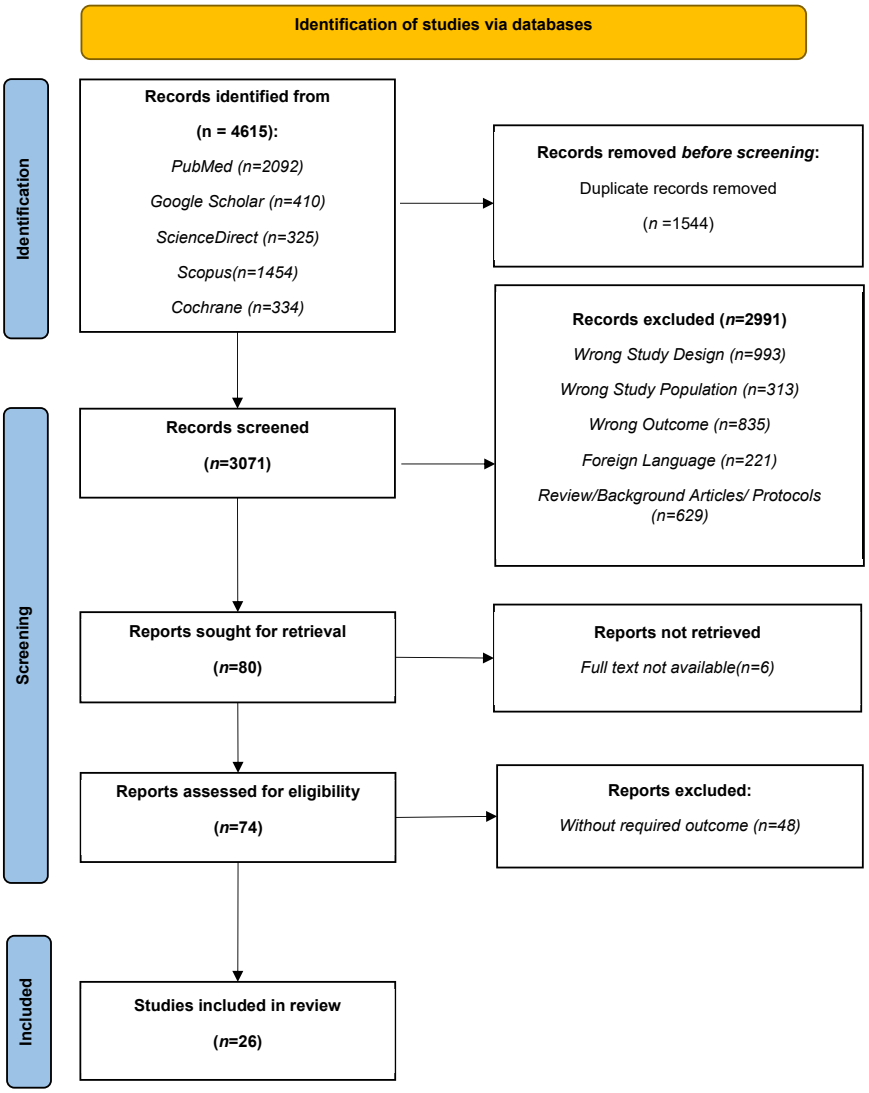

Fig. 1: PRISMA flowchart.

Author (Year)	Country	Type of Study	Number of cases screened	Type of Participants	Type of Iron	Arm 1 Sample Size	Arm 1 Frequency of Intervention	Arm 1 Dose of elemental iron	Arm 1 Hb levels before supplementation Mean ± SD (g/dL)	Arm 1 Hb levels after supplementation Mean ± SD (g/dL)	Arm 2 Sample Size	Arm 2 Frequency of Intervention	Arm 2 Dose	Arm 2 Hb levels before supplementation Mean ± SD (g/dL)	Arm 2 Hb levels after supplementation Mean ± SD (g/dL)	Risk of bias
Bhatla et al. 2009[1]	India	Randomized prospective trial	109	Healthy	Ferrous Sulphate	30	Daily	100 mg	11.79 ± 0.84	11.86 ± 1.15	30	once a week	200 mg	11.64 ± 0.62	11.25 ± 0.9	High
Bouzari et al. 2011[2]	Iran	Prospective simply randomized clinical trial	150	Healthy	Ferrous Sulphate	50	Daily	50 mg	12.44 ± 0.99	11.084 ± 0.82	50	once a week	100 mg	12.53 ± 0.77	11.62 ± 0.82	Low
Bouzari et al., 2011_2[2]	Iran	Prospective simply randomized clinical trial	150	Healthy	Ferrous Sulphate	50	Daily	50 mg	12.44 ± 0.99	11.084 ± 0.82	50	thrice a week	50 mg	12.62 ± 0.78	14.03 ± 0.78	Low
Casanueva et al. 2006[3]	Mexico	Randomized Control Trial	120	Healthy	Ferrous Sulphate	56	Daily	60 mg	12.87 ± 0.85	13.58 ± 1	60	once a week	120 mg	13.12 ± 0.97	12.63 ± 1.03	Low
Ekstrom et al. 2002[4]	Bangladesh	Community trial	209	Healthy	Elemental Iron	66	Daily	60 mg	11.04 ± 1.27	12.48 ± 1.61	74	once a week	120 mg	11.26 ± 1.39	12.26 ± 1.61	High
Gomber et al. 2002[5]	India	Prospective longitudinal study with observational design	80	Healthy	Ferrous Sulphate	29	Daily	100 mg	11.1 ± 1.3	11.7 ± 0.9	27	once a week	100 mg	10.8 ± 0.9	11.2 ± 0.9	High
Goonewardene et al. 2017[6]	Sri Lanka	Randomized Controlled Trial	292	Healthy	Elemental Iron	106	Daily	60 mg	11.9	11.8	106	once a week	120 mg	11.8	11.7	Low
Hanieh et al. 2017[7]	Viet Nam	Cluster randomized controlled trial	1258	Healthy	ferrous sulphate	336	Daily	60 mg	12.3 ± 1.4	12.5 ± 1.4	353	twice weekly	60 mg	12.1 ± 1.1	12.4 ± 1.1	Low
Hashim et al. 2012[8]	Malaysia	Randomised controlled trial	70	Mixed	Ferrous Fumarate	35	Daily	65 mg	10.4	10.5	35	once a week	65 mg	10.5	10.2	High
Hyder et al. 2003[9]	Bangladesh	Community trial	146	Healthy	Ferrous Sulphate	67	Daily	60 mg	11 ± 1.5	12.8 ± 1.8	79	once a week	60 mg	11.2 ± 1.3	13 ± 1.8	High
Karakoc et al. 2021[10]	Turkey	Randomized case–control study	217	Anaemic	Ferrous Fumarate	111	Daily	100 mg	9.8 ± 0.5	11.2 ± 0.8	106	alternate day	100 mg	9.8 ± 0.5	11.4 ± 0.7	High
Lam et al. 2021[11]	US	Prospective, randomized controlled trial	88	Anaemic	Ferrous Sulphate	45	Daily	65 mg	10.5 ± 0.4	11.3 ± 1	43	alternate day	130 mg	10.3 ± 0.6	10.9 ± 1.2	High
Mukhopadhyay et al. 2004[12]	India	Prospective randomized controlled study	111	Healthy	Elemental Iron	40	Daily	100 mg	11.1 ± 1	11.7 ± 1.1	40	once a week	200 mg	11.6 ± 0.9	11.4 ± 1.3	High
Mumtaz et al. 2000[13]	Pakistan	Double-blind, randomized, clinical trial	191	Anaemic	Ferrous Sulphate	84	Daily	60 mg	9.26 ± 1.41	11.36 ± 1.83	76	twice weekly	120 mg	9.58 ± 1.06	10.09 ± 1.23	Low
Muslimatun et al. 2001[14]	Indonesia	Randomized double blind community based trial	190	Mixed	Ferrous Sulphate	53	Daily	100 mg	11.13 ± 0.14	11.06 ± 0.15	66	once a week, iron	120 mg	11 ± 0.13	11.21 ± 0.14	High
Nisar et al. 2023[15]	Pakistan	Randomized Controlled Trial	266	Healthy	Ferrous Sulphate	131	Daily	60 mg	10.62 ± 0.14	11 ± 0.31	133	once a week	120 mg	10.59 ± 3.28	10.96 ± 0.27	High
Ranjan et al. 2018[16]	India	Randomized and longitudinal study	64	Anaemic	Ferrous Sulphate	32	Daily	65 mg	9.3 ± 2.2	11.93 ± 2.4	32	twice weekly	65 mg	9.41 ± 2.3	12.5 ± 2.6	High
Ridwan et al. 1996[17]	Indonesia	Random allocation	139	Mixed	Ferrous Sulphate	68	Daily	60 mg	10.6 ± 0.9	11 ± 0.7	71	once a week	120 mg	10.2 ± 1	10.8 ± 0.8	High
Robinson et al. 1998[18]	Indonesia	Randomised controlled trial	345	Healthy	Elemental Iron	161	Daily	60 mg	11.45 ± 0.08	12.25 ± 0.09	184	once a week	120 mg	11.35 ± 0.11	11.59 ± 0.09	High
Sadaf et al. 2023[19]	Pakistan	Randomized Controlled Trial	70	Healthy	Ferrous Sulphate	35	Daily	65 mg	12.14 ± 0.91	13.21 ± 0.93	35	once a week	130 mg	12.23 ± 0.97	12.86 ± 0.95	High
Shankar et al. 2016[20]	India	Randomized Controlled Trial	120	Anaemic	Ferrous Sulphate	30	Daily	100 mg	10.12 ± 0.14	10.88 ± 0.24	30	once a week	200 mg	9.92 ± 0.12	9.72 ± 0.25	Low
Shankar et al., 2016_2[20]	India	Randomized Controlled Trial	120	Healthy	Ferrous Sulphate	30	Daily	100 mg	12.11 ± 0.12	11.46 ± 0.14	30	once a week	200 mg	12.06 ± 0.12	11.28 ± 0.17	Low
Utari et al. 2017[21]	Indonesia	Pre-test post-test experimental design	96	Anaemic	Ferrous Sulphate	47	Daily	60 mg	10 ± 0.59	10.6 ± 0.99	47	once a week	60 mg	9.9 ± 0.54	10.4 ± 1.02	High
Yaznil et al. 2020[22]	Indonesia	Prospective cohort study	62	Healthy	Ferrous Fumarate	29	Daily	60 mg	11.6 ± 0.95	11.33 ± 0.74	33	twice weekly	60 mg	11.33 ± 0.96	11.27 ± 0.95	High

(Table 1 continues on next page)

Author (Year)	Country	Type of Study	Number of cases screened	Type of Participants	Type of Iron	Arm 1 Sample Size	Arm 1 Frequency of Intervention	Arm 1 Dose of elemental iron	Arm 1 Hb levels before supplementation Mean ± SD (g/dL)	Arm 1 Hb levels after supplementation Mean ± SD (g/dL)	Arm 2 Sample Size	Arm 2 Frequency of Intervention	Arm 2 Dose	Arm 2 Hb levels before supplementation Mean ± SD (g/dL)	Arm 2 Hb levels after supplementation Mean ± SD (g/dL)	Risk of bias
(Continued from previous page)																
Yekta et al. 2011[23]	Iran	Randomized, unsupervised field study	210	Healthy	Ferrous Sulphate	70	Daily	50 mg	12.06 ± 0.87	12.5 ± 0.93	62	once a week	100 mg	12.1 ± 0.81	12.4 ± 0.85	High
Yekta et al., 2011_2[23]	Iran	Randomized, unsupervised field study	210	Healthy	Ferrous Sulphate	70	Daily	50 mg	12.06 ± 0.87	12.5 ± 0.93	69	twice weekly	50 mg	11.9 ± 0.69	12.1 ± 0.78	High
Young et al. 2000[24]	Malawi	Randomized Controlled Trial	216	Mixed	Ferrous Sulphate	112	Daily	60 mg	10.57 ± 1.4	10.75	104	once a week	120 mg	10.44 ± 1.5	10.56	High
Zamani et al. 2008[25]	Iran	Randomized Controlled Trial	152	Healthy	Ferrous Sulphate	69	Daily	45 mg	13.3 ± 1.1	12.7 ± 1.5	53	once a week	90 mg	13 ± 1.2	12 ± 1.3	Low

Table 1: Study characteristics of the included studies.

Two types of oral iron supplementation were used in the studies, ferrous sulphate being the most common one (n = 20) followed by ferrous fumarate (n = 3). The type of supplementation was not mentioned for three studies; however, the dose of elemental iron was mentioned. The total daily elemental iron dose ranged from 60 to 100 mg (median dose: 60 mg/day, IQR:60–65 mg/day) and the intermittent elemental iron dose ranged from 50 to 120 mg (median dose: 120 mg/day, IQR: 65–120 mg/day). Nineteen studies gave iron supplementation along with folic acid, whereas 7 studies only administered iron supplementation. Intention to treat (ITT) analysis was used to measure the outcomes in 11 studies while per protocol analysis was used for 15 studies.

Risk of bias and quality of evidence

The risk of bias in the included studies is shown in Supplementary Appendix II. Five studies had a low risk of bias across all the domains, whereas 19 studies were categorised in the high risk of bias group for endpoint haemoglobin levels. The high risk of bias was due to the absence of allocation concealment in the randomisation process. The quality of evidence for the primary outcome has been summarised in Table 2. The summary of findings for the secondary outcomes of ferritin and side effects in included in Supplementary Appendices IV and V.

Primary outcome

Twenty-five studies reported the endpoint haemoglobin levels. Three studies had more than two arms, in such cases, data for the other arms was recorded as separate data in comparison to the daily supplementation group. The duration of iron supplementation in all studies ranged from 3 weeks to 20 weeks.

An overall comparison between the endpoint haemoglobin values among women supplemented daily versus those supplemented intermittently, irrespective of their anaemia status at baseline, was done among 25 studies (involving 4120 women). The pooled estimates of endpoint haemoglobin for the daily and intermittent subgroups were 11.80 g/dL (95% CI: 11.48 g/dL–12.11 g/dL) and 11.64 g/dL (95% CI: 11.26 g/dL–12.03 g/dL) (Supplementary Appendix V (a) & (b)). There was no significant difference (p = 0.18) between the mean haemoglobin levels of these two groups (SMD: 0.51, 95% CI: –0.23 to 1.24, I^2 = 97%, low certainty evidence) (Fig. 2a, Table 2) High heterogeneity was observed among the studies (I^2 = 97%) for this outcome. Further, a comparison between endpoint haemoglobin concentration among daily and once-a-week supplemented groups was done. Twenty studies (involving 2601 women) also showed no significant difference (p = 0.07) between the two groups (SMD: 0.89, 95% CI: –0.07 to 1.84, I^2 = 98%, low certainty evidence) (Fig. 2b, Table 2) raising the risk of type II

Summary of findings:

Daily oral iron compared to Intermittent oral iron for prevention of anaemia in pregnant women

Patient or population: Pregnant Women
Setting: Community Setting
Intervention: Daily oral iron
Comparison: Intermittent oral iron

Outcome № of participants (studies)	Anticipated absolute effects, SMD (95% CI)	Certainty	What happens
Endpoint haemoglobin (Daily versus Intermittent) № of participants: 4120 (25 RCTs)	SMD **0.51 SD higher** (0.23 lower to 1.24 higher)	⨁⨁◯◯ Low[a,b]	The evidence suggests that intermittent oral iron results in little to no difference in endpoint haemoglobin levels.
Endpoint haemoglobin (Daily versus Once-a-week) № of participants: 2601 (20 RCTs)	SMD **0.89 SD higher** (0.07 lower to 1.84 higher)	⨁⨁◯◯ Low[a,b]	The evidence suggests that once-a-week iron supplementation results in little to no difference in endpoint haemoglobin levels.
Endpoint haemoglobin (Daily versus More than Once-a-week) № of participants: 1114 (5 RCTs)	SMD **0.26 SD higher** (0.09 lower to 0.6 higher)	⨁⨁◯◯ Low[a,b]	The evidence suggests that more than once-a-week iron results in little to no difference in endpoint haemoglobin levels.
Endpoint haemoglobin in non-anaemic pregnant women (Daily versus Intermittent) № of participants: 2291 (18 RCTs)	SMD **0.01 SD higher** (0.51 lower to 0.53 higher)	⨁⨁◯◯ Low[a,b]	The evidence suggests that intermittent iron results in little to no difference in endpoint haemoglobin levels in non-anaemic pregnant women.
Endpoint haemoglobin in anaemic pregnant women (Daily versus Intermittent) № of participants: 1233 (9 RCTs)	SMD **0.77 SD higher** (0.45 lower to 1.99 higher)	⨁⨁◯◯ Low[a,b]	The evidence suggests that intermittent iron results in little to no difference in endpoint haemoglobin levels in anaemic pregnant women.

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; SMD: standardised mean difference. 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. [a]High risk of bias observed in studies as majority did not have allocation concealment. [b]High heterogeneity among the studies.

Table 2: **GRADE assessment table for primary outcome.**

error. The daily versus more than once-a-week supplementation comparison, reported in 5 studies, was also not significant (SMD: 0.26, 95% CI: –0.09 to 0.60, p = 0.14, I^2 = 81%, low certainty evidence) (Fig. 2c, Table 2).

Considering the WHO haemoglobin cut-off criteria for anaemia as 11 g/dL for the first and third trimesters and 10.5 g/dL for the second trimester, we evaluated the effect of oral iron supplementation of iron in those pregnant women who are anaemic and non-anaemia at baseline based on the mean haemoglobin level. The pooled estimates of endpoint haemoglobin for the daily and intermittent supplementation among the non-anaemic pregnant women were 11.92 g/dL (95% CI: 11.51 g/dL–12.33 g/dL) and 11.88 g/dL (95% CI: 11.44 g/dL–12.32 g/dL) (Supplementary Appendix V (c) & (d)). There was no significant difference (p = 0.97) between endpoint haemoglobin concentrations among the daily versus intermittent supplementation groups for non-anaemic pregnant women (SMD: 0.01, 95% CI: –0.51 to 0.53, I^2 = 93%, low-certainty evidence) (Fig. 2d, Table 2). The pooled estimates of haemoglobin for daily and intermittent supplementation among anaemic pregnant women were 11.09 g/dL (95% CI: 10.87 g/dL–11.31 g/dL) and 10.80 g/dL (95% CI: 10.17 g/dL–11.42 g/dL) (Supplementary Appendix V (e) & (f)). The anaemic group also did not show any significant difference between endpoint haemoglobin concentrations among the supplementation groups (SMD: 0.77, 95% CI: –0.45 to 1.99, I^2 = 94%, low certainty evidence) (Fig. 2e, Table 2).

Secondary outcome

Sixteen studies with 2132 participants reported endpoint ferritin levels between the daily versus intermittent supplementation was compared. The mean baseline ferritin levels for the daily supplementation group were 28.23 ng/mL whereas it was 25.68 ng/mL for the intermittent supplementation group. Among anaemic pregnant women mean baseline ferritin levels were 19.87 ng/mL and 19.72 ng/mL, for the daily and intermittent oral iron groups respectively. In the case of non-anaemic pregnant women, the mean ferritin levels at baseline were 29.41 ng/mL and 26.87 ng/mL for daily and intermittent oral iron groups. The difference in the endpoint ferritin levels between the two groups (daily versus intermittent) was statistically significant (SMD: 0.85, 95% CI: 0.15–1.54, p = 0.02, I^2 = 97%, low certainty evidence) (Fig. 3a, Supplementary Appendix III). Subgroup analysis of the endpoint ferritin among anaemic and non-anaemic pregnant women, found a significant difference in the daily versus intermittent supplementation groups for the non-anaemic women (SMD: 0.69, 95% CI: 0.11–1.28, p = 0.02, I^2 = 92%, low certainty evidence); however, the effect estimate was not significant for the anaemic group (SMD: 0.67, 95% CI: –0.12–1.46, p = 0.10, I^2 = 89%, low certainty evidence) (Fig. 3b and c, Supplementary Appendix III).

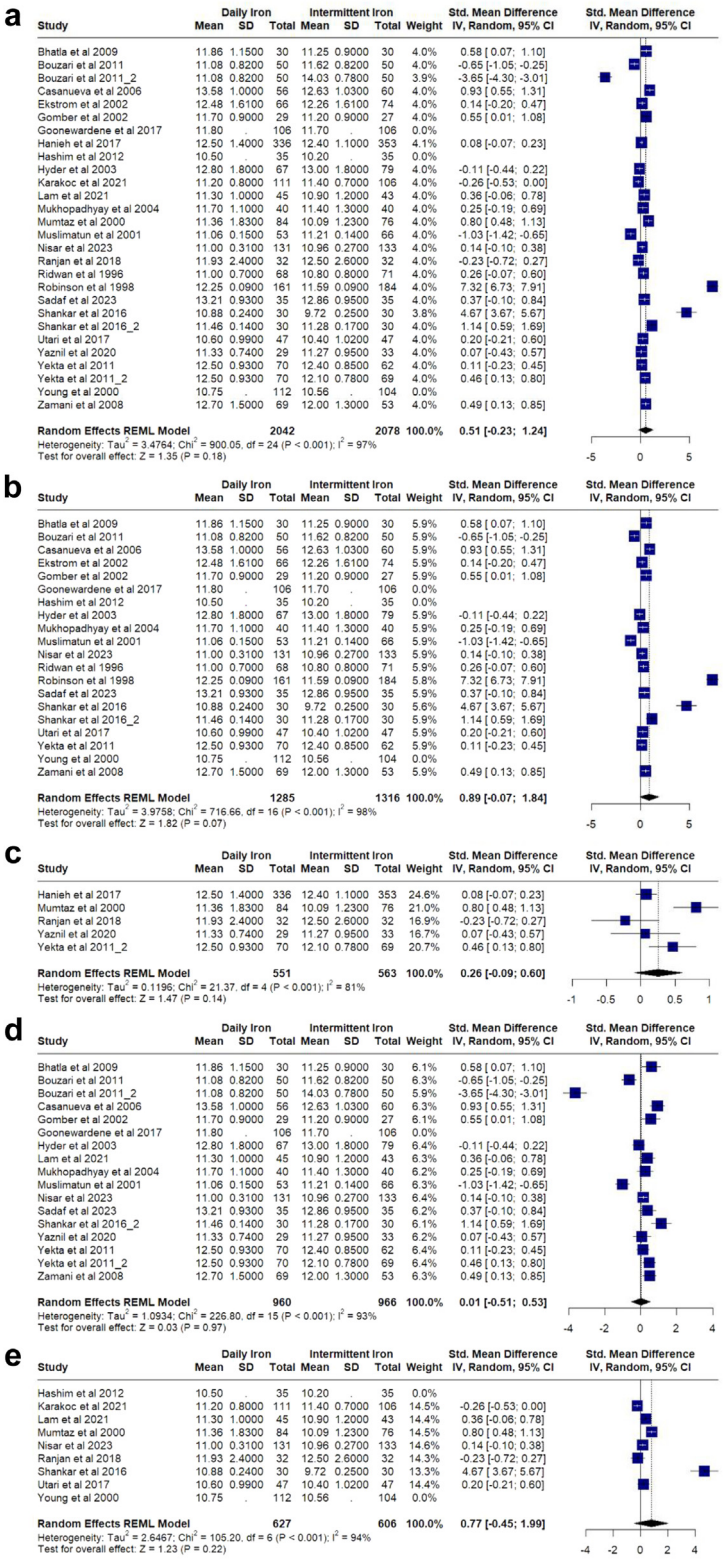

Fig. 2: Forest plot for Daily versus (a) intermittent supplementation across all studies (b) once-a-week supplementation across all studies (c) twice-a-week supplementation across all studies (d) intermittent supplementation among non-anaemic pregnant women (e) intermittent supplementation among anaemic pregnant women (SD:Standard deviation, CI:Confidence Interval, REML: Restricted maximum likelihood).

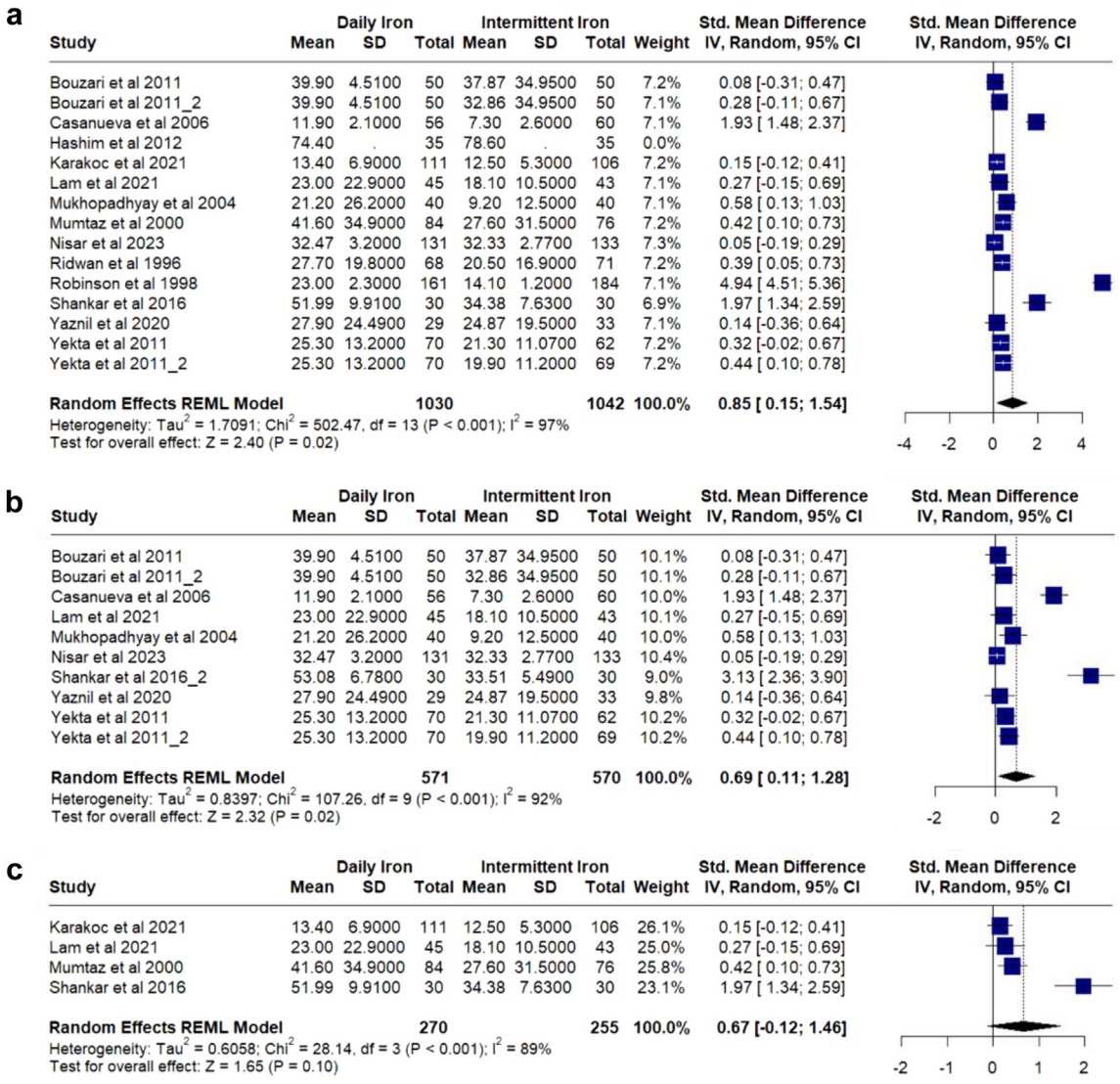

Fig. 3: Forest plots for endpoint serum ferritin levels in daily versus intermittent supplementation (a) across all studies (b) non-anaemic pregnant women (c) anaemic pregnant women (SD:Standard deviation, CI:Confidence Interval, REML: Restricted maximum likelihood).

Ten studies recorded the side effects of iron supplementation. Out of all the reported side effects, nausea, heartburn/acidity, vomiting, and constipation were the most commonly reported. Nausea was reported in 5 studies with a data of 995 participants. The nausea events were significantly higher in the daily group as compared to the intermittent supplementation group, (adjusted OR 3.56, 95% CI: 2.23–5.69, p < 0.001, moderate certainty evidence) (Fig. 4a, Supplementary Appendix IV). The heterogeneity was very low for this outcome (I^2 = 9%). The diarrhoea events were significantly different between the two groups (Adjusted OR 5.40, 95% CI: 1.90–15.33, p = 0.002, I^2 = 0%, low certainty evidence) (Fig. 4b, Supplementary Appendix IV). Similarly, the side-effect of vomiting, although higher in the daily group, was also not significant (adjusted OR: 3.22, 95% CI: 0.94–10.95, p = 0.06, I^2 = 28%, moderate certainty evidence) (Fig. 4c, Supplementary Appendix IV). Lastly, constipation was a significant side-effect in the daily supplementation group, reported in 3 studies with 841 participants (Adjusted OR 1.95, 95% CI: 1.21–3.14, p = 0.006, moderate certainty evidence) (Fig. 4d, Supplementary Appendix IV). There was no heterogeneity for the constipation outcome (I^2 = 0%).

Publication bias & sensitivity analysis

Sensitivity analysis excluding studies with a high risk of bias did not change the effect estimates for endpoint haemoglobin in daily versus intermittent supplementation groups (Supplementary Appendix VI). Similarly,

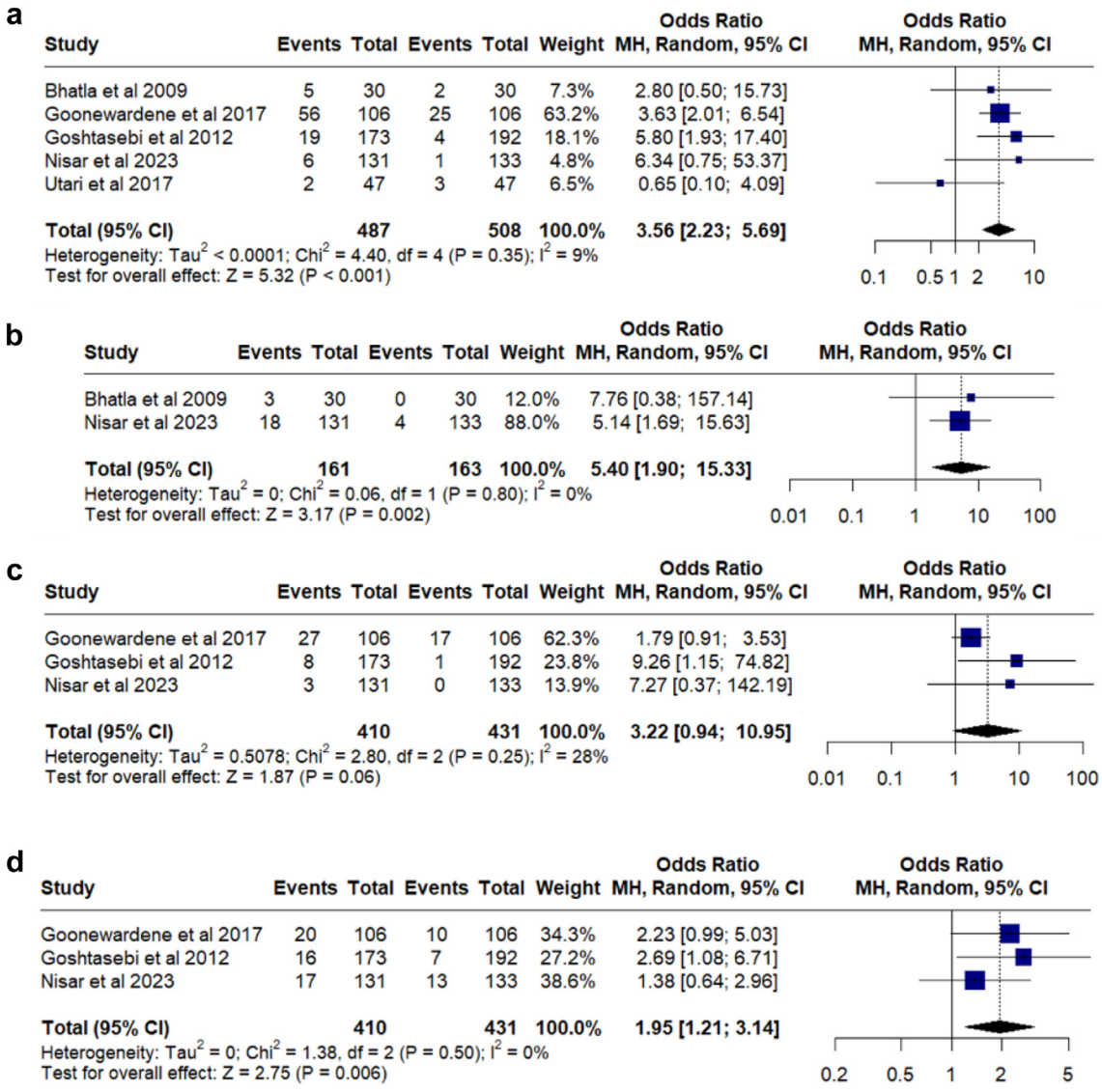

Fig. 4: Forest plots for side-effects due to iron supplementation in daily versus intermittent groups. (a) Nausea (b) diarrhoea (c) vomiting (d) constipation (SD:Standard deviation, CI:Confidence Interval, REML: Restricted maximum likelihood).

the effect estimates for endpoint ferritin levels did not lose significance after the removal of high risk bias studies (Supplementary Appendix VI).

Meta-regression

Meta-regression was performed to assess the effect of factors such as the method of haemoglobin estimation, type of iron salt used for supplementation, dosage in the intermittent arm, geographic region of the study population and the year of study publication. The meta-regression results show that none of the factors affected the endpoint haemoglobin levels and the endpoint ferritin levels significantly (Table 3). The number of studies reporting these factors for a healthy and anaemic group of participants was less than 10, hence meta-regression was not performed to assess the effect of these factors. The bubble plot for meta-regression of endpoint haemoglobin and ferritin values against these factors is included in Supplementary Appendix VII.

Discussion

Our systematic review and meta-analysis evaluated the impact of iron supplementation on the prevention of anaemia among pregnant women. Currently WHO recommends daily iron supplementation for pregnant women. We found that there was no significant difference in the endpoint haemoglobin levels between daily

Outcome	Moderator variable	No of studies reporting outcome	p value
Endpoint haemoglobin Levels	Year of publication	20	0.2533
	Geographic region of study population	25	0.6605
	Method of Hb estimation	20	0.1470
	Type of iron salt	22	0.5455
	Dosage for intermittent arm	20	0.1564
Endpoint Ferritin Levels	Year of publication	15	0.1254
	Geographic region of study population	15	0.4900
	Type of iron salt	13	0.2097
	Dosage for intermittent arm	15	0.4691

Table 3: **Summary of meta-regression analysis for moderators affecting the endpoint haemoglobin levels and endpoint ferritin levels.**

versus any intermittent oral iron supplementation with a low level of certainty. On sub group analysis by baseline anaemic status of pregnant women, frequency of intermittent supplementation did not have a significant effect on the endpoint haemoglobin status. The studies included to support this evidence had a high risk of bias.

The endpoint serum ferritin levels were significantly higher in pregnant women who were provided with daily oral iron supplementation compared to intermittent oral iron supplementation. Based on baseline anaemia status, endpoint ferritin pooled estimate in the non-anaemic group remained significant, while the same was not significant among anaemic women. In a study conducted by Milman et al., women with baseline serum ferritin concentrations below 70 ng/mL had a risk of developing iron deficiency anaemia during pregnancy or post-partum, thus suggesting the need for iron supplementation in these women. In our meta-analysis we found that for daily or intermittent supplementation of oral iron, the rise in ferritin was not beyond 70 ng/mL, suggesting that the pregnant women supplemented with either regimen might be at risk of developing anaemia.[48]

The side effects due to daily iron supplementation are one of the important reasons for the lack of compliance to supplementation among pregnant women. Ten studies recorded side effects, and the number of events were recorded for nausea, diarrhoea, vomiting and constipation. Occurrence of nausea, diarrhoea and constipation was significantly lower in the intermittent supplementation group. The median dose for intermittent supplementation was twice (120 mg/day, IQR: 65–120 mg/day) that of daily supplementation (60 mg/day, IQR:60–65 mg/day). However, the frequency of supplementation probably reduced the occurrence of adverse events. The lower number of events of nausea and constipation in pregnant women on intermittent oral iron supplementation were seen with moderate certainty.

A Cochrane review conducted by Pena-Rosas et al., in 2015 showed that intermittent supplementation could be considered an alternative strategy to the daily regimen for the prevention of anaemia in pregnancy.[11] However, recent WHO recommendations suggested daily supplementation of oral iron.[49] Our meta-analysis with a larger number of RCTs, including recently published RCTs, further strengthens the observations as the Cochrane review in terms of intermittent supplementation being an alternative to daily oral iron. Additionally, we found that the incidence of adverse effects like nausea and vomiting was much lower in the intermittent regimen group.

Excessive iron supplementation can also have adverse effects on maternal health and recent studies highlight the importance of carefully managing iron supplementation during pregnancy. While iron is essential for various physiological functions and metabolic pathways, excessive supplementation may lead to unintended consequences like small gestation age, risk of term low birth weight, hypertensive disorders among mothers and also impairs host immunity, particularly in populations at low risk of iron deficiency.[50] Research suggests that both deficiency and excess iron levels may have negative implications for pregnancy outcomes. Excessive iron supplementation can increase iron-mediated oxidative stress, disrupt microbiome homeostasis in the gastrointestinal tract, and potentially impact erythropoiesis, immune response, and placental blood flow.[51] In a retrospective study among pregnant women with gestational diabetes mellitus, there was a significant association of high maternal plasma ferritin with foetal macrosomia.[52] Similarly, in a large cohort study carried out among non-gestational diabetes mellitus women in China, IFA supplements were associated with foetal macrosomia and large for gestational age.[53]

Most of the studies in our systematic review were found to have a significant risk of bias with respect to random sequence generation. The high risk of bias, lower sample size in most of the studies make it difficult to generalize the outcome for all pregnant women, but it can be considered in non-anaemic pregnant women who experience adverse events and are unable to adhere to the daily regime.

Our study has some limitations. Firstly, the inability to include neonatal outcomes after daily versus intermittent oral iron and folic acid (IFA) supplementation limits the comprehensive understanding of the effects of different supplementation regimens on both maternal and neonatal health outcomes. This gap in the research highlights the need for further investigation in this area. Another limitation is that the number of studies included for the analysis of secondary outcome of adverse effects is very low. Additionally, potential bias during the review process is a common concern in meta-analyses. While efforts were made to minimize bias by defining selection criteria and involving multiple independent reviewers in data extraction and assessment, subjective biases could still influence the interpretation of the findings. Moreover, despite conducting

an exhaustive search of multiple databases and using predefined keywords, there is a possibility of missing relevant articles or conference papers not available online. Furthermore, restricting inclusion to articles published only in English may have resulted in the exclusion of valuable data published in other languages.

Despite these limitations, our meta-analysis provides valuable insights into the efficacy and side effects of intermittent iron supplementation during pregnancy. The findings suggest that intermittent supplementation may offer similar efficacy in increasing haemoglobin levels with fewer associated side effects compared to daily supplementation. However, the complexity of iron deficiency and overload warrants further well-designed randomized controlled trials with larger sample sizes to optimize IFA supplementation regimes and improve maternal and neonatal health outcomes while minimizing adverse effects and enhancing compliance.

In conclusion, our meta-analysis indicates that intermittent oral iron supplementation with a median dose of 120 mg/day demonstrates comparable efficacy to daily oral iron supplementation with a median dose of 60 mg/day in increasing haemoglobin levels among pregnant women. Importantly, this regimen is associated with a notable reduction in iron supplementation-related side effects. We recommend intermittent oral iron supplementation for individuals who are not able to adhere to the daily regime due to adverse events.

Contributors

NK: conceptualisation, data curation, methodology, project administration, supervision, writing—original draft, writing—review & editing.

SA: data curation, formal analysis, resources, software, visualisation, writing-review & editing.

AB: conceptualisation, data curation, methodology, project administration, supervision, writing—original draft, writing—review & editing.

NM: data curation, formal analysis, resources, writing-review & editing.

PS: data curation, formal analysis, resources, writing-review & editing.

VK: data curation, formal analysis, resources, writing-review & editing.

MM: supervision, writing—review & editing.

NK & AB verified all the data in the final manuscript before submission.

All authors read and approved the final version of the manuscript.

Data sharing statement

All the relevant data used to generate the information in this study can be found in the Supplementary file.

Declaration of interests

The Authors declare no competing interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102742.

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