Views Perspectives in Nutrition Science

Evidence of Multiple Micronutrient Supplementation (MMS) in Pregnancy

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Key messages

- Maternal multiple micronutrient (MM) deficiencies are common in many resource-poor settings, and although routine iron supplementation is recommended, prenatal MM supplement use is uncommon.
- Evidence gathered over the past decade or so indicates that a one-a-day MM supplement enhances birth outcomes, including improvement in birth weight and reduction in low birth weight and preterm birth, although not survival.
- New guidelines for recommending prenatal MM supplementation should be urgently considered, followed by planning of policies and program implementation in LMIC.

Background and history

There is sufficient evidence that micronutrient deficiencies are common, co-exist, are exacerbated during pregnancy, and are likely to influence maternal, fetal, and newborn health. Inadequate and poor-quality diets, cultural food beliefs, limited access and seasonal availability, gender bias, and illness all contribute to the chronic deficiency experienced by women of reproductive age in low and middle income countries (LMIC), where adverse birth outcomes – including high rates of fetal growth restriction, preterm birth, and neonatal and infant mortality – continue to be high.

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In the past, attention in these settings has been focused on adequate food (balanced energy-protein) supplementation and iron-folic acid use during pregnancy. Multiple micronutrient supplementation (MMS) as a strategy to enhance birth outcomes only began to receive attention recently. In contrast to this, in many high income countries, prenatal multivitamin-mineral supplement use is common and recommended, although not universal. Currently, as it has done in the past, the WHO recommends daily iron and folic acid supplement use as part of antenatal care for reducing the risk of low birth weight and maternal anemia and iron deficiency.[1]

In 1998, UNICEF/WHO and the UN University convened a technical meeting to discuss, and propose a formulation for, a prenatal micronutrient supplement intended for widespread use in developing countries.[2] The supplement was designed and called UNIMMAP (United Nations Multiple Micronutrient

Birth measurement in the JiVitA-3 trial, Bangladesh

Antenatal Preparation): it contained 15 micronutrients at dosages that approximated the recommended dietary allowances (RDA) for pregnancy (Table 1). The use of this supplement took place in subsequent research undertaken to substantiate its efficacy and safety, in part guided by WHO/UNICEF, who coordinated several studies. Daily prenatal supplementation was examined for its ability to enhance fetal growth and increase birth weight in various regions of the world. Several investigators also tested micronutrient supplements with formulations similar to, but not identical to, the UNIMMAP. Thus in the past decade and more, an impressive number of randomized controlled trials have been completed providing evidence of the impact of daily MMS during pregnancy on birth outcomes in diverse LMIC settings. Numerous systematic reviews, along with pooled and meta-analyses, have also been undertaken recently to evaluate the effects of "multiple" micronutrients, although supplements have contained anything from 8 to 29 different vitamins and minerals. This article aims to provide a summary of the findings of these trials and the current state of knowledge regarding evidence for an impact of this intervention strategy on pregnancy outcomes and implications for policy and programs for LMIC.

Efficacy trials of MMS: Study design and outcomes

Randomized controlled trials of antenatal multiple micronutrient supplementation (MMS) were conducted in most settings, using iron-folic acid as the control, although some included a placebo with iron-folic acid being provided to all pregnant women as a service. The MM supplement also contained the same amount of iron as found in the controls (30 mg) in most cases, although not all (Table 2). In some instances, the recommended 60 mg of iron was compared against 30 mg found in the UNIMMAP supplement, while in two instances the MM supplement was modified to contain the higher amount of iron to match the control. All except one trial did not include food supplementation, in which the MMS effect was compared within categories

TABLE 1: The UNIMMAP formulation

	IOM RDAs for Pregnancy|Lactation	UNIMMAP Formulation
Vitamin A (µg RE)	750/770	800
Vitamin D (µg)	5 (200 IU)	5
Vitamin E (mg)	15	10
Folic Acid (µg DFE)	600	400
Thiamin (mg)	1.4	1.4
Riboflavin (mg)	1.4	1.4
Niacin (mg)	18	18
Vitamin B_{12} (µg)	2.6	2.6
Vitamin B_6 (mg)	1.9	1.9
Vitamin C (mg)	80/85	70
Iron (mg)	27	30
Zinc (mg)	12/11	15
Iodine (µg)	220	150
Copper (µg)	1000	2000
Selenium (µg)	60	65

IOM: Institute of Medicine
RDA: Recommended Dietary Allowances
RE: Retinol Equivalents
DFE: Dietary Folate Equivalents

of early or late food supplementation.[19] In one trial, vitamin A was included in the control group receiving iron-folic acid.[4] The primary outcomes examined in the studies included birth weight, and other dimensions of birth size, rates of low birth weight, preterm birth, small-for-gestational-age, stillbirth, and neonatal mortality. Some studies followed infants through the first year of life or into childhood. Maternal anemia was an outcome in a majority of trials. Except for two trials, the majority of trials were not powered to find differences in neonatal or infant mortality as an outcome, but were designed to show significant effects on birth weight and reduction in the prevalence of low birth weight. Heterogeneity was high with respect to prevalence of low birth weight and levels of maternal undernutrition (low BMI and height) in populations, and beyond one trial in Nepal,[20] few examined prevalence of multiple micronutrient deficiencies during pregnancy.

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Summary of findings: Update

Since the last meta-analysis,[21] which included 16 trials, and the Cochrane systematic review, which included 21 trials,[22] a large MMS trial was completed in Bangladesh examining impact on infant mortality.[16] Another trial in China was also completed,[10] and provides additional data, although prevalence of low birth weight in this study was low. An update of the Cochrane systematic review is currently under way. However, we conducted a meta-analysis to include the new studies to the previous group of trials, which were all designed to test prenatal MMS of the UNIMMAP or a similar formulation. We excluded three trials originally that were previously included in the meta-analysis conducted by Ramakrishnan et al:[21] one that was done among HIV-infected mothers, one small clinic-based trial among undernourished women that contained an unusual supplement with 29 vitamins/minerals, and one small trial conducted in France. All three trials were deemed inappropriate for inclusion for the stated reasons. Thus in a total of 15 trials, we examined continuous outcomes of birth weight and gestational age, and dichotomous outcomes of low birth weight, preterm birth, small-for-gestational-age (SGA), stillbirth, and neonatal mortality (**Table 2**). Reported outcomes varied by study. We used either fixed or random effects models to generate effect size estimates depending on significant heterogeneity and I^2 of > 50%. Meta-analyses results and estimates

TABLE 2: Details of studies included in the meta-analysis

Country	Intervention	Control	Sample Size	Study | Reference
Pakistan	UNIMMAP (30 mg iron)	Iron (60 mg)-folic acid	2,378	Bhutta et al 2009 [3]
Nepal	MM (60 mg iron)	Iron (60 mg)-folic acid and vitamin A	1,340	Christian et al 2003 [4,5]
Bangladesh	UNIMMAP (30 mg iron)	Iron (30 mg)-folic acid	705	Eneroth et al 2010 [6]
Tanzania*	MM (no iron)	Placebo	7,866	Fawzi et al 2007 [7]
Zimbabwe*	MM (no iron)	Placebo	1,106	Friis et al 2004 [8]
Guinea-Bissau	MM (30 mg iron)	Iron (60 mg)-folic acid	740	Kaestel et al 2005 [9]
China	MM (30 mg iron)	Iron (60 mg)-folic acid	11,835	Liu et al 2013 [10]
Nepal	UNIMMAP (30 mg iron)	Iron (60 mg)-folic acid	1,052	Osrin et al 2005 [11]
Mexico	MM (60 mg iron)	Iron (60 mg)	633	Ramakrishnan et al 2003 [12]
Burkina Faso	UNIMMAP (30 mg iron)	Iron (60 mg)-folic acid	1,052	Roberfroid et al 2008 [13]
Indonesia	UNIMMAP (30 mg iron)	Iron (30 mg)-folic acid	11,101	Shankar et al 2008 [14]
Indonesia	UNIMMAP (30 mg iron)	Iron (30 mg)-folic acid	725	Sunawang et al 2009 [15]
Bangladesh	UNIMMAP (27 mg iron)	Iron (27 mg)-folic acid	26,808	West et al 2014 [16]
Niger	UNIMMAP (30 mg iron)	Iron (60 mg)-folic acid	2,550	Zagre et al 2007 [17]
China	UNIMMAP (30 mg iron)	Iron (30 mg)-folic acid	2,876	Zeng et al 2008 [18]

*Iron-folic acid was provided through antenatal care

of treatment effects are presented in the **Table 3** and **Figure 1** (for low birth weight) and **Figure 2** (for SGA).

There was an overall modest but significant increase in mean birth weight of 43.2 g with MMS and a resulting significant reduction in low birth weight of 12%. MMS influenced both preterm birth (10% reduction) and small-for-gestational-age (9% reduction) – two underlying causes of low birth weight, although the reduction in SGA was only marginally significant. Neither stillbirth nor neonatal mortality was significantly reduced with supplementation. Although these treatment effects appear somewhat more conservative than previously shown, they are derived from a more cohesive group of trials that were designed and executed to demonstrate the efficacy of a UNIMMAP or a similar MM formulation.

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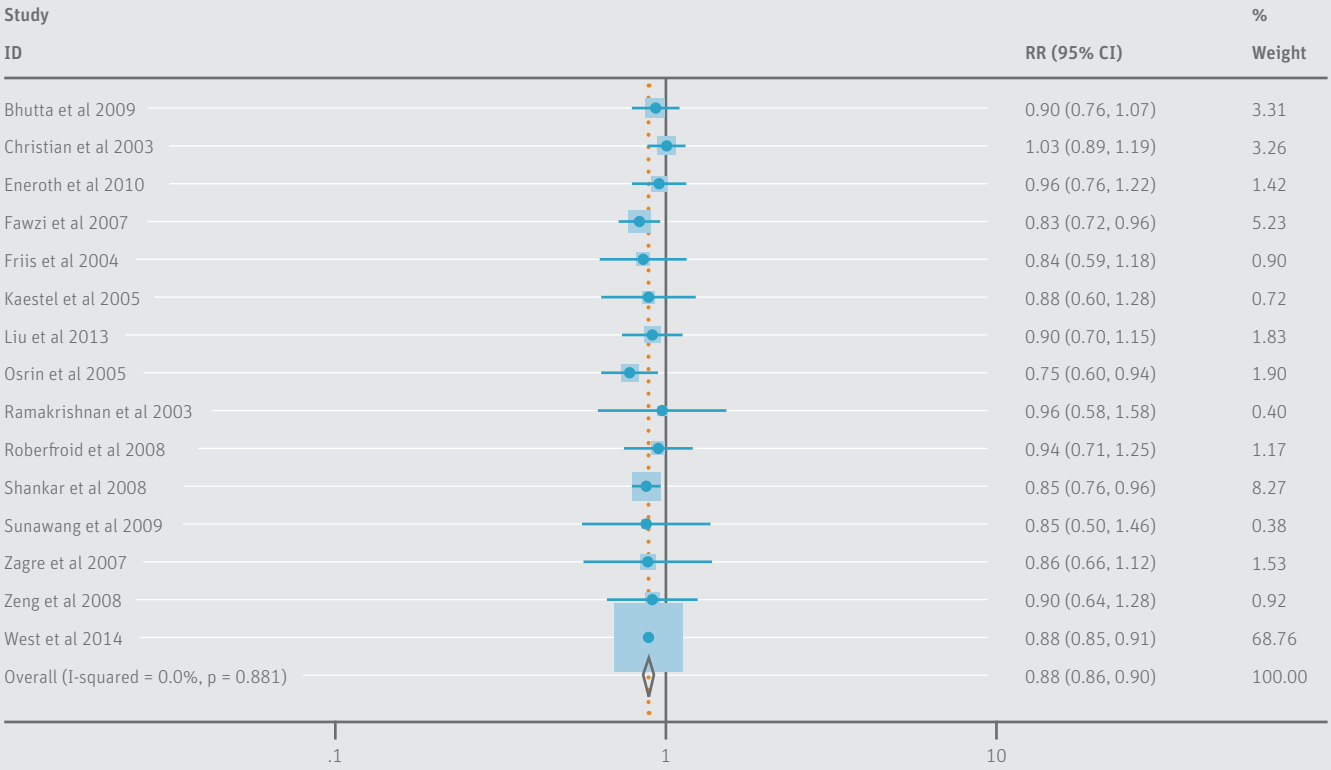
Effect modification

The meta-analysis by Ramakrishnan et al[21] identified several effect modifiers that merit discussion. One was a sub group analysis of five trials in which starting supplementation after

TABLE 3: Meta-analysis of multiple micronutrient supplementation effects using 15 trials conducted in LMIC settings

Outcomes	No. of trials	Treatment effects	95% CI
Birth weight, g	15	43.2	36.8–49.6
Gestational age, wk	10	0.11	0.00–0.21
Low birth weight (< 2.5 kg)	15	0.88	0.86–0.90
Preterm birth (< 37 wk)	10	0.90	0.84, 0.96
SGA (< 10th percentile)	7	0.91	0.84, 1.00
Stillbirth	12	0.94	0.87, 1.01
Neonatal mortality rate	12	0.98	0.91, 1.05

FIGURE 1: Treatment effects of multiple micronutrient supplementation on low birth weight (n=15)



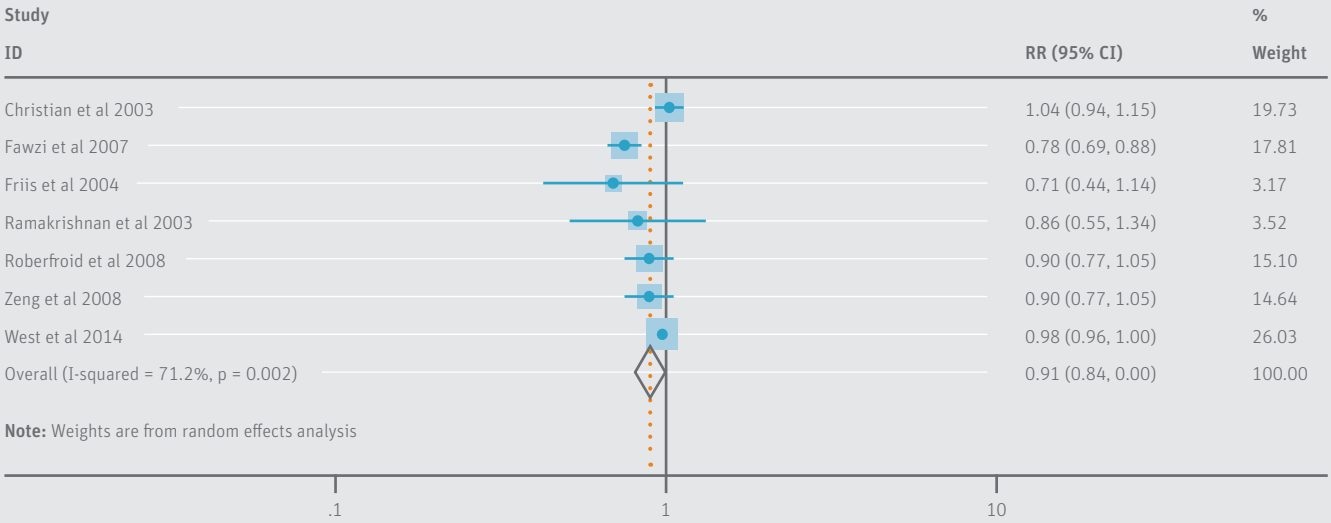
12 weeks of gestation vs. beginning earlier in the first trimester was found to be associated with an increased risk of neonatal mortality related to MMS (RR=1.38, 95%CI: 1.05–1.81). A previous pooled analysis,[23] when not all studies had been completed, also showed overall neonatal and perinatal mortality relative risks of > 1.0 associated with supplementation, although these were not statistically significant. Additionally, subgroup analyses indicated that MMS enhanced birth weight more in women with higher BMI, and an increased risk of large-for-gestational-age was also noted.

These findings raised concerns related to providing multiple micronutrients in settings where home deliveries were still common and both antenatal and obstetric care was poor. The increased risk of neonatal mortality in women who began supplementation later was not clearly understood and Ramakrishnan et al[21] noted that "findings from ongoing large trials in Bangladesh and China are awaited and may help clarify this issue." Both these trials are now included in the meta-analyses that were conducted (**Table 3**).

The recent findings from the Bangladesh trial[16] should be examined more closely. This RCT was called JiVitA-3. It was conducted between 2008 and 2013, and was designed and powered to show the effect of MMS on 6-month infant mortality as the primary outcome. The trial enrolled and supplemented over 44,000 pregnant women and included a total of 28,516 singleton live births. Maternal undernutrition was high in this rural Bangladeshi context, where 90% of women gave birth at home, 40% had early pregnancy BMI of < 18.5 and 50% had height < 150 cm. Low birth weight and SGA prevalence in the control group was 46% and 64%, and preterm birth rate was high at 22%. MMS had no impact on 6-month infant mortality (RR=0.95, 95% CI: 0.86–1.06), although there were significant interactions by sex and level of adherence. There was no mortality reduction in boys, but a statistically significant 17% reduction in mortality among girls. Significant increases in gestational age resulted in higher birth weight, length and other dimensions of size as well as significant reductions in rates of preterm birth, low birth weight, and a non-significant reduction in stillbirth.

Thus, in this undernourished setting there appeared to be beneficial effects of MMS on fetal and birth outcomes, without evidence of harm. In a post-hoc analysis, boys in the MM group were more likely to have a verbal-autopsy-based, physician-assigned, cause of death of birth asphyxia compared to those in the control. In contrast, girls did not experience this higher risk with supplementation, but had a lower risk of sepsis-related deaths if they were in the MM group. The strength of evidence from these analyses should be interpreted with caution, as verbal autopsy data are prone to misclassification and the study was not powered to examine cause-specific mortality differences by group. Overall, the JiVitA-3 trial results showed no reduction, but

FIGURE 2: Treatment effects of multiple micronutrient supplementation on small-for-gestational-age (n=7)



also no increase, in neonatal or infant mortality. This may alleviate previous concerns about potential harm, although it is likely that in environments where maternal short stature and constraint exist, there may be a risk of cephalopelvic disproportion and increased newborn morbidity with interventions targeted to achieve increased fetal growth and birth size. Countries will need to continue striving to improve facility-based delivery and skilled birth attendance in such settings, as everywhere else.

One should note that in all trials, the MM supplement (which included iron-folic acid) was compared to the current standard care of iron-folic acid, which itself is known to benefit birth outcomes. Haider et al,[24] in a systematic review of iron-folic acid supplementation trials (with 60 mg of iron), showed significant effects of the intervention relative to placebo on the outcome of birth weight (41.2 g, 95% CI: 1.2–81.2 g) and reduction in low birth weight (RR: 0.81, 95% CI: 0.71–0.93), although effects on preterm birth (RR: 0.84, 95% CI: 0.68–1.03) and SGA (RR: 0.85,95% CI: 0.67–1.08) were not significant. Folic acid included in the supplement is not considered to contribute to improvement in outcomes, which are probably attributable to iron, based on evidence from trials comparing prenatal folic acid alone vs. a placebo that have not shown a benefit.[4,10] In summary, it is important to recognize that the effects of MMS are over and above those achieved with iron-folic acid and are therefore likely to be larger (perhaps additive) if compared with no supplementation or a true placebo.

Policy implications and way forward

In conclusion, a strong body of research now appears to provide a solid evidence-base to support the widespread use of prenatal multiple micronutrient supplements. The two large trials completed recently may help address some of the uncertainties that existed for adopting a single multiple micronutrient supplement for global use, and the sum total of evidence is probably sufficient to show the public health value of prenatal micronutrient supplement use.

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