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Guideline:

Use of multiple micronutrient powders for home fortification of foods consumed by pregnant women

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Contents

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WHO Guideline[1]

Use of multiple micronutrient powders for home fortification of foods consumed by pregnant women

Summary

It is estimated that 41.8% of pregnant women worldwide are anaemic. Approximately 60% of these cases in non-malarious areas, and 50% in malaria-endemic settings, are assumed to be due to iron deficiency. Vitamin and mineral deficiencies in pregnancy are associated with adverse health outcomes in both the mother and her newborn. Member States have requested guidance from the World Health Organization (WHO) on the effects and safety of the use of multiple micronutrient powders for home fortification of foods consumed by pregnant women 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 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.

Currently, there is no evidence available to assess the potential benefits or harms of the use of multiple micronutrient powders for home fortification of foods consumed by pregnant women with regard to maternal and infant health outcomes. Thus the routine use of this intervention during gestation is not recommended as an alternative to iron and folic acid supplementation in pregnancy (strong recommendation).

[1] 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 use of multiple micronutrient powders for home fortification of foods consumed by pregnant women.

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, the eradication of extreme poverty and hunger (MDG 1), reduction of child mortality (MDG 4) and improvement of 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. Further details on the state of the art of this intervention are provided in the documents listed in the references.

Background

Pregnant women are particularly vulnerable to vitamin and mineral deficiencies because of the increase in metabolic demands to meet fetal requirements for growth and development (*1*). Iron deficiency is the most common micronutrient deficiency and is the leading cause of anaemia in the general population. An estimated 41.8% of pregnant women worldwide are anaemic (*2*), and approximately 60% of cases in non-malarious areas and 50% in malaria-endemic settings are assumed to be due to iron deficiency (*3*). In addition to iron deficiency, pregnant women, particularly those living in developing countries, are often deficient in multiple other nutrients (*1, 4*). The causes of the high burden of maternal micronutrient deficiencies include poor access to and consumption of foods with adequate micronutrient content, cultural practices and infections (*1*).

Vitamin and mineral deficiencies in pregnancy are associated with adverse health outcomes in both the mother and her newborn. For example, iron deficiency accounts for 18% of maternal mortality (*5*) and is associated with premature delivery and low birth weight (*6*). Iodine deficiency is the principal cause of preventable brain damage in childhood (*7*) and leads to thyroid under-function and goitrogenesis in adults (*8*). Nearly two billion people have insufficient iodine intake, and even subclinical iodine deficiency during pregnancy increases the risk of miscarriage and fetal growth restriction (*9*). Vitamin A deficiency affects approximately 19 million pregnant women worldwide and is associated with an increased risk of complications and death during pregnancy and in the postpartum period (*10, 11*). Severe vitamin A deficiency in the mother can also lead to low amounts of vitamin A reserves in the baby, which can negatively affect lung development and survival in the first year of life (*12, 13*). Other micronutrients of concern during pregnancy are folic acid, vitamin D, zinc and vitamin B_{12}.

Most women need additional iron to ensure sufficient iron stores to prevent iron deficiency during pregnancy (*14*). Direct iron supplementation in pregnant women is

extensively used in most low- and middle-income countries as a part of standard antenatal care to prevent and correct iron deficiency and anaemia during gestation. The provision of additional vitamins and minerals during gestation has been advocated on the basis of the assumption that in pregnant women with iron deficiency other micronutrient deficiencies may also be present, which together could compromise both maternal and neonatal outcomes (*15*).

Recent interest in alternative ways of providing micronutrients to populations where supplementation has been difficult to implement or where the target group is difficult to reach through mass fortification has led to the development of multiple micronutrient powders (that is, a mixture of vitamins and minerals in powder form) (*16*). The powders are supplied as single-serving packets, the contents of which can be added to any semi-solid food immediately before consumption (*17*). Although the primary motivation behind the use of micronutrient powders has been to prevent and treat anaemia and iron deficiency in infants and young children 6–23 months of age (*17*), in some countries they are being used in other target groups, including preschool-age children, pregnant women and emergency-affected populations.

Summary of evidence

A systematic review following the Cochrane methodology (*18*) was conducted to assess the effects and safety of use of home fortification of foods with multiple micronutrient powders in pregnant women with regard to neonatal and maternal outcomes. The review compared the provision of powders containing iron and at least two other vitamin and minerals with (i) no intervention or placebo, (ii) iron supplements, (iii) iron and folic acid supplements, and (iv) iron plus vitamin and mineral supplements to healthy women living in a variety of settings including malaria-endemic areas. The maternal outcomes ranked as critical by the Nutrition Guidance Expert Advisory Group (NUGAG) members were all-cause mortality at any time during pregnancy and anaemia, haemoglobin concentration, iron deficiency, iron deficiency anaemia, and serum and red blood cell folate concentrations at the end of pregnancy. Infant outcomes that were considered critical were low birth weight and premature delivery. The potential modifying effects of baseline anaemia and iron status, the iron content of the product, the provision regimen and the duration of the intervention were also considered.

The literature search for this review revealed no published trials to date assessing the benefits or harms of this intervention in pregnant women.

Indirect evidence from randomized controlled trials on daily supplementation with iron or iron and folic acid or iron and other multiple micronutrients in pregnant women show that the provision of multiple micronutrients is effective and safe, particularly when the iron dose ranges between 30 and 60 mg of elemental iron per day (*19*). Moreover, evidence of the effects and safety of home fortification with multiple micronutrient powders, from studies among children 6–23 months of age, shows that this intervention reduces iron deficiency and anaemia, although the information on malaria-related outcomes could not be properly assessed (*20*).

Recommendation

As there is currently no available evidence to directly assess the potential benefits or harms of the use of multiple micronutrient powders in pregnant women for improving maternal and infant health outcomes, routine use of this intervention during gestation is not recommended as an alternative to iron and folic acid supplementation (*strong recommendation*)[1].

Remarks

Evidence on the effects of home fortification of foods with multiple micronutrient powders in children supports further research into possible benefits and harms of this intervention in pregnant women.

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 has developed 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.

Implications for future research

Discussion of the evidence with NUGAG members and stakeholders highlighted the limited available evidence on home fortification of foods with multiple micronutrient powders to reduce vitamin and mineral deficiencies in pregnant women and the need for well-conducted randomized controlled trials to evaluate this intervention. In particular, future research should consider:

- population-relevant health outcomes, including side-effects of this intervention, in pregnant women and their babies;
- other factors such as acceptability and feasibility of and adherence to the intervention.

[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 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.

Guideline development process

This guideline was developed in accordance with the WHO evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development* (*21*).

Advisory groups

A 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 1). 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 2). 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. NUGAG 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 3). 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 guidelines 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 4). The questions were 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 these 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 the use of multiple micronutrient powders in pregnant women, along with the outcomes that were identified as critical and important for decision-making, are listed in PICO format in Annex 4.

WHO staff, in collaboration with researchers from other institutions, summarized and appraised the evidence, using the Cochrane methodology for randomized controlled trials (*18*). 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. If evidence had been found, "Summary of findings" tables would have been prepared according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the overall quality of the evidence (*22*). 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.

The results of the systematic review were used for drafting this guideline. The draft recommendation was reviewed by the WHO Nutrition Guidance Steering Committee and NUGAG members 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 5). 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. 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* (*23*), 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)* (*24*). The potential conflicts of interest declared by 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 received 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.
- Dr Gunn Vist co-authored the systematic review on the use of multiple micronutrient powders in pregnant women for this guideline. Dr Vist did not vote on the final draft recommendation but remained in the room during the discussions in order to answer questions regarding the systematic review.

Plans for updating the guideline

This guideline will be reviewed in 2013 as some ongoing trials may be able to provide the evidence that is currently lacking, particularly in malaria settings. 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 the *WHO handbook for guideline development* procedures (*21*). WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

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Annex 4 Questions in Population, Intervention, Control, Outcomes (PICO) format

Effects and safety of the use of multiple micronutrient powders in pregnant women

a. Should multiple micronutrient powders be used in pregnant women to improve health outcomes?
b. If so, at what dose, frequency and duration?

Population: Pregnant women (any trimester)
Subpopulation:
Critical

- By malaria transmission (four categories: 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
- By prevalence of anaemia in pregnant women: countries with a public health problem (5–19.9% mild; 20–39.9%, moderate; 40% or more, severe) versus no public health problem (less than 5%)
- By individual anaemia status: anaemic versus non-anaemic (defined as haemoglobin values less than 110 g/l)
- By iron status: iron-deficient versus non-iron deficient (as defined by ferritin, transferrin receptor, and/or zinc protoporphyrin/haem ratio (ZPPH) cut-offs)

Intervention: Micronutrient powder formulations containing iron and folic acid, with or without other micronutrients

- Subgroup analysis:

Critical

- By iron content of product: 30 mg versus 60 mg
- By number of micronutrients: two or fewer versus more than two
- By frequency: daily versus weekly versus flexible
- By duration of intervention:
  - During pregnancy alone: less than 3 months versus 3 or more months
  - During pregnancy and the early postpartum period (0–3 months): less than 3 months versus 3 or more months
- By level of exposure to the intervention: high versus low

Control:

- No provision of multiple micronutrient powders, or placebo
- Iron and folic acid supplements

Outcomes:

Maternal

Critical

- Haemoglobin values at term of pregnancy
- Anaemia at term of pregnancy
- Iron deficiency anaemia at term of pregnancy
- Iron status (as defined by trialists) at term of pregnancy
- Folate status at term of pregnancy
- All-cause mortality during pregnancy
  - Infections

For malaria-endemic areas only

- Malaria incidence and severity (parasitaemia with or without symptoms)
- Placental malaria

Newborns and infants

Critical

- Gestational age (less than 34 weeks versus more than 37 weeks versus 37 or more weeks)
- Birth weight (less than 1500 g versus less than 2500 g versus 2500 g or more)

For malaria-endemic areas only

- Malaria incidence and severity (parasitaemia with or without symptoms)

Setting: All countries

Annex 5 Summary of NUGAG members' considerations for determining the strength of the recommendation

Quality of evidence:	• There is no evidence available to assess this intervention
Values and preferences:	• The absence of evidence limits the ability to judge the possible value of this intervention
Trade-off between benefits and harm:	• There is uncertainty regarding the benefits and harms of this intervention
Cost and feasibility:	• Feasible in theory, but perhaps more costly that iron supplementation • No data available to make an estimation

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