Multiple micronutrient supplementation during pregnancy in developing-country settings: Policy and program implications of the results of a meta-analysis

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Abstract

Background. *An independent Systematic Review Team performed a meta-analysis of 12 randomized, controlled trials comparing multiple micronutrients with daily iron–folic acid supplementation during pregnancy.*

Objective. *To provide an independent interpretation of the policy and program implications of the results of the meta-analysis.*

Methods. *A group of policy and program experts performed an independent review of the meta-analysis results, analyzing internal and external validity and drawing conclusions on the program implications.*

Results. *Although iron content was often lower in the multiple micronutrient supplement than in the iron–folic acid supplement, both supplements were equally effective in tackling anemia. Community-based supplementation ensured high adherence, but some mothers still remained anemic, indicating the need to concomitantly treat infections. The small, significant increase in mean birthweight among infants of mothers receiving multiple micronutrients compared with infants of mothers receiving iron-folic acid is of similar magnitude to that produced by food supplementation during pregnancy. Larger micronutrient doses seem to produce greater impact. Meaningful improvements have also been observed in height and cognitive development of the children by 2 years of age. There were no significant differences in the rates of stillbirth, early neonatal death, or neonatal death between the supplemented groups. The nonsignificant trend toward increased early neonatal mortality observed in the groups receiving multiple micronutrients may be related to differences across trials in the rate of adolescent pregnancies, continuing iron deficiency, and/or adequacy of postpartum health care and merits further investigation.*

Conclusions. *Replacing iron–folic acid supplements with multiple micronutrient supplements in the package of health and nutrition interventions delivered to mothers during pregnancy will improve the impact of supplementation on birthweight and on child growth and development.*

Key words: Antenatal care, birthweight, iron–folic acid supplementation, multiple micronutrient supplementation, neonatal death, pregnancy, stillbirth

Introduction

Anemia affects one-quarter of the world's population and is concentrated in preschool-aged children and women [1], and in the latter group it accounts for at least 20% of maternal mortality [2]. Because iron deficiency makes a large contribution to anemia, global efforts to reduce the anemia burden have largely been directed toward increasing intake of iron through supplementation, food fortification, and diversification of diet. Pregnant women are often deficient in several other nutrients, all of which can negatively affect them as well as their infants' health, growth, and development across the life course [3]. Although most developing countries have policies promoting iron–folic acid supplementation for women during pregnancy and lactation, few address other nutritional requirements women may have throughout this critical time.

Because multiple micronutrient deficiencies often

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coexist in developing-country settings, the use of multiple vitamin and mineral supplements has been proposed by some authors as an alternative to the current standard World Health Organization (WHO) recommendation for iron–folic acid supplements in pregnancy [4]. In 1999, a consultation of experts in the field, convened by UNICEF, WHO, and the United Nations University (UNU), agreed on a formulation for a multiple micronutrient supplement for pregnant women for trial purposes [5]. This supplement, which later became known as the United Nations International Multiple Micronutrient Preparation (UNIMMAP), contains 13 vitamins and minerals in addition to iron–folic acid (**table 1**).

Populations facing emergencies, including natural disasters and conflicts, often have limited access to food, and presently some relief food supplies are still not fortified with vitamins and minerals. Recognizing this potential problem and that micronutrient needs are greater during pregnancy and lactation, WHO/World Food Programme (WFP)/UNICEF published a joint statement recommending the provision of multiple micronutrient supplements to young children and to pregnant and lactating women in emergency situations to help prevent and control multiple micronutrient deficiencies [6].

An assessment of the impact on health outcomes of the use of multiple micronutrient supplements compared with an iron–folic acid supplement during pregnancy outside of emergency settings could be expected to help policy makers determine optimal approaches to improving maternal and infant heath, and to consider multiple micronutrient supplements during pregnancy when feasible and appropriate. This paper discusses the results of the meta-analysis involving 12 studies assessing the impact of the use of multiple micronutrient supplements on micronutrient status, birthweight and gestational age, fetal losses, and neonatal mortality that are reported in this volume. This paper explores the internal and external validity of the results and discusses the policy implications for making preliminary recommendations aiming at improving programs.

TABLE 1. Composition of the World Health Organization/UNICEF/United Nations University multiple micronutrient supplement (United Nations International Multiple Micronutrient Preparation [UNIMMAP])

Nutrient	Amount
Vitamin A	800 μg
Vitamin D	200 IU
Vitamin E	10 mg
Vitamin C	70 mg
Vitamin B^{1}	1.4 mg
Vitamin B^{2}	1.4 mg
Niacin	18 mg
Vitamin B^{6}	1.9 mg
Vitamin B^{12}	2.6 μg
Folic acid	400 μg
Iron	30 mg
Zinc	15 mg
Copper	2 mg
Selenium	65 μg
Iodine	150 μg

Methods

The process that led to this meta-analysis is unusual and worthy of comment. This highly collaborative effort was performed by a diverse set of principal investigators, many of whom already had their own research funds, and who agreed to work together without a large amount of extra funding in order to increase the likelihood that their research would have policy and program impact. An initial meeting in 2002 of the principal investigators of nine efficacy and effectiveness trials of multiple micronutrient supplements from seven countries (Bangladesh, Guinea-Bissau, Indonesia, Nepal, Niger, Pakistan, and Tanzania) was held at the Institute of Child Health in London with funding support from the Micronutrient Initiative. The principal investigators, not all of whom were responsible for UNIMMAP trials, agreed to a standardized set of methods, including definition of outcome measures as well as consideration of a set of required and recommended confounders and effect modifiers that all should use [7]. A second meeting of the principal investigators of UNIMMAP trials (which included additional investigators from several other countries, including Burkina Faso and China, was held at the UNICEF Regional Office in Bangkok in 2004 to share preliminary results of the effectiveness trials that were already available [8] as well as to make initial explorations on how to do the meta-analysis of the efficacy trials. An independent Systematic Review Team was then commissioned by UNICEF/WHO/United Nations Standing Committee on Nutrition (SCN) to undertake a meta-analysis, and the principal investigators shared their data sets with them. A third meeting was held in October 2005 in Geneva under the aegis of the SCN, where the Systematic Review Team shared preliminary results of the meta-analysis with the principal investigators of 12 studies and began discussing the results obtained so far and further analysis to be undertaken. Tanzania and Vietnam were not included in the meta-analyses for operational reasons (such as lack of follow-up survey or lack of participation by investigators in meetings). It was agreed not to publish the results of the meta-analysis until each of the individual trials had been published. It was also agreed that all of the principal investigators would be part of the UNIMMAP study group team who would be the coauthors of the meta-analysis papers. A report of that meeting was prepared but not published because of the still confidential nature of the unpublished studies. Following completion of the meta-analysis, all of the principal investigators who were part of the UNIMMAP study group team agreed to the final versions of the four papers included in this volume [9–12].

It was also agreed at the principal investigators' meeting in Geneva that the policy and program members from the sponsoring agencies (SCN, UNICEF, and WHO) would review the results of these meta-analysis papers and independently make an analysis of the program and policy implications that stem from them. However, it is important to note that the funding agency (UNICEF) ensured that there was a strict firewall between the researchers at the University of Southampton who coordinated the meta-analysis and the sponsoring agencies [9] to ensure objectivity and their complete independence. Consideration of the policy and programmatic implications of the effect of micronutrient supplementation on birth outcomes requires several different perspectives, not least of which is to try to understand the possible mechanisms at play as well as what the biological significance of any such impact might be, and this is the purpose of this paper. Programmatic recommendations, as is well recognized, cannot always wait until there is perfect evidence for action, which may never come. The present writing group also took note that antenatal supplementation with multiple vitamins and minerals is the norm in many affluent countries and often for the affluent in poorer countries. In order to best interpret the results and to formulate conclusions and recommendations for policy and programs, this review looked at each of the outcomes and results that are reported in the meta-analysis papers. As well, the results in each of the individual trials were taken into account, along with a literature search using Medline and reference to existing normative program guidance.

Results

Trial population characteristics

As is to be expected of studies carried out on three different continents, the characteristics of the meta-analysis trial populations varied greatly. The review of methods and study characteristics by Margetts et al. [9] describes the large differences across the trials in baseline nutritional status. Mothers in Bangladesh [13], Indonesia [14, 15], Mexico [16], Nepal [17, 18], and Pakistan [19] were nearly 10 cm shorter than in those in Africa [20, 21] and China [22], whereas the mean body mass index (BMI) was highest in Guinea-Bissau [23], Mexico [16], and Zimbabwe [24]. Although the mean age did not differ across the trial populations, there were differences in parity, with 60% of mothers primiparous in China against only 19% in Pakistan. As Margetts et al. point out, the large differences in maternal size and parity across the trials need to be taken into consideration when interpreting the results of the meta-analysis [9].

Trial organization

There are important differences in the way the trials were organized that the review of trial characteristics does not capture entirely [9]. These organizational differences, summarized in **table 2**, relate to the way the trial effort and resources were employed. Some trials concentrated their efforts on delivering the supplements and carrying out the research, whereas others also tried to improve delivery of the supplements and improve compliance with supplement intake by the mothers, thus affecting the particular antenatal and postnatal health systems.

Most of the trials were carried out in predominantly rural populations, including Bangladesh, Burkina Faso, China, Indonesia (Indramayu and Lombok), Nepal (Sarlahi), Niger, and Vietnam. Only two of the trials, those in Guinea-Bissau (Bissau) and Zimbabwe (Harare), were carried out in urban settings. The remaining three trial populations, those in Mexico (Cuernavaca), Nepal (Janakpur), and Pakistan, were a rural–urban mix. Three trials, those in Guinea-Bissau, Nepal (Janakpur), and Zimbabwe, were "facility based," passively enrolling pregnant mothers coming to health centers. All other trials were "community based," actively seeking out mothers in the community early in pregnancy.

The way community surveillance was carried out also differed across the trials. In Bangladesh and Guinea-Bissau, the trials were conducted in the areas where existing health and demographic surveillance systems already had staff regularly recording vital events at the community level with follow-up household visits. In Burkina Faso, Mexico, and Nepal (Sarlahi), community-based surveillance was carried out by a trial workforce that had been employed for this purpose for the duration of the trial. In China, Indonesia, Niger, and Pakistan, the community surveillance was largely done by the existing community-based health workers as part of their regular job, although with varying levels of facilitation and extra training from the research project staff.

The trials also differed in the way resources were used to ensure adherence to the taking of the supplements, as well as to the collection of information and measurements. In the trials in Burkina Faso, Indonesia (Indramayu), Mexico, and Nepal (Sarlahi), a large part of the workers' efforts went into carrying out home visits to deliver supplements, take measurements, and record observations, with less or no effort going into improving the service delivery channels. In the

TABLE 2. Organizational aspects of the various trials of multiple micronutrient supplementation during pregnancy

Country of trial	Location Population size Rural or urban No. of births	Organizational focus/basis	Orientation of trial workforce	Stimulation of demand for services	Other components and comments
Bangladesh [13]	Matlab 225,000 Mostly rural 2,853	Community-focused DHSS and health facility for enrollment and examinations	DHSS workers check out all births and deaths in community Health service staff make household visits every 2 weeks to check adherence, take measurements, and collect data	Not reported	Food supplements made from local products provided through community-based organization as well as metronidazole to control bacterial vaginosis
Burkina Faso [21]	Hounde 12,000 Rural 1,260	Community-based surveillance and referral to health service for treatments, measurements, and delivery	Home visits monthly to check for pregnancies and household visits daily for supplement administration	None reported	Malaria treatment (2 types) and deworming 2× during pregnancy and vitamin A after delivery
China [22]	Shaanxi Population size not stated Rural 4,851	Community surveillance by village doctor and referral to township MCH facility as well as entry through health facility	Household visits every 2 weeks by village doctor to check adherence and by MCH staff after birth to take measurements and check vital events	Not reported	Not reported
Guinea-Bissau [23]	Bissau 90,000 Semiurban 2,100	Community for DHSS and health facility for enrolment and examinations	DHSS workers check out all births and deaths in community Health service staff make household visits to check compliance and to take measurements and collect information	Not reported	Malaria treatment and insecticide-treated bednets
Indonesia [14]	Indramayu 120,000 Rural 750	Community surveillance in research villages by research staff	Daily household visits for supplement administration. Weekly household visits for recording vital events and measurements	Not reported	Not reported

continued

TABLE 2. Organizational aspects of the various trials of multiple micronutrient supplementation during pregnancy *(continued)*

Country of trial	Location Population size Rural or urban No. of births	Organizational focus/basis	Orientation of trial workforce	Stimulation of demand for services	Other components and comments
Indonesia [15]	Lombok 2.1 million Mostly rural 28,426	Community-based facilitators linking to facility-based health workers (village midwives)	Household visits by both maternal data collectors and community-based facilitators to counsel	Social marketing and monthly household visits by community facilitators promoting health service utilization	Not reported
Mexico [16]	Cuernavaca Population size not stated Semirural 647	Community-based surveillance and research facility-based follow-up, plus referral as necessary to health service	Daily household visits for supplement administration	Not reported	High-quality antenatal care including referrals and treatment of infections. 1/3 of mothers were obese
Nepal [18]	Janakpur Population size not stated Rural and urban 1,052	Facility-based, with monthly clinic visits for examinations and measurements	Home visits monthly to check supplement administration and collect information	None reported	None reported
Nepal [17]	Sarlahi 650,000 Rural 4,130	Community-based surveillance and follow-up	Home visits monthly to check for pregnancies and household visits twice a week for supplement administration	Counseling on antenatal care and nutrition at the time of enrollment	Deworming and tetanus toxoid 2× during pregnancy Safe birthing kit for home-based delivery and flannel blanket for the newborn
Niger [20]	Maradi Population size not stated Mostly rural 2,550	Community workers (traditional birth attendants) actively seeking pregnant women and linking to nearest health facility	Traditional birth attendants dispensing supplements supported by community data collectors	Social marketing, plus outreach prenatal care from health facility to communities	Malaria chemoprophylaxis
Pakistan [19]	Sindh Population size not stated Rural and urban 1,613	Community health workers linking to facility (midwives) and community-based health workers (lady health workers), with referral as necessary to health system	Community health workers making household visits every 2 weeks to deliver supplements, make measurements, and collect information as appropriate	Social marketing and counseling at monthly household visit by community health workers	Not reported

Vietnam [25]	Red River Delta 515,000 Rural 1,579	Community surveillance by village health workers and referral to commune health facility	Research team collected routine health information from all 3 districts and did in-depth measurement and extra data collection through cluster surveys	Nutrition education for mothers during pregnancy through commune health facility	Not reported
Zimbabwe [24]	Harare Population size not stated Urban 1,106	Facility-based	Facility-based measurement, data and sample collection All supplements given at first contact and checked at birth	None	1/3 of mothers had untreated HIV infection

DHSS, Demographic Health Surveillance System; MCH, Maternal and Child Health

Indonesia (Lombok), Niger, Pakistan, and Vietnam trials, not only was the trial workforce used to help collect information and make measurements, but in addition extra efforts were put into trying to improve maternal adherence to the supplements by improving health service delivery mechanisms. Several trials even had social marketing and improved nutrition counseling that was aimed, not just at trial participants, but at the whole population of the communities in question.

In conclusion, the approaches used in organizing the trials varied considerably, ranging from a strictly research project approach to one of more in-depth program monitoring and evaluation. The strictly randomized control experimental approach provides greater scientific certainty that a treatment was delivered and that the only difference between the intervention group and the control group was the intervention being tested, assuming that measurements were done correctly. In the more programmatic approaches described above, delivery of the intervention relied more on getting the service delivery channel to function better, and then checking on compliance by a sample survey or some more indirect way. Community-based facilitation of service delivery can ensure early detection of pregnancy and increased uptake of health services, including micronutrient supplements. This energizing of the service delivery channel presumably improved all the antenatal and postnatal care. These organizational differences need to be taken into consideration when interpreting the results of the trials, and especially when trying to draw policy and program conclusions.

Adherence

Adherence was measured by pill counts or by observations of women actually consuming pills. The mean number of days women consumed the supplements was then reported as a percentage of the total number of possible days they could have consumed them (once they were recruited into the studies). If women consumed the supplements daily, adherence would be 100%. If women consumed them on average 5 days per week, adherence would be 71% (5/7 × 100). Adherence (often also referred to as compliance) was relatively high in all studies, with women consuming supplements on 69% to 98% of days (or, on average, 6 or 7 times per week (**fig. 1**).

The only true efficacy trials were the ones in Burkina Faso, Indramayu (Indonesia), and Mexico, where the research team administered the pills directly to the mothers in their homes on a daily basis. In Indramayu, Indonesia, two studies were conducted in parallel showing that the mean number of supplements consumed during pregnancy when women received them daily under direct observation was about 20% higher than the mean when they were distributed monthly

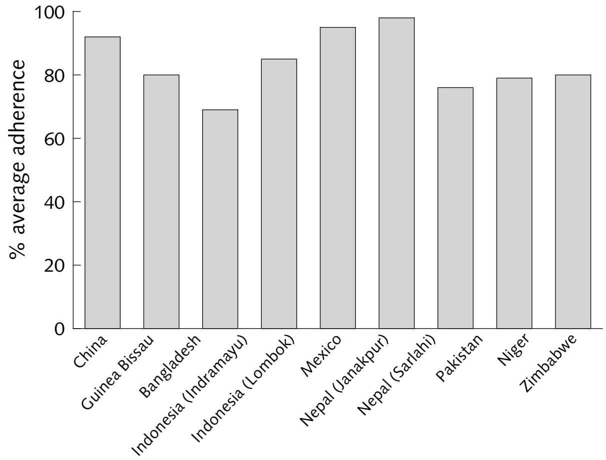

FIG. 1. Average adherence to supplementation in the meta-analysis studies

(130 vs. 107). The percentage adherence shown for Indramayu in **figure 1** is for the daily distribution group. In all other trials, the supplements were provided in batches in special bottles, and the number of pills not consumed was verified on replenishment. Early provision of supplements was made possible by the active "community-based" surveillance of pregnant women (in 8 of the 12 studies). Such early use of supplements meant that the numbers of supplements consumed in pregnancy in these studies were relatively high, ranging from 107 to 165, as compared with the WHO recommendation of 180 iron–folic acid supplements in pregnancy [26].

Micronutrient status

Maternal micronutrient status

The review by Allen and Peerson [10] reported that multiple micronutrient supplements had a similar impact on hemoglobin synthesis during pregnancy to that of iron–folic acid supplements alone, although often the multiple micronutrients contained lower amounts of iron. This may be because the women who received 60 mg of iron in an iron–folic acid supplement may not have absorbed it well, given the presence of inhibitors such as phytates and the likely low intakes of vitamin C, as is often the case among people in economically deprived settings with poor diets. The multiple micronutrient supplement, although containing only 30 mg of iron, also contained vitamin C, which may have helped absorption of the smaller amount of iron and so helped to ensure an equal effect in terms of the hematinic response.

Although micronutrient supplementation reduced anemia rates in all trials, significant levels of anemia still remained in most of them. In the Nepal (Sarlahi) study, 27.9% of women in the group receiving vitamin A and iron–folic acid and 37.7% in the group receiving multiple micronutrients were anemic in the third trimester, compared with 59.8% of those receiving only vitamin A. At 6 weeks postpartum, 15.2% and 12.2%, respectively, were anemic, although these levels were substantially lower than the level (39.8%) found in women who did not receive any iron in pregnancy [27]. Similar results were reported in Mexico, where about 30% of women in the group receiving multiple micronutrients and 32% of women in the iron–folic acid group had iron-deficiency anemia at 1 month postpartum [16]. In China, 45.1% of women who took iron–folic acid and 42.1% of those in the group receiving multiple micronutrients were anemic in the third trimester, compared with 61.0% of those who took folic acid alone [22].

One possible reason that anemia rates remained high among supplemented mothers in the meta-analysis trials is the lack of systematic control of infectious diseases. In Sarlahi, Nepal, intestinal parasites were presumptively treated twice during pregnancy, since previous studies had shown that women given albendazole in the second trimester of pregnancy had a lower rate of severe anemia during the third trimester [28]. The trials in Burkina Faso, Guinea-Bissau, and Niger included routine treatment of malaria. In Bangladesh, bacterial vaginosis was treated as one arm of the experiment, but the results of these interventions have not been reported yet. In Zimbabwe, a third of the mothers had HIV infections, although these were not treated.

Few trials assessed the impact of supplements beyond anemia, and they often did not look more broadly at maternal micronutrient status, especially for those nutrients contained in the multiple micronutrient supplements. In their accompanying review, Allen and Peerson [10] report inconsistent results for serum retinol status and suggest this may be due to poor absorption of the vitamin because of limited fat intake in the diet or to measurement problems. The Janakpur (Nepal) and the Indramayu (Indonesia) trials showed improvement in serum retinol in the mothers receiving multiple micronutrients compared with those receiving iron–folic acid, but this was not the case in the Pakistan trial. The Janakpur trial also showed improvement in serum vitamin E levels in mothers receiving multiple micronutrients that was not seen in the iron–folic acid group. Difficulties in assessment of zinc status may be the reason that the Indramayu trial showed no impact of the multiple micronutrient supplement on serum zinc levels and that the Pakistan trial is the only one that showed depressed serum zinc in the iron–folic acid group postpartum as compared with the group receiving multiple micronutrients, although similar results have been shown in multiple micronutrient supplementation of infants [29]. Several other studies have reported that concurrent deficiencies of nutrients other than iron are common in the trial sites, with the one in Mexico showing that zinc and folate deficiencies affected between 30% to 40% of women and that more than half had two concurrent deficiencies [16]. In Guinea-Bissau, 14% had low serum vitamin A values and 60% had poor serum folate status [30]. The Sarlahi study found that the rates of vitamin deficiency among control women in the third trimester were 66.9% for vitamin B_{12}, 88.4% for vitamin B_6, 63.6% for riboflavin, and 24.3% for vitamin D and that the levels of deficiency of these micronutrients were 35% to 77% lower among women who consumed multiple micronutrient supplements [31].

Impact on breastmilk and infant's micronutrient status

Very few trials in the meta-analysis reported the impact of maternal micronutrient supplementation on the micronutrient content of breastmilk or infants' micronutrient status. There is, however, considerable evidence from the literature that levels are improved by supplementation [32]. Maternal nutrient status during pregnancy affects the infant's nutritional status for many nutrients by improving infant stores and enhancing the micronutrient content of breastmilk [33, 34].

Size at birth

The meta-analyses observed a mean increase in birthweight of 22 g, with a range across studies from 4.9 to 75.5 g and with a larger impact on birthweight in infants of heavier women [11]. The effect of multiple micronutrient supplementation on birthweight was manifested by a positive shift in the entire birthweight distribution, with decreases in the numbers of low-birthweight (LBW) and small-for-gestational-age (SGA) babies and increases in the number of babies with weights at the other end of the curve. Fall et al. [11] report this increase as a higher rate of large-for-gestational-age (LGA) infants, which was defined as "birthweight above the within-each-population 90th percentile." Normally babies above 4 kg are considered LGA, and only in China, Guinea-Bissau, Lombok (Indonesia), and Zimbabwe were there several birthweights above 4 kg. There were no differences between infants of mothers supplemented with iron–folic acid and infants of mothers supplemented with multiple micronutrients in birth length or in head circumference of the newborns.

Birthweight differences can be a reflection of either shortened gestation, suboptimal fetal growth, or both, each with a different significance and prognosis [35]. The meta-analysis found no differences between infants of mothers supplemented with iron–folic acid and infants of mothers supplemented with multiple micronutrients in the rates of preterm birth or increased gestational length. Even though the meta-analysis noted some problems with measurement of gestational age in some of the studies, notably those in Niger and Pakistan, these results were no different if the improbable values were removed. This strongly suggests that the increase in birthweight of infants whose mothers received multiple micronutrients as compared with those whose mothers received iron–folic acid is a result of improved intrauterine growth, not decreased prematurity. The meta-analysis finding that the positive effect of multiple micronutrient supplementation on birthweight was greatest in infants of heavier women and was low or even negative among infants of women with low BMI is discussed later, but it is thought likely to be an artefact or to reflect that benefits accrue more to the mother and less to the fetus in women with low BMI than in women with higher BMI.

Further evidence from the individual UNIMMAP trials suggests that the impact of micronutrient supplementation during pregnancy on birthweight would be greater with larger doses of micronutrients. The study in Guinea-Bissau, which had two different multiple micronutrient supplements, one containing the RDA for nutrients and the other containing the same amount of iron but double the RDA for other nutrients, reported greater increases in birthweight with higher levels of micronutrients in the supplements (49 g for one multiple micronutrient vs. 88 g for two multiple micronutrients adjusted for malaria parasitemia, anemia, infant's sex, and season of birth [23]). Although the meta-analysis found no evidence that starting the supplement earlier in pregnancy increased the effect of the multiple micronutrient supplements on birthweight, the Niger trials found that the effect was greater when the duration of supplementation increased, so that the difference between infants in the multiple micronutrient group and those in the iron–folic acid group was 78 g for those whose mothers received the supplement for more than 150 days, compared with just 56 g for those whose mothers received the supplement for less than that period ($p < .001$) [20].

Several of the UNIMMAP intervention trials have now begun to report on growth and development outcomes later in childhood. In Nepal, children at the age of 2.5 years whose mothers had taken multiple micronutrients during pregnancy were heavier and although not taller, had larger head, chest, hip and mid-upper arm circumference, as well as lower systolic blood pressure of greater body size than those born to mothers who had only received iron–folic acid supplements [36]. A trial in Bangladesh reported small but significant improvements in measures of motor skills in children of mothers with low BMI who received multiple micronutrients during pregnancy [13]. The Vietnam trial in this volume reported that the increase in mean birthweight of approximately 100 g found in the districts of the Red River Delta supplemented with multiple micronutrients translated into a 30% reduction in stunting at 2 years of age [25].

Fetal and infant survival

The meta-analyses of mortality found no statistically significant differences between infants of mothers supplemented with iron–folic acid and infants of mothers supplemented with multiple micronutrients, be it for stillbirth rates in the 12 trials or for neonatal deaths in the 9 trials that reported on mortality after birth [12]. However, the early neonatal mortality rate was increased by 23%, although nonsignificantly, and when data from Lombok, Indonesia, were removed from the analyses because of significant heterogeneity ($p < .10$), there was a statistically significant higher odds ratio of early neonatal mortality in the groups receiving multiple micronutrients compared with the comparison groups (OR = 1.46; 95% CI, 1.09 to 1.95).

The lack of effect of the multiple micronutrient supplement on neonatal mortality, or even perhaps a negative effect in some locations, is surprising, considering the increase in birthweight achieved compared with the controls supplemented with iron–folic acid. Increased birthweight has consistently been found to be associated with a reduced risk of dying in infancy [37–39]. Even in Sarlahi (Nepal), an increase of 59 g in the mean birthweight of infants of women who were dewormed during pregnancy was associated with a 41% decrease in infant mortality at 6 months [28]. It seems strange that in the same Sarlahi population, similar increases in birthweight were reported to cause a decrease in mortality in one instance and an increase in another [40]. One possibility that has been suggested is that the multiple micronutrient supplements reduce early fetal losses but that infants then die later in the neonatal period [41].

Discussion

The success of these studies in attaining high rates of adherence to supplementation in both the multiple micronutrient and the iron–folic acid groups is noteworthy. Although daily iron supplementation is reported to cause more side effects than weekly supplementation [42], the findings of this meta-analysis confirm the findings of many other studies over the last two decades that women will consume iron, as well as multiple micronutrient supplements, as long as they have access to them and are adequately counseled on their use [43–45]. Furthermore, the meta-analysis found no significant differences in adherence between the multiple micronutrient and the iron–folic acid groups, even though the latter often received higher amounts of iron, and side effects were uncommonly reported. As commented by Margetts et al. [9], in 8 of the 12 studies, women were provided with supplements within the first 4 months of pregnancy. This early provision of supplements was made possible by the active community-based surveillance of pregnant women and is very different from the provision through facility-based approaches that is more commonly found in most Maternal and Child Health program settings. Such early use of supplements meant that the numbers of supplements consumed in pregnancy in these studies were relatively high, ranging from 107 to 165, as compared with the WHO recommendation of 180 iron–folic acid supplements in pregnancy [26].

The multiple micronutrient supplements were as effective as the iron–folic acid supplements in terms of the hemoglobin response, even though they often contained lower amounts of iron. In addition to vitamin C, which improves iron absorption, other nutrients in the multiple micronutrient supplements are likely to have contributed to improved hematopoiesis, such as retinol and selenium. These other nutrients are likely to have contributed to improving the nutritional status of the mother and, through her, the nutritional status of the infant, although these effects of the multiple micronutrients have so far been little researched. Another potentially important advantage of multiple micronutrients over the iron–folic acid supplements that is not apparent from the meta-analysis but that is beginning to raise concern, especially in the Indian subcontinent where many mothers are vegetarian, is the realization that giving iron–folic acid supplements without vitamin B_{12} can cause an imbalance in the metabolism of vitamin B_{12} and folate, which contributes to the metabolic programming of the offspring [46]. A study in Pune, India, has shown that children born to mothers with low vitamin B_{12} and high folate concentrations have higher insulin resistance [47]. Furthermore, a third of the mothers had low vitamin B_{12} status, and therefore giving them iron–folic acid supplements without vitamin B_{12} could well be contributing to the insulin resistance increasingly commonly seen in Indian children.

Why participants remained anemic in these trials, even though they were taking seemingly adequate amounts of supplemental iron, is not clear, but this has been seen in many effectiveness trials over the years. It may be that initiating supplementation in pregnancy is too late for many women, especially those with pre-existing anemia. A study conducted in Vietnam showed that the use of weekly iron–folic acid prior to and during pregnancy was associated with better iron status in the first and second trimesters of pregnancy and with reduced prevalence of LBW compared with pregnant women who only received daily iron–folic acid supplementation during pregnancy [48]. However, studies by Ekstrom et al. in Bangladesh comparing weekly and daily iron supplements found that a maximum hemoglobin effect was achieved by just 40 tablets each containing 60 mg of iron, whether taken as a daily or a weekly regimen, which led them to suggest that the level of iron supplementation currently being recommended might be too high [49]. However, anemia still persisted in these Bangladeshi women, even when the maximum hemoglobin response had been reached, with 20% still affected in the weekly and 14% in the daily regimes. This suggests that something else is involved in the causality of the anemia besides just iron availability.

One possible reason that supplemented mothers remain anemic could be infections, since these were not systematically treated across the trials. WHO/UNICEF program guidance for the control of anemia recommends the treatment of infections, and in particular of malaria, tuberculosis, HIV/AIDS, and helminth infections, in addition to the provision of iron supplements [50]. Inflammation associated with infections has been shown to contribute to low hemoglobin levels in iron-replete anemic pregnant women in Malawi [51] and Nepal [52], and the positive effects of multiple micronutrient supplements on hemoglobin levels in Kenyan adults with HIV/AIDS were only seen in subjects with no inflammation [53]. Furthermore, studies in schoolchildren in Kenya [54], South Africa [55], and Vietnam [56] all show that deworming, together with extra iron (either by supplementation or by fortification), resolves the problem of anemia better than either treatment alone.

Although none of the studies included in the meta-analysis have yet reported on the impact of maternal micronutrient supplementation on breastmilk composition or infant micronutrient status, there is considerable evidence from the literature indicating that these are improved. Maternal nutrient status during pregnancy affects the infant's nutritional status for many nutrients by improving infant stores and enhancing the micronutrient content of breastmilk [33, 35]. A study using antenatal multiple micronutrient supplements in Mexico found that vitamin A levels were improved in breastmilk [57] compared with the control group that received only iron. Studies in the Gambia have shown that riboflavin, vitamin A, and ascorbic acid concentrations in breastmilk can also be improved by micronutrient supplementation of lactating women [58–60]. In a double-blind study of low-income, lactating women in the United States, breastmilk levels of vitamin B_6, vitamin B_{12}, and folate increased in the micronutrient supplement group [61]. Zinc supplementation of Amazonian women during lactation doubled the retinol levels in breastmilk at 5 months postpartum compared with women receiving placebo [62]. Multiple micronutrient supplementation of HIV-positive mothers in Tanzania during pregnancy and lactation was associated with increased vitamin A and vitamin E status and decreased prevalence of vitamin B_{12} deficiency in infants at 6 weeks and 6 months postpartum [63]. Further research to demonstrate such linkages and benefits would be important to carry out. Many of the trials have collected samples that have yet to be analyzed and for which the results have not been published, and every effort should be made to ensure that this is done. Infants born with enhanced nutrient status are likely to be at an advantage for health and development.

It is remarkable that the increase in birthweight achieved by the multiple micronutrient supplement is of a similar order of magnitude to that produced by food supplementation during pregnancy. Kramer and Kakuma [64], in their Cochrane review of randomized, controlled trials of balanced energy–protein supplementation during pregnancy, reported a mean difference in increased birthweight of 37.6 g. Five of the nine trials that used UNIMMAP produced increases in mean birthweight greater than 30 g. The increase in mean birthweight achieved by use of the multiple micronutrient supplement is of course on top of any increase that might be achieved by the iron–folic acid supplements. Without a true placebo, we can only speculate on whether the iron–folic acid supplements also improved birthweight. However, there is a growing body of evidence which suggests that iron supplementation does improve birthweight, even in nonanemic women, suggesting benefits to maternal health beyond that seen for maternal anemia and iron deficiency, which may act through improving placental or fetal metabolism to facilitate fetal growth through pathways that do not involve maternal hemoglobin concentration [65].

Several newer trials, which were not included in the Cochrane review of multiple micronutrient supplementation [66] or in this meta-analysis that complements it, have also shown that multiple micronutrient supplementation during pregnancy increases birthweight. In a hospital-based trial among apparently healthy, well-nourished French women, a multiple micronutrient supplement without iron taken during the last 6 months of pregnancy not only improved blood levels of vitamin B_2, vitamin B_6, vitamin C, vitamin E, β-carotene, and folate, but also increased birthweight by 251 g as compared with the placebo [67]. The results of a hospital-based trial among thin (BMI < 18.5) and/or anemic women in New Delhi, India, showed that a supplement containing 29 vitamins and minerals taken in addition to the regular iron–folic acid supplement during the last trimester of pregnancy increased birthweight by 98 g, increased birth length by 0.80 cm, and reduced early neonatal morbidity by 50% [68], as compared with placebo. The increase in mean birthweight meant that the incidence of LBW was reduced from 43.1% to 16.2%, which seems truly remarkable in the Indian context, where a third of all births are LBW. If the results of this New Delhi trial can be replicated in other locations, multiple micronutrient supplementation could provide an important new tool for trying to solve the LBW problem in India.

The meta-analysis finding that the positive effect of multiple micronutrient supplementation on birthweight was greatest in heavier women and was low or even negative among women with low BMI is not easy to interpret. It may in part be an artefact caused by the way mothers' BMI status was determined, whereby weight on entry was regressed linearly to 15 weeks. Since weight gain in pregnancy is not linear, this will overclassify as thin those who entered the study early. Although admitting that the trials were not designed to examine interactions with maternal size, Fall et al. [11] hypothesized that the thinner mothers were not able to utilize the micronutrients because they were energy deficient. This seems unlikely, however, since among undernourished mothers (assessed by mid-upper-arm circumference < 23.5 cm) in the Lombok (Indonesia) trial, the multiple micronutrient supplement had a stronger positive effect on birthweight than the iron–folic acid supplement [15], a result similar to that seen in the trial of multiple micronutrients among thin women in New Delhi [68]. Furthermore, a similar partitioning was shown in mothers receiving food supplements, with the benefits accruing more to the mothers and less to the fetus in mothers with low BMI as compared with mothers with higher BMI [69]. This suggests that the partitioning of effect observed in women with low BMI who receive micronutrient supplements either is an artefact produced by the method of analysis or is due to something other than, or in addition to, energy sufficiency.

A low BMI in a mother can also be a reflection of younger age and greater immaturity. In the United States, where menarche occurs at around 12 years of age and girls continue to grow until 18 years of age on average, late-maturing girls tend to be thinner and grow taller than early-maturing girls [70, 71]. In developing-country settings, many girls, especially those in rural areas, are still growing into their late teens and even past 20 years of age [72]. Research in the United States has shown that if a still-growing adolescent becomes pregnant, her growth hormones favor the partitioning of growth to the mother at the expense of the fetus [73]. In energy-rich environments such as the United States, this results in the still-growing adolescent's accumulating extra fat at the end of the pregnancy. In energy-poor environments of rural Bangladesh, however, pregnancy and lactation during adolescence result in weight loss and depletion of fat and lean body mass, as well the cessation of linear growth of the mother [74]. A study in Mexico also found that multiple micronutrient supplements increase energy intake by the mother during pregnancy [75], which in an energy-rich environment is likely to contribute to increased fat accretion.

These partitioning and energy-saving mechanisms, which operate under hormonal control during first pregnancies among still-growing adolescents, could be attenuated more by the multiple micronutrient supplements than by the iron–folic acid control supplements. Zinc supplementation has been shown to increase growth and the production of insulin-like growth factors in Vietnamese children [76]. It may be that the zinc in the multiple micronutrients stimulates the production of growth hormone factors, which promote the growth of the young, still-growing child–mother at the expense of the growth of her fetus.

For most biological outcomes, the optimal birthweight is greater than the mean birthweight, and although the highest risk of an undesirable outcome is usually found for birthweights below 2.5 kg, the lowest risk is usually in the 3.5- to 4-kg group [77]. The outcomes that follow this pattern are many and include infant mortality in populations with high levels of intrauterine growth retardation (IUGR) [78] and cognitive function in the United Kingdom [79], for example. Thus, when a small increase in mean birthweight occurs and is evenly distributed across the whole population, as is the case for the increase in birthweight associated with the use of multiple micronutrient supplements, the whole population benefits. In the meta-analyses, very few if any infants had birthweights above 4 kg except for those in China, Guinea-Bissau, Lombok (Indonesia), and Zimbabwe.

Optimal fetal and infant growth is increasingly recognized to confer many benefits across the life course. As shown in the Vietnam trial reported in this volume, the small increase in mean birthweight achieved by multiple micronutrients as compared with iron–folic acid resulted in a 30% reduction in stunting rates in these children at 2 years of age [25]. These findings are similar to those achieved by food supplements provided during the last 3 months of pregnancy to mothers in Java, Indonesia, whereby a birthweight increase of nearly 100 g resulted in a 20% reduction in stunting at 5 years of age [80]. Reducing the rate of LBW is recognized to confer substantial economic benefits [81], and improved fetal and infant growth is recognized to contribute greatly to improving human capital across the life course [82], including reduction in the risk of diabetes and high blood pressure later in life [83].

It is of great concern that although the meta-analysis of mortality found no statistically significant differences in the rates of stillbirth or neonatal death between the groups of mothers supplemented with multiple micronutrients and those supplemented with iron–folic acid, the risk of early neonatal mortality was increased by 23% [12]. Although not statistically significant, this effect was seen in all trials except the two in Indonesia. Although the meta-analysis found no significant difference in the effect on the rate of premature births between mothers supplemented with multiple micronutrients and those supplemented with iron–folic acid, evidence from the trials in China [22] and Sarlahi (Nepal) [17] suggests that both multiple micronutrient and iron–folic acid supplements reduced the rate of premature births as compared with a control. However, the multiple micronutrient supplements not only reduced the rate of premature births but also reduced the rate of IUGR and shifted the whole birthweight distribution upward [84]. It may be that larger babies are the source of the possible excess neonatal mortality, causing problems for young adolescent primiparous mothers with relatively narrow, immature birth canals in particular. The rate of premature births also appears to be higher in this group of mothers, so conversely, excess neonatal mortality may be due to increased mortality among nonviable premature neonates born to young adolescent primiparous mothers.

But perhaps what is most surprising is that the apparently negative effect of the multiple micronutrient supplement is in the neonatal part of the reproductive losses. If multiple micronutrients were causing harm to the fetus, one would expect it to manifest itself more in stillbirths, but this did not occur. However, not only is there no evidence of harm to the fetus, but to the contrary, there seems to be benefit, as reflected in lower stillbirth rates and greater birthweight. Any possible negative impact seems to be in the neonatal part of the reproductive losses, which is more likely to be a reflection of the condition of the mother and placenta, the standard of health care during delivery and postpartum, or both.

The meta-analysis of mortality outcomes did not look at the possible interactions of the effects of micronutrient supplementation with maternal BMI and/or parity, as was done in the meta-analysis of birth size. However, several of the individual trials reported that the lack of effect, or even the negative effects, of the multiple micronutrient supplement compared with the iron–folic acid supplement occurred mainly in primiparous mothers. In Lombok (Indonesia) the beneficial effects of multiple micronutrient supplements on 90-day mortality found overall was not seen in primiparous mothers or young mothers (< 19 years of age). In Burkina Faso, the negative effect of multiple micronutrient supplements was associated with primiparity, although the effect was not statistically significant ($p = .11$) [21].

Some insights into the possible causes of the lack of impact, or even the possible negative impact, of the multiple micronutrient supplements on neonatal mortality are afforded by looking at the results obtained by trials that used other "controls" and different types of multiple micronutrient supplements. The Sarlahi (Nepal) trial [85] found no significant difference in 90-day mortality between the group receiving vitamin A plus iron–folic acid and the group receiving multiple micronutrients as compared with the local "control" mothers receiving only vitamin A supplements. But although both vitamin A plus iron–folic acid and multiple micronutrient supplements significantly reduced mortality among preterm infants as compared with controls, and both increased birthweight, the multiple micronutrient supplement, but not the iron–folic acid supplement, increased birthweight across the whole distribution [84]. Interactions between these differences in neonatal mortality and maternal parity, age, or BMI were not reported, but other studies at the Sarlahi trial site have found that in primiparae, young maternal age (< 18 years) is associated with an increased risk of preterm delivery as compared with a maternal age of 19 to 25 years [86]. The offspring of younger mothers also have a higher neonatal mortality rate [87]. The possibility that the decreased rate of preterm deaths and the increased rate of term deaths in the group receiving multiple micronutrients in Sarlahi were concentrated in still-growing adolescent mothers whose birth canals had not yet fully developed seems a likely one.

Prematurity was also part of the picture in the China trial [22], where the groups receiving multiple micronutrient and iron–folic acid supplements were compared with the "control" mothers receiving supplements of folic acid. Although there were no differences in the mean duration of gestation between the group receiving iron–folic acid and the group receiving multiple micronutrients, there were significant increases in duration of gestation in both groups compared with the folic acid control group. Furthermore, even though birthweight increased only in the group receiving multiple micronutrients, early neonatal mortality was significantly reduced only in the iron–folic acid group as compared with the folic acid control group. Although there were more first pregnancies in the Chinese than in the Sarlahi mothers (63% vs. 26%), the Chinese mothers were on average 2 years older and 8 cm taller, and only 1% of the Chinese mothers were under 18 years of age. Zeng et al. [22] further suggested that the difference in early neonatal mortality in the China trial was caused by the different levels of iron in the supplement (60 mg in the iron–folic acid supplement and 30 mg in the multiple micronutrient supplement), and that the differences in neonatal mortality seen in all the other trials except Lombok (Indonesia) were also caused by this difference between supplements in iron level.

Unlike all the other trials, the risk of early neonatal mortality was greater in the iron–folic acid group in both the Lombok and the Indramayu trials in Indonesia. This was the case even though in the Indramayu trial, the multiple micronutrient supplement contained 30 mg of iron and the iron–folic acid supplement contained 60 mg of iron, as opposed to the Lombok trial, in which both supplements contained 30 mg of iron. Furthermore, the beneficial effects of the multiple micronutrient supplement on early infant mortality in the Lombok trial were improved when the supplement was provided by the local village midwife and the birth attendant was a trained one. A large nationwide study in Indonesia has shown that the provision of postnatal care has a strong protective effect on neonatal mortality, with a progressive reduction in the risk of neonatal death as the percentage of deliveries by trained birth attendants increases [88]. It seems likely that the difference in the effect of the multiple micronutrient supplement on early neonatal mortality in Indonesia as compared with elsewhere is a reflection of the greater adequacy of perinatal health care provided by its extensive network of village midwives.

Care is needed before drawing rapid and inappropriate conclusions from the meta-analysis of mortality. The Lombok (Indonesia) trial was removed from the meta-analysis of mortality primarily because of its contribution to the between-study heterogeneity for the early neonatal mortality outcome. But it was not removed for the other outcomes, such as birthweight. The heterogeneity of the effect of multiple micronutrient supplements on early neonatal mortality may well be more a reflection of the adequacy of perinatal health care than of differences in the biological causes of early neonatal mortality and/or of the conditions of the mother rather than those of the fetus. Furthermore, in Lombok, mortality in the second and third months of life was 25% lower among infants of mothers who had received multiple micronutrients than among infants of mothers who had received iron–folic acid [15]. It is worth remembering also that the relationship between birthweight and infant mortality is population specific, and consequently the same birthweight interval does not have the same mortality risk in different ethnic or racial groups [89].

The meta-analysis raises the question as to whether the increase in birthweight caused by the multiple micronutrient supplement is potentially dangerous and might be contributing to increased neonatal mortality, as suggested by the investigators in the Sarlahi trial [84]. However, as the meta-analysis of birth size pointed out, the part of the body most likely to increase the risk of cephalopelvic disproportion is the head, and head circumference was not increased by the multiple micronutrient supplements. One study that has looked at the effect of food supplementation on birthing difficulties in detail is a trial in the Gambia where food supplements fed to mothers during pregnancy produced an increase in mean birthweight of 126 g, which was not associated with increased birth complications, and the increase in head circumference was only of the order of 1 mm [90]. Although the UNIMMAP trials were not powered to test the effect on maternal mortality, there was no evidence that the multiple micronutrient supplements increased maternal deaths in the large Lombok (Indonesia) trial, for example, and the Guinea-Bissau trial reported "substantial reductions in maternal mortality" in the group receiving multiple micronutrients [23], although the authors did not present the data and the trial was obviously not powered to look at this outcome.

The proportion of women with BMI less than 18.5 was relatively low in Africa (5.5% in Guinea-Bissau and 11% in Burkina Faso) and in the Asia-Pacific region (8.3% in Indonesia and 10.7% in China) but was higher in South Asia (20.4% in Pakistan, 27.9% in Janakpur, and 28.5% in Bangladesh). This may be a reflection of teenage pregnancy rates, which are well known to be high in the Indian subcontinent. For example, the proportion of women who have begun childbearing by age 17 is 20% in Nepal [91] and 37% in Bangladesh [92], which indicates the need for more attention to this issue from a children's rights perspective. Although 21% of women in Burkina Faso have also begun childbearing by age 17, they are taller than women in the Indian subcontinent when they begin childbearing [93]. The percentage of women aged 15 to 19 with height below 145 cm is less than 1% in Burkina Faso compared with 14.2% in Nepal and 15.7% in Bangladesh. It is essential that programs in South Asia address the nutritional status of women throughout the life course in order to reduce the prevalence of low BMI, low height, and associated health issues during pregnancy, for the sake of both the mother and the child. In these contexts, food-based supplements should be the product of choice, but in addition to rather than instead of multiple micronutrients (or through a fortified-food supplement, such as a lipid-based nutrient supplement or a ready-to-use supplementary food). In other populations, screening women for low BMI and low height and providing such women with increased food intake along with multiple micronutrients would be appropriate. These actions should go hand-in-hand with improving delivery and neonatal care, along with ongoing efforts to improve health and education systems, health and nutrition services capacity, and water and sanitation interventions.

Clearly there is a need for a single, consolidated source of WHO policy and program guidance on maternal nutrition during pregnancy and lactation, expanding on the program guidance on mothers' health and nutrition that is contained in the Global Strategy on Infant and Young Child Feeding [94]. Given the existing recommendation on the use of multiple micronutrients in emergencies, urgent attention needs to be paid to why the use of multiple micronutrients has not been expanded, when many women are experiencing the same negative factors while in a supposedly non-emergency situation.

Although there is a WHO recommendation that blanket supplementation with balanced protein–energy foods should be provided to women during pregnancy where LBW rates are greater than 15% [95], this is not widely appreciated, and neither is there program guidance on how to do it. The WHO Reproductive Health Strategy [96] mentions the word nutrition only twice and anemia not at all. Further discussions and review of existing program guidance are also contained in the SCN Policy Paper No. 18 on Low Birthweight [97], but little or none of this program guidance covers issues related to adolescent nutrition and teenage pregnancy. Although the need for a continuum of health and nutrition care across antenatal and early childhood periods in order to promote optimal fetal and infant growth and development is increasingly recognized, the translation of this into comprehensive programmatic guidelines for delivering the appropriate packages of interventions is still lacking and is urgently needed.

The lack of program guidance is perhaps a reflection of the complexity of the relationships between maternal nutrition and reproductive health outcomes and the failure of the nutrition community to adequately describe them to date. There is an urgent need to develop and strengthen the monitoring and evaluation of programs aimed at promoting improved maternal, fetal, infant, and young child nutrition, growth and development [98].

What are the implications of our findings for public health? Given the apparent benefits of multiple micronutrient supplementation, any suggestion of possible harm must be carefully reviewed to consider alternative explanations and to balance the potential gains and harms. Improving micronutrient intake during pregnancy reduces micronutrient deficiencies in mothers and increases birthweight. The surprising finding in the meta-analyses of a higher rate of early neonatal mortality in the group receiving multiple micronutrient supplementation when Lombok (Indonesia) was excluded underscores the need to enhance maternal and neonatal health care services in developing countries to improve the nutritional status of women prior to pregnancy and to protect maternal and neonatal health care during delivery. This conclusion is strongly reinforced by other aspects of maternal health and mortality and the inadequate progress towards Millennium Development Goal 6. The fact that women with low BMI are disadvantaged in many ways also reinforces the recommendations of the final report of the WHO Commission on Social Determinants of Health, which suggests, among other actions, increased focus on adolescent girls and on the circumstances of childbirth, as well as on child development, education, and social protection [99]. Increased attention must be given to improved community care to address households and pregnant women while current efforts to strengthen health systems go ahead. Whatever is recommended, and however cautiously the findings of the meta-analysis are interpreted, program and policy makers, donors, or indeed researchers, should not be let off the hook with regard to the need to make public health changes, given the urgent need to do something about the unnecessary deaths and poor development of millions of mothers and children in poor environments; somehow the intergenerational cycle of growth failure needs to be broken.

Conclusions

In summary, improving micronutrient intake during pregnancy reduces micronutrient deficiencies in mothers and increases birthweight. This paper suggests that multiple micronutrients are just as effective as iron–folic acid in reducing anemia and that good adherence can be achieved with maternal micronutrient supplements during pregnancy when the supply is guaranteed and mothers are counselled positively, including counselling on normal side effects. When so provided, multiple micronutrients increase mean birthweight and reduce the incidence of LBW, which also leads to improved child growth and development. The findings point to the need for improving maternal nutritional status before as well as during pregnancy, since intervening in pregnancy is too late. In settings where there is a significant number of undernourished pregnant women, supplementary feeding is also needed. The findings point to the importance of an integrated approach to addressing infectious disease (worms, malaria) along with nutritional status during pregnancy in order to bring about the necessary improvement in birthweight. The finding again reinforces the message that we cannot address Millennium Development Goal 4 without addressing Millennium Development Goal 5. Furthermore, there is an urgent need to take on the issue of adolescent pregnancy from a both from a children's rights and children's protection perspective, as well as from a gender perspective. This is perhaps one of the most urgent and critical of gender issues to be resolved in Millennium Development Goal 3, and that also has implications for the achievement of many of the other Millennium Development Goals.

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