Multiple micronutrient supplements in pregnancy:
Technical Reference Material I

The Benefits of Multiple Micronutrient Supplements in Pregnancy Technical Brief for Policy Makers: Bangladesh

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Multiple Micronutrient Supplementation in Pregnancy
TECHNICAL ADVISORY GROUP

This **Technical Brief for Policy Makers** describes the potential benefits of multiple micronutrient supplementation (MMS) during pregnancy compared to iron and folic acid supplementation (IFA), and provides a rationale for transitioning from MMS to IFA in low and middle income countries (LMIC) that see a high prevalence of micronutrient deficiencies in pregnant women and women of reproductive age (WRA), and/or poor pregnancy outcomes. Data from Bangladesh is used for illustrative purposes, but the document can be adapted to other LMICs, assuming the data exists at the national level to complete the information needs of this analysis.

Policy makers and operational managers may also want to consult a separate document which contains a set of Frequently Asked Questions (FAQ) to address often raised concerns about the switch from IFA to MMS.

The document is structured as follows:

- Overview
- The importance of micronutrients in pregnancy
- Maternal micronutrient status and pregnancy outcomes in Bangladesh
- Global evidence of the benefit of multiple micronutrient supplementation for improvement of pregnancy outcomes
- Cost effectiveness analysis for Bangladesh to switch from IFA to MMS
- Operationalizing the WHO Guidelines in Bangladesh
- Barriers to successful implementation of MMS
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The Benefits of Multiple Micronutrient Supplements in Pregnancy

Technical Brief for Policy Makers: Bangladesh

Overview

Adequate nutrition is necessary throughout the life-cycle but is especially important during pregnancy to ensure positive outcomes for both the mother and her infant. In particular, micronutrients (vitamins and minerals) are essential to placental and fetal development stages throughout gestation, in addition to maintaining maternal health. Recent meta-analyses have demonstrated that multiple micronutrient supplementation (MMS), containing 13–15 different micronutrients (including iron and folic acid)*, can reduce the risk of several adverse pregnancy outcomes in addition to iron-folic acid alone. In this document, the importance of micronutrients in pregnancy and the potential benefits of MMS for pregnant women are examined, based on available data on micronutrient status and pregnancy outcomes for Bangladesh.

The importance of micronutrients in pregnancy

Many micronutrients are critical during pregnancy, especially vitamins A, B6, B9 (folic acid), B12, C, D, E, and the minerals iron, zinc, iodine, copper, and selenium[1]. Recommended intakes increase for most of these nutrients by as much as 50%[1] during pregnancy to accommodate higher maternal, placental, and fetal requirements. For example, while women of reproductive age (WRA) need 18 mg of iron/day, pregnant women need 27 mg of iron/day; similarly, the daily requirements for zinc increase from 8 mg to 11 mg and the daily requirements for iodine increase from 150 µg to 220 µg, respectively[1].

Unfortunately, micronutrient deficiencies in pregnancy remain widespread globally, particularly in LMIC as a result of women entering pregnancy malnourished combined with the increased nutritional demands of pregnancy. Consequently, micronutrient deficiencies in pregnancy are associated with adverse birth outcomes such as pregnancy loss, birth defects, and low birth weight (LBW) and may influence long-term outcomes for the offspring, such as cognition and cardiometabolic risk[1]. For example, it is known that folate during the periconceptional period prevents neural tube defects (brain and spinal cord abnormalities), iodine in pregnancy prevents physical and cognitive stunting (impaired development), and zinc prevents preterm delivery[1].

Maternal micronutrient status and pregnancy outcomes in Bangladesh

Globally, it is estimated that 19.2% of pregnant women in LMIC suffer from iron deficiency anemia (IDA), 15.3% have vitamin A deficiency, 28.5% have iodine deficiency, and 17.3% are at risk of zinc deficiency[2].

Looking specifically at Bangladesh, almost a fifth (18.2%) of mothers of children aged 0-5y and pregnant women suffer from acute malnutrition: 11.9% in urban areas; 19.9% in rural areas[3]. Data from the National Micronutrients Status Survey 2011-12[4,5] indicate that women of reproductive age (WRA) (15–49y, non-lactating and non-pregnant) also suffer from a variety of micronutrient deficiencies and have sub-optimal intakes of various micronutrients, as shown in the Table 1.

Table 1 – Deficiencies and average daily intake of micronutrients among Bangladeshi women of reproductive age (15–49y)[4,5]

Micronutrient	Area	Intake (median)	Daily needs (RDA*)	Blood analysis: % with deficiency
Vitamin A	Total	372 RE**	700 RE**	**5.4**
	Urban	316 RE**		5.4
	Rural	467 RE**		4.9
	Slum	413 RE**		6.9
Vitamin B9 (folate)	Total	N.A.		**9.1**
	Urban	N.A.		8.6
	Rural	N.A.		11.4
	Slum	N.A.		7.9
Vitamin B12	Total	2.1 mcg	2.4 mcg	**6.1**
	Urban	2.0 mcg		5.7
	Rural	2.4 mcg		7.5
	Slum	2.1 mcg		6.5
Vitamin D	Total	N.A.		**71.5**
	Urban	N.A.		N.A.
	Rural	N.A.		N.A.
	Slum	N.A.		N.A.
Iodine	Total	N.A.		**42.1**
	Urban	N.A.		44.7
	Rural	N.A.		33.3
	Slum	N.A.		33.5
Zinc	Total	N.A.	8 mg	**57.3**
	Urban	4.9 mg		57.5
	Rural	4.5 mg		54.5
	Slum	3.6 mg		66.4
Iron	Total	6.64 mg	15-18 mg	**7.1**
	Urban	6.42 mg		6.7
	Rural	7.27 mg		8.7
	Slum	6.68 mg		7.4

*N.A. = Not Available; *RDA = Recommended Dietary Allowance; ** Retinol Equivalents*

The same survey shows that more than one in four (26%) WRA have anemia, with the women from rural areas (27.4%) more affected than the women living in urban areas (21.4%)[4]. Among pregnant Bangladeshi women, this prevalence increases to 35%[6].

Bangladesh also has a high burden of poor pregnancy outcomes, namely stillbirths, neonatal mortality (<28 days), infant mortality (<365 days), LBW (<2500 g at birth), SGA births (birth weight below the 10th percentile for infants of the same gestational age), and preterm births (gestational age at birth <37 weeks). The estimated prevalence of these outcomes are represented in the Table 2[7]. Data stratified by urban and rural areas shows that rural populations, which represent the majority of the total Bangladeshi population and register the highest number of annual births, also have the higher prevalence of adverse pregnancy outcomes, including maternal anemia, maternal underweight, neonatal mortality and infant mortality. One in every four infants is born with LBW, which is a strong indicator of a newborn's chances for survival, growth, long term health and psychosocial development.

Table 2 – Population size, annual births, and pregnancy outcomes in Bangladesh (adapted from Engle-Stone et al, 2018[7])

Outcome	**Urban areas**	**Rural areas**
Demographic characteristics		
Total population, n	66,217,830	99,776,312
Total annual births, n	1,101,038	1,898,474
Pregnancy outcomes		
Maternal anemia, %	31.4%	43.2%
Maternal underweight, %	16%	28%
Stillbirth rate, deaths per 1000 live births	4.78	21.17
Early neonatal mortality rate, deaths per 1000 live births	10.87	21.76
Neonatal mortality rate, deaths per 1000 live births	12.94	25.91
Infant mortality rate, deaths per 1000 live births	24.5	34.4
Low birth weight*, %	20.93%	21.66%
Preterm** and SGA*** births, %	2.57%	2.68%
Term and SGA births, %	30.15%	31.46%

**Low birth weight: weight <2500 g at birth*
***Preterm: gestational age at birth <37 weeks*
****SGA (small for gestational age): smaller than normal for the baby's gender and gestational age, usually defined by weight below the 10th percentile for infants of the same gestational age.*

Global evidence of the benefit of MMS for improvement of pregnancy outcomes

Two recent systematic reviews have found that MMS reduces the risk of adverse birth outcomes. A 2017 Cochrane review examined trials that compared iron and folic acid (IFA) supplementation alone and MMS supplementation, which includes IFA, during pregnancy. The reviews found that MMS reduces the risk of LBW and SGA by 12% and 8%, respectively[8]. In a 2017 individual participant data meta-analysis, data from 17 trials were reanalyzed which confirmed the outcomes of the Cochrane review and found additional positive effects of MMS on the reduction of risks of stillbirths, infant mortality and preterm births[9]. These additional benefits of MMS were even greater among female infants, anemic women, and underweight women, as detailed in Box 1. One of the clinical trials included in this review, conducted in rural Bangladesh, included 44,567 pregnant woman who were provided with MMS or IFA from early pregnancy to 12 weeks post-partum. In the group of Bangladeshi mothers who received MMS, there was a 11% reduction in stillbirths, 15% fewer preterm births and 12% fewer LBW, when compared to the group of mothers who received IFA.[10]

Box 1 – Benefits of multiple micronutrient supplementation (MMS), compared to supplementation of iron and folic acid (IFA) alone:

- Reduced risk of stillbirth
  - by 8% in the overall population of pregnant women
  - by 21% in the group of anemic pregnant women
- Reduced risk of infant 6-month mortality
  - by 29% in the group of anemic pregnant women
  - by 15% in female infants
- Reduced risk of low birth weight (<2500g)
  - by 12% in the overall population of pregnant women
  - by 19% in the group of anemic pregnant women
- Reduced risk of preterm (<37 weeks)
  - by 8% in the overall population of pregnant women
  - by 16% in the group of underweight women
- Reduced risk of being born small-for-gestational age
  - by 3% in the overall population of pregnant women
  - by 8% in the group of anemic pregnant women

Reference: Smith ER, Shankar AH, Wu LS-F, et al. 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. 2017;5(11):e1090-e1100.
Note: one of the 17 trials included in this meta-analysis was conducted in Bangladesh (n= 44,567 pregnant women).

Cost effectiveness analysis for Bangladesh to switch from IFA to MMS

One concern cited by the WHO about the use of MMS is the increased cost per dose over IFA. However, overall estimates of the increased cost vary. For example, the WHO estimates that cost per pregnancy per woman will be $3 for MMS vs. $1 for IFA[11]. UNICEF estimates the cost to be just $1.90 vs. $0.94 per woman, per pregnancy, for MMS and IFA respectively (A. Fleet, personal communication, April 18, 2018). While some of the increased cost is attributable to the price of additional raw materials, an increase in demand for MMS is expected to reduce the cost difference between IFA and MMS. Additionally, a Cost Effectiveness Analysis commissioned by the Sackler Institute for Nutrition Science performed in Bangladesh revealed that while the cost of the supplement itself is indeed higher for a single MMS tablet compared to an IFA one, the *total cost* of the program is only marginally higher[12]. This is because the portion of cost attributable to the product itself is only a fraction of the total program cost. The estimates projected for Bangladesh show that replacing IFA with MMS (assuming a dose of 180 tablets, costing an additional ~US$0.88 per covered pregnancy) would cost approximately $39 per case of LBW averted, $85 per case of preterm birth averted, $62 to $104 per case of SGA averted (depending on the used child growth standards), and $239 per case of infant mortality averted (with the current coverage scenario of 50%)[12]. If coverage was 100% (i.e. all pregnant women were treated with a regimen of 180 tables consumed over their pregnancies), shifting from IFA to MMS would save approximately 15,000 young lives (stillbirths and infant mortality) in one year in Bangladesh, and approximately 30,000 cases of preterm birth would be averted[12].

Operationalizing the WHO Guidelines in Bangladesh

The current World Health Organization (WHO) antenatal care (ANC) guidelines recommend the use of IFA supplementation during pregnancy, suggesting a daily oral dose of 30-60mg of iron and 0.4mg of folic acid[13]. Bangladesh currently uses IFA supplementation during pregnancy (60mg iron and 0.4mg folic acid[14]) as part of the antenatal care provided in this country.

Importantly, however, the WHO ANC guidelines also states that "policy-makers in populations with a high prevalence of nutritional deficiencies might consider the benefits of MMS on maternal health". The fact that the WHO ANC guidelines do not contain a general recommendation for the use of MMS in pregnancy is due in part to concern for the *non-significant* evidence (at the time of the WHO guideline development) of potential harm—in terms of increased infant mortality with MMS; but a recent reanalysis of the evidence demonstrated that MMS in pregnancy did not significantly increase the risk of infant mortality (or stillbirth or neonatal or 6-month mortality), in neither the overall group nor in any of the 26 subgroups[9, 2].

Bangladesh has an estimated 3 million livebirths per year, with a significant percentage of adverse pregnancy outcomes: about 14% of preterm births, more than 20% of LBW, and more than a third are born SGA[15]. This, in conjunction with the high prevalence of micronutrient deficiencies in the WRA in this country, including a high prevalence of anemic and underweight women, suggest that Bangladeshi pregnant women and their infants would benefit more from the use of MMS than IFA. Bangladesh should therefore consider switching from IFA supplementation to MMS in pregnant women, which would be supported by the exception provided for MMS in the WHO ANC guidelines.

Barriers to successful implementation of MMS

Like all supplementation regimes, MMS is most effective when coverage and adherence among pregnant women are high. Unfortunately, data from the Bangladesh Household Food Security and Nutrition Assessment (2009)[3] suggest that only half the women (50.3%) received iron and folic acid supplementation during their pregnancy , with a lower percentage in the rural areas (47.4%) than in the urban areas (60.7%). This could be partially explained by the lower attendance to ANC visits (an important vehicle for the provision of supplements), given that 40% of pregnant women in Bangladesh did not have one ANC visit, in 2011[16]. Additionally, from those women who had at least one ANC visit, a quarter did not receive or purchase any IFA supplements. This could reflect inadequate supply, inadequate provider knowledge and/or inadequate provider practices. For the women who are provided with IFA, it is not known how many take it through the recommended period of 180 days[16]. Therefore, the benefits of switching to MMS may not achieve their full potential unless modifications are made to improve the distribution, supply chain, education and compliance of supplementation.

Summary

Recent scientific evidence supports the use of supplements containing multiple micronutrients (including IFA) during pregnancy in low and middle income countries, where nutritional deficiencies are common[9]. Given the high prevalence of multiple micronutrient deficiencies in Bangladesh, particularly among pregnant women, the use of MMS should be considered a cost-effective intervention to improve their micronutrient status and reduce the risk of adverse pregnancy outcomes. Particular attention should be given to the rural areas, where the pregnancy outcomes are worse and coverage by ANC supplements is lower.

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