World Health Organization

Guideline:

Intermittent iron and folic acid supplementation in menstruating women

WHO Library Cataloguing-in-Publication Data

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1.Iron – administration and dosage. 2.Folic acid – administration and dosage. 3.Anaemia, Iron-deficiency – prevention and control. 4.Menstruation – complications. 5.Women. 6.Dietary supplements. 7.Guidelines. I.World Health Organization.

ISBN 978 92 4 150202 3 (NLM classification: WD 160)

Design and layout: Alberto March

Suggested citation

WHO. *Guideline: Intermittent iron and folic acid supplementation in menstruating women*. Geneva, World Health Organization, 2011.

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Acknowledgements

This guideline was coordinated by Dr Luz Maria De-Regil under the supervision of Dr Juan Pablo Peña-Rosas, with technical input from Dr Metin Gulmezoglu, Dr Jose Martines and Dr Lisa Rogers. Thanks are due to Dr Regina Kulier and the staff at the Guidelines Review Committee Secretariat for their support throughout the process. Thanks are also due to Dr Davina Ghersi for her technical advice and assistance in the preparation of the technical consultations for this guideline and Mr Issa T. Matta and Mrs Chantal Streijffert Garon from the World Health Organization (WHO) Office of the Legal Counsel for their support in the management of conflicts of interest procedures. Ms Grace Rob and Mrs Paule Pillard from the Micronutrients Unit, Department of Nutrition for Health and Development, provided logistic support.

WHO gratefully acknowledges the technical input of the members of the WHO Nutrition Steering Committee and the Nutrition Guidance Expert Advisory Group (NUGAG), especially the chairs of the meetings, Dr Janet King, Dr Rebecca Stoltzfus and Dr Rafael Flores-Ayala. WHO is also grateful to the Cochrane Developmental, Psychosocial and Learning Problems Group staff for their support during the development of the systematic review used to inform this guideline.

Financial support

WHO thanks the Government of Luxembourg for providing financial support for this work.

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.