TECHNICAL BRIEF

Prenatal Multiple-Micronutrient Supplementation: Current State of Knowledge and Priorities

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BACKGROUND

Micronutrient deficiencies in pregnant women are a major public health problem in low-income countries, although there remains an urgent need to collect more prevalence and health related outcome data in this area (1–5). Micronutrients are required for the increased metabolic demands and the physiological changes that occur during pregnancy, including fetal growth and development. Inadequate intake of vitamins and minerals can have adverse effects on the health, function, and survival of the mother and fetus. For example, iodine deficiency can impair neural, intellectual, and physical development (6); iron deficiency can result in poor pregnancy outcomes such as low birth weight (4,7); folic acid deficiency can cause neural tube defects (8,9); and vitamin A deficiency can lead to maternal night blindness (10) and higher maternal mortality (11). Prenatal multiple-micronutrient supplement use is nearly universal in industrialized countries. However, the full health benefits and safety of supplying prenatal multiple-micronutrients are not yet entirely understood, especially across different high-risk populations where undernutrition and poor pregnancy outcomes are common.

In 1998, UNICEF, the United Nations University (UNU), and World Health Organization (WHO) convened a technical meeting to discuss and propose a formulation for a prenatal micronutrient supplement intended for use in developing countries. The supplement (called UNIMAP, for UN Multiple Micronutrient Preparation) remains in use today in emergency situations and research studies. It contains 14 micronutrients at dosages that approximate the recommended dietary allowances (RDA) for pregnancy (12). The use of this supplement was considered tentative until subsequent research could substantiate its efficacy and safety, as well as guide any necessary modifications. UNICEF coordinated studies of this daily prenatal supplement to test its ability to enhance fetal growth and increase birth weight in different regions of the world. In addition, several other investigators have tested, or are presently testing, the effects of supplements similar to UNIMAP on birth weight and other health outcomes. Neonatal mortality, however has been measured in only two of these studies, both in Nepal.

This brief summarizes the findings of the multiple micronutrient supplementation trials among non-HIV-affected women published to date, recognizing that data from several trials in different areas of the world currently remain unpublished. Two recent trials in Nepal are highlighted for their potential lessons learned. The findings reviewed here are inconclusive about the public health benefits and risks of multiple prenatal micronutrient supplement use, but illustrate the potential for supplements to have health benefits and pose risk in some populations, depending on the outcome examined. There is a need to conduct rigorous, adequately-sized prenatal supplementation trials in different regions of the world. These can assess the spectrum of public health benefits from prenatal multiple micronutrient supplement use in order to inform and guide policy decisions.

EFFICACY AND SAFETY OF MATERNAL MULTIPLE MICRONUTRIENT SUPPLEMENTATION

Five randomized controlled trials have been published on the efficacy of prenatal multiple-micronutrient supplementation of non-HIV-affected women (Table 1). The supplement formulation used in each study is described in Table 2. In Mexico, where women were randomized to receive either iron (60 mg) or a multiple-micronutrient supplement containing iron, there was no observed difference in birth weight between groups (13). A study in Zimbabwe, which included both HIV-1 infected and uninfected pregnant women, found a small

overall reduction in low birth rate. In non-HIV-1 infected women, there was a 26 g increase in mean birth weight and a 26 percent reduction in risk of low birth weight; neither effect was statistically significant (Table 1) (14). In this study, all women received 60 mg of iron and 400 µg of folic acid as per the national policy.

A trial in Guinea-Bissau showed no significant impact of a multiple-micronutrient supplement containing a single recommended dietary allowance, or RDA, for all nutrients on birth size when compared to iron-folic acid supplement use (15). However, supplementation with twice the RDA for all nutrients significantly increased birth weight by 88 to 95g, depending on the level of adjustment in the analysis. The use of this supplement also showed a significant reduction in miscarriage, but the study was not designed to evaluate this outcome and no explanation was provided for this effect. There was no difference in perinatal or neonatal mortality associated with the increased birth weight attributed to this supplement, although the study was not of sufficient size to show differences in this outcome.

One of two double-blind trials in Nepal, conducted in the southern plains District of Sarlahi, compared four combinations of micronutrients taken from early pregnancy through six weeks postpartum to a control supplement (7,16). The test supplements contained folic acid alone, folic acid+iron, folic acid+iron+ zinc, or a multiple-micronutrient formulation with folic acid+iron+zinc and eleven other micronutrients. All supplements contained the RDA of vitamin A (11). Folic acid supplementation alone did not affect birth weight, but was associated with a non-significant 20 percent reduction in neonatal mortality. The entire effect, however, was observed in preterm infants, among whom mortality was lowered by over 60 percent ($p<0.001$). Adding iron to folic acid improved maternal hemoglobin concentration, increased mean birth weight, and reduced the prevalence of low birth weight, without improving infant survival beyond that achieved with folic acid alone. Adding zinc antagonized beneficial effects of iron but without affecting infant survival. Intake of the 14-nutrient supplement conferred the greatest increase in mean birth weight (by 64 g), but failed to benefit infant survival compared to the control group. When comparing the effects of maternal multiple micronutrient use to that of iron-folic acid, representing a secondary comparison, there was a non-significant 49 percent increase in neonatal mortality.

A second randomized trial was conducted in the nearby District of Dhanusa, also in the southern plains of the country but based out of a clinic. This study also reported a significant increase in birth weight (77 g, 95% CI: 24–130) among infants born to mothers receiving the UNIMAP supplement daily compared to infants whose mothers took an iron-folic acid supplement (17). Here too, an increase in birth size did not improve infant survival. Compared to the iron-folic acid supplement, there was a non-statistically significant 53 percent increase in neonatal mortality among infants born to mothers assigned to the multiple-micronutrient group.

Photo courtesy of L. Lartigue.

A mother and child in Guinea

Given that both trials in Nepal were independent, had similar designs in populations of similar risks, and still represent the only two such trials published in South Asia, their findings were pooled to examine tentative effects of prenatal multiple micronutrient versus iron-folic acid use on early infant mortality in this local rural setting (18). Notwithstanding caveats about the need for more trial data, the pooled analysis yielded 36 percent and 52 percent increases in perinatal and neonatal mortality, respectively. This was associated with prenatal multiple micronutrient use. The reasons for an increased risk of mortality are not known. Explanations have so far focused on an upward shift in the entire distribution of birth weight, which could place larger infants at increased risk of birth asphyxia due to intrauterine constraint in a chronically stunted and undernourished population. In Sarlahi, adverse effects on infant survival were not observed in the iron-folic acid group compared to controls. Perhaps of relevance is that iron-folic acid appeared to only increase weight in the lower tail of the birth weight distribution (19). Other explanations include increased uterine sensitivity to oxytocin (18) and

improved intrauterine survival of infants born to multiple-micronutrient supplemented mothers who may have otherwise been stillborn (20). In Sarlahi, where infants were followed for one year, there was no reversal of the higher mortality that might have been expected had the micronutrient supplement only delayed mortality after birth. In the Dhanusa study, the number of stillbirths in the multiple micronutrient group was slightly lower than in the iron-folic acid group (n=15 vs.18). The pooled analysis has stirred needed debate about the generalizability of the findings, mechanisms for the observed effects, and the need for definitive research (20–22) given that some proportion of infants might incur risk from prenatal multiple-micronutrient supplement use in some settings. Recently, a systematic Cochrane analysis was undertaken by Haider and Bhutta of outcome data from published and unpublished trials of prenatal micronutrient supplementation (23). This analysis compared two of more nutrients vs. a placebo, no supplement, or a supplement with a single nutrient. A sub-analysis also compared multiple micronutrients vs. iron-folic acid. The main conclusion of this review was that a) there was no evidence to suggest that iron-folate should be replaced with multiple micronutrients, b) there was insufficient evidence to demonstrate either benefit or harm caused by multiple micronutrient supplementation and c) further research was needed to demonstrate benefit or potential adverse effects (23).

In summary, research has so far not provided a clear platform of evidence to support the widespread use of prenatal multiple-micronutrient supplements. The current uncertainty that exists questions the wisdom of adopting for global use a single multiple-micronutrient supplement at this time.

Several maternal multiple micronutrient trials have been recently completed in different areas of the world. Although pooled analyses of data from these trials are underway, there is an urgent need for all findings to be peer-reviewed and published and the information appropriately assimilated to understand the regional and global relevance of prenatal micronutrient use. It is likely that findings from the current available trials will not resolve uncertainties that exist about the public health value of prenatal micronutrient supplement use.

PRIORITIES AND FUTURE DIRECTIONS

Maternal micronutrient deficiencies are widespread and their prevention may improve the health of women and their infants in the developing world. However, the extent to which this can occur through multiple micronutrient supplementation is not known. It is essential that prenatal micronutrient supplement policies be grounded in scientific evidence of efficacy (benefit with respect to a range of plausible outcomes) and safety (posing minimal risk for all major outcomes). There is, thus, an urgent and practical research agenda facing prenatal micronutrient supplementation over the next several years. In each high-risk region of the world, the prevalence and severity of concurrent maternal micronutrient deficiencies should be estimated in broadly representative populations. Adequately designed intervention trials should be carried out to assess the ability of prenatal multiple micronutrient supplementation to reduce risks of a) preterm delivery, b) intrauterine growth retardation via multiple measures of birth size, c) still birth, d) neonatal and postneonatal infant mortality, and e) improved infant growth and development. There is also evidence that peri-conceptional maternal micronutrient nutriture may influence infant health, which provides a "new" window of maternal dietary supplement exposure that merits a critical research strategy. Finally, while this brief focuses on prenatal supplementation, there is an equal need to evaluate the health impact of maternal dietary interventions to improve micronutrient status prior to conception, during pregnancy, and during lactation.

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Table 1. Prenatal Multiple Micronutrient Supplementation Impacts on Birth Weight, Low Birth Weight and Preterm Delivery and Neonatal/Infant mortality

Study Reference	Population	Study Design/ Groups	Birth Weight Mean (SD), g Diff (95% CL)	Low birth weight % RR (95% CL)	Preterm delivery, % RR (95% CL)	Neonatal mortality, /1000 births, RR (95% CL)	Remarks
Ramakrishnan et al; 2003 (13) Ramakrishnan et al; 2003 (13)	Semi-urban Mexico	Control:Fe (n=323) MM: (n=322) MM vs. Control	2977 (393) 2981 (391) -	8.89 8.49 -	6.54 7.48 -	Not reported.	Acceptable nutritional status. Low LBW rates
Friis et al; 2004 (14)	Harare, Zimbabwe antenatal clinics –HIV-negative	Control: PL (n=361) MM (n=364) MM vs. Placebo	3044 3070 26 (-38, 91)	9.7 7.1 0.74 (0.45, 1.20)	16.2 12.7 0.79 (0.55, 1.13)	Not reported.	Women received iron-folic acid; high loss to follow-up
Kaestel et al; 2005 (15)	Guinea-Bissau, antenatal clinics	Control: FeFA (n=366) MMx1RDA (n=360) MM2xRDA (n=374) MM1 vs. FeFA MM2 vs. FeFA	3022 (2952, 3051) 3055 (3000, 3110) 3097 (3049, 3145) 49 (-22, 121)[2] 88 (17, 159)[2]	13.6 12.0 10.1 0.88 (0.57, 1.37)[2] 0.70 (0.44, 1.11)[2]	Not reported	42 50 44 1.15 (0.63, 2.10)[2] 1.09 (0.60, 1.99[2]	Birth weight missing for 974 infants
Christian et al; 2003 (7,14)	Rural Nepal	Control: VA (n=685) FAFe: (n=635) MM: (n=705) FAFe vs. Control MM vs. Control	2587 (445) 2652 (436) 2659 (446) 37 (-16, 90)[1] 64 (12, 119)[1]	43.4 34.3 35.3 0.84 (0.72, 0.99) 0.86 (0.74, 0.99)	20.4 23.1 20.6 1.13 (0.90, 1.40) 1.01 (0.82, 1.26)	45.7 36.3 54.0 0.80 (0.50, 1.27) 1.19 (0.77, 1.83)	Number for mortality outcome is: 876, 772 & 870 for Ctrl, FAFe & MM
Osrin et al; 2005 (17)	Nepal, urban/rural, antenatal clinics	Control: FeFA (n=523) MM: (n=529) MM vs. Control	2733 (422) 2810 (529) 77 (24, 130)	25 19 0.69 (0.52, 0.93)	10 8 0.85 (0.57, 1.29)	20 30.6 1.53 (0.72, 3.23)	Number for mortality outcome: 568 and 571 for Control and MM

Low birth weight : <2500 g
Preterm delivery: gestational duration of <37 wk

[1] Adjusted for maternal weight at baseline
[2] Adjusted for malaria parasitemia, anemia, infant sex, and seasons of birth.

Table 2. Composition of the multiple micronutrient supplements tested in the various studies

NUTRIENTS	STUDY				
	Ramakrishnan et al., 2003 (Mexico)	**Friis et al., 2004 (Zimbabwe)**	**Kaestel et al., 2005 (Guinea-Bissau[1])**	**Christian et al., 2003 (Nepal)**	**Osrin et al., 2005 (Nepal[1])**
Vitamin A	650 µg RE	3000 µg RE; ß-carotene 3.5 mg	800 µg RE	1000 µg RE	800 µg RE
Vitamin D	7.7 µg	10 µg	5 µg	10 µg	5 µg
Vitamin E	3.8 mg	10 mg	10 mg	10 mg	10 mg
Thiamine	0.93 mg	1.5 mg	1.4 mg	1.6 mg	1.4 mg
Riboflavin	1.87 mg	1.6 mg	1.4 mg	1.8 mg	1.4 mg
Niacin	15.5 mg	17 mg	18 mg	20 mg	18 mg
Folic acid	215 µg		400 µg	400 µg	400 µg
Vitamin B6	1.94 mg	2.2 mg	1.9 mg	2.2 mg	1.9 mg
Vitamin B12	2.04 µg	4 µg		2.6 µg	2.6 µg
Vitamin C	66.5 mg	80 mg	70 mg	100 mg	70 mg
Zinc	12.9 mg	15 mg	15 mg	30 mg	15 mg
Iron	62.4 mg		30 mg	60 mg	30 mg
Magnesium				100 µg	
Vitamin K				65 µg	
Iodine			150 µg		150 µg
Selenium		65 µg	65 µg		65 µg
Copper		1.2 mg	2 mg	2 mg	2 mg

[1]This formulation is the UNU/UNICEF/WHO supplement called UNIMAP

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