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Intermittent iron and folic acid supplementation in non-anaemic pregnant women

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Contents

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WHO Guideline [1]

Intermittent iron and folic acid supplementation in non-anaemic pregnant women

Summary

It is estimated that 41.8% of pregnant women worldwide are anaemic. At least half of this anaemia burden is assumed to be due to iron deficiency. Member States have requested guidance from the World Health Organization (WHO) on the effectiveness and safety of different schemes of iron and folic acid supplementation in pregnant women as a public health measure to improve pregnancy outcomes in support of their efforts to achieve the Millennium Development Goals.

WHO developed the present evidence-informed recommendations using the procedures outlined in the *WHO handbook for guideline development*. The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and (v) planning for dissemination, implementation, impact evaluation and updating of the guideline. The *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) methodology was followed to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

The guideline advisory group for nutrition interventions, the Nutrition Guidance Expert Advisory Group, comprises content experts, methodologists, representatives of potential stakeholders and consumers. These experts participated in several WHO technical consultations concerning this guideline, held in Geneva, Switzerland, and Amman, Jordan, in 2010 and 2011. Members of the External Experts and Stakeholders Panel were identified through a public call for comments, and this panel was involved throughout the guideline development process. Guideline advisory group members voted on the strength of the recommendation, taking into consideration: (i) desirable and undesirable effects of this intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the interventions in different settings; and (iv) the cost of options available to health-care workers in different settings. All the members of the guideline advisory group completed a Declaration of Interests Form before each meeting.

Intermittent iron and folic acid supplementation is recommended in non-anaemic pregnant women to prevent development of anaemia and to improve gestational outcomes (*strong recommendation*). The quality of the evidence for low birth weight, birth weight, premature birth, maternal anaemia at term, iron deficiency anaemia at term, and side-effects was very low.

[1] This publication is a WHO guideline. A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

Scope and purpose

This guideline provides global, evidence-informed recommendations on intermittent iron and folic acid supplementation as a public health intervention for the purpose of improving pregnancy outcomes and reducing maternal anaemia in pregnancy.

The guideline will help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the Millennium Development Goals, in particular, reduction of child mortality (MDG 4) and improvement in maternal health (MDG 5). The guideline is intended for a wide audience including policy-makers, their expert advisers and technical and programme staff at organizations involved in the design, implementation and scaling-up of nutrition actions for public health.

This document presents the key recommendation and a summary of the supporting evidence. Further details of the evidence base are provided in Annex 1 and other documents listed in the references.

Background

It is estimated that 41.8% of pregnant women worldwide are anaemic (*1*). At least half of this anaemia burden is assumed to be due to iron deficiency (*2*), with the rest due to other conditions such as folate, vitamin B_{12} or vitamin A deficiencies, chronic inflammation, parasitic infections and inherited disorders. A pregnant woman is considered to be anaemic if her haemoglobin concentration during the first and third trimester of gestation is lower than 110 g/l, at sea level; in the second trimester of pregnancy, the haemoglobin concentration usually decreases by approximately 5 g/l (*3*). When anaemia is accompanied by an indication of iron deficiency (e.g. low ferritin levels), it is referred to as iron deficiency anaemia (*2*).

Low haemoglobin concentrations indicative of moderate or severe anaemia during pregnancy have been associated with an increased risk of premature delivery, maternal and child mortality, and infectious diseases (*4*). Growth and development may also be affected (*2*), both in utero and in the long term (*5*). Conversely, haemoglobin concentrations greater than 130 g/l at sea level may also be associated with negative pregnancy outcomes such as premature delivery and low birth weight (*6, 7*).

Interventions aimed at preventing iron deficiency and iron deficiency anaemia in pregnancy include iron supplementation, fortification of staple foods with iron, health and nutrition education, control of parasitic infections, and improvement in sanitation (*8*). Delayed umbilical cord clamping is also effective in preventing iron deficiency among infants and young children (*9*). During pregnancy, there is an increase in maternal iron requirements to support both maternal and fetal needs, and most women require additional iron intake to ensure sufficient iron stores at conception as well as during pregnancy to prevent iron deficiency (*10*). The use of daily iron and folic acid supplements throughout pregnancy has been the standard approach to cover this gap and in turn prevent and treat iron deficiency anaemia. Despite its proven efficacy, the use of daily iron supplementation has been limited in programme settings, possibly due to a lack of compliance because of common side-effects (e.g. nausea, constipation, dark stools or metallic taste), concerns about the safety of this intervention among women with an adequate iron intake, and variable availability of the supplements at community level (*11*).

Intermittent use of oral iron supplements (i.e. once, twice or three times a week on non-consecutive days) has been proposed as an effective alternative to daily iron supplementation for prevention of anaemia in women of reproductive age, including those who are pregnant (*12,13*). The rationale behind this intervention has traditionally been that intestinal cells turn over every 5–6 days and have limited iron absorptive capacity. Thus intermittent provision of iron would expose only the new intestinal epithelial cells to this nutrient, which, in theory, should improve its absorption (*14*). This mechanism has recently been questioned. Intermittent supplementation also reduces oxidative stress and the other side-effects of daily supplementation (*15, 16*) and may minimize blockage of absorption of other minerals due to the high iron levels in the gut lumen and in the intestinal epithelial cells. Experience has shown that intermittent regimens may be more accepted by women, with increased adherence to supplementation programmes (*17*).

Summary of evidence

An existing Cochrane systematic review (*18*) assessing the benefits and harms of iron supplementation alone or in combination with folic acid or other vitamins and minerals in pregnant women on neonatal and pregnancy outcomes was updated for this guideline. The updated review (*19*) compared the intermittent use of iron supplements alone, or in combination with folic acid or other micronutrients, with no intervention or placebo, and with the same supplements given on a daily basis to pregnant women living in a variety of settings, including malaria-endemic areas.

The infant outcomes ranked as critical for decision-making by the Nutrition Guidance Expert Advisory Group members were low birth weight, weight at birth, prematurity, perinatal death and congenital anomalies including neural tube defects. The maternal outcomes considered critical were anaemia, iron deficiency and iron deficiency anaemia at term, as well as the presence of any side-effects, clinical malaria and infections during pregnancy. The potential effects of baseline anaemia prevalence, gestational age at the start of supplementation, malaria setting and the weekly dose of iron were also evaluated.

The review included 21 trials, but only 18 trials (with 4072 women) contributed data to the review. The trials were carried out in the past two decades in countries across the globe (Argentina, Bangladesh, China, Guatemala, India, Indonesia, Iran, Malawi, Mexico, Pakistan, South Korea and Thailand). Most of the trials included both anaemic and non-anaemic women. All the studies were conducted in countries with some degree of malaria risk (*20*), however it was not clear from the reports whether malaria prevention and control programmes were in place at the time when these studies were conducted or whether concomitant malaria interventions were made available to the study participants.

None of the studies included in the review compared the effects of intermittent iron supplementation with the effects of no iron supplementation. This likely is because the studies involving intermittent supplementation were carried out in countries whose legislatures require all pregnant women to be given iron supplements.

For the comparison between daily and intermittent regimens, the methodological quality of the trials included in the analysis was mixed, with most studies reporting high losses to follow-up. The total weekly iron dose in the arm that received intermittent supplements ranged from 80 mg to 200 mg of elemental iron as ferrous sulfate or ferrous fumarate per week, whereas the folic acid dose ranged from 400 µg (0.4 mg) to 3500 µg (3.5 mg) per week.

There was no detectable difference between women taking iron supplements intermittently (alone or in combination with other micronutrients) and those receiving daily supplements with regard to maternal anaemia at term (average relative risk (RR) 1.22, 95% confidence interval (CI) 0.84–1.80, four studies), the risk of having a low birth weight (RR 0.96, 95% CI 0.61–1.52, seven studies) or a preterm (RR 1.82, 95% CI 0.75–4.40, four studies) baby and infant birth weight (mean difference –8.62 g; 95% CI 52.76 to 35.52 g, eight studies). There were no maternal deaths (six studies) or women with severe anaemia (six studies).

Fewer side-effects were reported in women receiving intermittent rather than daily iron and folic acid supplements (RR 0.56; 95% CI 0.37–0.84, 11 studies). High haemoglobin concentrations (more than 130 g/l) during the second and third trimester of pregnancy were also less frequent among women using supplements intermittently (RR 0.48; 95% CI 0.35–0.67, 13 studies).

The intervention seems to be equally effective among populations with different prevalences of anaemia, and in settings described as malaria endemic, and regardless of whether the supplementation was initiated earlier or later than 20 weeks of gestation or whether the dose of elemental iron per week was lower or higher than 120 mg.

The quality of the evidence for low birth weight, birth weight, premature birth, maternal anaemia at term, iron deficiency at term, and side-effects was very low (Annex 1).

Recommendation

Intermittent use of iron and folic acid supplements by non-anaemic pregnant women is recommended to prevent anaemia and improve gestational outcomes (*strong recommendation*)[1, 2].

A suggested scheme for intermittent iron and folic acid supplementation in non-anaemic pregnant women is presented in Table 1.

[1] A strong recommendation is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. The recommendation can be either in favour of or against an intervention. Implications of a strong recommendation for patients are that most people in their situation would want the recommended course of action and only a small proportion would not. Implications for clinicians are that most patients should receive the recommended course of action, and that adherence to this recommendation is a reasonable measure of good-quality care. With regard to policy-makers, a strong recommendation means that it can be adapted as a policy in most situations.

[2] Considerations of the guideline advisory group for determining the strength of the recommendation are summarized in Annex 2.

Table 1

Suggested scheme for intermittent iron and folic acid supplementation in non-anaemic pregnant women

Supplement composition	Iron: 120 mg of elemental iron[a] Folic acid: 2800 µg (2.8 mg)
Frequency	One supplement once a week
Duration	Throughout pregnancy. Iron and folic acid supplementation should begin as early as possible
Target group	Non-anaemic[b] pregnant adolescents and adult women
Settings	Countries where prevalence of anaemia among pregnant women is lower than 20%.

[a] 120 mg of elemental iron equals 600 mg of ferrous sulfate heptahydrate, 360 mg of ferrous fumarate or 1000 mg of ferrous gluconate.

[b] Haemoglobin concentrations should be measured prior to the start of supplementation to confirm non-anaemic status (*3*).

Remarks

- If a woman is diagnosed with anaemia at any time during pregnancy, she should be given daily iron and folic acid supplements throughout pregnancy as per current guidance (*21*).
- The implementation of this recommendation may require a strong health system to facilitate confirmation of non-anaemic status prior to the start of supplementation and to monitor anaemia status throughout pregnancy.
- As there is limited evidence for the effective dose of folic acid in intermittent supplementation, the recommendation for the folic acid dosage is based on the rationale of providing seven times the recommended daily supplemental dose during pregnancy. Folic acid requirements are increased in pregnancy because of the rapidly dividing cells in the fetus and increased urinary losses. As the neural tube closes by day 28 of pregnancy, by when pregnancy may not have been detected, folic acid supplementation after the first month of pregnancy may not prevent neural tube defects. However, it will contribute to other aspects of maternal and fetal health.
- In malaria-endemic areas, iron and folic acid supplementation programmes should be implemented in conjunction with measures to prevent, diagnose and treat malaria during pregnancy (*20, 22-23*).

- An iron supplementation programme may form part of an integrated programme of antenatal and neonatal care (*24, 25*) that promotes adequate gestational weight gain, screening of all women for anaemia at antenatal and postpartum visits, use of complementary measures to control and prevent anaemia (e.g. hookworm control), and a referral system to manage cases of severe anaemia.

- The implementation of a behaviour change communication strategy to communicate the benefits of the intervention and management of side-effects, along with provision of high-quality products with appropriate packaging, is vital to improving the acceptability of and adherence to recommended supplementation schemes. The strategy can also serve to promote the use of dietary diversity and intake of food combinations that improve iron absorption.

- Oral supplements are available as capsules or tablets (soluble, tablets, dissolvable and modified-release tablets) (*26*). Establishment of a quality assurance process is important to guarantee that supplements are manufactured, packaged and stored in a controlled and uncontaminated environment (*27*).

- The selection of the most appropriate delivery platform should be context-specific, with the aim of reaching the most vulnerable populations and ensuring a timely and continuous supply of supplements.

Implications for future research

Discussion with the guideline advisory group members and stakeholders highlighted the limited evidence available in some areas, meriting further research on intermittent iron and folic acid supplementation in non-anaemic pregnant women, particularly in the following areas:

- the most effective and safe weekly dose of folic acid to improve folate status and improve pregnancy outcomes;

- effects of other vitamins and minerals on haematological, nutritional and other health outcomes as well as the best formulation to provide multiple micronutrients on a weekly basis;

- mechanisms through which intermittently delivered iron is absorbed and regulated by the intestinal cells;

- potential use of slow-release formulations in terms of efficacy, cost and side-effects, in comparison with standard iron and folic acid tablets.

Dissemination, adaptation and implementation

Dissemination

The current guidelines will be disseminated through electronic media such as slide presentations, CD-ROMs and the World Wide Web, either through the World Health Organization (WHO) Micronutrients and United Nations Standing Committee on Nutrition (SCN) mailing lists, the WHO nutrition web site, or the WHO e-Library of Evidence for Nutrition Actions (eLENA). This library aims to compile and display WHO guidelines related to nutrition, along with complementary documents such as systematic reviews and other evidence that informed the guidelines, biological and behavioural rationales, and additional resources produced by Member States and global partners. The guideline will also be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. It will also be published in the WHO Reproductive Health Library.

Adaptation and implementation

As this is a global guideline, it should be adapted to the context of each Member State. Prior to implementation, an intermittent iron supplementation programme should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication channels, and potential stakeholders. Ideally, iron and folic acid supplementation should be implemented as part of an integrated programme for antenatal and neonatal care. The implementation in this guideline may require a strong health system to facilitate the diagnosis of anaemia prior to starting supplementation and to monitor anaemia status throughout pregnancy.

To ensure that WHO global guidelines and other evidence-informed recommendations for micronutrient interventions are better implemented in low- and middle-income countries, the Department of Nutrition for Health and Development works with the WHO Evidence-Informed Policy Network (EVIPNet) programme. EVIPNet promotes partnerships at country level between policy-makers, researchers and civil society to facilitate policy development and implementation through use of the best available evidence.

Monitoring and evaluation of guideline implementation

A plan for monitoring and evaluation with appropriate indicators is encouraged at all stages. The impact of this guideline can be evaluated within countries (i.e. monitoring and evaluation of the programmes implemented at scale) and across countries (i.e. the adoption and adaptation of the guidelines globally). The WHO Department of Nutrition for Health and Development, jointly with the Centers for Disease Control and Prevention (CDC) International Micronutrient Malnutrition Prevention and Control (IMMPaCt) programme, and with input from international partners, developed a generic logic model for micronutrient interventions in public health to depict the plausible relationships between inputs and expected MDGs by applying the micronutrient programme evaluation theory (*28*). Member States can adjust the model and use it in combination with appropriate indicators, for designing, implementing, monitoring and evaluating the successful scaling-up of nutrition actions.

For evaluation at global level, the WHO Department of Nutrition for Health and Development is developing a centralized platform, for sharing information on nutrition actions in public health practice implemented around the world. By sharing programmatic details, specific country adaptations and lessons learnt, this platform will provide examples of how guidelines are being translated into nutrition actions.

Guideline development process

This guideline was developed in accordance with WHO evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development* (*29*).

Advisory groups

The WHO Steering Committee for Nutrition Guidelines Development, led by the Department of Nutrition for Health and Development, was established in 2009 with representatives from all WHO departments with an interest in the provision of scientific nutrition advice, including Child and Adolescent Health and Development, Reproductive Health and Research, and the Global Malaria Programme. The Steering Committee guided the development of this guideline and provided overall supervision of the guideline development process (Annex 3). Two additional groups were formed: an advisory guideline group and an External Experts and Stakeholders Panel.

The Nutrition Guidance Expert Advisory Group, was also established in 2009 (Annex 4). There were four subgroups: (i) Micronutrients, (ii) Diet and Health, (iii) Nutrition in Life course and Undernutrition, and (iv) Monitoring and Evaluation. Its role is to advise WHO on the choice of important outcomes for decision-making and in the interpretation of the evidence. The group includes experts from various WHO expert advisory panels and those identified through open calls for specialists, taking into consideration a balanced gender mix, multiple disciplinary areas of expertise and representation from all WHO regions. Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process) and consumers. Representatives of commercial organizations may not be members of a WHO guideline group.

The External Experts and Stakeholders Panel was consulted on the scope of the guideline, the questions addressed and the choice of important outcomes for decision-making, as well as with regard to review of the completed draft guidelines (Annex 5). This was done through the WHO Micronutrients and SCN mailing lists that together include over 5500 subscribers, and through the WHO nutrition web site.

Scope of the guideline, evidence appraisal and decision-making

An initial set of questions (and the components of the questions) to be addressed in the guideline was the critical starting point for formulating the recommendation. The questions were drafted by technical staff from the Micronutrients Unit, Department of Nutrition for Health and Development, based on policy and programme guidance needs of Member States and their partners. The population, intervention, control, outcomes (PICO) format was used (Annex 6). The questions were discussed and reviewed by the Steering Committee and feedback was received from 48 stakeholders.

The first nutrition guideline advisory group meeting was held on 22–26 February 2010 in Geneva, Switzerland, to finalize the scope of the questions and rank the critical outcomes and populations of interest. The nutrition guideline advisory group – Micronutrients Subgroup discussed the relevance of the questions and modified them as needed. The guideline group members scored the relative importance of each outcome from 1 to 9 (where 7–9 indicated that the outcome was critical for a decision, 4–6 indicated that it was important and 1–3 indicated that it was not important). The final key questions on iron and folic acid supplementation in pregnant women, along with the outcomes that were identified as critical and important for decision-making, are listed in PICO format in Annex 6.

WHO staff, in collaboration with researchers from other institutions, summarized and appraised the evidence, using the Cochrane methodology for randomized controlled trials[1]. For identifying unpublished studies or studies still in progress, a standard procedure was followed to contact more than 10 international organizations working on micronutrient interventions. In addition, the International Clinical Trials Registry Platform (ICTRP), hosted at WHO, was systematically searched for any trials still in progress. No language restrictions were applied in the search. Evidence summaries were prepared according to the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) approach to assess the overall quality of the evidence (*30*). GRADE considers: the study design; the limitations of the studies in terms of their conduct and analysis; the consistency of the results across the available studies; the directness (or applicability and external validity) of the evidence with respect to the populations, interventions and settings where the proposed intervention may be used; and the precision of the summary estimate of the effect.

Both the systematic review and the GRADE evidence profiles for each of the critical outcomes were used for drafting this guideline. The draft recommendation was reviewed by the WHO Nutrition Guidance Steering Committee and the nutrition guideline advisory group at a second consultation, held on 15–18

[1] As part of the Cochrane pre-publication editorial process, reviews are commented on by external peers (an editor and two referees external to the editorial team) and the group's statistical adviser (http://www.cochrane.org/cochrane-reviews). The Cochrane handbook for systematic reviews of interventions describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health-care interventions.

November 2010 in Amman, Jordan, and at the third consultation, held on 14–16 March in Geneva, Switzerland, where the guideline advisory group also voted on the strength of the recommendation, taking into account: (i) desirable and undesirable effects of this intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings (Annex 2). Consensus was defined as agreement by simple majority of guideline group members. WHO staff present at the meeting as well as other external technical experts involved in the collection and grading of the evidence were not allowed to vote. One member voted against the use of intermittent iron and folic acid supplements as an alternative to daily supplementation in non-anaemic pregnant women.

A public call for comments on the final draft guidelines was then released. Interested stakeholders became members of the External Experts and Stakeholders Panel but were only allowed to comment on the draft guideline after submitting a signed Declaration of Interests Form. Feedback was received from 15 stakeholders. WHO staff then finalized the guideline and submitted it for clearance by WHO before publication.

Management of conflicts of interest

According to the rules in the WHO *Basic documents* (*31*), all experts participating in WHO meetings must declare any interest relevant to the meeting prior to their participation. The conflicts of interest statements for all guideline group members were reviewed by the responsible technical officer and the relevant departments before finalization of the group composition and invitation to attend a guideline group meeting. All guideline group members and participants of the guideline development meetings submitted a Declaration of Interests Form along with their curriculum vitae before each meeting. In addition, they verbally declared potential conflicts of interest at the beginning of each meeting. The procedures for management of conflicts of interests strictly followed WHO *Guidelines for declaration of interests* (*WHO experts*) (*32*). The potential conflicts of interest declared by the members of the guideline group are summarized below.

- Dr Héctor Bourges Rodriguez declared being chair of the executive board of the Danone Institute in Mexico (DIM), a non-profit organization promoting research and dissemination of scientific knowledge in nutrition, and receiving funds as chair honorarium from DIM. Some of the activities of the DIM may generally relate to nutrition and are funded by Danone Mexico, a food producer.

- Dr Norm Campbell at the first meeting declared owning stock in Viterra, a wheat pool for farmers that neither manufactures products nor undertakes activities related to this guideline. In 2011, Dr Campbell declared no longer owning stocks in this company. He serves as a Pan American Health Organization (PAHO) consultant and has been an adviser to Health Canada and Blood Pressure Canada, both of which are government agencies.

- Dr Emorn Wasantwisut declared serving as a technical/scientific adviser to the International Life Sciences Institute (ILSI)/South East Asia's Food and Nutrients in Health and Disease Cluster and as a reviewer of technical documents and speaker for Mead Johnson Nutritionals. Her research unit received funds for research support from Sight and Life and the International Atomic Energy Agency (IAEA) for the use of stable isotopes to define interactions of vitamin A and iron.

- Dr Beverley Biggs declared that the University of Melbourne received funding from the National Health and Medical Research Council (NHMRC) and Australian Research Council (ARC) for research on intermittent iron and folic acid supplementation in pregnancy, conducted in collaboration with the Research and Training Center for Community Development (RTCCD), the Key Centre for Women's Health and the Murdoch Childrens Research Institute.

Plans for updating the guideline

This guideline will be reviewed in 2015. If new information is available at that time, a guideline review group will be convened to evaluate the new evidence and revise the recommendation if needed. The Department of Nutrition for Health and Development at the WHO headquarters in Geneva, along with its internal partners, will be responsible for coordinating the guideline update following formal *WHO handbook for guideline development* (*29*) procedures. WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

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Annex 1 GRADE "Summary of findings" tables

Any intermittent oral iron supplementation versus any daily iron supplementation for women during pregnancy–infant outcomes

Patient or population: women during pregnancy

Settings: community settings

Intervention: intermittent supplementation with iron alone or plus any other micronutrients

Comparison: any intermittent oral iron supplementation versus any daily iron supplementation

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Low birth weight (less than 2500 g)	**RR 0.96** (0.61–1.52)	1111 (7 studies)	⊕⊖⊖⊖ **very low** [1]	
Birthweight (g)	**MD–8.62** (-52.76 to 35.52)	10 608 (8 studies)	⊕⊖⊖⊖ **very low**[2]	
Premature birth (less than 37 weeks of gestation)	**RR 1.82** (0.75–4.40)	382 (4 studies)	⊕⊖⊖⊖ **very low**[3]	
Neonatal death (death within first 28 days of life)	**Not estimable**	0 (0 studies)	See comment	No studies reported data for this outcome
Congenital anomalies (including neural tube defects)	**Not estimable**	0 (0 studies)	See comment	No studies reported data for this outcome

CI, confidence interval; RR, risk ratio

* GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Six of the studies contributing data had high levels of attrition, none had blinding and five had high or unclear risk of bias for allocation concealment. Proportion of events was low and there was some imprecision in the estimate. The results were consistent and statistical heterogeneity was nil ($I^2 = 0\%$).

[2] Seven of the studies contributing data had high levels of attrition, none had blinding and five had high or unclear risk of bias for allocation concealment. 95% confidence intervals were wide for this outcome, although the results were consistent and statistical heterogeneity was nil ($I^2 = 0\%$).

[3] Three of the included studies had high attrition, lacked blinding and had unclear or high risk of bias for allocation concealment. Proportion of events was low. The results were consistent and statistical heterogeneity was nil ($I^2 = 0\%$).

For details of studies included in the review, see reference (*19*).

Any Intermittent oral iron supplementation versus any daily iron supplementation for women during pregnancy–maternal outcomes

Patient or population: women during pregnancy

Settings: community settings

Intervention: intermittent supplementation with iron alone or plus any other micronutrients

Comparison: any intermittent oral iron supplementation versus any daily iron supplementation

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Anaemia at term (haemoglobin lower than 110 g/l at 37 weeks' gestation or more)	**RR 1.22** (0.84–1.80)	676 (4 studies)	⊕⊖⊖⊖ **very low**[1]	
Iron deficiency at term (as defined by the trialists, based on any indicator of iron status at 37 weeks' gestation or more)	**Not estimable**	0 (0 studies)	See comment	No studies reported data for this outcome
Iron deficiency anaemia at term (as defined by the trialists)	**RR 0.71** (0.08–6.63)	156 (1 study)	⊕⊖⊖⊖ **very low**[2]	
Maternal death	**Not estimable**	0 (0 studies)	See comment	No studies reported data for this outcome
Side-effects (any reported throughout the intervention period)	**RR 0.56** (0.37–0.84)	1777 (11 studies)	⊕⊖⊖⊖ **very low**[3]	
Severe anaemia at any time during second and third trimester (haemoglobin lower than 70g/l)	**Not estimable**	1240 (6 studies)	See comment	While this outcome was reported in six studies there were no events
Maternal clinical malaria	**Not estimable**	0 (0 studies)	See comment	This outcome was not reported in any of the included studies
Maternal infection during pregnancy	**Not estimable**	0 (0 studies)	See comment	This outcome was not reported in any of the included studies

CI, confidence interval; RR, risk ratio

* GRADE Working Group grades of evidence:

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Half of the studies contributing data had high risk of bias for attrition, one had unclear allocation concealment. 95% confidence intervals were wide for all of these studies. The results were consistent and statistical heterogeneity was nil (I^2 = 10%).

[2] The single study contributing data had unclear methods to generate the random sequences and no blinding. 95% confidence intervals were wide.

[3] Several studies were at high or unclear risk of allocation and attrition. The size and direction of treatment effect varied in these studies and heterogeneity was high (I^2 = 87%).

For details of studies included in the review, see reference (*19*).

Annex 2 Summary of the considerations by the Nutrition Guidance Expert Advisory Group for determining the strength of the recommendation

Quality of evidence:	• The quality of the evidence was low and may be insufficient to support the use of intermittent supplementation in settings where daily iron and folic acid supplementation is standard practice
Values and preferences:	• This may be a solution in areas with low prevalence of anaemia in pregnant women in whom daily programmes have failed to deliver • Intermittent iron and folic acid supplementation is likely to achieve higher coverage than daily supplementation. However, it requires screening for anaemia status of pregnant women, which is not common in most communities
Trade-off between benefits and harm:	• Non-anaemic pregnant women can still be iron deficient; therefore intermittent iron supplementation may result in iron deficiency later on during pregnancy. If this intervention is combined with weekly iron supplementation in menstruating women, it may be more successful in preventing anaemia • Benefits outweigh harms but it is an area where more research is needed
Costs and feasibility:	• Intermittent supplementation with iron and folic acid during pregnancy is presumably cheaper than daily supplementation and feasible in populations with low rates of iron deficiency or where daily iron supplementation is not available

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Annex 6 Questions in Population, Intervention, Control, Outcomes (PICO) format

Effects and safety of iron and folic acid supplementation in pregnant women

a. Could iron and folic acid supplements given to pregnant women improve maternal and infant health outcomes?

b. If so, at what dose, frequency and duration for the intervention, and in which settings?

Population: Non-anaemic pregnant women

Subpopulation:

Critical

- By malaria-endemic versus non-malaria-endemic area (no transmission or elimination achieved, susceptibility to epidemic malaria, year-round transmission with marked seasonal fluctuations, year-round transmission with consideration of *Plasmodium falciparum* and/or *Plasmodium vivax*)
- By use of concurrent malarial measures, in particular, intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP)
- By human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) status: HIV positive versus HIV negative
- By individual's status of iron deficiency: iron deficiency versus non-iron deficiency
- By individual's status of anaemia: anaemic versus non-anaemic
- By anaemia status of population: 20% or less versus 20–40% versus more than 40%

Intervention: Iron plus folic acid supplementation

Subgroup analysis:

Critical

- By frequency: daily versus once weekly versus twice weekly versus other
- By duration: 3 months or less versus more than 3 months
- By nutrient: iron versus iron plus folic acid versus iron plus other micronutrients
- By iron content
- By folic acid content

Control:

- No iron supplementation
- Placebo
- Same supplement without iron or folic acid on a daily basis

Outcomes: Maternal

Critical

- Severe anaemia
- Maternal mortality
- Anaemia at term
- Haemoglobin concentrations
- Iron deficiency anaemia at term
- Iron deficiency at term
- Morbidity from malaria – incidence and severity (parasitaemia with or without symptoms)
- Adverse effects

Neonate/infant

Critical

- Neural tube defects
- Iron deficiency anaemia at birth
- Low birth weight: less than 2500 g
- Birth weight
- Iron deficiency at term
- Length at birth
- Anaemia at birth
- Preterm birth: less than 37 weeks' gestation
- Neonatal mortality: within 28 weeks after birth

Setting: All settings

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