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Guideline:

Daily iron and folic acid supplementation in pregnant women

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WHO Guideline[1] Daily iron and folic acid supplementation in 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 daily 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 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. 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 intervention 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.

Daily oral iron and folic acid supplementation is recommended as part of the antenatal care to reduce the risk of low birth weight, maternal anaemia and iron deficiency (*strong recommendation*). The overall quality of the evidence for iron supplementation versus no iron was moderate for low birth weight, preterm birth, maternal anaemia at term and maternal iron deficiency at term. The evidence was of low quality for birth weight, neonatal death, congenital anomalies, maternal death, maternal severe anaemia, and infections during pregnancy; whereas it was of very low quality for side-effects.

[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 daily 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 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, 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 burden is assumed to be due to iron deficiency (*2*), with the rest due to conditions such as folate, vitamin B_{12} or vitamin A deficiency, 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 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*). Iron deficiency anaemia may affect growth and development both in utero (*2*) and in the long term (*5*). 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, women need to consume additional iron to ensure they have sufficient iron stores to prevent iron deficiency (*10*). Therefore, in most low- and middle-income countries, iron supplements are used extensively by pregnant women to prevent and correct iron deficiency and anaemia during gestation.

A standard supplemental dose of 60 mg of elemental iron was first established in 1959, based on estimates of iron requirements in pregnant women (*11*); this dose has since been endorsed by several expert consultations (*4, 12, 13*). A prophylactic dose of 300 µg (0.3 mg) per day throughout pregnancy was suggested in 1968 by the World Health Organization (WHO). The supplemental dose was increased to 400 µg (0.4 mg) of folic acid per day in 1998 following publication of several studies supporting

the periconceptional use of this nutrient in the prevention of neural tube defects. This dose was deemed to provide more folic acid than required to produce an optimal haemoglobin response in pregnant women. If supplementation is started after the first trimester of pregnancy it will not help prevent birth defects (*13*).

Gastrointestinal distress is a common observation in women consuming large amounts of supplemental iron, particularly on an empty stomach. Thus gastrointestinal side-effects are considered as the critical adverse effect on which to base the tolerable upper level of intake for iron. Use of high-dose iron supplements is commonly associated with constipation and other gastrointestinal effects, including nausea, vomiting and diarrhoea, with the frequency and severity depending on the amount of elemental iron released in the stomach.

Summary of evidence

An existing Cochrane systematic review (*14*) assessing the benefits and harms of iron supplementation in healthy pregnant women was updated for this guideline. The updated review (*15*) compared the daily provision of iron supplements alone or in combination with folic acid or other micronutrients with no intervention, placebo or versus the use of the same supplements but without iron (e.g. only folic acid) among 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 were low birth weight, weight at birth, prematurity, perinatal death and congenital anomalies, including neural tube defects. The maternal outcomes considered were anaemia, iron deficiency and iron deficiency anaemia at term, as well as the presence of any side-effects, clinical malaria or infections during pregnancy. The potential effects of baseline anaemia status, gestational age at the start of supplementation, malaria setting and the daily dose of iron were also evaluated.

The review included 60 randomized controlled trials with 27 402 women from 30 different countries in all continents. Only 43 trials contributed data to the review, albeit not all of them reported on all the outcomes; 16 of the trials were of high quality according to the pre-established criteria. Twenty-three studies were conducted in countries that in 2011 had some malaria risk in parts of the country. In some of these countries/territories, malaria is present only in certain areas or up to a particular altitude. Only two of these studies reported malaria outcomes. It was not always 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.

Overall, women taking daily iron supplements were less likely to have low birth weight babies compared with controls (average relative risk (RR) 0.81, 95% confidence interval (CI) 0.68 – 0.97, 11 studies) and the mean birth weight was 30.81g greater for those infants whose mothers received iron during pregnancy (95% CI 5.94 – 55.68 g, 14 studies). There was no significant effect on preterm birth or neonatal death.

Daily iron supplementation reduced the risk of maternal anaemia at term by 70% (RR 0.30, 95% CI 0.19 – 0.46, 14 trials) and iron deficiency at term by 57% (RR 0.43, 95% CI 0.27 – 0.66, seven studies), but it had no significant effect on the risk of infections during pregnancy (RR 1.16, 95% CI 0.83 – 1.63, two studies). Women receiving iron had 8.88 g more haemoglobin per litre at or near term (95% CI 6.96 – 10.80, 19 studies) than those who did not receive iron. At the same time, women who received iron supplements tended to report more frequently side-effects (RR 2.36, 95% CI 0.96 to 5.82, 11 studies) and were at increased risk of high haemoglobin concentrations (i.e. greater than 130 mg/L) during the second and third trimesters of pregnancy (RR 2.26, 95% CI 1.40 – 3.66, 10 studies).

The intervention seems to be effective among populations with different prevalences of anaemia, and in settings described as malaria-endemic, when compared with settings where malaria is sporadic or absent, and regardless of whether the supplementation was initiated earlier or later than 20 weeks of gestation or whether the daily dose of elemental iron was 30 mg or less, 31–59 mg, or 60 mg or higher. However, women receiving 60 mg of iron or more were more likely to have haemoglobin concentrations above 130 g/L and report side effects (RR 6.52, 95% CI 1.13, 37.69) than dose women receiving 30 mg per day or less (RR 1.01, 95% CI 0.84 – 1.21).

The overall quality of the evidence for iron supplementation versus no iron was moderate for low birth weight, preterm birth, maternal anaemia at term and maternal iron deficiency at term. The evidence was of low quality for birth weight, neonatal death, congenital anomalies, maternal death, maternal severe anaemia, and infections during pregnancy; whereas it was of very low quality for side-effects (Annex 1).

Recommendation

This guideline updates the WHO recommendations published previously (*2*).

Daily oral iron and folic acid supplementation is recommended as part of the antenatal care to reduce the risk of low birth weight, maternal anaemia and iron deficiency (*strong recommendation*)[1,2].

A suggested scheme for daily iron and folic acid supplementation in pregnant women is presented in Table 1.