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Guideline:

Intermittent iron and folic acid supplementation in menstruating women

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Contents

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WHO Guideline[1]

Intermittent iron and folic acid supplementation in menstruating women

Summary

Women of reproductive age are at increased risk of anaemia because of chronic iron depletion during the menstrual cycle. It is estimated that worldwide there are 469 million anaemic women of reproductive age. At least half of the cases are attributed to iron deficiency. Member States have requested guidance from the World Health Organization (WHO) on the effects and safety of intermittent supplementation with iron and folic acid in menstruating women as a public health measure to prevent anaemia 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 used to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews.

The guideline development group for nutrition interventions, the Nutrition Guidance Expert Advisory Group (NUGAG), 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 in 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. NUGAG 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 intervention in different settings; and (iv) the cost of options available to health-care workers in different settings. All NUGAG members completed a Declaration of Interests Form before each meeting.

Intermittent iron and folic acid supplementation is recommended as a public health intervention in menstruating women living in settings where anaemia is highly prevalent, to improve their haemoglobin concentrations and iron status and reduce the risk of anaemia (strong recommendation). The overall quality of the evidence for anaemia, haemoglobin, iron deficiency and ferritin was found to be low for the comparison between intermittent iron supplementation and no intervention or placebo. When this intervention was compared with daily iron supplementation, the quality of the evidence for anaemia was moderate, low for haemoglobin and ferritin, and very low for iron deficiency.

[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 the intermittent use of iron and folic acid supplements as a public health measure for the purpose of reducing anaemia and improving iron status among menstruating women.

The guideline will help Members States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the Millennium Development Goals, in particular, promotion of gender equality and empowerment of women (MDG 3) 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 the global prevalence of anaemia in non-pregnant women is 30.2% (*1*). Anaemia has multiple causes that very often coexist; it can result from parasitic infections, inflammatory disorders, inherited disorders of haemoglobin structure, or vitamin and mineral deficiencies, including iron and vitamins A, B_{12} and folate. At least half the burden of anaemia is associated with iron deficiency (*2*). Iron deficiency is the result of prolonged negative iron balance, which can be caused by inadequate iron intake (due to insufficient dietary iron content or absorption), increased iron requirements or chronic loss of iron due to bleeding. Women of reproductive age are at higher risk of developing iron deficiency because of losses during menstruation (*2*).

Anaemia in women of reproductive age is usually diagnosed when the haemoglobin concentration in the blood is below 120g/l, at sea level (*3*). A diagnosis of iron deficiency anaemia is made when there is both anaemia and iron deficiency, the presence of which is established by measuring the concentration of ferritin or another indicator of iron status, such as serum soluble transferrin receptors (*4*). Iron deficiency anaemia impairs resistance to infection in all age groups, and reduces physical capacity and work performance among adolescents and adults (*2, 5*). In addition, women entering pregnancy with suboptimal iron reserves may be at higher risk of negative maternal and neonatal outcomes (*6*).

Daily supplementation with iron and folic acid for a period of 3 months has been the standard approach for the prevention and treatment of iron deficiency anaemia among women of reproductive age. Despite its proven efficacy, there has been limited success with the daily regimen public health programmes, which is thought to be primarily due to low coverage rates, insufficient tablet distribution and, low and adherence because of the side-effects (e.g. constipation, dark stools or metallic taste) (*7*).

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 to prevent anaemia among menstruating women (*8, 9*). The proposed rationale behind this intervention is 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 epithelial cells to this nutrient, which should, in theory, improve the efficiency of absorption (*10, 11*). Intermittent supplementation may also reduce oxidative stress and the frequency of other side-effects associated with daily iron supplementation (*6, 8*) as well as minimize blockage of absorption of other minerals due to the high iron levels in the gut lumen and in the intestinal epithelium. Experience has shown that intermittent regimens may also be more acceptable to women and increase compliance with supplementation programmes (*12, 13*). Use of these regimens may also result in improvement in women's iron and folate status prior to pregnancy, to help prevent neural tube defects (*14*).

Summary of evidence

A Cochrane systematic review (*15*) assessing the effect and safety of intermittent iron supplementation on anaemia and its associated impairments was conducted for this guideline. This review compared the intermittent use of iron supplements alone, or in combination with folic acid or other micronutrients, versus no intervention or placebo, and versus the same supplements given on a daily basis to pubescent girls and menstruating women, living in a variety of settings, including malaria-endemic areas.

The outcomes considered to be critical for decision-making by the Nutrition Guidance Expert Advisory Group (NUGAG) were anaemia, iron deficiency, iron deficiency anaemia and morbidity, particularly malaria incidence and severity. The potential modifying effects of baseline anaemia status, dose of elemental iron per week, duration of the supplementation, supplement formulation, and malaria endemicity were also considered relevant.

The review included 21 randomized controlled trials involving 10 258 postmenarchal women from 15 countries in Latin America, Asia, Africa and Europe. The baseline prevalence of anaemia was different across the trials. Five studies were performed in areas described as malaria-endemic.

Women taking intermittent iron supplements (alone or in combination with folic acid or other micronutrients) had higher haemoglobin (mean difference (MD) 4.58 g/l, 95% confidence interval (CI) 2.56–6.59, 13 studies) and ferritin concentrations (MD 8.32 µg/l, 95% CI 4.97–11.66, six studies) and were less likely to develop anaemia (average risk ratio (RR) 0.73; 95% CI 0.56–0.95, 10 studies) than those who did not receive the supplements or were given a placebo.

Compared with women receiving daily iron supplements, women who received iron supplements intermittently were more likely to be anaemic (RR 1.26, 95% CI 1.04–1.51, six studies) and have higher ferritin concentrations (MD –11.32 µg/l, 95% CI –22.61

to –0.02, three studies), although they had similar haemoglobin concentration (MD –0.15 g/l, 95% CI –2.20 to 1.91, eight studies). There was no statistical evidence of differences in the risk of having iron deficiency (RR 4.30, 95% CI 0.56–33.20, one study) or clinical malaria, but these findings should be interpreted with caution as very few studies have assessed these outcomes.

The intervention was effective regardless of whether the supplements were given once or twice weekly, for less or more than 3 months, contained less or more than 60 mg of elemental per week or in areas with different prevalence of anaemia or malaria.

The overall quality of the evidence for anaemia, iron deficiency, haemoglobin and ferritin was found to be low for the comparison between intermittent iron supplementation and no intervention or placebo. When this intervention was compared with daily iron supplementation, the quality of the evidence for anaemia was moderate, low for haemoglobin and ferritin, and very low for iron deficiency (Annex 1).

On the programme experience side, weekly supplementation with iron and folic acid in menstruating women has been successfully implemented using different delivery mechanisms in several countries (including Cambodia, Egypt, India, Laos, the Philippines and Viet Nam), reaching over half a million women. In general, the reported compliance has been high, with a decrease in the prevalence of anaemia between 9.3% and 56.8% (*16*).

Recommendation

This recommendation replaces those published in a previous WHO statement (*17*).

Intermittent iron and folic acid supplementation is recommended as a public health intervention in menstruating women living in settings where anaemia is highly prevalent, to improve their haemoglobin concentrations and iron status and reduce the risk of anaemia (*strong recommendation*)[1].

A suggested scheme for intermittent iron and folic acid supplementation in menstruating 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. This 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.

Table 1

Suggested scheme for intermittent iron and folic acid supplementation in menstruating women

Supplement composition	Iron: 60 mg of elemental iron[a] Folic acid: 2800 µg (2.8 mg)
Frequency	One supplement per week
Duration and time interval between periods of supplementation	3 months of supplementation followed by 3 months of no supplementation after which the provision of supplements should restart. If feasible, intermittent supplements could be given throughout the school or calendar year
Target group	All menstruating adolescent girls and adult women
Settings	Populations where the prevalence of anaemia among non-pregnant women of reproductive age is 20% or higher

[a] 60 mg of elemental iron equals 300 mg of ferrous sulfate heptahydrate, 180 mg of ferrous fumarate or 500 mg of ferrous gluconate.

Remarks

- Intermittent iron and folic acid supplementation is a preventive strategy for implementation at population level. If a woman is diagnosed as having anaemia in a clinical setting, she should be treated with daily iron (120 mg of elemental iron) and folic acid (400 µg or 0.4 mg) supplementation until her haemoglobin concentration rises to normal (*18*). She can then switch to an intermittent regimen to prevent recurrence of anaemia.
- 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 supplemental dose to prevent neural tube defects (400 µg or 0.4 mg daily). Further limited experimental evidence suggests this dose can improve red cell folate concentrations to levels associated with a reduced risk of neural tube defects (*17*, *19*).
- In malaria-endemic areas, the provision of iron and folic acid supplements should be made in conjunction with adequate measures to prevent, diagnose and treat malaria (*20*).

- The provision of iron and folic acid supplements on an intermittent basis can be integrated into national programmes for adolescent and reproductive health (*21, 22*). However, to ensure that the daily needs are met and not exceeded, supplementation should be preceded by an evaluation of the nutritional status of women of reproductive age and of the existing measures to control anaemia and folate insuficiency, such as programmes for hookworm control, food fortification or adequate diet promotion.
- Intermittent iron and folic acid supplements could be given to women planning pregnancy to improve their iron stores. On confirmation of pregnancy, women should receive standard antenatal care including daily or intermittent iron and folic acid supplementation depending on their anaemia status (*23, 24*).
- The establishment of a quality assurance process is important to guarantee that supplements are manufactured, packaged and stored in a controlled and uncontaminated environment according to prespecified conditions (e.g. colour and size of pills) (*25*).
- 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 supplements with appropriate packaging, may improve the acceptability and adherence to iron and folic acid supplementation. Such a strategy can also serve to promote dietary diversification and the intake of food combinations that improve iron absorption.
- 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.
- Oral supplements are available in tablet and capsule form (*26*). Tablets (soluble tablets, effervescent tablets, dissolvable tablets for use in the mouth, and modified-release tablets) are solid dosage forms containing one or more active ingredients. They are manufactured by single or multiple compression (in certain cases they are moulded) and may be uncoated or coated. Capsules are solid dosage forms with hard or soft shells, which are available in a variety of shapes and sizes, and contain a single dose of one or more active ingredients. Capsules are intended for oral administration and may allow modified release of their contents.

Dissemination, adaptation and implementation

Dissemination

The current guideline 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 or the WHO nutrition web site. The Department of Nutrition for Health and Development is developing 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. This 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 and folic acid 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. Supplementation programmes should start with a pilot and scaled up as experience and evidence grow and resources allow. Ideally, intermittent iron and folic acid supplementation should be part of a national strategy to control nutritional deficiencies and should be integrated into national programmes focused on adolescent and reproductive health.

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 national or regional scale) and across countries (i.e. the adoption and adaptation of the guideline globally). The WHO Department of Nutrition for Health and Development, Micronutrients Unit, jointly with the US Centers for Disease Control and Prevention (CDC) International Micronutrient Malnutrition Prevention and Control (IMMPaCt) programme, and with input from international partners, has 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. 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 (*27*).

For evaluation at the 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.

Examples of programmes implemented in two WHO regions have been recently published (*16*, *28*).

Implications for future research

Discussion with meeting participants and stakeholders highlighted the limited evidence in some areas, meriting further research on intermittent iron and folic acid supplementation in menstruating women, in particular, in the following areas:

- benefits of this intervention on work and productivity, and pregnancy outcomes;
- the most effective and safe weekly dose of folic acid to improve folate status and prevent neural tube defects;
- effects of other vitamins and minerals on haematological, nutritional and other health outcomes, as well as the best formulation to provide multiple micronutrients on an intermittent basis;
- mechanisms through which intermittent 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;
- the optimal time interval between periods of supplementation in terms of cost-effectiveness and long-term sustainability of the intervention.

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 and the Department of Research Policy and Cooperation, 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 2). Two additional groups were formed: an advisory guideline group and an External Experts and Stakeholders Panel.

The Nutrition Guidance Expert Advisory Group, NUGAG, was also established in 2009 (Annex 3). NUGAG consists of 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 guideline (Annex 4). 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 this guideline was the critical starting point for formulating the recommendation. The questions were drafted by technical staff at 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 5). The questions were discussed and reviewed by the WHO Steering Committee for Nutrition Guidelines Development and feedback was received from 48 stakeholders.

The first NUGAG 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 NUGAG – Micronutrients Subgroup discussed the relevance of the questions and modified them as needed. 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 menstruating women, along with the outcomes that were identified as critical and important for decision-making, are listed in PICO format in Annex 5.

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 to the search. Evidence summaries were prepared according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach to assess the overall

[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.

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 discussed by the WHO Nutrition Guidance Steering Committee and NUGAG at a second NUGAG consultation, held on 15–18 November 2010 in Amman, Jordan, and at the third consultation, held on 14–16 March 2011 in Geneva, Switzerland, where NUGAG members 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) cost of options available to health-care workers in different settings (Annex 6). Consensus was defined as agreement by simple majority of the 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. There were no strong disagreements among the guideline group members.

A public call for comments on the final draft guideline was then released. All 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 members of the guideline group are summarized on the following page.

- 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 has 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 Beverly 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 weekly 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* procedures (*29*). 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

Intermittent use of supplements with iron alone or with other micronutrients versus no supplementation or placebo in menstruating women

Patient or population: Menstruating women
Settings: All settings including malaria-endemic areas
Intervention: Intermittent supplementation of iron alone or with any other micronutrients
Comparison: Placebo or no intervention

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Anaemia (as defined by the trialists)	**RR 0.73** (0.56–0.95)	2996 (10 studies)	⊕⊕⊖⊖ **low**[1,2]	
Iron deficiency anaemia (anaemia and one indicator of iron deficiency)	**RR 0.07** (0–1.16)	97 (1 study)	⊕⊖⊖⊖ **very low**[1,3,4]	Only one study reported on this outcome
Iron deficiency (as defined by the trialists)	**RR 0.5** (0.24–1.04)	624 (3 studies)	⊕⊕⊖⊖ **low**[1,3]	
All-cause morbidity	**RR 1.12** (0.82–1.52)	119 (1 study)	⊕⊖⊖⊖ **very low**[1,4]	Only one study reported on this outcome
Haemoglobin (g/l)	**MD 4.58** (2.56–6.59)	2599 (13 studies)	⊕⊕⊖⊖ **low**[1,2]	
Ferritin (µg/l)	**MD 8.32** (4.97–11.66)	980 (6 studies)	⊕⊕⊖⊖ **low**[1,3]	

CI, confidence interval; RR, risk ratio; MD, mean difference.
*GRADE Working Group grades of evidence:
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We have moderate confidence 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 quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.
[1] In several trials, the method of allocation concealment was not clear and there was lack of blinding.
[2] There was high heterogeneity and some inconsistency in the direction of the effect.
[3] Wide confidence intervals.
[4] Only one study reported on this outcome.

Note: For cluster-randomized trials the analyses only include the estimated effective sample size, after adjusting the data to account for the clustering effect.

For details of studies included in the review, see reference (*15*).

Intermittent use of supplements with iron alone or with other micronutrients versus daily use of supplements in menstruating women

Patient or population: Menstruating women
Settings: All settings including malaria-endemic areas
Intervention: Intermittent supplementation of iron alone or with any other micronutrients
Comparison: Daily supplementation with iron alone or with any other micronutrients

Outcomes	Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Anaemia (as defined by the trialists)	**RR 1.26** (1.04–1.51)	1492 (6 studies)	⨁⨁⨁⨀ **moderate**[1]	
Iron deficiency anaemia (anaemia and one indicator of iron deficiency)	Not estimable	0 (0 studies)	See comment	No studies reported on this outcome
Iron deficiency (as defined by the trialists)	**RR 4.30** (0.56–33.20)	198 (1 study)	⨁⨀⨀⨀ **very low**[2]	
All-cause morbidity	Not estimable	0 (0 studies)	See comment	No studies reported on this outcome
Haemoglobin (g/l)	**MD –0.15** (–2.20 to 1.91)	1676 (8 studies)	⨁⨁⨀⨀ **low**[1,3]	
Ferritin (µg/l)	**MD –11.32** (–22.61 to –0.02)	657 (3 studies)	⨁⨁⨀⨀ **low**[1,3]	

CI, confidence interval; RR, risk ratio; MD, mean difference
*GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We have moderate confidence 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 quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.
[1] In several trials, the method of allocation concealment was not clear and there was lack of blinding.
[2] Only one study with approximately 25% losses to follow-up reported on this outcome; wide confidence intervals.
[3] There was high statistical heterogeneity and some inconsistency in the direction of the effect.

Note: For cluster-randomized trials the analyses only include the estimated effective sample size, after adjusting the data to account for the clustering effect.

For details of studies included in the review, see reference (*15*).

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Annex 5

Effects and safety of iron and folic acid supplementation in menstruating women (i.e. women of reproductive age)

a. Should iron and folic acid supplements be given to menstruating women to improve health outcomes?
b. If so, at what dose, frequency and duration for the intervention, and in which settings?

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

Population: Menstruating 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 antimalarial measures introduced in the study: yes versus no
- By antimalarial measures implemented by the health system: yes versus no
- By woman's status of anaemia: anaemic versus non-anaemic
- By woman's status of iron deficiency: iron deficient versus non-iron deÿcient

Intervention: Iron plus folic acid supplementation
- Subgroup analysis:

Critical
- By iron content: 30 mg versus 60 mg versus other
- By folic acid content: 400 µg versus other
- By frequency: daily versus weekly versus twice weekly versus other
- By duration: 3 months or less versus more than 3 months
- By nutrient: iron plus folic acid versus iron alone versus iron plus others

Control:
- No iron supplementation
- Placebo
- Same supplement without iron or folic acid

Outcomes: *Critical*
- Anaemia
- Morbidity
  - Malaria incidence and severity (parasitaemia with or without symptoms)
- Iron deficiency
- Iron deficiency anaemia

Setting: All countries

Annex 6 Summary of NUGAG members' consideration for determining the strength of the recommendation

Quality of evidence:	• Low-quality evidence from randomized controlled trials but adequate when country experience is considered
Values and preferences:	• Women prefer a weekly preventive measure rather than a daily dose • There is strong evidence from field programmes; it is a good public health practice
Trade-off between benefits and harm:	• Benefits outweigh the possible harms • Improved iron status at this age is likely to improve quality of life and improve reproductive health
Costs and feasibility:	• Supplements may not always be cheap and there is a need for more cost–benefit and feasibility analyses. However, intermittent supplementation with iron and folic acid has been feasible and cost-effective in country programmes and has been shown to be cheaper than daily supplementation • Supplementation for 6 months followed by 6 months off supplementation may increase the success of this intervention

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