

Switching from Iron and Folic Acid Supplementation to Multiple Micronutrient Supplementation in Pregnancy:

Frequently Asked Questions (FAQ)



Decision-makers and operational managers often have many technical questions when trying to decide whether and how to add MMS to existing nutritional services. Following are responses to some of the frequently asked questions concerning multiple micronutrient supplements in pregnancy.

1. What are the specific health benefits of switching from taking iron and folic acid (IFA) to multiple micronutrient supplements (MMS) during pregnancy?

Multiple micronutrient deficiencies co-exist among women and micronutrients requirements are increased in pregnancy. Inadequate intake of micronutrients can lead to adverse effects on the mother and developing fetus.

Multiple micronutrient supplementation (MMS) has been shown to significantly improve birth outcomes, by reducing the risk of low birth weight, being born small-for-gestational age (SGA), and preterm births, as compared to use of iron and folic acid supplementation (IFA) alone.^{1,2}

While the benefits of the MMS on birth outcomes are universal, women who are nutritionally vulnerable, that is, women who are anemic and/or underweight during their pregnancy experience even greater benefits. This includes a reduced risk of SGA, low birthweight, and 6-month mortality among infants born to anemic women and an even greater reduction in the risk of preterm birth among underweight women. Additionally, female infants born to mothers who received MMS, have a 13% reduced risk of mortality throughout the first year of life.²

2. What are the long-term benefits for children of giving prenatal MMS?

To date, few studies have examined the long-term physical and developmental benefits of taking MMS during pregnancy, and findings are mixed.³ However, SGA and preterm birth have long-term effects (e.g., an increased risk of stunting and mortality), so by preventing these conditions one can hypothesize the long-term benefits of MMS use.

3. What are the proxy measures for nutritional deficiencies among pregnant women?

In general, nutritional deficiencies among women of reproductive age (WRA) are relatively common in low- and middle-income countries (LMICs). While data for specific countries are often limited, there are a number of data sources that can help indicate the prevalence of nutritional deficiencies. Ideally, micronutrient biomarker data from a representative sample of WRA will provide the most direct and quantitative assessment of nutritional deficiencies. However, should these data not be available, the prevalence of anemia, dietary intake data, dietary diversity scores, and the Hidden Hunger Index⁴ can be used to assess nutritional status. Prevalence of adverse birth outcomes can also be used as a proxy measure for poor nutritional status. For

example, a high prevalence of low birth weight (LBW), SGA and preterm births would suggest nutritional deficiencies.

4. What is the rationale for the United Nations International Multi-Micronutrient Antenatal Preparation (UNIMMAP) formulation?

Building on the considerable experience and documented, positive effect of IFA on pregnant women with nutritional deficiencies, there is now general consensus about the utility and formulation of a multiple micronutrient supplementation program for pregnant women. This consensus was built around a recognition that multiple micronutrient deficiencies co-exist among women of vulnerable populations with three additional facts:

- i) improvements in diet are difficult to achieve over a short time span for vulnerable populations;*
- ii) several nations have worked to achieve fortification of basic foodstuffs on a large-scale, yet fortification goals are often not fully realized for the most vulnerable populations; and*
- iii) the high nutrient needs of pregnancy are almost impossible to cover through dietary intake alone.⁶*

To address the need for a standardized MMS that can meet the increased micronutrient requirements of pregnant women, as well as be used in clinical trials to test the efficacy of MMS vs IFA, an expert group was assembled by the World Health Organization, UNICEF & United Nations University, in July 1999. The work of that expert group resulted in identification of the United Nations International Multi-Micronutrient Antenatal Preparation – otherwise known as the UNIMMAP formulation.

The selection of nutrients for the UNIMMAP formulation was based on nutrient requirements, risk of nutrient deficiencies, potential nutrient toxicities, and on the potential interactions between nutrients if combined into one tablet. Other considerations included cost, size of the resulting supplement, and possible side effects. Based on these criteria, the resulting formulation included 15 micronutrients (vitamins A, C, D, E, B1 (thiamine), B2 (riboflavin), B3 (niacin), B6, B12, folic acid, Fe, Zn, Cu, I, Se).⁵ See Table 1 for the full description of the technical specifications of the UNIMMAP formulation.

The benefits of the UNIMMAP formulation vs. IFA alone on birth outcomes has been demonstrated.^{1,2}

5. Is the iron in the MMS formulation readily bioavailable?

No recommendation for the optimal form(s) of iron to use in MMS currently exists; currently, different forms are used by different manufacturers. Major manufacturers of MMS in the U.S. and Europe currently use the ferrous fumarate or ferrous sulfate forms of iron. However, when comparing different oral preparations using a human intestinal model, results demonstrate that there are differences in dissolution times and iron uptake, with varying physical characteristics of the preparation (e.g., tablet, capsule, syrup) and iron form (e.g. sulfate, fumarate, and gluconate), and, whether iron is alone or with vitamins, minerals, or both.⁶ This issue requires further study.

6. How does the amount of iron in the UNIMMAP formulation compare to the recommendations of the World Health Organization (WHO) Antenatal Guidelines?

The original rationale for the UNIMMAP formulation, which specifies 30 mg of iron (rather than 60 mg) was based on, among other things, the following:^{5 (p. 12)}

- *Iron absorption in the UNIMMAP formulation is enhanced (as compared to the IFA) due to the inclusion of vitamin C, vitamin A, and riboflavin.*
- *Most pregnant women suffer from mild or moderate anemia, which can be addressed with 30 mg of iron.*
- *Larger amounts of zinc may be needed if 60 mg of iron were used to counteract the possible negative influence of higher amounts of iron on zinc absorption.*
- *Increased risk of side effects caused by higher amounts of iron, which may reduce adherence to supplementation.*

The current rationale for retaining 30 mg of iron in the UNIMMAP formulation is consistent with the recent World Health Organization (WHO) Antenatal Guidelines, which recommend iron supplementation to be between 30-60 mg/day.

7. Are there any benefits or negative consequences of using 30 mg of iron rather than 60 mg of iron during pregnancy?

Recent evidence suggests that in the context of prenatal micronutrient supplementation, there are no negative or positive consequences to using 30 mg of iron in MMS versus 60 mg of iron in IFA⁷.

8. What is the optimal amount of iron for women during pregnancy?

The optimal dose of iron during pregnancy and the consequences of excess iron are unclear and remain high priority research questions. However, the following guidance may be helpful:

Prevention:

The guidance given here is intended to clarify that MMS is a public health intervention, it is not guidance for treatment. In settings where maternal anemia is present, generally 30 – 60 mg of supplemental iron is sufficient to prevent poor birth outcomes.

Treatment:

In cases of severe anemia in pregnancy (as defined by local health authorities), the causes and treatment should be determined by a healthcare professional. Existing guidelines, suggest that anemia (if determined to be caused by iron deficiency) could be treated by 120 mg per day of iron until hemoglobin level rises to normal.^{8 (p. 23).}

Toxicity:

Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake likely to pose no risk of adverse health effects. For iron the UL is 45 mg/day, which was set based on the highest dose likely to not cause gastrointestinal side effects. While toxicity from iron overdose can occur, these have only been reported at much higher doses.⁹*

**Note: There is no globally accepted UL for iron, as recognized by multiple regulatory authorities (e.g., the European Food Safety Authority (EFSA) (hyperlink to reference: [EFSA UL for iron](#)). However, some regulatory authorities do state an UL for iron. For example, the US Institute of Medicine and the Australia Ministry of Health state 45 mg/day during pregnancy as UL (hyperlinks to references: [US UL for iron](#), [Australia UL for iron](#))*

9. Can MMS and IFA be taken simultaneously? What side-effects can be expected with simultaneous use of MMS + IFA?

MMS is a preventive measure that should reduce the likelihood of maternal anemia. However, if pregnant woman is identified to be anemic while taking MMS, it is important to refer her to a healthcare professional to determine whether it is due to iron deficiency or other causes (e.g. malaria) and provide the adequate treatment according to the etiology of anemia. Due to the multifactorial nature of anemia, this condition should be managed by the health care professional, and in accordance with local guidelines.

While the MMS is sufficient for most pregnant women, in individual cases of severe anemia caused by iron deficiency, MMS can be used in conjunction with iron tablets to achieve a more rapid increase in hemoglobin concentration.^{5 (p. 12)} In populations affected by an emergency, pregnant women should continue taking the IFA tablets while receiving the MMS.¹⁰

The evidence shows that the most common complaints among women consuming IFA (60 mg iron) or MMS include constipation, nausea, vomiting, and diarrhea.^{1,11,12,13} If MMS and IFA are taken simultaneously, it would result in an iron intake of 90 mg/day, with some increased risk of gastrointestinal side effects.

10. Does MMS use lead to larger birth size, especially for boys? Could this lead to birth complications in pregnancy for women of short stature?

While some research suggests that MMS may significantly increase the risk of being born large-for-gestational-age (LGA) based on the Intergrowth standard,^{2 (p. e1096 – e1098)} the risk of LGA with MMS use does not vary by sex of offspring and does not increase the subsequent risk of stillbirth or neonatal mortality.

Conclusion: Large-scale deployment should be implemented, even among populations of with a high prevalence of maternal stunting.^{2 (p. e1096 – e1098)}

11. Should there be variations of the UNIMMAP formula? Does possible benefit outweigh the likely cost?

The UNIMMAP formulation was carefully developed based on multiple criteria (see Q. 4),^{5 (p. 1& 7-10)} and the benefits of using UNIMMAP and similar MMS formulations have been demonstrated across multiple countries.^{1,2} The benefits of MMS formulations that are considerably different from the UNIMMAP formulation and the acceptable range for each micronutrient has yet to be established.

There is ongoing consideration to enhance the UNIMMAP formulation. However, if a different formulation is eventually agreed to, it would take years to demonstrate safety and efficacy for a new formulation. In addition, there would need to be an examination of the additional costs and/or feasibility issues related to manufacturing and procurement of the new product. Health services should not wait to deploy the UNIMMAP MMS product in hopes that a new formulation of MMS will be made readily available in the near future.

12. Is the level of any of the micronutrients in the UNIMMAP formulation teratogenic (e.g., vitamin A)?

*No, none of the micronutrient concentrations in the UNIMMAP formulation is teratogenic. The UL is the highest level of daily intake that is likely to pose no risk of adverse health effects in almost all individuals of a specified life stage. **Across all 15 ingredients in the UNIMMAP formulation, none exceed the UL for the target age groups (see Table 1).***

A recent study examined the potential of reaching the UL of the nutrients provided by the UNIMMAP formulation based on the daily consumption of the supplement on top of a diet that already included the recommended intake of the same nutrients. Only three nutrients met or exceeded the UL (folate, iron, and niacin) and the risk of multiple micronutrient consumption leading to excess intake of micronutrients was considered to be low.¹⁴

With regard to vitamin A specifically, although normal embryonic and fetal development require sufficient maternal vitamin A intake, consumption of excess preformed vitamin A during pregnancy causes birth defects, especially during the first trimester. An increased risk of vitamin A-associated birth defects has not been observed at supplemental doses below 3,000 µg (10,000 IU)/day of preformed vitamin.⁹ Thus the UL of vitamin A for pregnant women ≤ 18 years is 2,800 µg and for those 19-50 years is 3,000 µg. The amount of vitamin A in the UNIMMAP formulation is 800 µg (2,667 IU)/day which is only 29% and 27% of the UL for these age groups, respectively. Even if a pregnant woman consumed the RDA for vitamin A (750 µg retinol activity equivalents/day), and took the UNIMMAP supplement, her intake would still be below the UL for vitamin A.

13. What is the recommended number of MMS tablets to be taken during pregnancy?

Optimally, one MMS tablet would be taken on each day during pregnancy. However, the minimum number of MMS tablets that is needed to accrue the benefits of MMS use for a positive birth outcome is not known. Data from the clinical trials suggest that MMS significantly reduces the risk of neonatal mortality and infant mortality among women with high adherence (≥95%), compared to those with lower adherence (<95%).

Complicating this issue is that MMS use, as for IFA use, is unlikely to occur starting on the date of conception, and that pregnant women generally don't have their first antenatal care visit until well into their first trimester – both of which impedes optimal initiation of MMS or IFA use.

Moreover, the cost of both MMS and IFA, which is now about the same, is still a factor regarding decision-making about the number of doses and format of MMS tablet packaging. Currently, where there is no local research that suggests otherwise, the expert consensus (of the Task Force for Multiple-micronutrient Supplementation for Pregnant Women) and practical field experience is that MMS tablets should be packaged in 180 count bottles, and that the full bottle should be given to the pregnant women at her first antenatal care visit or at the time she is first contacted by a community-based provider.

14. What is the best timing for initiating MMS use by pregnant women to optimize the known effect of MMS on SGA, pre-term babies, underweight, and stunting?

Research suggests that early (< 20 weeks' gestation) and extended (> 20 weeks' gestation) adherence to a daily MMS regimen throughout the period of pregnancy decreases risk of preterm, SGA, LBW, and infant mortality.² Thus, starting MMS as soon after conception as possible, and continuing MMS use throughout the pregnancy is the most optimal pattern of use to encourage. While it is optimal to start MMS supplementation as early as possible after conception, it may still be valuable to initiate MMS anytime in pregnancy.

15. Is there any benefit for giving MMS during pre-conception?

More research is needed to determine benefits on birth outcomes of taking MMS during the pre-conceptional period. However, folic acid supplementation should be commenced as early as possible (ideally before conception) to prevent neural tube defects (NTD), which most often occur within the first few weeks of pregnancy.⁸ (p. 23 footnote c)

In populations considering switching from IFA to MMS completely, supplementation with MMS during the pre-conception period should be considered for the prevention of NTDs.

16. Is there any benefit for giving MMS during the period of lactation?

More research is needed to determine effects of MMS during the period of lactation. However, the expert committee that developed the UNIMMAP formulation also took lactating women into consideration. Due to the high nutrient demands during early lactation and to help support recovery after delivery, they suggest continuing the use of UNIMMAP into lactation. However, when resources are limited, it is recommended that MMS be targeted towards pregnant women, given that its impact during this life stage has been clearly demonstrated on the mother and newborn.

17. Wouldn't populations be best served by focusing on overall improvement of diet rather than promotion of a "pill based" solution that could take resources away from efforts to improve diets?

While recognizing that these micronutrients should ideally be obtained from food, improvements in diet may be difficult to achieve over a short time span for populations in most resource-poor countries. Some countries have established programs to increase micronutrient intake through food fortification, but many more have yet to achieve appropriate food fortification goals. In addition, food fortification programs usually do not address the 15 nutrients commonly provided in MMS and the increased micronutrient requirements posed by pregnancy are especially challenging to cover through dietary intake. In fact, in most industrialized countries, it is common for women to take MMS during pregnancy and lactation.

18. Is there any group or combination of groups that provides technical and/or financial assistance to demonstration activities to: i) advise on demonstration project design, ii) review planning for data analysis, iii) assist with interpretation of results, and/or iv) facilitate dissemination of findings

A Technical Advisory Committee was created by the New York Academy of Sciences with funding from the Bill & Melinda Gates Foundation. There is also a website (www.nyas.org/mms) to help disseminate information to those who are interested in learning more about what the group is doing and planning to do; individual questions can be submitted in the section “Request more information” on the website or by emailing nutrition@nyas.org.

19. What should a “Demonstration Project” for early adopters attempt to learn or achieve?

Demonstration projects are generally undertaken to identify information that will make large scale implementation occur more smoothly or to answer questions on how to optimize policies that guide implementation – but NOT for the purpose of replicating research to prove the worth of the intervention. The following suggested uses for a demonstration project for early adopters of MMS would be to determine:

- *Acceptance: How to improve acceptance of MMS during pregnancy?*
 - *Adherence: How to improve adherence to MMS during pregnancy?*
 - *Optimal answers to policy or operational implementation issues, including:*
 - *When is the earliest time during pregnancy that women can be reached to receive MMS in a given country?*
 - *What configuration of behavior change communication optimizes adherence/use in a given country?*
 - *What is the right packaging in terms of number of doses to dispense at a time (e.g., 180 tablets per bottle)?*
 - *What is the optimal supply amount to give at one time (e.g., give full supply all at once or as a monthly supply)?*
 - *What are the optimal points for accessing MMS (e.g., in-facility antenatal visits, family planning clinics, at the time of mandatory marriage counseling, through community health workers, etc.)?*
 - *Can MMS distribution effectively reach eligible beneficiaries with the right dose at the right time, when scaled (e.g., reach, dose, adherence)?*
 - *What are the cost implications of changes in implementation?*
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20. Should introduction and scaling-up of MMS always be based on the results of implementing a demonstration project?

No, the introduction and scaling-up does not always need to be based on the results of implementing a demonstration project, especially in cases where a functioning IFA platform exists and/or lessons from other demonstration projects can be applied.

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Table 1. Finished Product Specifications

MMS Tablets or Capsules—Vitamins and Minerals for Pregnant Women
(UNIMMAP per WHO, UNICEF, & UNU¹)

| Ingredient/Form ² | Label Claim UNIMMAP | Tolerable Upper Levels (ULs) | | | |
|------------------------------|------------------------|------------------------------|--------|----------|--------|
| | | 14-18 y | | 19+y | |
| | | UL | % UL | UL | %UL |
| Vitamin A | 800 µg RE (2667 IU) | 2,800 µg | 29% | 3,000 µg | 27% |
| Vitamin C | 70 mg | 1,800 mg | 3.9% | 2,000 mg | 3.5% |
| Vitamin D | 200 IU (5 µg) | 100 µg | 5% | 100 µg | 5% |
| Vitamin E (10 mg α-TE) | 10 mg (15 IU) | 800 mg | 1.3% | 1,000 mg | 1% |
| Vitamin B1 | 1.4 mg | ND | ND | ND | ND |
| Vitamin B2 | 1.4 mg | ND | ND | ND | ND |
| Vitamin B3 | 18.0 mg | 30 | 60% | 35 | 51.4% |
| Vitamin B6 | 1.9 mg | 80 | 2.34% | 100 | 1.9% |
| Folic Acid | 400 µg | 800 µg | 50% | 1000 µg | 40% |
| Vitamin B12 | 2.6 µg | ND | ND | ND | ND |
| Iron | 30 mg | 45 mg | 67% | 45 mg | 67% |
| Iodine | 150.0 µg | 900 µg | 16.7% | 1,100 µg | 13.64% |
| Zinc | 15.0 mg | 34 mg | 44.1% | 40 mg | 37.5% |
| Selenium | 65.0 µg | 400 µg | 16.25% | 400 µg | 16.25% |
| Copper | 2.0 mg | 8.0 mg | 25% | 10.0 mg | 20% |

¹ Composition of MMS for pregnant women is formulated to provide the daily Recommended Dietary Allowance (RDA) of each nutrient. From Report of a United Nations Children’s Fund (UNICEF), World Health Organization (WHO), United Nations University (UNU) Workshop, *Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries. Report of a Workshop. New York, UNICEF, 1999.*

² Several forms of each ingredient may be appropriate for use. It is necessary to refer to WHO specifications (when available, e.g., iron) and the manufacturer