WHO recommendation on multiple micronutrient supplementation during pregnancy

31 July 2020

Recommendation

Antenatal multiple micronutrient supplements that include iron and folic acid are recommended in the context of rigorous research*.

(Context-specific recommendation - research)

* The GDG clarified that rigorous research includes implementation research using high-quality methods appropriate to the specific research questions.

Publication history

First published: November 2016

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Assessed as up-to-date: July 2020

Remarks

- This recommendation updates and supersedes the WHO recommendation found in the WHO ANC guideline issued in 2016 (1).
- The evidence is derived from trials using multiple micronutrient supplements (MMS) containing 13 to 15 micronutrients (including iron and folic acid [IFA]) and the widely available United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP), which contains 15 micronutrients, including 30 mg of iron and 0.4 mg of folic acid.
- As the evidence was mainly derived from low- and middle-income countries, its applicability to high-income countries or to populations not at risk of micronutrient deficiencies – for example, due to an adequate diet and food fortification programmes – is unclear.
- Research in this context therefore includes:
  - controlled clinical trials in which early pregnancy ultrasound is used to establish gestational age with certainty**, with assessment of critical maternal and perinatal outcomes, and follow-up of infants sustained into childhood; and
  - where programmes of MMS are being considered, implementation research to establish the impact of switching from iron and folic acid supplements to MMS, including evaluation of acceptability, feasibility, sustainability, equity and cost-effectiveness.
- Many MMS contain 30 mg or less of elemental iron and WHO recommends antenatal iron and folic acid supplements containing 60 mg of elemental iron in populations where anaemia is a severe public health problem (a prevalence of 40% or higher) (2). Therefore, countries should consider their population magnitude and distribution of anaemia, its nutritional determinants (i.e. iron deficiency), as
well as the magnitude and distribution of the complex low birthweight and its component parts (i.e. preterm, small for gestational age [SGA] or a combination of these) (3), when undertaking any research in the context of this recommendation.

- Pregnant women should be supported and encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy, balanced diet consistent with guidelines on healthy eating (4).

** Gestational age accurately assessed by ultrasound emerged as an important feature of future trials because of the conflicting and confusing differences in intervention effects found on low birthweight and its component parts (preterm birth, and SGA).

Background

Pregnancy requires a healthy diet that includes an adequate intake of energy, protein, vitamins and minerals to meet increased maternal and fetal needs. However, for many pregnant women, dietary intake of fruit, vegetables, meat and dairy products is often insufficient to meet these needs, and may lead to micronutrient deficiencies. In resource-poor countries in sub-Saharan Africa, south-central Asia and south-east Asia, maternal undernutrition is highly prevalent and is recognized as a key determinant of poor perinatal outcomes (5). However, a clear understanding of the individual requirements and contributions of all essential vitamins and minerals to optimize maternal and fetal health during the antenatal period is limited (6).

Methods

In April 2019, following pre-established prioritization criteria, the Executive Guideline Steering Group prioritized updating of the recommendation on multiple micronutrient supplements (MMS). This resulting recommendation updates and supersedes the previous recommendation on antenatal MMS issued in the 2016 WHO ANC guideline (1). WHO convened a virtual Guideline Development Group (GDG) – an international group of experts assembled for the purpose of developing this guideline – meeting to review and update this recommendation on 4–5 December 2019, organized from Geneva, Switzerland. The recommendation was developed initially using the standardized operating procedures described in the WHO handbook and updated based on the WHO ‘living guideline’ approach for maternal and perinatal health recommendations (7, 8).

An updated Cochrane systematic review was the primary source of evidence on effectiveness of oral antenatal MMS. The scientific evidence supporting the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) and Confidence in the Evidence from Reviews of Qualitative Research (GRADE-CERQual) approaches, for quantitative and qualitative evidence, respectively. Data from the Cochrane review were customized to reflect the key comparisons, GDG - specified subgroup analyses, and outcomes relevant to the ANC guideline. The DECIDE (Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence) framework – an evidence-to-decision tool that includes intervention effects, values, resources, equity, acceptability and feasibility criteria – was used to guide the formulation and approval of the recommendation. The latest versions of two qualitative systematic reviews commissioned by the WHO Steering Group for the 2016 guideline development process and systematic reviews of cost-effectiveness informed this framework (9,10). The GDG members reviewed, discussed and made judgements on the impact of the interventions for each of the EtD criteria.

Further information on procedures for developing this recommendation are available here.
**Recommendation question**

For this recommendation, we aimed to answer the following question:

- For pregnant women (P), does antenatal MMS (I) that includes IFA compared with routine IFA supplementation (C) improve maternal and perinatal health outcomes (O)?

**Evidence summary**

This evidence was derived from a Cochrane systematic review that included 20 trials involving 141,849 women; however, only 16 trials contributed data to the updated WHO analysis (11). Of these 16 trials, six evaluated supplements with 13 or 14 micronutrients, including IFA; and 10 evaluated supplements with 15 micronutrients including vitamins A, D, E; niacin; folic acid; vitamins B1, B2, B6, B12, C; zinc, iron, iodine, selenium and copper, as per the UNIMMAP formulation (12). All the trials were conducted in LMICs. The GDG-specified WHO analyses were updated with these revised data to include:

- Comparison 1: MMS with 13 to 15 micronutrients compared with IFA supplements.
- Comparison 2: UNIMMAP supplements compared with IFA supplements.

The GDG also requested additional subgroup analyses according to the dose of iron in the control group because most trials in the review evaluated MMS containing 30 mg of elemental iron, and this was compared with IFA controls that employed either 30 mg or 60 mg of iron. Evidence from sensitivity analyses was not graded.

**Comparison 1: MMS with 13 to 15 micronutrients compared with IFA supplements**

**Maternal outcomes**

High-certainty evidence shows that MMS probably make little or no difference to maternal anaemia compared with IFA supplements (eight trials; risk ratio [RR]: 1.03, 95% confidence interval [CI]: 0.92 to 1.15). Compared to IFA supplements, low-certainty evidence indicates that MMN supplements probably make little or no difference to caesarean section rates (four trials; RR: 1.04, 95% CI: 0.76 to 1.43) and low-certainty evidence suggests that they may have little or no difference on maternal mortality (six trials; RR: 1.06, 95% CI: 0.72–1.54) compared to IFA supplements. Subgroup findings and sensitivity analyses were consistent with the overall findings for these outcomes.

**Fetal and neonatal outcomes**

High-certainty evidence suggest that MMS reduce the risk of having a low birth weight neonate (16 trials; RR: 0.88, 95% CI: 0.86 to 0.91) compared to IFA supplements but moderate-certainty evidence shows that MMS probably makes little to no difference to the risk of having a small for gestational age neonate compared to IFA supplements (15 trials; RR: 0.98, 95% CI: 0.96 to 1.00). Moderate-certainty evidence shows that MMS make little or no difference to preterm birth rates compared to IFA supplements (16 trials; RR: 0.94, 95% CI: 0.88 to 1.00).

Subgroup findings for the effect on perinatal mortality differed according to the dose of iron (30 mg or 60 mg) in the IFA supplements and therefore subgroup data were not pooled. Moderate-certainty evidence for the 60 mg iron subgroup suggests there is probably little or no difference between MMS and IFA supplements (nine trials; RR: 1.15, 95% CI: 0.93 to 1.42); whereas moderate-certainty evidence for the 30 mg iron subgroup suggests that MMS are probably associated with lower perinatal mortality than IFA supplements (four trials; RR: 0.92, 95% CI: 0.86 to 0.98). Some subgroup evidence suggested that IFA...
supplements with 60 mg iron may be associated with lower neonatal mortality than MMS. Other subgroup evidence suggested that, when MMS were compared with IFA supplements containing the same dose of iron (30 mg), MMS may be associated with lower perinatal mortality than IFA supplements. However, these findings were uncertain.

**Comparison 2: UNIMMAP formulation compared with IFA supplements**

**Maternal outcomes**

The evidence on maternal outcomes was consistent with Comparison 1, and suggests little or no difference in the relative effects of UNIMMAP compared with IFA supplements (30 mg or 60 mg) on maternal anaemia, caesarean section and maternal mortality.

**Fetal and neonatal outcomes**

Moderate-certainty evidence suggests that the UNIMMAP supplement probably reduces the risk of having an SGA neonate compared with IFA supplements. Consistent with Comparison 1, moderate-certainty suggests that the UNIMMAP supplement probably reduces the risk of having a low-birthweight neonate compared with IFA supplements.

Consistent with Comparison 1, subgroup findings for perinatal and neonatal mortality differed according to the dose of iron in the IFA supplements. For perinatal mortality, moderate-certainty evidence for the 60 mg iron subgroup suggests that IFA supplements were favoured (six trials; RR: 1.20, 95% CI: 0.95 to 1.51); while moderate-certainty evidence for the 30 mg iron subgroup, suggested that UNIMMAP was favoured (three trials; RR: 0.90, 95% CI: 0.80 to 1.01). However, neither of these effect estimates was statistically significant. For neonatal mortality, moderate-certainty evidence for the 60 mg iron subgroup also suggested IFA supplements were favoured (six trials; RR: 1.25, 95% CI: 0.94 to 1.67) and UNIMMAP in the 30 mg iron subgroup (three trials; RR: 0.90, 95% CI: 0.78 to 1.05); however, both subgroup estimates included the possibility of no difference. In the sensitivity analysis restricted to studies using 0.4 mg of folic acid, there was a trend in favour of 60 mg IFA supplements that became statistically significant (five trials; RR: 1.38, 95% CI: 1.05 to 1.82).

**Additional considerations**

- In general, the research evidence suggests there may be some beneficial effects with MMS and that they may cause little harm compared with IFA supplements; however, this evidence was derived mostly from trials using MMS containing 30 mg of iron and 0.4 mg of folic acid, i.e. UNIMMAP. Many LMICs use IFA supplements with a higher dose of iron than 30 mg. Due to some uncertainty about the effects of switching from a higher dose of iron to a lower dose, more research is needed.
- All evidence was derived from studies in LMICs; its applicability to other country settings is unclear.
- WHO advises that 60 mg iron be taken daily by pregnant women and adolescent girls in settings with a high prevalence of anaemia (1).
- A non–Cochrane review of MMS in LMIC countries (13) found that MMS reduced the risk of low birthweight by 14% (8–19%), preterm birth by 7% (2–13%) and SGA births by 6% (2–10%) on average compared with IFA supplements; the effects on low birthweight and SGA were greater among anaemic women than non-anaemic women. The review also found that, whilst there was no difference in neonatal mortality overall (RR: 0.99, 95% CI: 0.89 to 1.09), MMS were associated with lower neonatal mortality among female neonates by about 15% (4–25%). The review used individual patient data for 112 953 pregnant women from 17 RCTs comparing MMS with IFA supplements alone. In meta-analyses, data were pooled using a fixed effects model. Two trials, SUMMIT, 2008 (14) and West et al., 2014 (15), which used 30 mg and 27 mg of iron in the control arms, respectively, contributed more than two-thirds of the data. Trials among anaemic and/or malnourished pregnant women were also included in this review. These factors may explain differences in effect estimates between the Cochrane data used by WHO and the Smith et al. (2017) review (13). The latter also
noted, however, that “some subgroups given multiple micronutrient supplements with low-dose iron (30 mg) had higher stillbirth and neonatal mortality than iron-folic acid alone with 60 mg iron”.

- A meta-analysis of neonatal mortality data for the MMS versus 60 mg iron IFA comparison has also been the focus of a separate paper in which study methods are not reported in detail (16). This meta-analysis included data from the 60 mg study group of the MINIMat trial (17) that were not available in the 2019 Cochrane review (the latter only included data for the 30 mg IFA study group from this trial). Sudfeld and Smith (2019) also included data from one trial (18) that was excluded from the WHO analyses because its multiple MMS comprised fewer than 13 micronutrients.

- Point estimates for RRs from these two additional trials favoured MMS and, overall, 11 trials included in their neonatal mortality analysis gave an RR of 1.05 (95% CI: 0.85 to 1.30), suggesting little or no difference in effect between MMS and IFA supplements.  
- A review of the effects of antenatal MMS compared with IFA supplements on health benefits for children used data from nine of the trials included in the 2015 Cochrane review (19), six of which assessed UNIMMAP (20). This review found no evidence of additional health benefits in the longer term with MMS, specifically for child mortality (nine trials), weight-for-age (four trials), height-for-age (six trials), head circumference (three trials) and cognitive function (four trials).

Resources

Two economic analyses published in 2019 found MMS to be cost-effective compared with IFA supplements (21,22).

Equity

The WHO State of inequality report (2015) shows that women who are poor, least educated, and residing in rural areas have lower health intervention coverage and worse health outcomes than the more advantaged women in LMICs (23). ANC coverage of at least four visits differed according to the women’s education and income levels; inequalities in ANC coverage of at least one visit were also demonstrated, though to a lesser extent. In 50% of study countries, infant mortality was at least eight deaths per 1000 live births higher in rural than in urban areas and, in about a quarter of the study countries, neonatal mortality was at least 15 deaths per 1000 live births higher among the least educated. Stunting prevalence in children under 5 was also substantially unequal between the least and most educated mothers.

Acceptability

Qualitative evidence suggests that women in a variety of settings tend to view ANC as a source of knowledge and information and that they generally appreciate any advice (including dietary or nutritional) that may lead to a healthy baby and a positive pregnancy experience (high confidence in the evidence) (10). However, health-care providers have noted the lack of appropriate training, resources and time to deliver the service in the informative, supportive and caring manner that women want (high confidence in the evidence) (10).

Feasibility

On the demand side, qualitative evidence shows that women may be less likely to engage with services when there are additional costs associated with supplementation (high confidence in the evidence) or where the recommended intervention is unavailable because of resource constraints (low confidence in the evidence) (10). Additionally, in a number of LMIC settings, healthcare providers felt that that a lack of resources – both in terms of the availability of the supplements and the lack of suitably trained staff to deliver nutritional information – may limit the implementation of this intervention (high confidence in the evidence).

Further information and considerations related to this recommendation can be found in the WHO guidelines, available in the Annex of this publication: https://www.who.int/publications/i/item/9789240007789
Implementation considerations

- The successful introduction of evidence-based policies related to antenatal care into national programmes and health care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. These processes may include the development or revision of national guidelines or protocols based on this recommendation.
- The recommendation should be adapted into locally-appropriate documents and tools that are able to meet the specific needs of each country and health service. Modifications to the recommendation, where necessary, should be justified in an explicit and transparent manner.
- An enabling environment should be created for the use of this recommendation, including changes in the behaviour of health care practitioners to enable the use of evidence-based practices.
- Local professional societies may play important roles in this process and an all-inclusive and participatory process should be encouraged.
- Antenatal care models with a minimum of eight contacts are recommended to reduce perinatal mortality and improve women’s experience of care. Taking this as a foundation, the GDG reviewed how ANC should be delivered in terms of both the timing and content of each of the ANC contacts, and arrived at a new model – the 2016 WHO ANC model – which replaces the previous four-visit focused ANC (FANC) model. For the purpose of developing this new ANC model, the ANC recommendations were mapped to the eight contacts based on the evidence supporting each recommendation and the optimal timing of delivery of the recommended interventions to achieve maximal impact.

Research implications

During the recommendation development process, the GDG identified the following important knowledge gap that needs to be addressed through primary research:

- What is the impact of switching from routine antenatal IFA supplements (either with 30 mg or 60 mg elemental iron) to MMS on important health outcomes (maternal, perinatal, child), equity, acceptability, feasibility, sustainability and health-care resources in different country settings?

Related links

WHO recommendations on antenatal care for a positive pregnancy experience (2016) - full document and evidence tables

WHO Programmes: Department of Maternal, Newborn, Child, Adolescent Health and Ageing

WHO Programmes: Department of Nutrition and Food Safety

Pregnancy, Childbirth, Postpartum and Newborn Care: A guide for essential practice

Managing Complications in Pregnancy and Childbirth: A guide for midwives and doctors

WHO Programmes: Sexual and Reproductive health

Maternal Health

External link: BMJ Global Health editorial on WHO recommendations on antenatal nutrition: an update on multiple micronutrient supplements
References


Citation: WHO Reproductive Health Library. WHO recommendation on multiple micronutrient supplementation during pregnancy (July 2020). The WHO Reproductive Health Library; Geneva: World Health Organization.


Published on RHL (https://extranet.who.int/rhl)