Multiple micronutrient supplements in pregnancy: Technical Reference Material II

Generic Training Materials

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Multiple Micronutrient Supplementation in Pregnancy
TECHNICAL ADVISORY GROUP

Introduction

Under a grant from the Bill and Melinda Gates Foundation, the Nutrition Program at the New York Academy of Sciences (NYAS) prepared a series of Technical Reference Materials (TRMs) to support the distribution of multiple micronutrient supplements (MMS) to pregnant women in the context of Antenatal Care programs. The TRMs include advocacy materials, training modules and job aids. All the TRMs presented in this series are "generic" and need to be adapted to each country context, taking into account the specifics of the ANC program (e.g. the level of decentralization of services, personnel qualifications, etc.); the type of Health Management Information System in that particular country and other local aspects (transport, storage infrastructure, etc.).

This present document describes the generic training materials and job aids developed to support the use of MMS in low and middle income countries (LMICs). The individual TRMs are found in companion documents, available through the links provided in the text, or directly from NYAS.

1. Training modules

Two training modules were developed:

1.1. A pre-service training module for healthcare professionals

This power point presentation (~45 minutes), should be used for pre-service training of qualified healthcare professionals (physicians, nurses, trained midwives). It provides information about the scientific rationale for using MMS, comparing in particular to the use of iron and folic acid (IFA) in ANC programs. This information can also be used in conferences and public presentations to other scientific audiences.

1.2. An in-service training module for frontline health workers

This power point presentation, a shortened and simplified version of 1.1 (~20 minutes), should be used for in-service training courses. It can also be used in refresher training sessions, to update and reinforce the initial training received by frontline health workers on MMS. Its purpose is to educate frontline health workers, who may not have formal health care training, on the rationale for using MMS (comparing particularly to IFA) in ANC programs. It also aims to demonstrate the role of CHWs and frontline healthcare workers in explaining the benefits of MMS to clients of ANC clinics, and suggestions for increasing compliance with the regimen, and for expanding coverage among women of reproductive age.

2. Job Aids

Job aids include counseling cards, posters, leaflets to distribute to ANC clients, and a decision algorithm to help frontline workers guide women in the use of MMS. Those are briefly described below.

2.1. Decision algorithm

This tool helps frontline health integrate MMS-related content in to the different antenatal care (ANC) contacts ("visits"), incorporating those with other nutrition actions recommended by the WHO ANC guideline. For example, in addition to the provision of MMS, healthcare professionals should advise pregnant women on healthy eating, ideal weight gain and the need to limit caffeine intake; and check their hemoglobin level at certain time points. This algorithm also stresses the need to record all the services provided in the ANC register. It is relevant to all healthcare workers who conduct ANC consultations, whether for pregnant women or for WRA who are planning a pregnancy, and a protected (e.g. plastified) copy should be kept permanently in each ANC clinic.

2.2. Leaflets for pregnant women

A simple educational leaflet was produced for distribution to pregnant women, providing them with the information and instructions that should accompany the delivery of the MMS (whether packaged or bottled). It explains, in plain language:

- The reason why they need to take the MMS
- When they should start taking the MMS
- How they should take the MMS
- What to do if they forget to take the MMS
- What to do if they feel sick after taking the MMS
- Why it is important to comply with the recommended dose of the supplements.

The front page offers space to write the date of the next ANC contacts, the name and contact of the healthcare worker that the woman should call if she has additional questions or a concern arises; and the unique code number assigned to this woman in the ANC system, assuming that such a scheme is used by the program. The leaflet should be given to the woman at the time she is provided with the MMS by the person who hands out the supplements. Depending on the distribution system in place, it may be delivered at the ANC clinic (ideally on the first visit), at a healthcare facility or in the community itself, e.g by community health volunteers or by skilled birth attendants who have taken one of the training modules.

A simplified version of the leaflet was also prepared that delivers the same messages but using more visual representations of the information and very little text, for women with limited or no

reading skills. This also minimizes the risk of misinterpreting the messages during translation into local languages.

2.3. Counselling cards flip chart

This tool helps frontline workers communicate the importance of MMS to pregnant mothers. The chart book contains 6 counseling cards, covering the following key aspects:

1. The role of micronutrients in pregnancy and the increased micronutrient needs of pregnant women
2. The potential consequences of micronutrient deficiencies on pregnancy and birth outcomes
3. The benefits of MMS during pregnancy
4. Dose, frequency and duration of MMS during pregnancy
5. Side effects of MMS and their management
6. Importance of healthy eating in pregnancy

These counselling cards can be used both for individual or group counselling. Each card consists of an illustration to be shown to the pregnant women, accompanied by text to be used by the educator to convey the message. When showing the illustration, the educator should ask first "what do you see in the picture?" to initiate a discussion, and build on what the pregnant woman knows to articulate the key message. Before moving to a new card, the educator should review the key points discussed to ensure the woman has understood the messages correctly. The educator can select which card to use in a given counselling session depending on whether it is a first or return ANC contact, or whether there are other education topics to cover.

2.4. Posters to display at point of care

These two posters were created to:

- remind the pregnant women or those who are planning for pregnancy about the new program of MMS; it may be displayed on the walls of clinics, hospitals, health centers and other facilities delivering ANC programs
- remind healthcare professionals (medical doctors, nurses, midwives) or community health workers for the need to distribute the MMS during the first time they contact with a pregnant women, and the need to assess and encourage full compliance in every antenatal care visit. It can be displayed, for example, on the wall of staff office/room of healthcare facilities, or in the office allocated to community health workers.

1.1

Pre-service training module for healthcare professionals

The Importance of Multiple Micronutrient Supplementation during pregnancy

Training module for
healthcare professionals

Multiple Micronutrient
Supplementation in Pregnancy
TECHNICAL ADVISORY GROUP

Objectives

At the end of this session, you will be able to:

- Appreciate the essential role of key micronutrients in pregnancy and the increased micronutrient needs of pregnant women
- Understand that micronutrient deficiencies are common among women of reproductive age and are associated with adverse pregnancy and birth outcomes
- Understand the scientific rationale for selecting MMS over IFA and identify the different benefits provided by antenatal MMS compared to IFA
- Educate and guide pregnant women about the importance of MMS during pregnancy
- Detect potential reasons for poor compliance to MMS and help the patient improve compliance

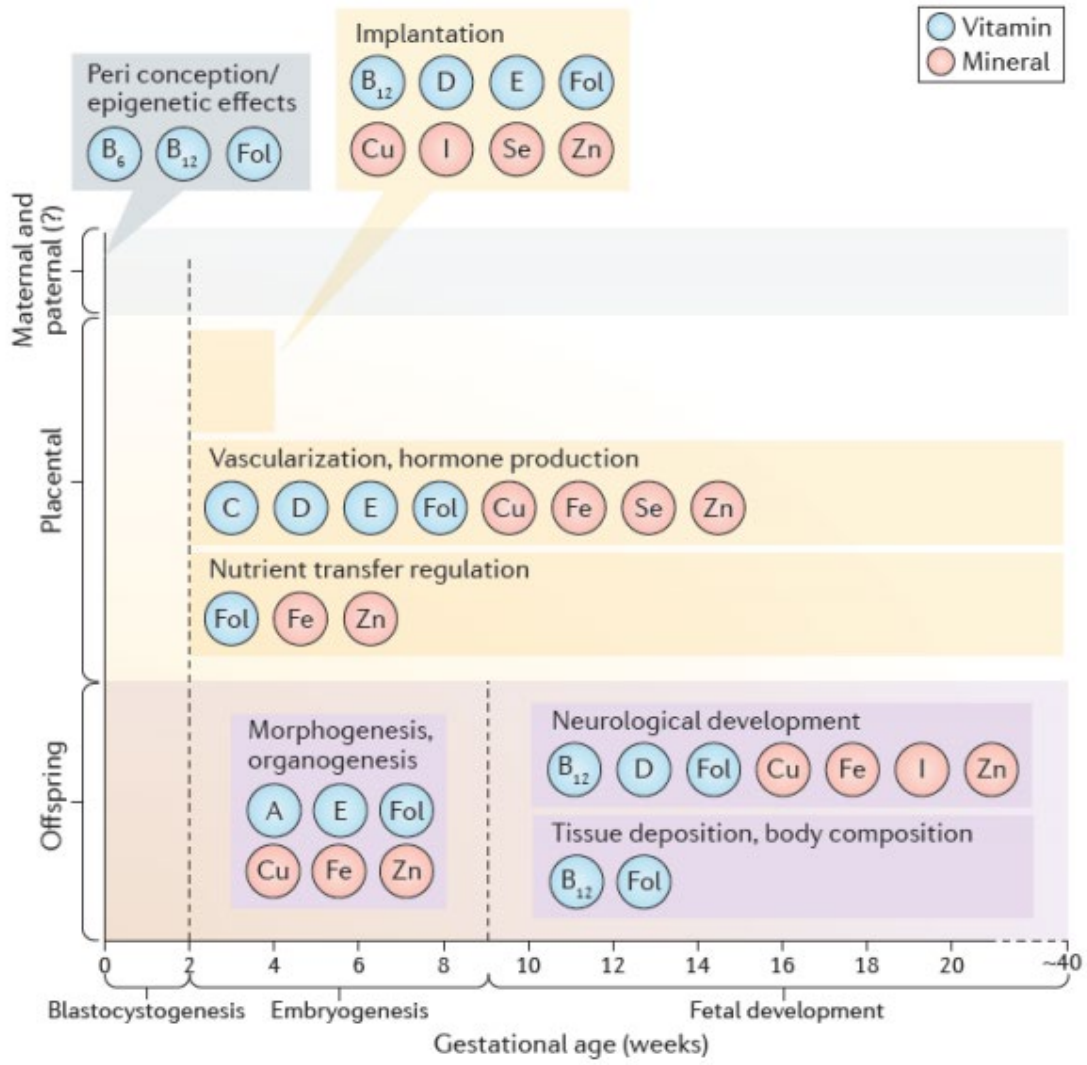
Contents of this Training Module

I. The role of micronutrients in pregnancy

Different vitamins and minerals affect the successive stages of fetal development

- implantation and vascularization of the placenta
- offspring morphogenesis and organogenesis
- neurological development and accumulation of fetal nutrient stores
- tissue deposition and body composition

(figure on the right, reproduced from Gernand et al., 2016).



Fol – folate; Cu – copper; I – iodine; Se – selenium; Zn – zinc; Fe - iron

*Suggested reading: Gernand A.D., et al. 2016. Nat Rev Endoc **12**: 274–289.*

Examples of the micronutrient (group) roles in several stages of fetal development:

- Zinc, folate, niacin, riboflavin, and vitamins B_6 and B_{12} are considered particularly important in early gestation as these micronutrients are:
  - involved in one-carbon metabolism, which is essential for cell proliferation, growth, and protein synthesis in the earliest stages of gestation
  - involved in the rapid demethylation of maternal and paternal genomes immediately following conception, as well as the sustained remethylation of the fetal genome during gestation
- Zinc, vitamin D and vitamin E contribute to adequate placental implantation, development, vascularization and metabolism
- Iron, folate, zinc, niacin, and vitamins B_6 and A support the organogenesis and development of the fetal central nervous system
- Iodine, through its incorporation to the thyroid hormones, has a crucial role in early brain development (for adequate neuronal growth, migration and myelinization at different sites)

*Suggested reading: Gernand A.D., et al. 2016. Nat Rev Endoc **12**: 274–289.*

The role of individual micronutrients and consequences of their deficiency during pregnancy

Nutrient	Primary function	Function in pregnancy	Consequences of deficiency in pregnancy
Vitamin A	Required for normal vision (essential component of rhodopsin, a protein that absorbs light in the retinal receptors; normal differentiation and functioning of the conjunctival membranes and cornea); cell growth and differentiation; antioxidant properties.	Cellular differentiation (related to embryonic development and immunity, induced by retinoic acid); positive effect on iron metabolism and hemoglobin production by enhancing non-heme iron absorption; anti-infective properties; fetal uptake in late pregnancy.	Xerophthalmia; vitamin A-deficiency anemia; maternal mortality; slower infant growth and development.
Vitamin B1 (Thiamine)	Essential to key reactions in energy metabolism (hence growth, development and function of cells); thiamine diphosphate is an essential cofactor for several enzymes involved in glucose, amino acid and lipid metabolism.	Fetal growth and development, and production of adenosine triphosphate (ATP) from glucose in the brain.	Beriberi which is associated with extensive neurological and/or cardiovascular damage.
Vitamin B2 (Riboflavin)	Essential component of two coenzymes (flavin mononucleotide and flavin adenine dinucleotide) that play major roles in energy production; cellular function, growth, and development; and metabolism of fats, drugs, and steroids; involved in the metabolism of other B vitamins (B3, B6 and B9).	No additional roles in pregnancy were identified.	Possibly preeclampsia (decreased levels of flavocoenzymes could cause mitochondrial dysfunction, increase oxidative stress and interfere with nitric oxide release and thus blood vessel dilation); cardiac outflow tract defects and preterm birth.

Sources:
- *Institute of Medicine 1990. Nutrition During Pregnancy: Part I: Weight Gain, Part II: Nutrient Supplements. Washington, DC: The National Academies Press.*
- *Gernand A.D., et al. 2016. Nat Rev Endoc 12: 274–289*
- *United Nations. 1999. Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries.*
- *https://ods.od.nih.gov/*
- *https://lpi.oregonstate.edu/mic/life-stages/pregnancy-lactation*

The role of individual micronutrients and consequences of their deficiency during pregnancy (cont.)

Nutrient	Primary function	Function in pregnancy	Consequences of deficiency in pregnancy
Vitamin B3 (Niacin)	Its metabolically active form, the coenzyme nicotinamide adenine dinucleotide, is required by more than 400 enzymes including those involved in glycolysis, fatty acid metabolism, and tissue respiration.	No additional roles in pregnancy were identified.	Pellagra, which clinically presents as dermatitis, diarrhea, and dementia.
Vitamin B6 (Pyridoxine)	B6 vitamers are required for the function of numerous enzymes including those involved in nervous system function, red blood cell formation and function, steroid hormone function, nucleic acid synthesis, and niacin formation.	Some primary functions are augmented during pregnancy (e.g. increase of blood by >40% requires more vit. B6 for red blood cell formation); fetal uptake in late pregnancy.	Impaired fetal nervous system development.
Vitamin B9 (Folate)	Cofactor required in single-carbon transfers in the synthesis of DNA and RNA and metabolism of amino acids; involved in methylation reactions and conversion of homocysteine to methionine.	Cell proliferation and growth in the early stages (materno-placental tissue expansion and fetal growth); increased maternal erythropoiesis	Anomalies in the fetus and placenta in early pregnancy; neural tube defects; and megaloblastic anemia.

Sources:
- *Institute of Medicine 1990. Nutrition During Pregnancy: Part I: Weight Gain, Part II: Nutrient Supplements. Washington, DC: The National Academies Press.*
- *Gernand A.D., et al. 2016. Nat Rev Endoc 12: 274–289*
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The role of individual micronutrients and consequences of their deficiency during pregnancy (cont.)

Nutrient	Primary function	Function in pregnancy	Consequences of deficiency in pregnancy
Vitamin B12 (Cobalamin)	Coenzyme in single-carbon transfers in the synthesis of DNA and RNA and metabolism of amino acids; involved in methylation reactions and conversion of homocysteine to methionine.	Normal cell division and protein synthesis during pregnancy (gene expression, cell differentiation and the formation of organs); fetal uptake in late pregnancy.	Slowed DNA synthesis and its consequences, such as neural tube defects; elevated homocysteine and megaloblastic anemia; deficiency may be masked by folic acid supplementation
Vitamin C	Antioxidant function (as a reducing agent, protects against free-radical-induced oxidative damage and regenerates other antioxidants within the body, e.g. vit. E); synthesis of L-carnitine, some neurotransmitters and collagen, an essential component of connective tissue, which plays a vital role in wound healing; immune function (stimulates the production and function of leukocytes); increases the bioavailability of non-heme iron by enhancing its intestinal absorption.	In addition to the crucial "primary functions" which also apply to the developing fetus, vitamins C and E may help to prevent preeclampsia because oxidative stress has been implicated in the pathogenesis of this condition; positive effect on iron metabolism and hemoglobin production.	Scurvy and impaired synthesis of collagen, a protein that gives structure to bones, cartilage, muscle and blood vessels.
Vitamin D	Maintenance of bone mineralization through the regulation of calcium and phosphorus homeostasis; non-skeletal effects on the immune, endocrine, and cardiovascular systems	Promotes placental vascular endothelial growth factor (VEGF) production; modulates immune function; supports implantation and placental metabolism; fetal uptake in late pregnancy.	Possible increased risk of preeclampsia, low birth weight and preterm birth

Sources:
- *Institute of Medicine 1990. Nutrition During Pregnancy: Part I: Weight Gain, Part II: Nutrient Supplements. Washington, DC: The National Academies Press.*
- *Gernand A.D., et al. 2016. Nat Rev Endoc 12: 274–289*
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The role of individual micronutrients and consequences of their deficiency during pregnancy (cont.)

Nutrient	Primary function	Function in pregnancy	Consequences of deficiency in pregnancy
Vitamin E	Vitamin E functions as a chain-breaking antioxidant that prevents the propagation of free radicals in membranes and plasma lipoproteins; cell-mediated immunity (e.g. by improving the formation of an adhesive junction between naïve T lymphocytes and antigen-presenting cells).	Required to protect essential fatty acids from oxidative degradation during embryogenesis; may promote vascularization of the placenta, presumably by enhancing expression of angiogenic factors, such as the vascular endothelial growth factor (VEGF); required for fetal uptake in late pregnancy.	Possible increased risk of pregnancy complications involving oxidative stress, such as pre-eclampsia.
Copper	Required for the function of numerous enzymes, including those involved in red blood cell formation and free radical defense.	Required for iron metabolism for erythropoiesis.	Animal models suggest neurological and vascular deficits in offspring, as well as stillbirth.
Iodine	Required for thyroid hormones, which regulate metabolism.	Required for fetal and child brain development.	Poor physical and cognitive development; hypothyroidism, goiter; deafness; and stillbirth.

Sources:
- *Institute of Medicine 1990. Nutrition During Pregnancy: Part I: Weight Gain, Part II: Nutrient Supplements. Washington, DC: The National Academies Press.*
- *Gernand A.D., et al. 2016. Nat Rev Endoc 12: 274–289*
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The role of individual micronutrients and consequences of their deficiency during pregnancy (cont.)

Nutrient	Primary function	Function in pregnancy	Consequences of deficiency in pregnancy
Iron	Required for the function of numerous enzymes and proteins (including hemoglobin).	Required for increasing blood cell mass and delivering oxygen to tissues; fetal uptake in late pregnancy.	Increases risk for low birth weight, preterm birth and perinatal mortality.
Selenium	Required for antioxidant activity of glutathione peroxidase, which catalyzes hydrogen peroxide to water.	Required to prevent fetal and maternal oxidative stress.	Causes a frequently fatal cardiomyopathy for mothers and infants, known as Keshan disease. Also associated with infertility, miscarriage and disruption of fetal nervous and immune systems and low birth weight.
Zinc	Required for nucleic acid and protein metabolism; the synthesis of DNA and RNA; and initiation of transcription.	Essential for every phase of gestation, including implantation and cell division to neurological development.	Increases risk of congenital abnormalities, impaired intrauterine growth, low birth weight, and pre-eclampsia. Animal studies have shown zinc restriction during pregnancy has teratogenic effects on organs, especially skeletal and central nervous systems, as well as deleterious effects on the immune system and growth retardation.

Sources:
- *Institute of Medicine 1990. Nutrition During Pregnancy: Part I: Weight Gain, Part II: Nutrient Supplements. Washington, DC: The National Academies Press.*
- *Gernand A.D., et al. 2016. Nat Rev Endoc 12: 274–289*
- *United Nations. 1999. Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries.*
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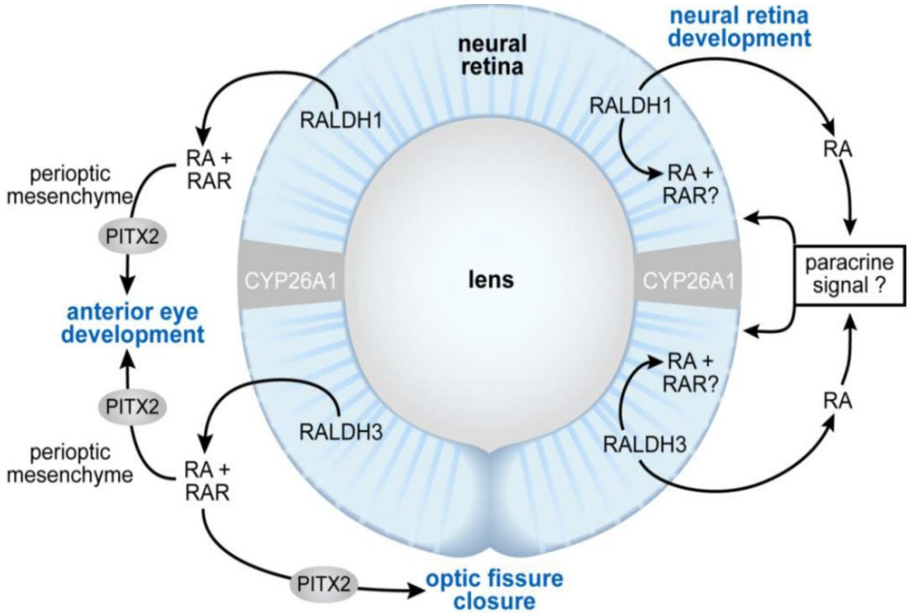
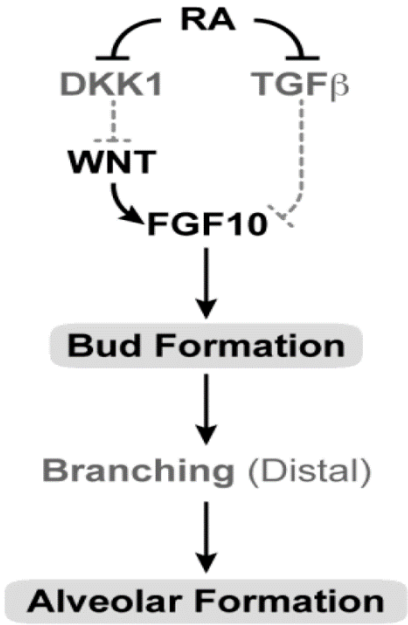
Examples: vitamin A and eye and lung development

Retinoic acid (RA), a vitamin A metabolite, is essential for many events in the developing embryo, such as eye morphogenesis and differentiation (figure on the left) and lung development (figure on the right).



There are various proposed sites of RA function during eye morphogenesis and differentiation: at early stages of eye development, RA acts as a paracrine signal binding to RARs (nuclear RA receptors) located in the perioptic mesenchyme to support anterior eye segment development and closure of the optic fissure.
At a later stage, RA promotes differentiation of the neural retina (probably through a paracrine effect of RA outside of the neural retina or a direct effect on the cells within the retina itself) - reproduced from Clagett-Dame et al., 2011.

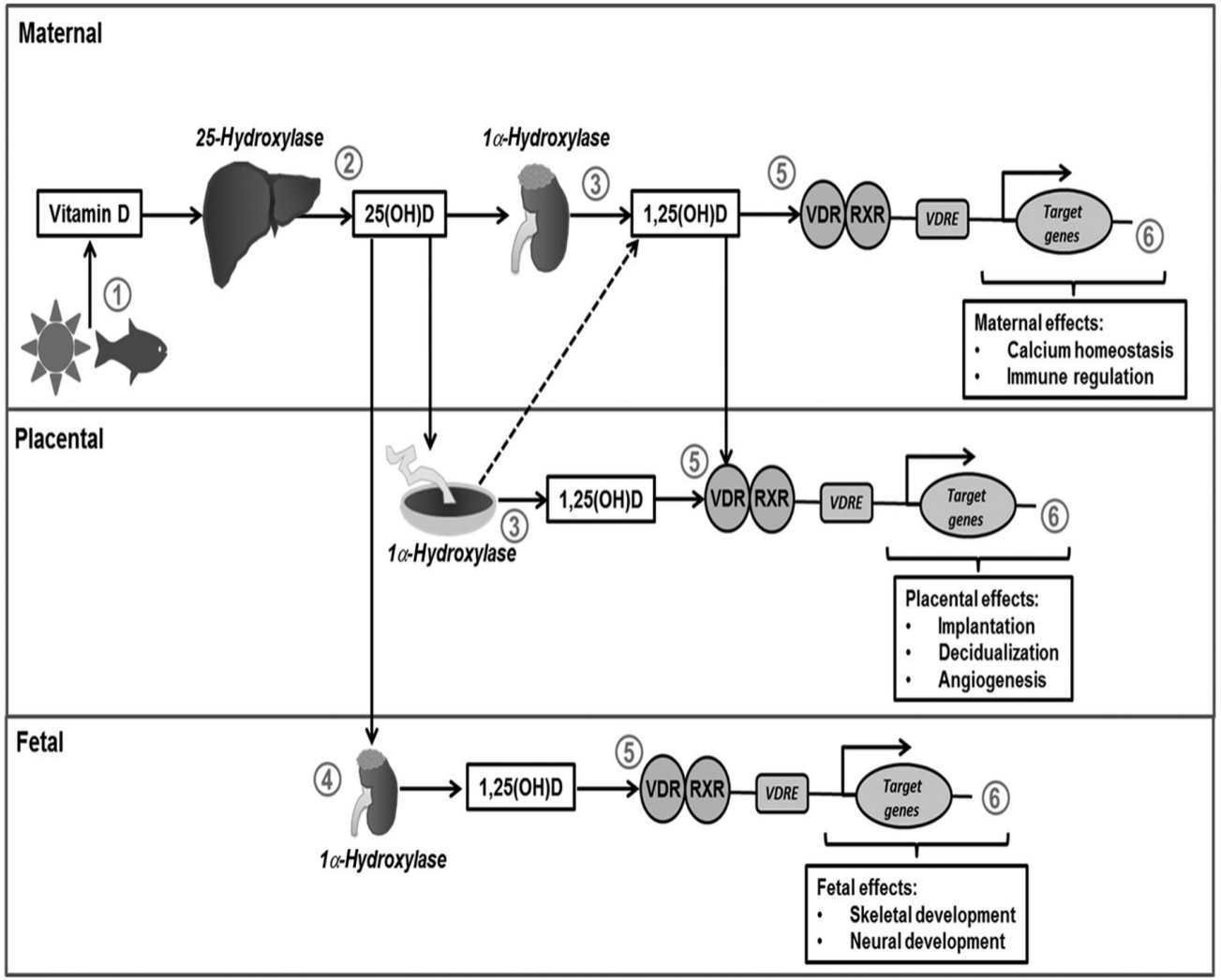


There are different proposed sites of RA action in lung development, from primary bud formation in the developing embryo to a downstream role in alveolar formation. During induction of the lung buds, RA regulates mesodermal *Fgf10* levels by negatively regulating Tgfβ and enabling induction of the Wnt pathway by repression of the Dickkopf homolog 1 (*Dkk1*) known to antagonize Wnt ligand-receptor binding. RA may also influence the response of the foregut endoderm (origin of lung progenitors) to *Fgf10* - reproduced from Clagett-Dame et al., 2011.

Suggested reading: Clagett-Dame et al., 2011. Nutrients. 3(4): 385–428

Examples: vitamin D and metabolic pathways during pregnancy

- This figure illustrates various Vitamin D metabolic pathways during pregnancy, at the maternal, fetal and placental level.
- Vitamin D is absorbed into maternal circulation via UVB-catalyzed synthesis in the skin or dietary intake (1). It is then then converted to 25(OH)D via hepatic 25-hydroxylase, in the liver (2), and subsequently hydroxylated to the active form (1,25(OH)D) in various tissues, including the kidney and placenta (3).
- The precursor 25(OH)D can also directly cross the placenta (6), where it is hydroxylated to the active form in the kidney of the fetus (4).
- The active form of vitamin D then elicits genomic effects through binding to the vitamin D receptor (VDR) (which dimerizes with the retinoid X receptor (RXR)) in target tissues, including the placenta (5). This induces the transcription of target genes via vitamin D response element (VDRE), thus enabling the regulation of a range of important processes during gestation (6), such as maternal immune regulation, placental angiogenesis and skeletal and neural development.

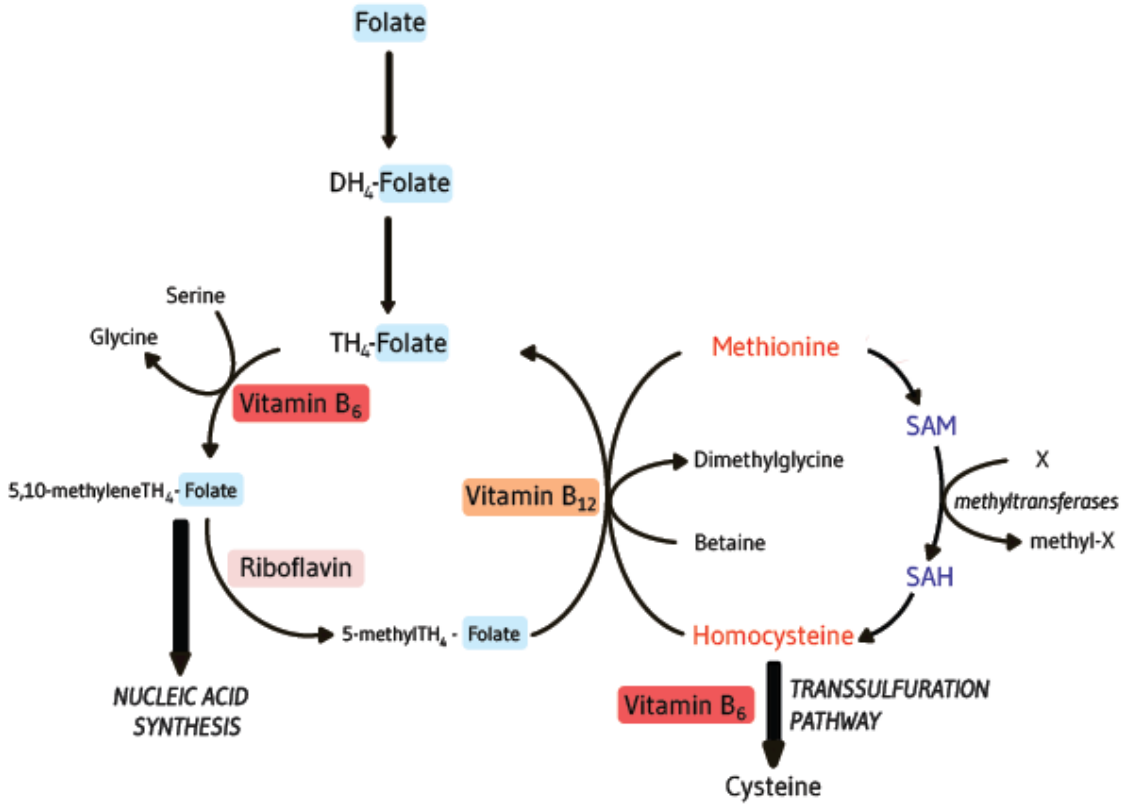


Reproduced from Yates et al, 2017

Suggested reading: Yates et al, 2017. Reproduction. 153(5):R163-R171

Examples: complex B vitamins (folate, vitamins B2, B6 and B12) and one–carbon metabolism

- This figure shows that several B complex vitamins (folate, vitamins B2, B6 and B12) are the source of coenzymes that participate in one-carbon metabolism.
- One-carbon metabolic pathways drive the synthesis of proteins, biogenic amines and lipids required for early growth, together with the synthesis and methylation of DNA and histones essential for the regulation of gene expression.
- This demonstrates the importance of these vitamins on cell proliferation, growth and protein synthesis in the earliest stages of gestation.

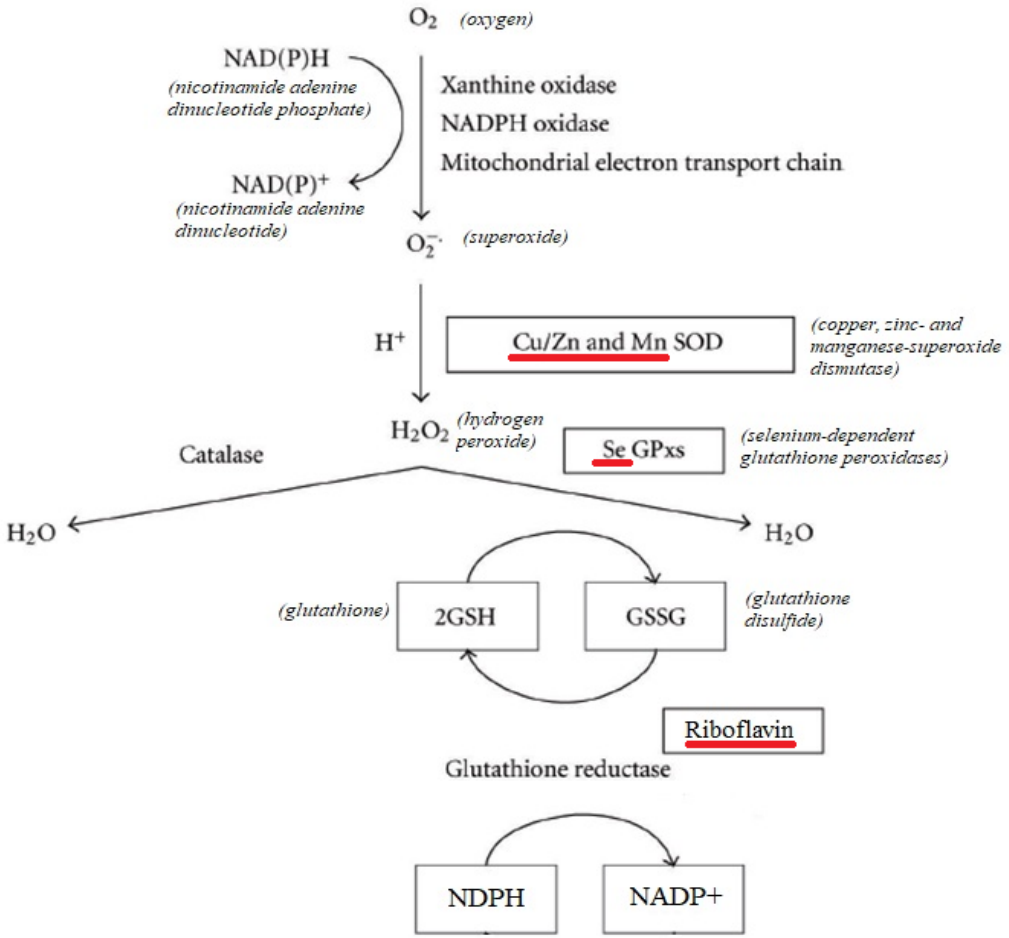


5,10-methylenetetrahydrofolate is required for the synthesis of nucleic acids, and 5-methyltetrahydrofolate is required for the formation of methionine from homocysteine. Methionine, in the form of methyl donor S-adenosylmethionine (SAM), is essential to many biological methylation reactions, including DNA methylation. Methylenetetrahydrofolate reductase (MTHFR) is a riboflavin (FAD)-dependent enzyme that catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. *SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; TH_4-Folate, Tetrahydrofolate.*

Reproduced from https://lpi.oregonstate.edu/mic/vitamins/folate

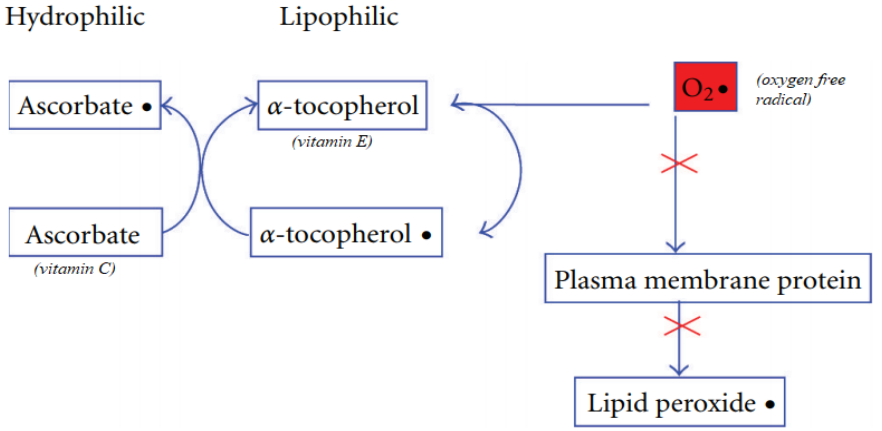
Suggested readings:
Steegers-Theunissen at al. 2013. Hum Reprod Update. Nov-Dec;19(6):640-55.
https://lpi.oregonstate.edu/mic/vitamins/folate

Examples: antioxidant micronutrients and reduction of oxidative stress and lipid peroxidation



Major pathways of reactive oxygen species generation and metabolism, highlighting the role of micronutrients as essential cofactors for enzymes with antioxidant activity *(adapted from Mistry et. al 2011).* The placenta is armed with antioxidant defenses, including the selenium-dependent glutathione peroxidases and copper/zinc and manganese superoxide dismutases represented in the figure.

Suggested reading: Mistry et al. 2011. Oxid Med Cell Longev.; 2011:841749.



Synergistic mechanisms of vitamin C (ascorbate) and vitamin E (α-tocopherol) to prevent lipid peroxidation (*reproduced from Mistry et. al 2011).*

- Oxidative stress is generated during normal placental development, but there are a number of mechanisms whereby antioxidant micronutrients protect the fetus and placenta against oxidative damage (see examples on figures, left and above).

- However, when the supply of antioxidant micro-nutrients is limited, exaggerated oxidative stress (placenta and maternal circulation) occurs, leading to adverse pregnancy outcomes, such as preeclampsia and fetal growth restriction.

Recommended dietary allowances (RDA) increase during pregnancy

- Increased maternal, placental and fetal nutrient demands, elevate the recommendations for some of the nutrients' intake by up to ~50% during pregnancy.

- The nutritional requirements of malnourished pregnant women may be even higher than those listed here (which are estimated for well nourished populations in the US and Canada), as pre-existing micronutrient deficiencies may need to be corrected.

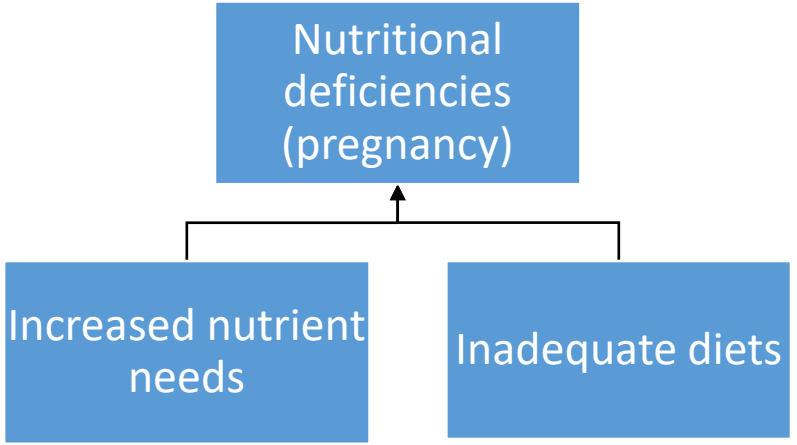
Nutrient	Non-pregnant and non-lactating women	Pregnant women
Vitamin A	700 µg RAE	770 µg RAE
Vitamin B1 (thiamine)	**1.1 mg**	**1.4 mg (+27%)**
Vitamin B2 (riboflavin)	**1.1 mg**	**1.4 mg (+27%)**
Vitamin B3 (niacin)	**14 mg**	**18 mg (+28%)**
Vitamin B6 (pyridoxine)	**1.3 mg**	**1.9 mg (+46%)**
Vitamin B9 (folate)	**400 µg DFE**	**600 µg DFE (+50%)**
Vitamin B12 (cobalamin)	2.4 µg	2.6 µg
Vitamin C	75 mg	85 mg
Vitamin D	600 IU	600 IU
Vitamin E	15 mg	15 mg
Copper	900 µg	1000 µg
Iodine	**150 µ**	**220 µg (+47%)**
Iron	**18 mg**	**27 mg (+50%)**
Selenium	55 µg	60 µg
Zinc	**8 mg**	**11 mg (+38%)**

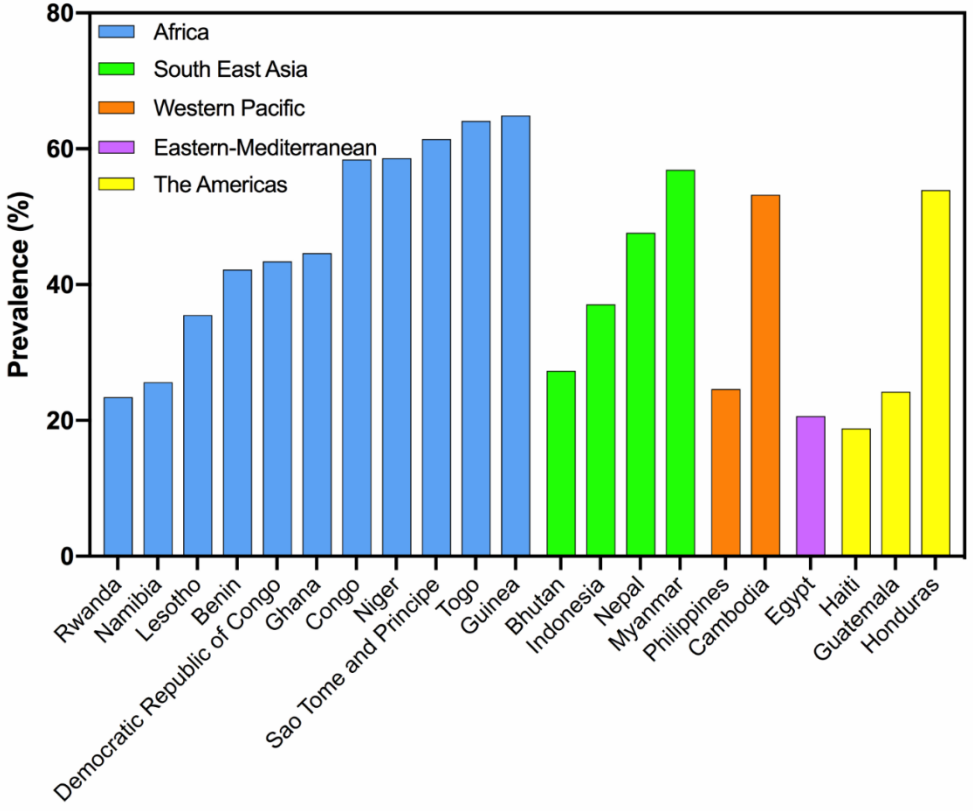
*Suggested reading: Gernand A.D., et al. 2016. Nat Rev Endoc **12**: 274–289.*

Source: Institute of Medicine reports on Dietary Reference Intakes for each nutrient (http://fnic.nal.usda.gov/dietary-guidance/dietary-referenceintakes/dri-nutrient-reports)

II. Micronutrient deficiencies in women of reproductive age and during pregnancy in LMIC

The increased nutrient needs of gestation in addition to the monotonous and nutrient-poor diets common in LMIC place pregnant women at risk of nutritional deficiencies in micronutrients, energy, protein and some fatty acids.





Data from 21 national and regional surveys in LMIC, published between 2013-2017, show that 32% of pregnant women suffer from anemia (hemoglobin < 120 g/L). This prevalence is even higher in Africa (48%) and South-East Asia (45%) – figure on the left, adapted from Bourassa et al, 2019.

It is estimated that half of these values are attributed to iron deficiency anemia.

Suggested reading: Bourassa M.W., et al. 2019.. Ann. N. Y. Acad. Sci. Submitted for publication.

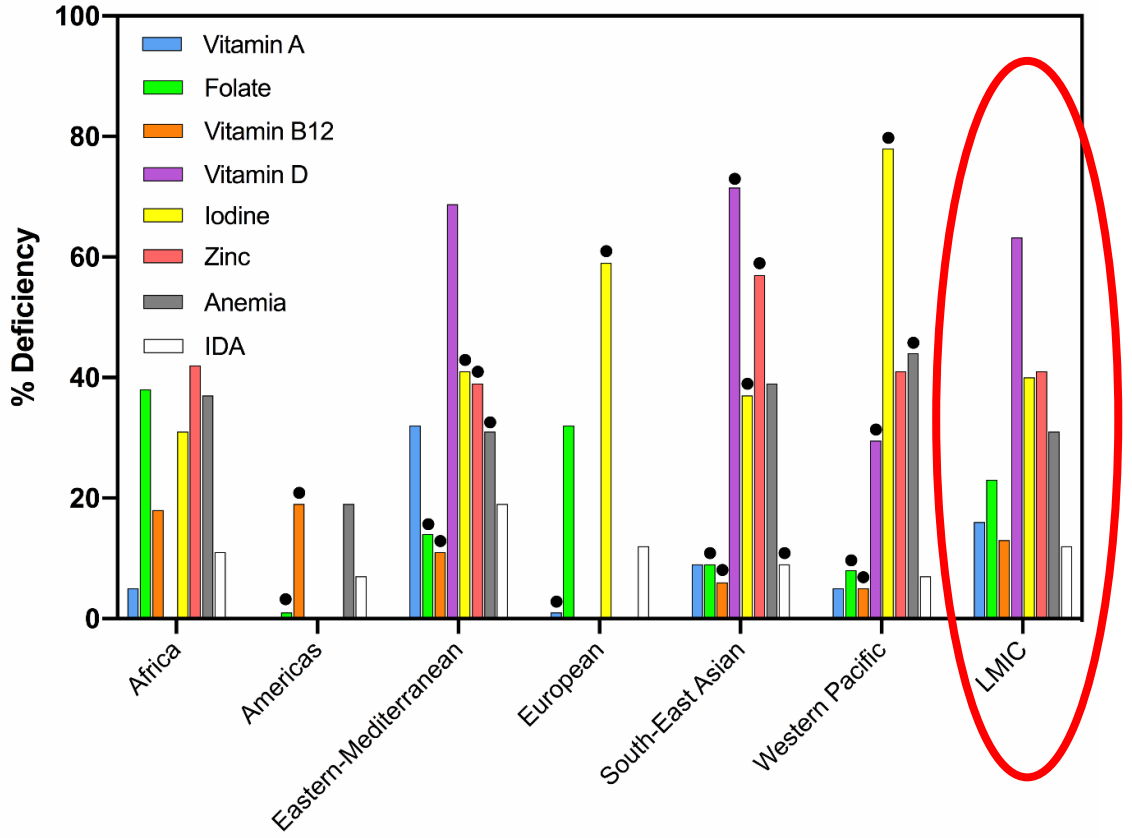
II. Micronutrient deficiencies in women of reproductive age and during pregnancy in LMIC (cont.)

The average prevalence of micronutrient deficiencies in women of reproductive age in LMIC are:

- 16% for vitamin A
- 23% for folate
- 13% for vitamin B12
- 63% for vitamin D
- 40% for iodine
- 41% for zinc
- 31% for anemia (similarly to the prevalence of pregnant women)
- 12% for iron deficiency anemia

<u>Multiple micronutrient deficiency is a public health concern in most LMIC!</u>

Regional estimates of micronutrient deficiencies and anemia in women of reproductive age (52 national and regional surveys, published between 2013-July 2017)



IDA – iron deficiency anemia; LMIC - Low- and Middle-Income Countries.
Missing bars means no data were found for that micronutrient in the specific region

- *Not representative (<3 countries).* Adapted from Bourassa et al, 2019.

Suggested reading: Bourassa M.W., et al. 2019. Ann. N. Y. Acad. Sci. Submitted for publication; https://www.who.int/news-room/fact-sheets/detail/preterm-birth.

III. Adverse pregnancy outcomes (maternal and child) in LMIC

- **Preterm birth** *(<37 weeks of gestation)*

Prematurity is the world's number one cause of death in children under 5 years of age.
More than 80% of preterm babies were born in Asia (7.8 million, or 10.4% of live births) and Sub-Saharan Africa (4.2 million, or 12.0% of live births).

- **Small for gestational age** ((SGA), *birth weight < 10th percentile for a given gestational age*)

19.3% of all live births were SGA and 21.9% of all neonatal deaths were attributable to SGA.
South Asia has the highest prevalence (34%) of SGA.

Both preterm and SGA infants have an increased neonatal mortality risk: 6·82 (95% CI 3·56–13·07) and 1·83 (95% CI 1·34–2·50), respectively (Lancet. 2013 Aug 3; 382(9890): 417–425).

Adverse pregnancy outcomes associated with maternal micronutrient deficiencies are common in LMIC

Adverse pregnancy outcomes in various regions	Sub-Saharan Africa	Asia	South East Asia	South Asia	World
Preterm births (2014) (%)	12.0	10.4	N/R	N/R	10.6
Small for gestational age (2012) (%)	16.5	N/R	21.6	34.2	19.3
Low birth weight (2009-2013) (%)	13.0	N/R	N/R	28	16
Stillbirths (2015) (per 1000 total births)	28.7	N/R	12.2	25.5	18.4
Neonatal mortality (2016) (per 1000 live births)	27.7	N/R	13.5	27.6	18.6

N/R – not reported
adapted from Bourassa et al, 2019

Suggested reading: Bourassa M.W., et al. 2019.. Ann. N. Y. Acad. Sci. Submitted for publication; https://www.who.int/news-room/fact-sheets/detail/preterm-birth.

III. Adverse pregnancy outcomes (maternal and child) in LMIC (cont.)

- **Low birth weight** (weight <2500g)

Caused by either intrauterine growth restriction or preterm birth, LBW affects 16% of all live births; South Asia has the largest burden (28%)

- **Stillbirths**

Though not often reported as an adverse outcome; available data suggest that the highest incidence is in sub-Saharan Africa (28.7 per 1000 total births)

- **Neonatal mortality** (< 28 days)

Most prevalent in sub-Saharan Africa: 27.7 per 1000 live births.

Other adverse maternal and child outcomes associated with micronutrient deficiencies in pregnancy include:

- maternal depression
- maternal and child cognitive impairment
- premature rupture of membranes
- insufficient gestational weight gain
- congenital anomalies and pre-eclampsia

*Suggested reading: Nguyen P.H. et al. 2017. BMC Womens. Health 17: 44; Prado E.L. et al. 2012. Maternal multiple micronutrient supplements and child cognition: a randomized trial in Indonesia. Pediatrics 130(3):e536-46; Prado E.L., et al. 2012.. PLoS One **7**: e32519 ; Prado E.L. et al. 2017. Lancet Glob. Heal. 5: e217–e228; Hofmeyr G.J et al. 2014. BJOG An Int. J. Obstet. Gynaecol. 121: 951–957.*

IV. Interventions to improve micronutrient nutrition in pregnant women

In order to address micronutrient malnutrition in the general population, World Health Organization (WHO) and the Food and Agricultural Organization of the United Nations (FAO) suggest:

1) nutrition education leading to increased diversity and quality of diets;

2) food fortification and biofortification;

3) disease control measures; and

4) supplementation

Currently only routine iron-folic acid is recommended in pregnancy, along with context-specific recommendations for protein-energy, calcium, vitamin A and zinc.

Source: https://www.flickr.com/photos/unicefethiopia/18199055126/in/photostream/

Suggested reading: Allen L.H., B. de Benoist, O. Dary, et al. 2006. Guidelines on Food Fortification With Micronutrients. WHO & FAO

IV. Interventions to improve micronutrient nutrition in pregnant women (cont.)

Challenges associated with these strategies:

- Food fortification is a long-term measure used to tackle nutritional deficiencies in a population, and therefore may not cover the immediate needs of a pregnant women
- Nutrition education using local foods can be challenging because even optimized local diets are likely to be insufficient to meet the high nutritional requirements of pregnancy

  For example, in order to reach the recommended **daily** intake of 27mg of iron for a pregnant woman, she would need to consume:

4.5 cups of boiled lentils, OR

5.5 portions (3oz) of beef liver

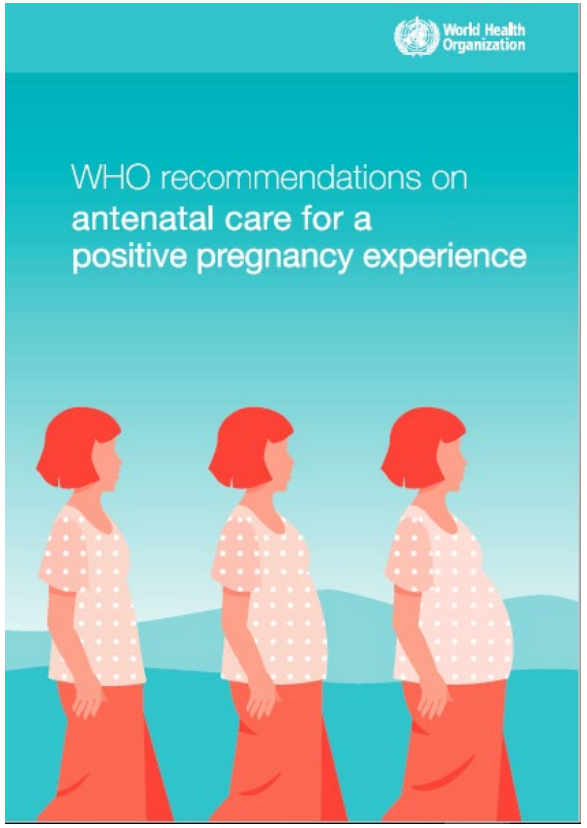
When food-based solutions are not practical, supplementation can help

Sources: https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/
https://www.maxpixel.net/India-Asian-Daal-Dal-Bowl-Toor-Dal-Dhal-Toor-1740205

V. Existing guidelines on micronutrient supplementation in pregnancy

The WHO Guidelines for Antenatal Care (ANC), from 2016:

- Recommend daily oral IFA for pregnant women. Thus, IFA is currently the recommended standard of care for pregnant women in many countries
- Do not recommend that MMS replace IFA as routine standard of care because of "…*some evidence of risk, and some important gaps in the evidence*" but:
- Comments "*that policymakers in* ***<u>populations with a high prevalence of nutritional deficiencies might consider the benefits of multiple micronutrient supplements on maternal health</u>*** *to outweigh the disadvantages [such as cost], and may choose to give multiple micronutrient supplements that include iron and folic acid*."



Suggested reading: WHO. 2016. "World Health Organization Recommendations on Antenatal Care for a Positive Pregnancy Experience."

VI. New evidence to support the switch from IFA to MMS in Pregnancy

Since the release of the WHO 2016 guidelines, two new systematic reviews were published comparing supplements of iron (with or without folic acid) vs. MMS :

Cochrane Review (2017 update)

Individual Patient Data (IPD) Meta-analysis (2017)

Suggested reading: Haider B. et al. 2017. Cochrane Database Syst. Rev. 4: CD004905; Smith E.R. et al. 2017. Lancet Glob. Heal. 5: e1090–e1100.

The 2017 Cochrane Review

- Included 15 studies in LMIC
- Focused on the overall effects of the available trials
- MMS resulted in a 12% reduction in LBW and a 8% reduction in SGA births, compared to IFA
- No effect on other outcomes

Overall effects of MMS vs. IFA on birth outcomes in LMIC	Cochrane Review (15 RCTs) Relative Risks (RR (95% CI))	IPD Meta-analysis (17 RCTs) Relative Risks (RR (95% CI))	
	Random effects	Random effects	Fixed effects
SGA (<10th percentile)	**0.92 (0.86-0.98)[a]**	0.94 (0.90-0.98) [b]	0.97 (0.96–0.99)[b]
LBW (<2500g)	**0.88 (0.85-0.91)**	0.86 (0.81-0.92)	0.88 (0.85–0.90)
VLBW (<2000g)	**Not Reported**	Not Reported	0.78 (0.72-0.85)
Preterm Birth (<37 weeks)	**0.96 (0.90-1.03)**	0.93 (0.97-0.98)	0.92 (0.88–0.95)
Very Preterm Birth (<34 weeks)	**Not Tested**	Not Reported	0.87 (0.79-0.95)
LGA (>90th percentile Oken)	**Not Tested**	1.04 (0.92-1.18)	1.05 (0.95–1.15)
LGA (>90th percentile INTERGROWTH)	**Not Tested**	Not Reported	1.11 (1.04-1.19)
Stillbirth	**0.97 (0.87-1.09)**	0.97 (0.85-1.11)	0.92 (0.86–0.99)
Neonatal Mortality (≤28 days)	**1.06 (0.92-1.22)**	0.99 (0.89-1.09)	0.98 (0.90–1.05)
Infant Mortality (≤365 days)	**Not Reported**	0.97 (0.88-1.06)	0.97 (0.88–1.06)

[a]SGA defined by authors of trials; [b]SGA defined by the INTERGROWTH-21 standard
MMS, multiple micronutrient supplementation; IFA iron with or without folic acid; IPD, individual participant data; RCTs, randomized controlled trials; SGA, small for gestational age; LBW, low birthweight; VLBW, very low birthweight; LGA, large for gestational age. RR in green show a significant decrease in RR.

Suggested reading: Haider B. et al. 2017. Cochrane Database Syst. Rev. 4: CD004905.

The 2017 Individual Patient Data (IPD) Meta-analysis

- Included 17 studies in LMIC (13 included in the Cochrane review)
- MMS resulted in a **reduced risk of stillbirth, very LBW (VLBW), LBW, very preterm birth, preterm birth, and SGA**, when compared with IFA
- These additional benefits (when compared with the Cochrane review) may be explained by the differences in the methodology and number of included studies.

Note: in a IPD meta-analysis, rather than extracting summary (aggregate) data from study publications, the original research data are sought directly from the researchers responsible for each study, to be re-analyzed centrally and combined in meta-analyses. This can improve the quality of data and the type of analyses that can be done, producing more reliable results. For this reason an IDP is a 'gold standard' of systematic reviews.

(https://methods.cochrane.org/ipdma/about-ipd-meta-analyses)

Overall effects of MMS vs. IFA on birth outcomes in LMIC	Cochrane Review (15 RCTs) Relative Risks (RR (95% CI))	IPD Meta-analysis (17 RCTs) Relative Risks (RR (95% CI))	
	Random effects	**Random effects**	**Fixed effects**
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Preterm Birth (<37 weeks)	0.96 (0.90-1.03)	**0.93 (0.97-0.98)**	**0.92 (0.88–0.95)**
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LGA (>90th percentile Oken)	Not Tested	**1.04 (0.92-1.18)**	**1.05 (0.95–1.15)**
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Neonatal Mortality (≤28 days)	1.06 (0.92-1.22)	**0.99 (0.89-1.09)**	**0.98 (0.90–1.05)**
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[a]SGA defined by authors of trials; [b]SGA defined by the INTERGROWTH-21 standard
MMS, multiple micronutrient supplementation; IFA iron with or without folic acid; IPD, individual participant data; RCTs, randomized controlled trials; SGA, small for gestational age; LBW, low birthweight; VLBW, very low birthweight; LGA, large for gestational age. RR in green show a significant decrease in RR and those in red a significant increase in RR.

Suggested reading: Smith E.R. et al. 2017. Lancet Glob. Heal. 5: e1090–e1100.

Subgroup analyses of the 2017 IDP Meta-analysis: some effect modifiers

26 subgroup analyses were conducted for a variety of outcomes. Results showed **larger benefits of MMS** among women who:

- Were **anemic** compared to non anemic (hemoglobin <110 g/L vs >110 g/L)
  - 19% vs 9% reduction on LBW
  - 29 % vs 7% reduction on 6-month infant mortality
- Were **underweight** compared with non-underweight (BMI <18.5 vs >18.5 kg/m^2)
  - 16% vs 6% reduction on preterm birth
- **Started supplementation earlier** compared to later initiation (<20 weeks vs >20 weeks of gestation)
  - 11% reduction vs. no change on preterm birth
- Had **higher supplement adherence** compared to lower adherence (≥95% vs <95%)
  - 12 % reduction vs 5% increase on neonatal mortality
  - 15 % reduction vs 6% increase on infant mortality
- Were **carrying a female fetus** compared to a male fetus
  - 15 % reduction vs 6% increase on neonatal mortality
  - 15 % vs 2% reduction on 6-month mortality
  - 13 % reduction vs 5% increase on infant mortality

Source: https://www.flickr.com/photos/unicefethiopia/13753414204/in/album-72157643732848944/

Suggested reading: Smith E.R. et al. 2017. Lancet Glob. Heal. 5: e1090–e1100.

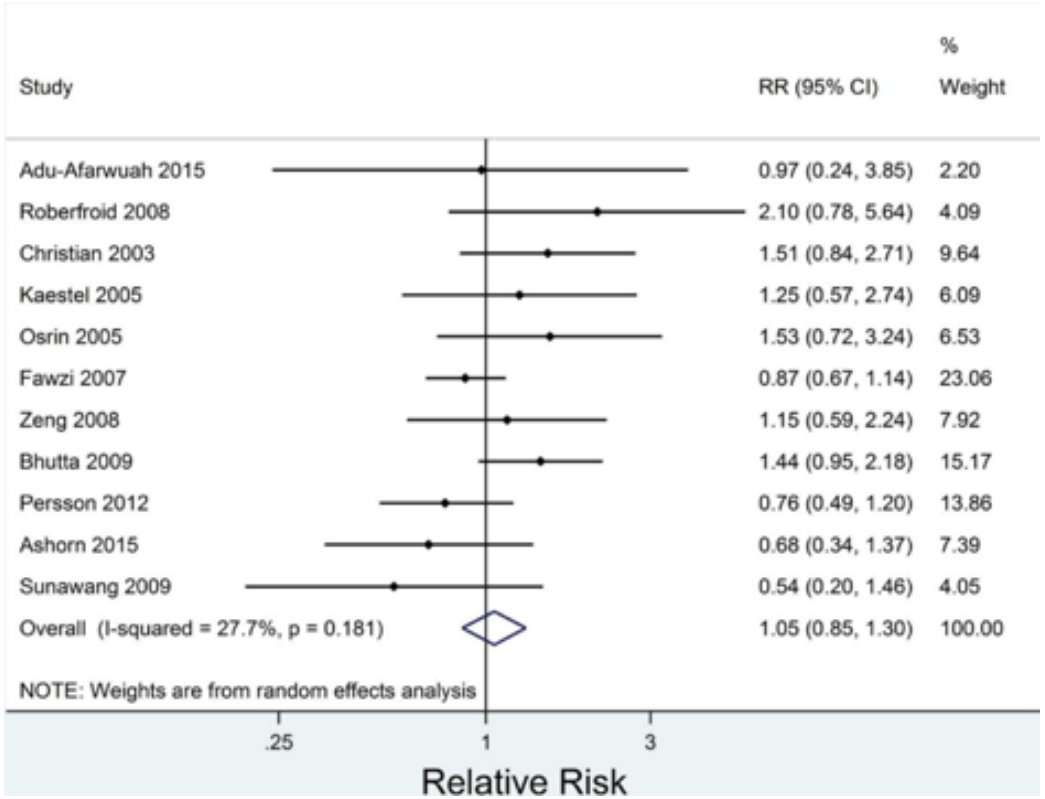
VII. The risks and concerns about antenatal MMS

Risk of Neonatal Mortality

- The WHO ANC Guidelines had raised concern about the potential risk of increased neonatal mortality in those receiving MMS, when compared to the group of IFA containing 60 mg of iron (6 trials, RR: 1.22, 95% CI 0.95-1.57).

- A recent, updated analysis of these data plus five more studies found **no increased risk of neonatal mortality associated with MMS** (11 trials, RR: 1.05, 95% CI 0.85-1.30) – figure on the right.

Forest plot for the effect of MMS vs. IFA (with 60 mg of iron and any dose of folic acid) in the control group on neonatal mortality (reproduced from Sudfeld and Smith, 2018)



Suggested reading: Bourassa M.W., et al. 2019.. Ann. N. Y. Acad. Sci. Submitted for publication;
Sudfeld C.R. & E.R. Smith. New evidence should inform WHO policy on multiple micronutrient supplementation in pregnancy. J. Nutr.

Side Effects and Adherence Data

- Both side effects and adherence to supplementation can influence the effectiveness of the intervention, but these are not consistently reported in many trials comparing MMS and IFA.

- Available data show no significant differences in side effects between IFA and MMS in 6 trials; 1 additional trial showed more vomiting in the MMS group compared to the IFA groups (MMS, 11.6%; IFA (60 mg iron), 6.9% (p = 0.002); and IFA (30 mg iron), 7.1% (p = 0.003))

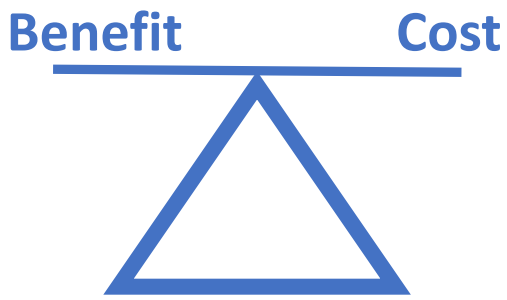
- There is no trend towards better adherence to IFA versus MMS: available data show differences on adherence rates between both groups are lower than 2%

Source: https://www.goodfreephotos.com

Suggested reading: Bourassa M.W., et al. 2019.. Ann. N. Y. Acad. Sci. Submitted for publication

Cost Effectiveness

- WHO ANC Guidelines also expressed concern about the increased cost of MMS per dose over IFA.
- A cost-effectiveness analysis of switching from IFA to MMS (single-year, complete and immediate switching) in Bangladesh, estimated that it costs:



  - an additional US$0.88 per covered pregnancy
  - $39 per case of LBW averted,
  - $85 per case of preterm birth averted,
  - $62 to $104 per case of SGA averted (INTERGROWTH-21st and Oken standards, respectively),
  - $239 per case of infant mortality averted
  - $13.3 per disability-adjusted life year (DALY) averted.

  Other interventions to improve maternal/neonatal health, e.g. pneumococcus and rotavirus vaccines and mother's groups were estimated to cost more than $100 per DALY averted

- If coverage was 100% in Bangladesh, 15,000 young lives (stillbirths and infant mortality) would be saved/year, and 30,000 cases of preterm birth would be averted, by shifting from IFA to MMS
- Cost-effectiveness of replacing IFA with MMS will be most favorable in countries with well-performing IFA distribution programs

Suggested reading: Engle-Stone R. et al. 2018. Ann. N. Y. Acad. Sci. Submitted for publication

VIII. Aspects to consider when switching from IFA to MMS in pregnancy

Formulation

- United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) is most commonly used in MMS trials with pregnant women, providing 15 vitamins and minerals, including iron and folic acid (see composition on the right).

- UNIMMAP provided with a nutrient-rich diet is unlikely to result in excessive intakes for the various nutrients. There is no risk of toxicity.

Composition of the UNIMMAP:

Vitamin A - 800 µg
Vitamin D - 200 IU
Vitamin E - 10 mg
Vitamin C - 70 mg
Vitamin B1 - 1.4 mg
Vitamin B2 - 1.4 mg
Vitamin B3 - 18 mg
Vitamin B6 - 1.9 mg
Vitamin B12 - 2.6 µg
Folic Acid - 400 µg
Iron - 30 mg
Zinc - 15 mg
Copper - 2 mg
Selenium - 65 µg
Iodine - 150 µg

Suggested readings: Bourassa M.W., et al. 2019. Ann. N. Y. Acad. Sci. Submitted for publication ;
United Nations. 1999. Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries; Gernand A.D. 2018. The upper limit – examining risk of excess micronutrient intake in pregnancy from antenatal supplements. Ann. New York Acad. Sci. York Acad. Sci. In prep; National Research Council. 1989. "Recommended Dietary Allowances: 10th Edition." Washington, DC: The National Academies Press.

Delivery of supplements

HOW

- A minimum of 180 tablets should be provided to the pregnant women, in the first antenatal care visit/contact.
- The healthcare provider should inform the pregnant women (both verbally and in writing) about the importance of MMS during pregnancy (see educational leaflet to be handed to pregnant women, which contains information about why they need to take the MMS, how they should consume the supplements, what to do in case of side effects, etc).
- The importance of a healthy and varied diet should also be stressed, based on available resources. MMS does not cover other nutritional needs such as protein, essential fatty acids, energy, calcium, antioxidant compounds, etc. which need to be obtained from the diet.

WHEN

- The earlier supplementation starts, the better and ideally before conception, given the role of folic acid in preventing neural tube defects in the first weeks of pregnancy.

Compliance and adherence to regimen

- As for all supplementation regimes, MMS is most effective when compliance (taking the pill every day throughout pregnancy) is high.
  - Results show larger benefits (on neonatal and infant mortality) of MMS among women with higher adherence to MMS regime.
- MDs and other healthcare professionals have a crucial role in **assessing and reinforcing compliance to MMS in every ANC visit/contact.**
- It is important to understand the causes for a client's poor compliance, and follow this by appropriate advice. Poor compliance may be due to:
  - lack of knowledge/awareness
  - misconceptions about possible undesirable outcomes (e.g. afraid of delivering a larger baby),
  - forgetfulness
  - side effects
- Advice might include strategies to avoid side effects (e.g. take the supplement just before going to sleep) or on how to avoid forgetting to take the supplement.

https://www.flickr.com/photos/unicefethiopia/45860398804/in/album-72157705337531074/

Coverage

- In addition to ensuring compliance, it is important to maximize the number of pregnant women who have access to and receive MMS supplements
- Unfortunately data from various LMIC countries show that IFA only reaches 10-50% of all the target population. These numbers are even lower in rural areas
- ANC visits are an important vehicle for the provision of IFA, but if attendance is low, it is necessary to identify other suitable vehicles to reach this population
- A multidisciplinary team effort is needed to reach the whole population of pregnant women. This may involve medical doctors, nurses, midwives, community health volunteers, birth attendants and other personnel involved in the antenatal care.
- Continued professional education about the importance of MMS in pregnancy is warranted

https://www.flickr.com/photos/unicefethiopia/13102277025/in/album-72157642245083673/

IX. Conclusions

- Inadequate micronutrient intakes are common in LMIC, especially among pregnant women, who have increased micronutrient requirements.
- This can lead to an increase in adverse pregnancy and birth outcomes.
- IFA is still the standard of antenatal care for pregnant women in most LMIC, but recent meta-analyses demonstrate that
  - MMS can reduce the risks of preterm birth, LBW, SGA and stillbirth in comparison to IFA alone.
  - These benefits are greater for anemic and underweight women.
- MMS does not lead to an increased risk of harm for the pregnant women or their infants
- Cost effectiveness analyses also show the long term economic and health benefits of MMS over IFA.
- In settings with inadequate micronutrient intakes, practitioners should consider supplementing pregnant women with MMS as a cost-effective method to reduce the risk of adverse birth outcomes.
- MMS should be started as early as possible in pregnancy, and compliance to MMS should be frequently monitored and reinforced.

X. Key references

- Bourassa M.W., S.J.M. Osendarp, S. Adu-Afarwuah, *et al.* 2019. Review of the Evidence Regarding the Use of Antenatal Multiple Micronutrient Supplementation in Low- and Middle-Income Countries. *Ann. New York Acad. Sci.* Submitted for publication
- Haider B., Z. Bhutta, H. Ba, *et al.* 2017. Multiple-micronutrient supplementation for women during pregnancy. *Cochrane Database Syst. Rev.* **4**: CD004905.
- Smith E.R., A.H. Shankar, L.S.-F. Wu, *et al.* 2017. Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries. *Lancet Glob. Heal.* **5**: e1090–e1100.
- World Health Organization. 2016. "*World Health Organization Recommendations on Antenatal Care for a Positive Pregnancy Experience.*
- Gernand A.D., K.J. Schulze, C.P. Stewart, *et al.* 2016. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. *Nat Rev Endoc* **12**: 274–289
- Engle-Stone R. & S.A. Vosti. Replacing Iron-Folic Acid with Multiple Micronutrient Supplements among Pregnant Women in Bangladesh and Burkina Faso: Single-year Assessment of Costs, Impacts, and Cost-Effectiveness. *Ann. New York Acad. Sci.* Submitted for publication
- Gernand A.D. 2018. The upper limit – examining risk of excess micronutrient intake in pregnancy from antenatal supplements. *Ann. New York Acad. Sci.* Submitted for publication
- *United Nations. 1999. Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries*

1.2

In-service training module for frontline health workers

Multiple micronutrient supplementation for a positive pregnancy experience

Training module/refresher course for community health workers

Multiple Micronutrient Supplementation in Pregnancy
TECHNICAL ADVISORY GROUP

Objectives

At the end of this session, you should:

- Appreciate the essential role of key micronutrients in pregnancy and the increased micronutrient needs of pregnant women
- Understand that micronutrient deficiencies are common in this population and are associated with poor pregnancy and birth outcomes
- Understand the rationale for selecting MMS over IFA and identify the different benefits provided by antenatal MMS compared to IFA
- Be able to educate and guide pregnant women about the importance of MMS during pregnancy
- Detect potential reasons for poor compliance to MMS and help the patient improve compliance

Content

I. The role of micronutrients and increased nutritional needs in pregnancy

II. Micronutrient deficiencies during pregnancy/reproductive age

III. Poor pregnancy, maternal and child outcomes in LMIC

IV. Interventions to improve micronutrient nutrition in pregnant women

V. Rationale to recommend MMS in pregnancy

VI. Risks and concerns of MMS during pregnancy

VII. Other important aspects to consider while switching from iron and folic acid supplements to MMS in Pregnancy

- Formulation
- Delivery of supplements
- Compliance

VIII. Conclusions

I. The role of **micronutrients** and increased nutritional needs in pregnancy

- Micronutrients are vitamins and minerals that we need to consume every day in small quantities.
- Every person needs enough micronutrients from their diet, but this is particularly important for pregnant women. They need additional nutrients for the healthy development of their baby and placenta.
- For example, folic acid is needed to prevent birth defects of the brain and spine; iodine is needed to prevent physical and cognitive stunting; zinc helps to prevent preterm delivery and iron reduces the risk of anemia and low birth weight.
- Micronutrients are also needed for the baby to accumulate nutrient stores in his/her body (during the second and third trimester of pregnancy), which are necessary for a healthy infancy.

*Suggested reading: Gernand A.D., et al. 2016. Nat Rev Endoc **12**: 274–289.*

Fol – folate; Cu – copper; I – iodine; Se – selenium; Zn – zinc; Fe - iron

- The requirements of some nutrients, such as folate, iodine, zinc, vitamin B6 and iron are up to 50% higher during pregnancy

- Pregnant women also need more energy, protein and other essential fatty acids, which need to be promoted through a healthy and varied diet.

- This presentation focuses on micronutrients and how we can help women consume enough vitamins and minerals for a good pregnancy and a healthy baby.

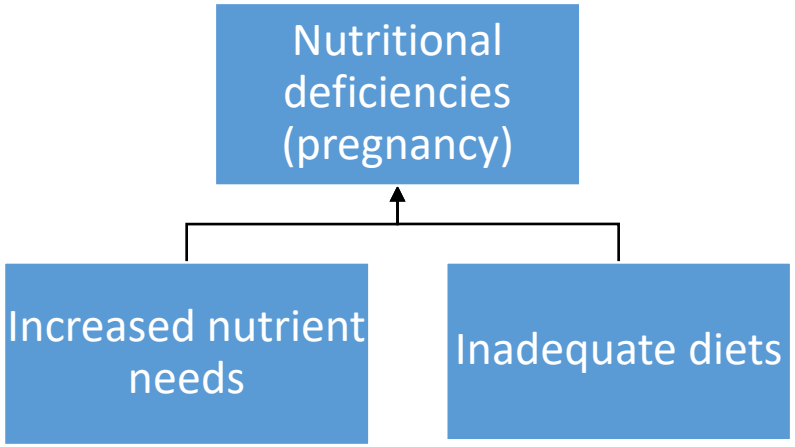
Recommended intakes for some micronutrients of a non-pregnant and pregnant women.

Nutrient	Non-pregnant and non-lactating women	Pregnant women
Vitamin A	700 µg RAE	770 µg RAE
Vitamin B6	**1.3 mg**	**1.9 mg (+46%)**
Vitamin B12	2.4 µg	2.6 µg
Folate	**400 µg DFE**	**600 µg DFE (+50%)**
Vitamin C	75 mg	85 mg
Vitamin D	600 IU	600 IU
Vitamin E	15 mg	15 mg
Copper	900 µg	1000 µg
Iodine	**150 µ**	**220 µg (+47%)**
Iron	**18 mg**	**27 mg (+50%)**
Selenium	55 µg	60 µg
Zinc	**8 mg**	**11 mg (+38%)**

Source: Institute of Medicine reports on Dietary Reference Intakes for each nutrient (http://fnic.nal.usda.gov/dietary-guidance/dietary-referenceintakes/dri-nutrient-reports)

II. Micronutrient deficiencies during pregnancy/reproductive age

The increased nutrient needs of pregnancy in addition to the inadequate diets frequent is low and middle income countries (LMIC) leave pregnant women at risk of nutritional deficiencies.



Below are the estimates of micronutrient deficiencies in women of reproductive age in LMIC:

- 16% for vitamin A
- 23% for folate
- 13% for vitamin B12
- 63% for vitamin D
- 40% for iodine
- 41% for zinc
- 31% for anemia (similarly to the prevalence of pregnant women)
- 12% for iron deficiency anemia (anemia caused by iron)

III. Poor pregnancy, maternal and child outcomes in LMIC

Poor pregnancy outcomes associated with micronutrient deficiencies during pregnancy are common in LMIC. These include:

- **Preterm birth** *(<37 weeks of gestation)*

Prematurity is the world's number one cause of death in children under 5 years of age.

- **Small for gestational age** (*birth weight < 10th percentile for a given gestational age*)

Both preterm and SGA infants have an increased risk of death.

- **Low birth weight** (birth weight <2500g)
- **Stillbirths**
- **Neonatal mortality** (< 28 days)
- **Others:** congenital anomalies, maternal and child cognitive impairment, maternal depression, etc.

IV. Interventions to improve micronutrient nutrition in pregnant women

- Food fortification is a long term measure used to tackle nutritional deficiencies in a population, and therefore do not cover the immediate needs of a pregnant women
- Nutrition education using local foods is also challenging because even optimized local diets are likely to be insufficient to meet the high nutritional requirements of pregnancy

  For example, in order to reach the recommended daily intake of **27 mg of iron** for a pregnant woman, she would need to eat:

4.5 cups of boiled lentils every day, OR

5.5 portions (3oz) of beef liver every day

When food-based solutions are not practical, supplementation can help

Sources: https://ods.od.nih.gov/factsheets/Iron-HealthProfessional/
https://www.maxpixel.net/India-Asian-Daal-Dal-Bowl-Toor-Dal-Dhal-Toor-1740205

V. Rationale to recommend MMS in pregnancy

Until recently, supplements containing only 2 micronutrients (iron and folic acid) were provided to pregnant women, in many countries.

However, recent high quality studies show that there are additional benefits of using MMS when compared to iron and folic acid supplements alone:

- **Reduced risk of stillbirth,** particularly among anemic pregnant women
- **Reduced risk of low birth weight**, particularly among anemic women
- **Reduced risk of preterm birth**, particularly among underweight women
- **Reduced risk of being born small for gestational age**, particularly among anemic pregnant women
- Reduced risk of the baby dying at 6 months in the group of anemic pregnant women

Source: https://www.flickr.com/photos/unicefethiopia/18199055126/in/photostream/

V. Rationale to recommend MMS in pregnancy (cont.)

These studies also show that the benefits of providing MMS to pregnant women are greater among women who:

- Started supplementation earlier compared to later initiation (<20 weeks vs >20 weeks of gestation)

This shows the importance of starting the MMS as early as possible.

- Had higher supplement adherence compared to lower adherence (≥95% vs <95%)

This shows the importance of taking the full recommended dose of MMS (compliance).

- Were carrying a female baby, which led to reduced risk of death in females (and no effect in males).

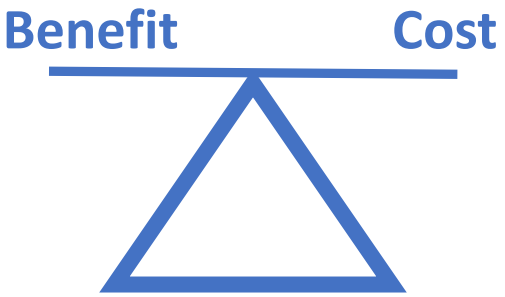
Source: https://www.flickr.com/photos/unicefethiopia/13753414204/in/album-72157643732848944/

Suggested reading: Smith E.R. et al. 2017. Lancet Glob. Heal. 5: e1090–e1100.

VI. Risks and concerns of MMS during pregnancy

Research shows that, when compared with iron and folic acid supplements, the use of MMS in pregnancy:

- does not increase the risk of neonatal mortality (infant death in the first 28 days after birth), or the risk of the baby being born too large
- has similar (small) side effects
- has a similar level of adherence (compliance)
- is highly effective in relation to its cost (i.e. is cost-effective), compared with other interventions designed to improve maternal and baby health.



VII. Other important aspects to consider when comparing IFA to MMS in Pregnancy

Formulation

- The most commonly used formulation, developed by the United Nations for pregnant women (UNIMMAP), contains 15 vitamins and minerals, including iron and folic acid (see composition on the right).

- UNIMMAP provided with a nutrient-rich diet is unlikely to result in excessive intakes for any of the micronutrients.

- If is possible that the amount of iron of the UNIMMAP (30 mg) is lower than the amount of iron from the old iron and folic acid supplement (e.g. 60 mg iron). This is no reason for concern, as it is within the recommended dose of iron for pregnant women (30-60mg) and the presence of other micronutrients (e.g. vitamin C) in the MMS increases iron absorption.

Composition of the UNIMMAP:

Vitamin A - 800 µg
Vitamin D - 200 IU
Vitamin E - 10 mg
Vitamin C - 70 mg
Vitamin B1 - 1.4 mg
Vitamin B2 - 1.4 mg
Vitamin B3 - 18 mg
Vitamin B6 - 1.9 mg
Vitamin B12 - 2.6 µg
Folic Acid - 400 µg
Iron - 30 mg
Zinc - 15 mg
Copper - 2 mg
Selenium - 65 µg
Iodine - 150 µg

Delivery of supplements

- A **minimum of 180 tablets** should be provided to the pregnant women, in the **first antenatal care visit** (in the healthcare center or at home), as she may not be able to attend other visits.
- The **earlier the supplementation starts, the better** (ideally before conception, given the role of folic acid in preventing birth defects of the brain, spine, or spinal cord in the first weeks of pregnancy)
- It is your responsibility to **inform the pregnant women about the importance of MMS during pregnancy**. You should carry educational leaflets with you that can give and explain to the women at the same time you deliver the bottle of MMS supplements. It contains relevant information, such as the reason why they need to take the MMS, how they should consume the supplements, what to do in case of side effects, etc.
- It is still important to advise pregnant women to follow a healthy and varied diet. MMS does not cover other nutritional needs of pregnancy, such as protein, essential fatty acids, energy, calcium, antioxidant compounds, etc. which need to be obtained from the diet.

Compliance

https://www.flickr.com/photos/unicefethiopia/45860398804/in/album-72157705337531074/

- Like all supplementation regimes, MMS is most effective when compliance among pregnant women is high
- You have a crucial role in assessing and reinforcing compliance to MMS in every ANC visit/contact
- **At every visit, try to understand any causes of poor compliance, and give appropriate advice.** A pregnant women may not be taking the MMS because of:
  - **lack of knowledge**

    It is your role to inform and deliver written and verbal information about why and how the MMS should be taken
  - **misconceptions about possible undesirable outcomes** (e.g. afraid of delivering a larger baby)

    You can reassure the woman that the MMS will not make the baby grow or gain weight in excess.
  - **forgetfulness**

    You can advise the woman to take the supplement at the same time everyday (to create a routine), and ask a close family member to remind her.
  - **side effects (e.g. nausea, vomiting, stomach pain)**

    If the woman complains of side effects, you can advise her to take the supplement just before going to sleep, or to take it with a meal instead of on an empty stomach; you can also assure that these side effects may be temporary and it is important to continue taking the supplements.

VIII. **Conclusions**

- Pregnant women have higher needs of micronutrients. Various nutritional deficiencies are common in this population and can lead to poor pregnancy and birth outcomes.
- Recent studies show that MMS, when compared to iron and folic acid alone, can reduce the risks of preterm birth, low birth weight, being born small for gestational age and stillbirth. These benefits are even greater for anemic and underweight women.
- A minimum of 180 tablets/pills of MMS should be delivered as early as possible in the pregnancy
- Compliance to MMS should be frequently monitored and reinforced on antenatal care visits

2.1

Job aid - Decision algorithm

Algorithm for multiple micronutrient supplementation and other nutritional interventions in pregnancy and childbearing age

Multiple Micronutrient Supplementation in Pregnancy
TECHNICAL ADVISORY GROUP

Ask and/or assess
- Pregnant?

→ **Not pregnant**

Counsel on:
- Planning for pregnancy
- Starting MMS, or folic acid supplements, before conception
- Taking MMS daily during the whole pregnancy

↓ **Pregnant**

- Assess gestation period
- First or return antenatal care (ANC) contact?

↓ **First contact**

Check and/or provide:
- ANC booklet (if applicable)
- Provide MMS, ideally full quantity (minimum of 180 tablets)
- Check hemoglobin level (ideally through full blood count testing; otherwise, by hemoglobinometer)
- Counsel as appropriate (see below)

↘ **Return contact**

Check and/or provide:
- ANC booklet (if applicable)
- Check if MMS tablets were given in the previous contact
- Ask how many MMS tablets were taken and assess reason for poor compliance
- Check hemoglobin level on gestation week 12, 26 and 36; if anemic, refer to treatment
- Counsel as appropriate (see below)

↓ ↓

Counsel on:
- MMS in pregnancy: explain the benefits, dose, frequency, duration and how to manage side effects. A leaflet that contains this information should be given to the pregnant women at the same time she receives the MMS
- Healthy eating* and physical activity**, for pregnant women to stay healthy and prevent excessive weight***
- In malnourished women: counsel on increasing energy and protein intake
- If dietary calcium is low in the local population: provide calcium supplements (1.5-2g oral elemental calcium/day)
- If caffeine intake is greater than 300mg/day: counsel on reducing caffeine intake
- In case of constipation: counsel on adequate intake of water and dietary fiber; alternatively provide wheat bran or other fiber supplements
- In case of leg cramps: may provide magnesium or calcium supplements (2-4 weeks) and advise on non-pharmacological treatment options (e.g. muscle stretching, massage, heat therapy and dorsiflexion of the foot)
- When to return next ANC contact and for more MMS (if needed), which can be written on the leaflet as a reminder

Record:
- In the ANC register all services provided, including number of MMS given

** Aims to provide adequate macro and micronutrients, obtained through the consumption of a variety of foods, including green and orange vegetables, fruits, dairy products, meat, fish, eggs, beans, nuts and wholegrains.*
*** Aims to maintain a good level of fitness throughout pregnancy through aerobic physical activity and strength-conditioning exercise*
**** The ideal weight gain during pregnancy is dependent on baseline weight (weight at the start of pregnancy):*
- If underweight (i.e. BMI < 18.5 kg/m^2): weight gain between 12.5 and 18 kg
- If normal weight (i.e. BMI 18.5–24.9 kg/m^2): weight gain between 11.5 and 16 kg
- If overweight (i.e. BMI 25–29.9 kg/m^2): weight gain between 7 and 11 kg
- If obese (i.e. BMI > 30 kg/m^2): weight gain between 5 and 9 kg

*References: WHO. 2016. "World Health Organization Recommendations on Antenatal Care for a Positive Pregnancy Experience"; Bourassa M.W., et al. 2019. Review of the Evidence Regarding the Use of Antenatal Multiple Micronutrient Supplementation in Low- and Middle-Income Countries. Ann. New York Acad. Sci. Submitted for publication; Smith E.R., et al. 2017. Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomized trials in low-income and middle-income countries. Lancet Glob. Heal. **5**: e1090–e1100.*

2.2 a)

Job aid - Leaflet for pregnant women

Did you know...

Pregnancy increases the amount of nutrients you need?

Patient ID: _____

Antenatal care schedule:

Contact 1: _____

Contact 2: _____

Contact 3: _____

Contact 4: _____

Contact 5: _____

Contact 6: _____

Contact 7: _____

Contact 8: _____

If you have any questions, contact your healthcare professional:

_____

(name)

_____

(telephone number)

Multiple Micronutrient Supplementation in Pregnancy

WHAT DO I NEED TO KNOW?

WHY DO I NEED TO TAKE THIS SUPPLEMENT?

Pregnant women have **increased nutritional** needs. For example, a pregnant woman needs 40-50% more iron, iodine, zinc and vitamin B6 than a non-pregnant woman.

Unfortunately it can be difficult to obtain the nutrients that you and your baby need through diet alone. This is why experts recommend that you take a daily supplement, called a **multiple micronutrient supplement**, that contains several vitamins and minerals.

This supplement, compared to the traditional supplement of iron and folic acid alone, **decreases** the risk of:

- The baby dying in the womb (>28 weeks) or later, through the first 6 months of life
- The baby being born very small (low birth weight)
- The baby being born too early (before 37 weeks of pregnancy)

This supplement also helps you feel less tired and have more energy throughout the pregnancy.

WHEN SHOULD I START THIS SUPPLEMENT?

You should start to take this supplement ideally **before conception** (the beginning of your pregnancy); if not possible, start **as soon as possible after conception**. You should take it **every day**, until the end of your pregnancy.

If you **do not** take this supplement every day, it may not have the benefits that are expected.

As a pregnant mother, you can take action to improve the chances of having a healthy pregnancy and baby!

HOW SHOULD I TAKE THIS SUPPLEMENT?

It is important to **establish a routine** (e.g. take it at the same time every day) to avoid forgetting your daily supplement. For example, you can leave the supplement on the bedside and take it just before going to bed, or associated with a meal (e.g. at dinner). However, it is better to take it with a glass of water or fruit juice, instead of milk.

WHAT IF I FORGET?

If you forget to take this supplement, do not take the missing dose(s). Take the supplement **as soon as you remember**, and continue to take one pill per day.

WHAT IF I FEEL SICK?

This supplement does **not** lead to more side effects (such as nausea, vomiting or diarrhea) than the traditional supplement of iron and folic acid. If you feel any side effects, try taking the supplement before you go to bed and lay down. You could also try to **take it with a meal**, rather than on an empty stomach.

2.2 b)

Job aid - Leaflet for pregnant women (simplified)

Patient ID: _____

Did you know...

Pregnancy increases the amount of nutrients you need?

Antenatal care schedule:

Contact 1: _____

Contact 2: _____

Contact 3: _____

Contact 4: _____

Contact 5: _____

Contact 6: _____

Contact 7: _____

Contact 8: _____

Multiple Micronutrient Supplementation in Pregnancy

WHAT DO I NEED TO KNOW?

If you have any questions, contact:

_____

_____

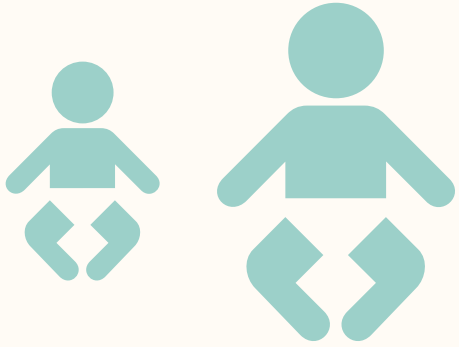
WHAT?

This is a pill with several essential vitamins and minerals

WHY?

1. For a healthy mom and healthy baby
2. Prevents the baby from:

- Dying in the womb
- Being born too small
- Being born too early



WHEN?

- As early as possible, before getting pregnant
- Everyday until the end of pregnancy

40 weeks

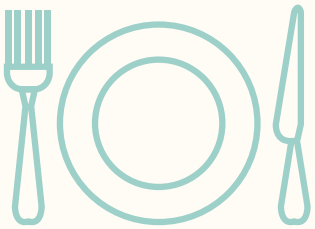
As a pregnant mother, you can take action to have a healthy pregnancy and baby!

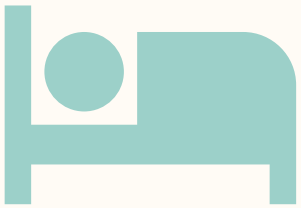
HOW?

- At the same time everyday
- Take with water or juice

SIDE EFFECTS

In case of nausea or vomiting, take it with a meal or before sleeping





2.3

Counselling cards flip chart

Multiple Micronutrient Supplementation in Pregnancy
TECHNICAL ADVISORY GROUP

The importance of multiple micronutrient supplementation during pregnancy:

Counselling cards

Source: https://www.flickr.com/photos/unicefethiopia/28560538057/in/album-72157697469939431/

How to use this flip chart of counselling cards

This flip chart of counselling cards is designed to help healthcare providers or community health workers (educators) to communicate effectively about the importance of MMS in pregnancy to the pregnant mothers. There are 6 cards covering the key messages:

1. The role of micronutrients in pregnancy and the increased micronutrient needs of pregnant women
2. Micronutrient deficiencies lead to poor pregnancy and birth outcomes
3. The benefits of multiple micronutrient supplements (MMS) during pregnancy
4. Dose, frequency and duration of MMS during pregnancy
5. Side effects of MMS and management
6. Importance of healthy eating in pregnancy

- Individual counselling of mothers on MMS is critical for improving compliance, although these counselling cards can be used both for individual or group counselling.
- Each card starts with a picture or illustration, which is intended to be viewed by the pregnant women, followed by a page with text to be viewed by the educator. While showing the picture/illustration to the pregnant woman, the educator should raise the first question “what do you see in the picture?”; this initiates a discussion where the other questions should be raised and, building on what the pregnant woman knows, the key messages should be covered. Before moving to a new card, the educator should review the key points discussed to ensure the woman has understood the messages correctly.
- The educator can select the appropriate card to use in a given counselling session (depending on whether it is a first or return antenatal care contact, or whether there are other education topics to cover).
- It is important to maintain eye contact with the pregnant women during counselling.

1. The role of micronutrients in pregnancy and the increased micronutrient needs of pregnant women

Ask:

- What do you see in the picture?
- Does the pregnant woman need more nutrients?
- Which nutrients? And for what?

Messages:

- The picture shows a developing baby (fetus), the umbilical cord and placenta
- A pregnant woman needs more nutrients for the healthy development of the baby and the placenta, such as energy, protein (from eggs, meat, milk), essential fats (from fish), and several vitamins and minerals.
- Examples of the roles of vitamins and minerals in pregnancy:
    - Folic acid is needed for the development of the brain and the spinal cord of the baby;
    - Vitamin D and calcium are needed for the growth of baby's bones;
    - Vitamin A are needed for healthy eyes of the baby and mother;
    - Iron and vitamin B12 are needed to make extra blood cells (and prevent anemia);
    - Iodine is needed for brain development
- The baby also accumulates nutrient stores in his/her body (during the second and third trimester of pregnancy), which are necessary for a healthy infancy

2. Micronutrient deficiencies lead to poor pregnancy and birth outcomes

Source: http://womensandinfantshealth.ca/conditions/intrauterine-growth-restriction-iugr-2/

Ask:

- What do you see in the picture?
- What other pregnancy problems can be caused by the lack of nutrients?

Messages:

- The picture shows a baby that was born with normal weight (on the right) and a baby that was born too small for his age (on the left)
- If the pregnant woman does not consume enough nutrients, the baby is more likely to:
    - Be born too early (premature, i.e. before 37 weeks of pregnancy) – this is one world's number one cause of death in children under 5 years of age.
    - Be born very small (low birth weight)
    - Die in the womb (stillbirth)
    - Die in the first month after birth
    - Be born with severe abnormalities, such as defects of the brain and spinal cord

3. The benefits of multiple micronutrient supplements (MMS) during pregnancy

Source: https://www.k4health.org/sites/default/files/hcp_ifas_counselling_guide_national_kenya_0.pdf

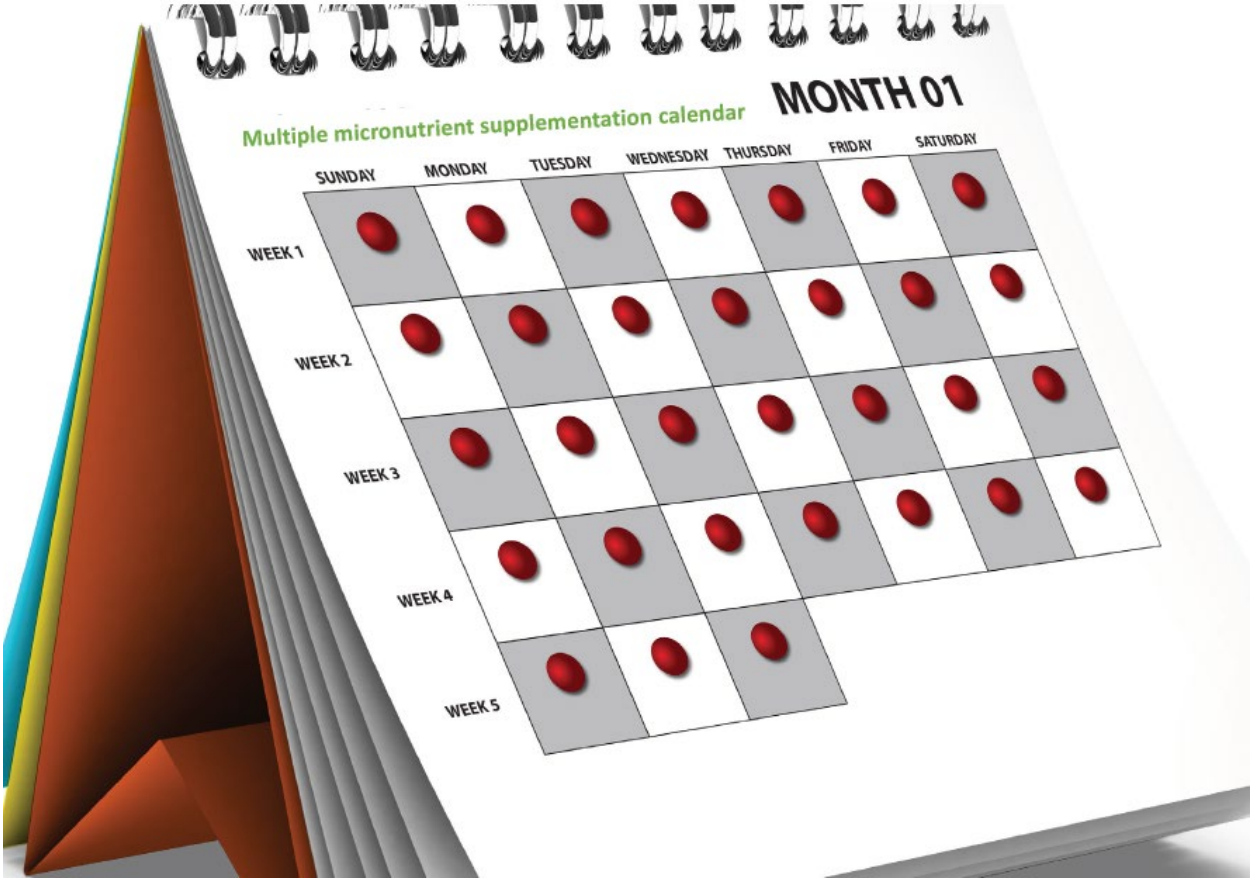
Ask:

- What do you see in the picture?
- If it is a first contact: have you ever taken MMS?
- If it is a return contact: are you currently taking MMS?
- Why do you need to take MMS?

Messages:

- The picture shows a happy mother holding her healthy baby
- The high nutrient needs of pregnancy and your developing baby are difficult to meet through diet alone; you need to take one supplement with several vitamins and minerals to meet these increased needs (it does not matter if you have anemia or not)
- This supplement reduces the risk of the baby dying in the womb or later (through the first 6 months of life) and the risk of having a baby born too small or too early; it also helps you feel less tired and have more energy throughout the pregnancy
- Taking a MMS is a simple measure to improve the chances of having a healthy pregnancy and baby

4. Dose, frequency and duration of MMS during pregnancy



Source (modified):
https://www.k4health.org/sites/default/files/hcp_ifas_counselling_guide_national_kenya_0.pdf

Ask:

- What do you see in the picture?
- If it is a return contact: are you taking MMS every day?
- When should you start taking this supplement? For how long?

Messages:

- This picture shows a calendar and the need to take one pill of these MMS every single day
- Each pill contains 15 vitamins and minerals that you and your baby need every day; if you don't take it every day, it may not have the expected benefits
- Take the supplement at the same time every day (to create a routine and avoid forgetting it); ask a close family member to remind you
- The earlier you start this supplement, the better. Ideally you should start it before getting pregnant, because folic acid (one the vitamins in this supplement) prevents birth defects of the brain or spinal cord in the first weeks of pregnancy; if not possible, start it as soon as possible during your pregnancy
- You should take this supplement at least until the end of your pregnancy
- If you run out of supplements, call your healthcare professional or community health worker to ask for additional supplements

Additional information:

If this is a return visit and the pregnant women states she is not taking the MMS every day, explore the causes (e.g. lack of knowledge, misconceptions about possible undesirable outcomes, forgetfulness and side effects) and give appropriate advice.

5. Side effects of MMS and management

Source (modified):
https://www.k4health.org/sites/default/files/hcp_ifas_counselling_guide_national_kenya_0.pdf

Ask:

- What do you see in the picture?
- If it is a return contact: have you ever experienced side effects of this supplement? How have you managed them?

Messages:

- The picture shows a pregnant woman and a healthcare professional discussing the possible side effects of taking MMS and how to manage them
- If you feel any side effect while taking this supplement (such as nausea, vomiting, stomach pain), you should try take the supplement just before going to sleep, or to take it with a meal instead of on an empty stomach
- These side effects may be temporary and it is important to continue taking the supplement
- MMS will not make the baby grow too much or gain weight in excess.

6. Importance of healthy eating in pregnancy

Source: https://www.k4health.org/sites/default/files/hcp_ifas_counselling_guide_national_kenya_0.pdf

Ask:

- What do you see in the picture?
- What foods should you eat during your pregnancy?
- How much weight should you gain during pregnancy?
- Is coffee or caffeinated drinks safe during pregnancy?

Messages:

- This image shows a variety of foods that pregnant women should eat to consume enough energy, protein, vitamins and minerals
- It is important to have a healthy diet with a variety of foods, including green and orange vegetables, fruit, meat, fish, beans, lentils, nuts, whole grains and milk products
- For a pregnant woman with a normal weight, she should gain between 11.5-16Kg during the whole pregnancy; underweight women should gain more weight, and should aim to eat more energy and protein
- A small amount of coffee or caffeinated drinks (1-2 small cups/day) is safe
- If you have leg cramps during pregnancy, some supplements of magnesium and calcium may help to prevent these cramps: speak with your healthcare professional

2.4

Posters to display at point of care

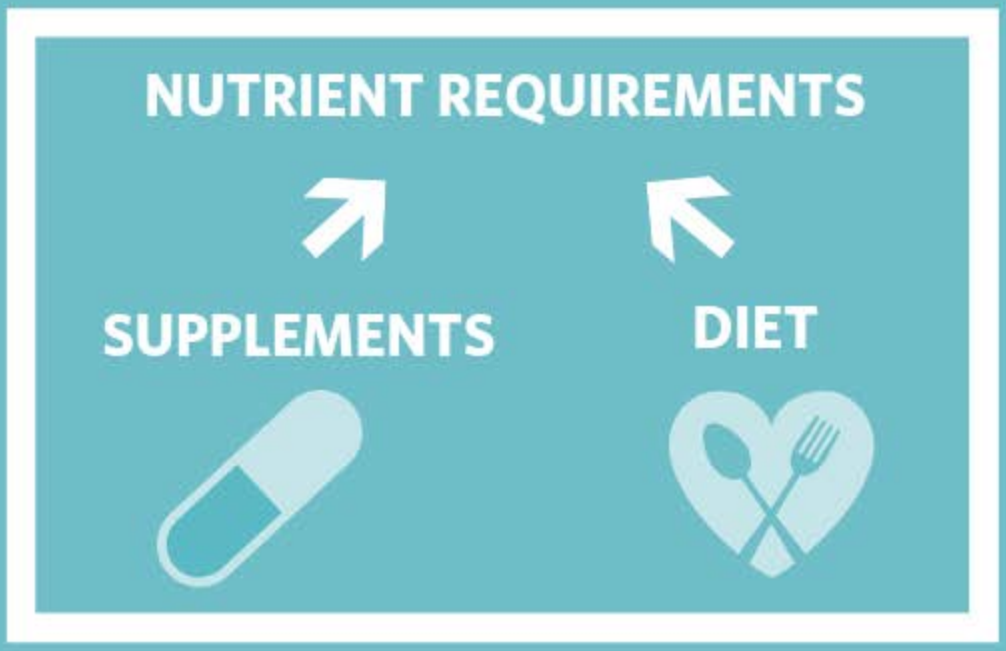
MULTIPLE MICRONUTRIENT SUPPLEMENTS

- A pill with several essential vitamins and minerals
- Contribute for a healthy pregnancy and healthy baby
- To be taken everyday until the end of your pregnancy

If you know you are pregnant or planning to get pregnant, ask your doctor to provide you these supplements.

MULTIPLE MICRONUTRIENT SUPPLEMENTS

A solution to meet the high nutrient requirements of pregnancy



REMEMBER:

- To distribute the micronutrient supplements the first time you see a pregnant woman (clinic/ home), regardless of hemoglobin status
- Assess and encourage full compliance during every antenatal care visit

To learn more go to:
www.nyas.org/MMS